Study supporting the Impact Assessment of the Revision of Directive 2002/98/EC on safety and quality of human blood and blood components and of Directive 2004/23/EC on safety and quality of human tissues and cells and of their implementing acts

Final Report

Written by ICF S.A.
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Final Report

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Glossary

Term	Definition / Interpretation
Audit	A process of checking the validity and quality of the system operated by a Member State to implement the oversight and inspection provisions of a legislative framework
Inspection	The procedure undertaken by a competent authority, to check the compliance of an authorised establishment regulated under the BTC legal framework, with that framework's requirements for quality, safety etc.
Measure	A specific policy intervention that forms a component of a policy option.
Option	A number of measures bundled together into a package that addresses one or more problem drivers
Theory of change	A narrative explanation of how planned policy actions are expected to lead to desired outcomes.

Acronyms and abbreviations

Term	Definition / Interpretation
AATB	American Association for Tissue Banks
ACI	Autologous chondrocyte implantation
ADM	Acellular dermal matrix
ADSC	Adipose-derived stem cells
ARM	Alliance for Regenerative Medicine
ART	Assisted reproductive technology
ATMP	Advanced therapy medicinal product
BE	Blood establishment
BTC	Blood, tissues and cells
CAGR	Compound annual growth rate
CAT	Committee for Advanced Therapies (within the EMA)
CCP	COVID Convalescent Plasma
DBM	Demineralised bone matrix
DHBM	Donor human breast milk
EBA	European Blood Alliance
ECDC	European Centre for Disease Prevention and Control
EDQM	European Directorate for the Quality of Medicines of the Council of Europe

Term	Definition / Interpretation
EMA	European Medicines Agency
EMBT	European Society for Blood and Marrow Transplantation
ESHRE	European Society of Human Reproduction and Embryology
ESI	Emergency Support Instrument
EU	European Union
EVs	Extra-cellular vesicles
FMT	Faecal microbial transplant
GMP	Global Manufacturing Processes
HTs	Hepatocyte transplantations
HSC	Hematopoietic Stem Cells
ICSI	Intracytoplasmic sperm injection
IVF	*In vitro* fertilisation
MAR	Medically assisted reproduction
MDR	Medical Devices Regulation
NCA	National competent authority
PBM	Patient blood management
PDMP	Plasma-derived medicinal products
Pharma	Pharmaceutical
PID	Primary immunodeficiencies
PMF	Plasma Master File
PPTA	Plasma Protein Therapeutics Association
PRP	Platelet-rich plasma
QALY	Quality adjusted life years
R&D	Research and development
RAB	Rapid alert system for blood
RATC	Rapid alert system for tissues and cells
SAE	Serious adverse events
SAR	Serious adverse reaction
SAREs	Serious adverse reactions and events
SEC	Single European Code

Term	Definition / Interpretation
SEDs	Serum eye drops
SoHO	Substances of human origin
SMEs	Small and medium enterprises
TE	Tissue establishment
US	United States
VISTART	Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction and Transplantation – Joint Action
VHD	Valvular heart disease
VUD	Voluntary and unpaid donation
WHO	World Health Organisation
WS	Workshop

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Disclaimer

1. Introduction

This is the **final report** of a study commissioned by the Health and Digital Executive Agency (HaDEA) to support the European Commission's assessment of the impacts of proposed reforms to Directive 2002/98/EC and Directive 2004/23/EC and their implementing acts - the European Union (EU)'s legislation on blood, tissues and cells (BTC).

It is informed by desk research, a series of stakeholder workshops, targeted data requests, surveys of national competent authorities (NCAs) and of BTC establishments and wider sector stakeholders, and a series of interviews with representatives of individual and representative organisations, competent authorities and other stakeholders. More information on the methodology can be found in Annex 4 of this document.

In this document 'Public Consultation' means the consultative process launched by the European Commission that was open between 21 January and 15 April 2021 on the Commission's "Have Your Say" portal.

'Establishment survey' and 'NCA survey' refer to two surveys administered to stakeholders and NCAs by ICF during June/July 2021. The former attracted responses from stakeholder groups beyond BTC establishments, as described in the text.

2. Problem definition

The problem definition for the legislative reforms has been developed in detail in the evaluation of the existing legislation[1]. This study was required to conduct supplementary research on two specific aspects of the existing problem:

- The impact of the COVID-19 pandemic; and
- The borderline issues between BTC and adjacent legislative frameworks.

This section provides a summary of this research. A detailed commentary of the results of the research undertaken on these issues is provided in Annex 3.

2.1. The impact of the COVID-19 pandemic on the sector

The COVID-19 pandemic affected the BTC sector in many ways, including through: reducing donor availability; reducing the capacity of collection establishments to accommodate donors due to social distancing measures; reducing the availability of staff at Substance of Human Origin (SoHO) facilities; changing demand for SoHO products; and causing issues with provision or distribution of critical materials, equipment, and SoHO products.

On the one hand, the BTC sector demonstrated an ability to adapt when faced with challenges created by the COVID-19 pandemic. New procedures to facilitate social distancing and increase infection control processes were implemented by establishments. Additionally, the COVID-19 pandemic highlighted the importance of EU cooperation with Member States and the BTC sector. This allowed several non-legislative actions to be undertaken in response to the pandemic.

For example, non-binding guidance on donor selection and testing was prepared by the European Centre of Disease Control (ECDC) in March 2020[2]. Furthermore, the European

[1] European Commission (2019). Commission Staff Working Document: Evaluation of the Union legislation on blood, tissues and cells {SWD(2019) 376 final}. Brussels. Available from: https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/swd_2019_376_en.pdf.

[2] Measures to mitigate the risk of COVID-19 transmission including the implementation of stricter donor selection criteria and donor deferral criteria, donor testing for COVID-19 and the use of viral inactivation techniques were outlined.

Commission committed €36 million to 24 projects to support Covid Convalescent Plasma (CCP) collection through the Emergency Support Instrument (ESI) and established the EUCCP Database through cooperation with Member States. The European Commission also published a guidance document on the preparation and use of CCP, as well as a clarification that SoHO are considered to be essential goods/services, for which free circulation within the EU is crucial.

On the other hand, based on the experiences of the pandemic, stakeholders (including non-governmental organisations) have argued that the SoHO supply chain is not adequately prepared for epidemiological emergencies and crises. Specific issues that were reported include:

- A decrease in the donation and collection of SoHO (mitigated initially by the reduction in elective procedures in hospitals), and difficulties in collecting and forecasting needs for SoHO after the first lockdown.
- Difficulties with oversight of BTC activities reported by many BTC establishments and NCAs. For example, it was not possible to do on-site inspections during the height of the pandemic; desk-based or remote inspections (sometimes with a virtual component) were undertaken instead.
- The legislative provisions in the BTC legislation could not be updated rapidly enough to address quality and safety impacts of COVID-19 on the BTC sector. For example, respondents to both the surveys undertaken with NCAs and establishments conducted for this study[3] identified the greatest weaknesses of the legislation in the context of the pandemic response to be the lack of a legally binding requirement that ECDC donor selection and COVID-19 testing guidance be followed. Respondents underlined that this might have resulted in the circulation of SoHO that did not comply with this guidance (as Member States could not insist on these requirements being mandatory).
- Other problems respondents identified were the lack of a provision for monitoring of the supply situation, lack of proportionate approach to the quick assessment of novel therapies (i.e. CCP) and lack of provision for export bans.

2.2. Borderline issues between adjacent regulatory frameworks

Specific borderline issues between adjacent regulatory frameworks, and the impacts of these, are detailed in case studies presented in Annex 9.

Evidence examined for the present study suggests that the lack of clarity on the regulatory status of emerging novel therapies has had a number of negative impacts for the sector as a whole and, that this may be contributing to inequitable patient access to novel therapies. This lack of clarity generally arises in relation to the medicinal product legislation, the Advanced Therapy Medicinal Product (ATMP) Regulation and Medical Devices Regulation (MDR). A recurrent issue demonstrated by the borderline case studies is that Member States' regulation of the borderlines is not harmonised. Lack of harmonisation was documented for autologous adipocyte cells, decellularised dermis, decellularised heart valves, demineralised bone, faecal microbiota transplants (FMT), donor human breast milk (DHBM), isolated hepatocytes, platelet rich plasma (PRP), and serum eye drops (SEDs).

Several definitions and terms used in the BTC legislation lack clarity. The resulting legal uncertainty leads to divergent interpretations and classifications of BTC products. The definitions or terms most frequently cited in this context are those intended to provide a clear demarcation between where the scope of the BTC legislation ends, and where the

[3] Information about the methodology of the data collection for this study is presented in Annex 4.

scope of 'adjacent' legislation begins. Terms which have caused uncertainties include "substantial manipulation" and "non-homologous use"; these are unclear determinants for classifying an ATMP. Other definitions that are considered to be contributors to the borderline problem are found in the MDR and other requirements related to medical devices: "placing on the market"; and "derivative". The perceived lack of clarity of terms such as "substantial manipulation" and "non-homologous use" led to a 2014 Committee for Advanced Therapies (the CAT) reflection paper on classification of advanced therapy medicinal products[4].

The evidence examined in the present study (detailed further in Annex 9) indicates that some borderline products may not meet uniform standards of quality and safety. For example, the case study on SEDs indicates a direct correlation between the regulatory approach (classification of a product) taken by a Member State and the ability of patients to access SEDs that conform to a standardised set of quality and safety procedures. This will potentially result in unequal patient access to safe, high quality products across the EU. It is well documented[5,6] that the co-factors of regulatory uncertainty and complexity create an environment inimical to innovation and a barrier to the free movement of products across the EU, which in turn affects patient access. Conversely, gaps or 'loopholes' in the legislation have led to patients being provided with access to unsafe/unproven borderline therapies.

The borderline problem also extends to the operation of the market as measured by innovation, affordability, and the economic viability of the sector. Despite the growth of public-private collaborations between academia and industry, feedback collected during the consultations frequently referred to that fact that an environment of regulatory uncertainty and complexity will negatively affect investment in research and development (R&D) and therefore reduce innovation (and interest from commercial actors who can scale up treatments and therapies) in Europe. Stakeholders from the European Medicines Agency (EMA) Taskforce reported that some developers leave the EU for the US due to difficulties with varied Member State requirements.

Some of the borderline substances are of restricted clinical applicability and therefore of limited interest for commercial companies/entities, thus potentially hampering patient access to these products.

In summary, the lack of clarity on the regulatory status of emerging novel therapies – which generally arises between the medicines legislation as a result of the definitions/terms used to classify different products – has led to the divergent interpretations and classifications of BTC products and reduced harmonisation in the regulation of novel products across the EU. In turn, this regulatory confusion has impacted on levels of quality and safety and challenged the pace of innovation.

3. Objectives

The specific objectives for the proposed reforms to the EU's BTC legislation are:

- Objective 1: Increase patient protection from all avoidable risks

[4] European Medicines Agency (2014). Reflection paper on classification of advanced therapy medicinal products. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-reflection-paper-classification-advanced-therapy-medicinal-products_en.pdf

[5] Pirnay, J. P., Vanderkelen, A., De Vos, D., Draye, J. P., Rose, T., Ceulemans, C., Ectors, N., Huys, I., Jennes, S., & Verbeken, G. (2013). Business oriented EU human cell and tissue product legislation will adversely impact Member States' health care systems. Cell and tissue banking, 14(4), 525–560. https://doi.org/10.1007/s10561-013-9397-6

[6] Verbeken G, Draye JP, Fauconnier A, Vanlaere I, Huys I, et al. (2020). The Magistral Preparation of Advanced Therapy Medicinal Products (ATMPs). J Surg Practice. 2020;2(1):16. DOI: 10.36879/JSP.20.000116. Available from: http://globalsciencelibrary.com/article/The+Magistral+Preparation+of+Advanced+Therapy+Medicinal+Products+%28ATMPs%29

- Objective 2: Strengthen and harmonise oversight among Member States
- Objective 3: Increase protection of BTC donors, and children born from donated sperm, eggs or embryos, from specific risks
- Objective 4: Facilitate innovation of safe BTC therapies
- Objective 5: Avoid shortages of critical BTC therapies

Policy measures have been developed to help achieve each objective. These are described in the following section and in further detail in Annex 3.

4. Option definition

4.1. Baseline scenario

The impacts of revising the EU's BTC legislation need to be assessed against a reference, or baseline scenario, that captures expectations of the future evolution of the regulated system, and the problems within it, under an assumption that the legal framework is not reformed. This baseline should be a forward projection of how the system is expected to evolve, rather than simply an assumption that the future looks exactly like today.

4.1.1. The BTC sector and its expected evolution

Blood, tissues, cells (and other SoHO) are used in a variety of medical therapies and in the creation of medical devices and medicinal products, as well as for research. Treatments based on these substances of human origin save lives (such as blood transfusion in case of trauma), improve the quality of life (such as ocular tissue transplants), and help create life (gametes and *in vitro* fertilisation).

Data on current activity levels and the scale of the BTC sector are provided in Annex 13. The EU27 host around 1400 blood establishments (BEs) and more than 3200 tissue and cell establishments (TEs)[7]. The sector encompasses public sector, not-for-profit and private sector establishments. Registered BTC establishments range from units within public hospitals to networked charitable enterprises, to independent commercial companies.

The blood sector comprises a largely public whole blood and blood components sub-sector, and a largely commercial plasma and plasma derivatives sub-sector. Whole blood and blood components donations are used mostly for transfusions, while plasma, the liquid component of blood that is recovered from donated whole blood or collected in plasmapheresis centres, is used to manufacture medicinal products (such as immunoglobulins or clotting factors, so-called plasma derivatives). Plasma collection is often conducted in for-profit centres and plasma donors often receive compensation[8].

The evaluation of BTC legislation previously conducted for the Commission noted that demand for blood for transfusion has plateaued, or even decreased slightly, due to the development of new therapies and to more restrictive transfusion protocols. In contrast, there has been a steady and significant global increase, over 9% per year[9] in the global use

[7] ICF analysis of Tissue and Cells Compendium data from June 2021 identified 3,238 establishments (Annex 13.3).

[8] ICF (2018). Study supporting the evaluation of the EU legislation on Blood and Tissues and Cells (SANTE/2017/B4/010) - Final report. Published by the European Commission. Available from: https://op.europa.eu/en/publication-detail/-/publication/c1c3414c-ec23-11e9-9c4e-01aa75ed71a1/language-en/format-PDF/source-239053397

[9] Allied Market Research (2018). Blood Plasma Derivatives Market by Type (Albumin, Factor VIII, Factor IX, Immunoglobulin, Hyperimmune Globulin, and Others), Application (Hemophilia, Hypogammaglobulinemia, Immunodeficiency Diseases, von Willebrands Disease (vWD), and Other Application), and End User (Hospitals, Clinics, and Other End Users) - Global Opportunity Analysis and Industry Forecast, 2016-2023. Available from: https://www.alliedmarketresearch.com/blood-plasma-derivatives-market

and market for plasma-derived medicinal products, and therefore in demand for plasma donation. The plasma is manufactured by fractionators into medicinal products such as clotting factors, albumin and immunoglobulins.

Detailed data on TEs are available from the online database maintained by the European Commission (Reference Compendia for the Application of a single European Coding System for Tissues and Cells). Four Member States – Germany, Spain, France and Italy – together host more than 60% of all these establishments, approximately proportionate to their share of EU population. Annex 13.3 provides further detail on the distribution of TEs across the EU and the type of activity they undertake, as well as information on the number and types of authorisations they hold.

The activities regulated by the EU's BTC legislation include areas where practices are comparatively mature (e.g., blood donation) through to those where significant further innovation in technology and practice is foreseen over the next ten years (e.g. certain applications of tissues and cells, and plasma). Due to limited time series data for the EU27, it has not been possible to fully profile changes in activity within the BTC sector, but there are some examples (illustrated by the data on transfusion recipients shown in Figure 1).

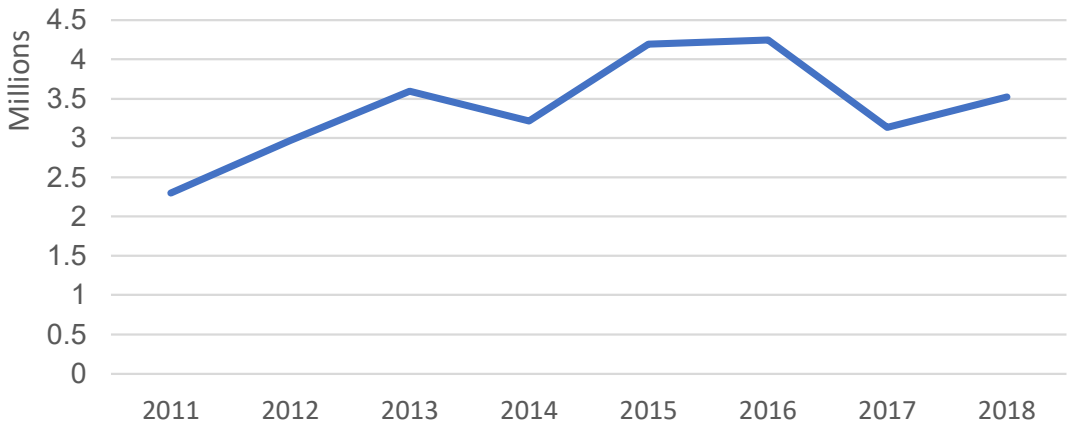


Figure 1: Number of blood recipients transfused, 2011-2018 as reported to the European Commission

Source: European Commission, 2020. Summary of the 2019 annual reporting of serious adverse reactions and events for blood and blood components (data collected from 01/01/2018 to 31/12/2018).

The research did not allow to develop reference scenarios projecting changes in future demand for BTC or changes in the numbers of establishments. It did, however, provide some information on expectations of future changes. Specific examples identified through stakeholder consultations are provided below.

- There is a general expectation of growth in demand for MAR services due to factors that include changes in rules in some Member States and demographic change. The number of cycles reported to the European Society of Human Reproduction and Embryology (ESHRE) consortium has been growing at 10% per year[10].
- There is also an expectation of growth in new and emergent applications, exploiting the results of research and innovation (which is also taking place in a growing commercial sector) and increasing the use of such treatments to benefit more patients (including applications on the borderlines with other regulatory regimes, as discussed further below), including use in personalised medicine.

[10] The total number of cycles submitted to the ESHRE Consortium is now increasing by about 10% per year". Statement dates from analysis issued in 2019 on data from 2016. Source: European pregnancy rates from IVF and ICSI 'appear to have reached a peak', ESHRE. News release 25.06.2019 https://www.eurekalert.org/news-releases/543795 . Accessed 11 August 2021.

- It is predicted that, through further innovation, there will be a flow of novel BTC, some of which may be classified as ATMPs.
- It is likely new genetic tests will become available that would be relevant to screening of donors involved in medically assisted reproduction (MAR) and other donors.
- There is an expectation of more processing options and applications of SoHO or products that use SoHO as starting material becoming possible, leading to more borderline products that pose classification challenges for regulators.
- There is likely to be an emergence of comparatively new types of services that might be brought into the scope of BTC legislation, such as human breast milk banks.
- There is likely to be increased automation in BTC technologies.
- Development of innovative red blood cell technologies is also expected.

The stakeholder consultations did not provide consensus on how the overall number of BTC establishments will change in the years ahead. Some expect a degree of consolidation in the sector, with fewer small establishments as a result of pressures that includes the burden of regulatory compliance. Others have expectations of expansion as a result of growth in demand across the sector as whole, particularly in MAR, and in new BTC applications.

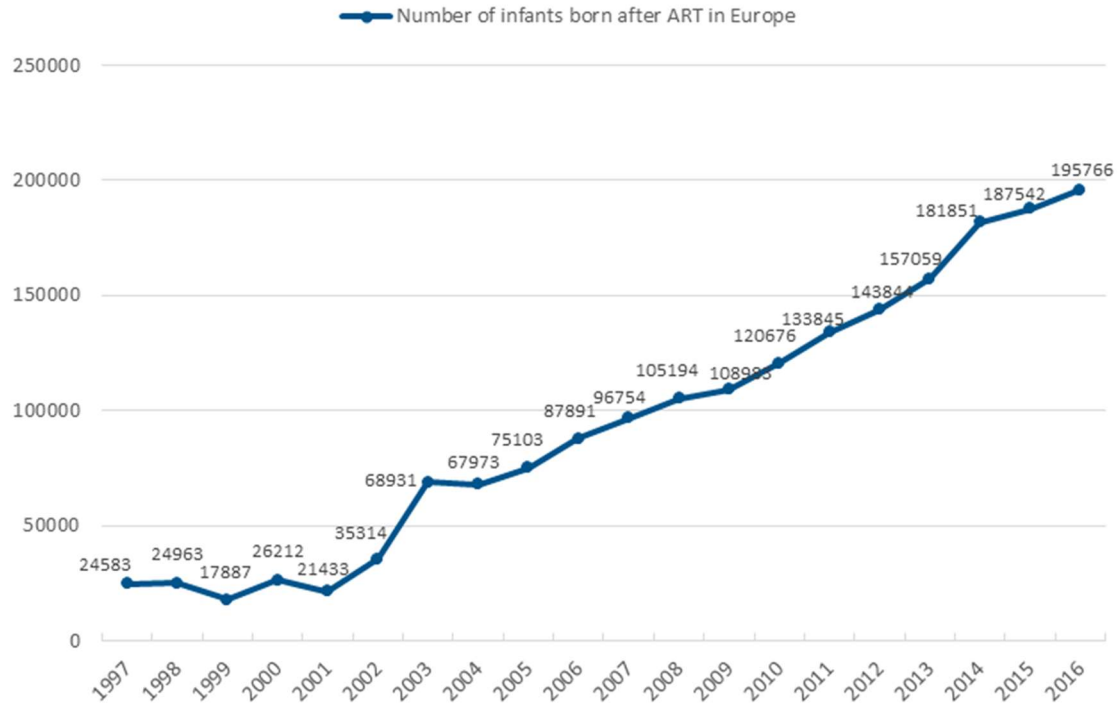


Figure 2: Numbers of children born from MAR in Europe[11]

Source: 20 years of the European IVF-monitoring Consortium registry: what have we learned? A comparison with registries from two other regions. Ch De Geyter et al. Human Reproduction, Volume 35, Issue 12, December 2020, Pages 2832–2849, https://doi.org/10.1093/humrep/deaa250

[11] Note: 'Europe' in this article includes more than the EU27 – beneficiaries of EU legislative reforms will be fewer. ESHRE data for 2017, covering 24 Member States estimate 125,779 ART infants, meaning infants born after IVF and ICSI cycles, which includes fresh and frozen cycles, cycles after preimplantation genetic testing, and cycles with donated oocytes, and excludes MAR techniques, such as ovarian stimulation or intra-uterine insemination

4.1.2. Expected evolution of problems

The following section considers how the issues identified in the evaluation of the EU's BTC legislation are expected to evolve in the future.

Responses to the establishments' survey[12] (whilst too few to be taken as fully representative of the sector) suggest the problems which the reforms are intended to address are expected to deteriorate further over the coming ten years if there is no reform of EU legislation (Figure 3). NCA respondents mostly expected either no change or the problems to get worse (Figure 4).

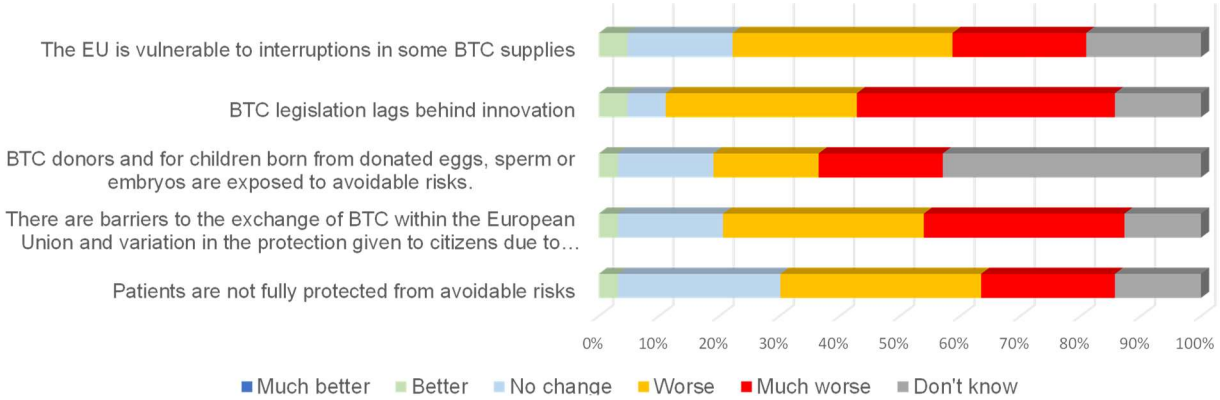


Figure 3: Establishment expectations of the future evolution of the problems that the reforms are intended to address

Source: Establishment survey. The European Commission has identified five problems with the current situation. In each case, how will the situation change over the next ten years if there is no change to EU legislation on BTC? n = 63

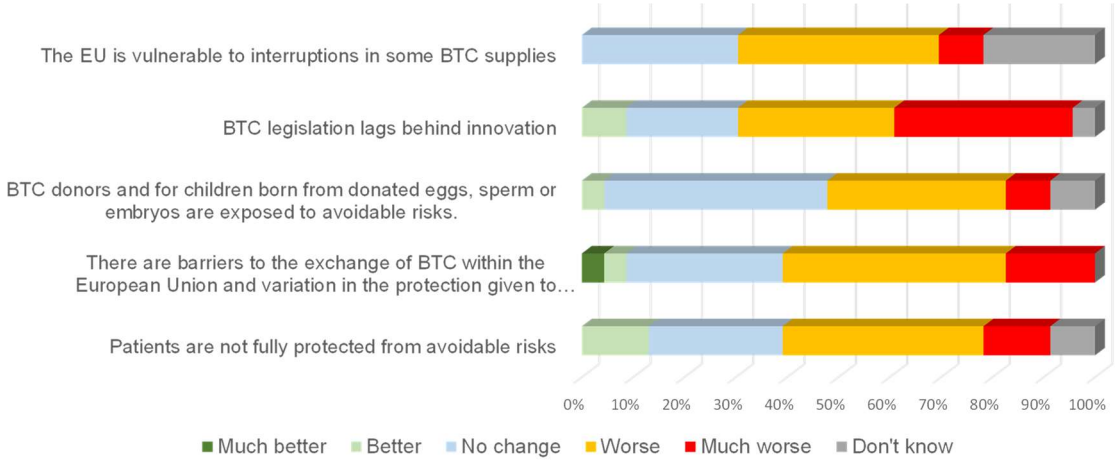


Figure 4: Few NCA respondents expect the current problems of concern to resolve themselves – most expect further deterioration or, at best, maintenance of the status quo

Source: NCA survey. The European Commission has identified five problems with the current situation. In each case, how will the situation change over the next ten years if there is no change to EU legislation on BTC? n = 23

These views are supported by comments in workshops and interviews, which regularly referenced issues such as increasing divergence of regulatory practice among Member States, lack of consistent standards of protection, increasing problems with exchange of BTC within the EU, and challenges in securing patient safety.

[12] Responses to this survey were not limited to BTC establishments but also concerned establishment activity (Annex 6).

Experts participating in the workshop on borderlines held in support of this study (attended by representatives of regulators and sector interests, see Annex 6 for a list of stakeholders consulted and Annex 11 for a summary of workshop notes) indicated that they expect to see increasing numbers of therapies being developed at the borderlines or crossing the borderlines with BTC / Pharma / ATMPs / Medical Devices[13].

The CAT also noted a 'clear increase' in applications for ATMP classifications and scientific advice, particularly since 2015/16, signalling that many more borderline or wider regulatory issues may arise that need resolving between adjacent frameworks. The recent formation of the EU-Innovation Network Borderline Classification Group (BLCG) – a new informal initiative that discusses borderline cases, some of which involve SoHO – also signals there will be a continued need to clarify the regulatory pathway for novel products.

There is a concern among stakeholders that the current regulatory framework for BTC does not support the EU's ambitions to be a leading centre for innovation, as reflected in programmes such as the Innovative Health Initiative[14]. In the EU a lack of harmonisation of regulations creates barriers to research and innovation, including facilitation of multi-country clinical investigations on novel BTC applications. The surveys suggest that the gap between legislation and the state of innovation will expand further in the absence of legislative reform (Figure 5).

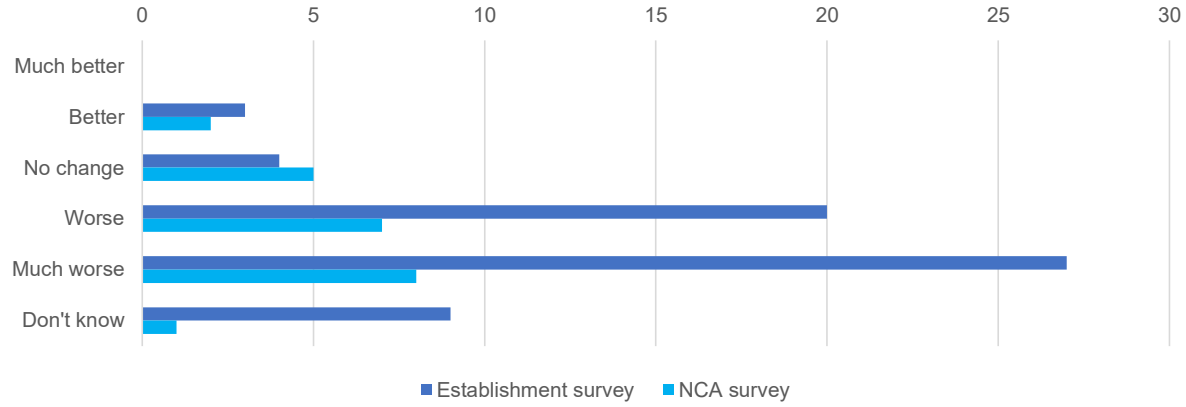


Figure 5: Stakeholders expect use of BTC in the EU to lag behind innovation in the baseline scenario – i.e., with no reform of EU law

Source: Establishment and NCA surveys. Question: "How will the situation change over the next ten years if there is no change to EU legislation on BTC?" Prompt – "BTC legislation lags behind innovation". N = 63 establishments, 23 NCAs.

The EU has historically been heavily reliant on the United States (US) for its supply of plasma. Actions taken by the Commission to help Member States cope with the COVID-19 pandemic (in helping Member States access machines used for the collection of CCP) have made some contribution to the EU's domestic capacity to collect plasma. But the structural barriers to achieving self-sufficiency in plasma are expected to continue in the baseline scenario, and the EU's dependency on US supplies is expected to persist.

A recurrent theme in consultations was the challenges associated with cross-border exchanges of BTC within the EU, with barriers created by differences in Member State regulations. Insofar as the Member States' regulatory environment is expected to continue as an extension of the current model in the baseline scenario, such challenges are expected to persist. Though data on exchange of BTC among the Member States are scarce and not

[13] Of 56 respondents to a poll at the workshop 36 responded 'very likely', 12 'likely' and 8 'possible' to the question *"With regards to future innovation, will there be increasing numbers of therapies developed at the borderlines or crossing the borderlines with BTC/Pharma/ATMPs/Medical Devices?"*

[14] The innovative Health Initiative is a public-private partnership which aims to "create an EU-wide health research and innovation ecosystem that facilitates the translation of scientific knowledge into tangible innovations" and contribute to a number of European policies, most notably Europe's Beating Cancer Plan, the new Industrial Strategy for Europe and the Pharmaceutical Strategy for Europe. More information can be found here: https://be.linkedin.com/company/innovative-health-initiative

systematically collected, the study gathered some key information on cross-border exchanges, which is provided in Annex 15.

Security of supply is expected to remain a concern. Barriers to exchange of BTC within the EU, caused in large part by variation in regulatory regimes, are expected to continue in the baseline scenario.

4.1.3. Regulatory baseline

Measures contained within the EU's legislative reforms will not impose additional burdens if they replicate requirements already adopted at Member State level. The variation in regulatory practice for BTCs around the EU means that this regulatory baseline varies by measure and by Member State. Research has been conducted to try to construct this aspect of the baseline scenario. Given the level of concentration of establishments in a few Member States, it was important to understand the regulatory *status quo ex ante* in Germany, France, Italy and Spain (the overall magnitude of impact of the proposed measures at EU level is particularly influenced by the extent to which equivalent measures are already implemented in those coutries). The current situation in these countries has been confirmed based on information provided by the relevant competent authorities. The situation in another 15 countries has been established through survey responses and email follow-up. Assumptions have been built for the residual Member States, as described in Annex 5.

4.1.4. Establishment risk assessments

The preparation and evaluation of establishment risk assessments as a regulatory requirement was explored in the NCA survey to inform the baseline situation for measures proposed under Objective 1. On the basis of the responses, and follow-up verification, it has been assumed that more than 80% of establishments are already subject to such requirements, either due to legal obligations or for quality and risk assurance practices (this is further explained in Annex 5). Some establishments will be performing activities equivalent to risk assessments even if not required by regulatory frameworks as part of good professional practice, in support of organisational quality management objectives, to meet the requirements of their customers, or for other strategic reasons. This practice has been confirmed by representative organisations and experts, and suggests the current use of risk assessments is likely to be higher than what is currently required by law.

4.1.5. Competent authority status and operating principles

There is variation in the organisational arrangements (e.g., centralised vs. regional) and operational set-up of NCAs. The evaluation found that designated functions are carried out by medicinal product authorities in some Member States, BTC specialist authorities in others and national or regional health administrations in others. Consequently, enforcement powers, levels of independence from the sector and from government, as well as technical competencies vary.

4.1.6. Competent authority financing

Imposition of additional obligations on institutions that do not have the power to raise their own income may undermine the achievement of legislative objectives. In this context, the mechanism by which BTC competent authorities are funded is a relevant element of the baseline scenario. Where authorities have a route to recovering cost increases through, for example, increasing fees levied on regulated institutions, the risk of EU legal reforms having negative impacts on their financial sustainability is reduced.

Survey evidence and consultations suggest a mix of financial models across the EU. The survey did not provide complete coverage of all Member States so some assumptions are required. Based on NCA survey responses and follow-up email exchanges with select

NCAs (outlined in Annex 6), it has been assumed that half the Member States operate a fee or levy system that would enable them to recover legitimate additional costs from BTC establishments[15]. The remaining competent authorities are assumed to rely on additional budget allocation from central or regional government, or release resources from internal sources, to fund any incremental costs resulting from EU BTC legislative reforms.

4.1.7. Risk-based approach to inspection

One of the measures proposed to strengthen and harmonise oversight (Objective 2), is to require competent authorities to adopt a risk-based approach to inspection.

Competent authorities from 15 Member States[16] have confirmed that they already have some form of risk-based inspection regime. The specification of this regime varies by country, with no major difference between the blood and the tissue and cell sector. While operating within the current legislative framework and its prescribed inspections regime, competent authorities in many Member States plan inspections more frequently than the prescribed two-year period for a sub-set of establishments, based on a set of criteria which define the need for closer monitoring and control.

These criteria include previous instances of non-compliance; high incidence of adverse events reported; changes in the organisational structure of the establishments; complexity and novelty of BTC processes; and whether the establishment has been active in the BTC sector for a long time, or whether it is newly established.

The extent to which the frequency of inspections is higher than currently stipulated under the legislation (i.e. every two years) varies across Member States, and even within the same Member State, depending on decisions made by competent authorities, according to the set of criteria listed above. The increased frequency of inspections ranges from yearly to even more frequent checks in some cases (e.g. to twice a year).

In general, the criteria defined above are not set in national laws or official documents but are rather part of the standard procedures applied by the competent authorities as part of their oversight role. Therefore, there is no official documentation on the risk definition or classification operating in Member States, nor on the distribution of establishments based on risk.

A rough estimation provided by the competent authorities interviewed defined the low-risk regulated entities as 70%-80% of the total, with the remaining 20%-30% being high-risk, with a slightly higher presence of high-risk establishments in the tissue and cells sector compared to the blood one.

The current risk-based inspection practices encompass a variety of inspection approaches and frequencies. Inspections can be *in situ*, when inspectors visit the establishment and examine documentation and the structure, but also desk-based only, which are less labour-intensive. Inspections can encompass the whole BTC activities of the regulated entity being inspected, or only a component (e.g., a specific preparation). The risk criteria listed above are considered when planning the frequency and scope of the inspections. In post-inspection follow-up, it is not uncommon to have more frequent follow-up only on the riskier

[15] Of the 15 Member States that replied (to the survey and/or a verification email), 8 operate a levy system – i.e. 53% of the replies. In all Member States identified as having a levy system the BEs/TEs have the same funding system, except for in Denmark where BEs are not charged but TEs are. The precise rules governing the costs eligible for inclusion in levies / charges in each Member State and in each context is undetermined.

[16] Those who responded to the impact survey (Annex 6)

or more controversial items identified by earlier inspections, and/or desk-based follow-up rather than on-site.

For the purposes of the impact analysis, extrapolating from the evidence gathered, it has been assumed that 83% of BEs/TEs are already subject to risk-based inspections, and that this approach is applied in 20 EU Member States[17].

4.1.8. Quality and safety requirements to protect donors and children born as a result of MAR

The codification of operating rules to protect donors is established practice for many establishments and will not be determined by regulatory requirements alone. The research did not identify any consistent significant changes expected in the decade ahead on donor rules, other than a general trend towards tightening of donor eligibility requirements in some areas. The same applies to children born as a result of MAR. Out of the 15 replies from NCAs to the online impact survey, 13 indicated that they had relevant practices to protect donors and children, leading to an estimate for the analysis in this study that 20 Member States have provisions in place.

4.1.9. Risk assessments of novel processes

Measures proposed under Objective 4 would require establishments to conduct risk assessment of novel processes and these would be evaluated by competent authorities. Information on the regulatory baseline for assessment for novel processes is provided by a survey conducted in 2019 of competent authorities in support of the Facilitating the Authorisation of the Preparation Process for Blood, Tissues and Cells (GAPP) project[18]. This found variation in systems for handling applications (Figure 6); and a majority (14 of 23) of respondents reported having no definition of what constitutes a new/novel activity, product, process, or clinical indication. In most instances, the process for managing applications for such an authorisation was linked to the inspection system (18 of 24 respondents). Only three of 19 authorities indicated that there was documentary guidance available to competent authorities on the evaluation of data to be submitted to support an application for product authorisation (note: GAPP has since provided guidance). Only four of 20 respondents had a mutually accessible database of national authorisations or details of the associated evaluation.

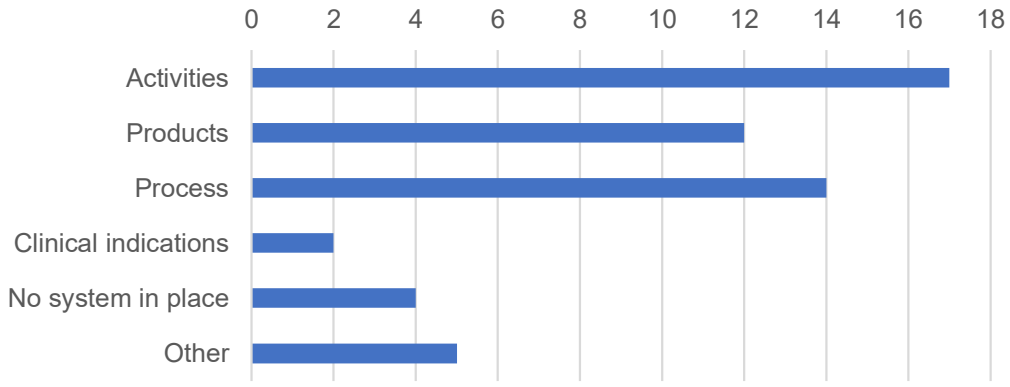


Figure 6: Authorisation systems in place to manage new/novel aspects

Source: GAPP WP5 Survey (2019) – Section 1, Question 14: Does your Competent Authority have a system in place to manage the authorisation of new / novel…" N = 24

[17] Details on the assumptions used for this estimation are in Annex 5.1.5.

[18] GAPP WP5 Survey. This has 24 responses, of which 23 were national competent authorities and 1 a regional authority.

4.1.10. Reporting shortages and supply issues

Measures proposed under Objective 5 (avoiding shortages of critical BTC therapies) would require establishments managing 'critical BTC' to report to regulators in the event of supply shortages. The definition of 'critical BTC' was established for tissues and cells by the European Directorate of Quality Medicines (EDQM) as part of a study for "Harmonising activity data collection exercises in the field of tissues and cells in Europe"[19]. For blood, the definition encompasses all key blood products (as shown in Annex 14). Responses to the NCA and establishment surveys suggested that systematic reporting of supply issues by establishments to competent authorities is present in about half of the Member States, with various frequencies and modalities.

4.1.11. Establishment contingency plans

Measures proposed under Objective 5 (avoiding shortages of critical BTC therapies) require emergency planning by competent authorities and for establishments managing 'critical BTC' to prepare contingency plans. Responses to the surveys conducted for this study identified that BTC establishments are required by NCAs to develop and maintain contingency plans in seven of the 15 Member States that responded. Research for the EDQM's Blood Supply Contingency and Emergency Plan project suggests that such emergency planning is widespread[20].

Based on survey responses and further verification with competent authorities, it has been assumed that 50% of BTC establishments are already subject to a requirement to develop and maintain a contingency plan equivalent to that which will be required under the proposed EU legislative reforms, either because of legal obligations or because of risk and quality assurance procedures.

Interviews and email exchanges with stakeholders confirm that some establishments are required to maintain contingency plans addressing supply risks to satisfy supply chain requirements, e.g. due to customer contractual terms. The prevalence of regulatory requirements for such plans does not provide a complete picture of the baseline situation (but it is recognised that the specification and content of plans will vary in the absence of standard guidance).

4.1.12. National law and Member State regulatory practices

The regulatory baseline includes national legislation and ancillary regulatory requirements as well as EU legislation. A key feature of the baseline is a lack of harmonisation of regulatory requirements at Member State level, and sometimes within Member States. A desire for harmonisation among operators of BTC establishments was a recurrent theme of stakeholder engagement processes and is an aspect of the status quo that the proposed reforms are intending to address.

When technology and other factors are changing, Member States may step in with new legislation if the EU does not act. The consultations suggest an expectation within the sector that this would happen, resulting in increased divergence in regulation at national level if EU legislation is not changed. This would, in turn, exacerbate the problems such as lack of consistent standards of patient safety, and barriers to exchange of BTC within the EU. If, for instance, competent authorities are authorising novel BTC on the basis of different rules, or assessing establishments against different operational standards, then this does not

[19] EDQM (2021). Harmonising activity data collection exercises in the field of tissues and cells in Europe: Conclusions and Recommendations of the Working Group. Work Package 7. Available online: https://www.edqm.eu/sites/default/files/medias/fichiers/Transplantation/Tissues_and_cells/tissues_and_cells_conclusions_and_recommendations_harmonising_activity_data_collection_exercises.pdf

[20] EDQM presentation on Blood Supply Contingency and Emergency Plan (B-SCEP Project). Not yet published.

foster mutual trust. Barriers to exchange among Member States may increase the risk of shortages.

4.1.13. Future evolution of adjacent EU laws

A new pharmaceutical strategy for Europe that is being developed by the European Commission[21] would happen independently of the reform of BTC legislation and so forms part of the baseline scenario. As the Commission published its Roadmap on the revision of the general pharmaceutical legislation in March 2021, the detailed content of this parallel revision is not known at the time of drafting this study.

Another change to the EU context may arise from the legislative proposal issued by the Commission in 2020 to expand the legal mandate of ECDC, with the aim to support Member States and the European Commission through: epidemiological surveillance; crisis and emergency preparedness and response planning, reporting and auditing; provision of non-binding recommendations and options for managing risks; increased capacity to mobilise and deploy EU Health Task Force to assist local response in Member States; and support to build a network of EU reference laboratories and a network for SoHO[22].

4.2. Alternative policy options

The Commission has defined policy options that codify alternative approaches to achieving the specific objectives. The policy options are distinguished by their approach to the setting of rules that need to be followed by BEs/TEs to (i) enhance safety and quality of BTC (to better protect patients (Objective 1) and donors and offspring (Objective 3)), (ii) improve contingency planning and sufficiency data reporting (Objective 5), and (iii) perform risk assessments for novel preparation processes of BTC (Objective 4).

The composition of the policy options and their component measures are described in Annex 2. At least one option has been prepared to address each specific objective.

The different approaches are defined as follows:

- Option 1 provides BEs/TEs with the freedom to make reference to a variety of national and international guidance when conducting risk assessments of their own activities;
- Option 2 requires BEs/TEs to conduct their risk assessments based on guidance developed and maintained by nominated EU expert bodies;
- Option 3 requires BEs/TEs to conduct their risk assessments based on rules defined in EU law.

Annex 2 provides more details on each of the measures provided within the three options proposed, and for each of the five objectives of the revision. Although the Commission has developed a distinct set of measures for each objective, the interventions are not completely independent – there is the potential for interactions between them (e.g. measures attached to one objective could also help to address the problem targeted by another objective) as the measures are deployed within the same integrated system.

Looking across the reform proposals as a whole, the majority of the measures (27 of 41) are common to all the options. A single set of measures to strengthen and harmonise oversight among Member States (Objective 2) is present in all options.

[21] European commission (2021). A pharmaceutical strategy for Europe. European Commission. Available from: https://ec.europa.eu/health/medicinal-products/pharmaceutical-strategy-europe_en Accessed 12 August 2021.

[22] ECDC (2020). Commission presents proposals for expansion of ECDC mandate. Available from: https://www.ecdc.europa.eu/en/news-events/commission-presents-proposals-expansion-ecdc-mandate. Accessed 24 December 2021.

5. Impacts

This chapter considers the expected health and economic impacts which may arise as a result of the proposed changes to the EU's BTC legislation.

Annex 4.7 explains in greater detail the process by which the indicators presented in this section were identified. Statements of impact have been developed for each option based on evidence gathered during the research phase.

5.1. Health impacts

This part of the report examines the expected impacts of the options on public health and the public health system, focusing on indicators relevant to the following policy objectives:

- Increasing patient protection from avoidable risks.
- Increasing quality and safety for donors and offspring.
- Quality of governance: strengthening and harmonisation of oversight among Member States.
- Access to BTC therapies – resilient supply in times of crisis and access to innovations.

The operational impacts on the BTC supply chain and cost impacts on health system regulators (i.e. NCAs) are discussed in the sections that follow (Section 5.2).

5.1.1. Increase patient protection from all avoidable risks (Objective 1)

This section looks at the impacts of the proposed measures on Objective 1 and the differences between the policy options proposed.

Stakeholders affected by measures intended to increase patient protection from avoidable risks

All recipients of BTC in the EU may benefit from the measures proposed to provide a consistent, high level of quality and safety.

Estimates of the number of people that will benefit from the reforms' impact on quality and safety are provided in Table 1 (overleaf), based on the best available data. The table shows that the reforms have the potential to improve quality and safety of healthcare for millions of people each year.

As all policy options cover the same activities, the number of patient beneficiaries is constant across options. The distribution of beneficiaries will vary across the EU based on the distribution of the relevant activities, as BTC activity is higher in some Member States than others, and in some Member States more stringent measures and protocols are already in place (i.e. some Member States already implement measures in their national legislation that are being proposed in the revision). This is discussed in the description of individual impacts in the rest of this section.

Table 1 – Estimated number of patients benefiting from measures that improve quality and safety (per year)

Category	Illustrative data on number of people benefitting	Source
Patients - blood	An estimated 4.6 million patients receive a blood transfusion in EU27 Member States annually.	EU27 estimate calculated using 2019 annual figures for Serious Adverse Reactions and Events (SAREs) for Blood and Blood Components[23] (data collected from 01/01/2018 to 31/12/2018) and the Manifesto for European Action on Patient Blood Management (PBM) (2020)[24].
MAR	MAR patients are supported through ~900 thousand assisted reproduction cycles	Estimate based on information collected by the European Commission[25].
Patients – tissues	An estimated 115,000 patients a year receive some kind of transplant, across all the tissue types for EU27.	ICF analysis based on data captured by the EDQM[26].
Hematopoietic stem cells (HSC)	31,881 new patients treated with autologous and allogenic HSCs annually in the EU.	Data obtained directly from the European Group for Blood and Marrow Transplant (EMBT)[27].
Recipients of FMT	1,095 recipients of FMT[28].	Estimate provided from Baunwall et al (2021)[29].

Note: the beneficiary population is the same under all options

The reforms will impact BEs/TEs, organisations in the sector's supply chain (e.g. ATMP manufacturers) and regulators. The quality and safety measures will affect an estimated 3,238[30] TEs and around 1,400[31,32] BEs. The proposed extension of scope of the legislation will put circa 200[33] breast milk banks under the regulatory oversight of BTC competent

[23] European Commission (2020). Summary of the 2019 Annual Reporting of Serious Adverse Reactions and Events for Blood and Blood Components. Available from: https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/2019_sare_blood_summary_en.pdf

[24] International Foundation for Patient Blood Management (2020). Manifesto for European action on Patient Blood Management (PBM). Available from: https://www.ifpbm.org/images/EU%20PBM%20Manifesto%20February%202020%2024.pdf

[25] European Commission (2020). DG SANTE Infographic. Available from: https://ec.europa.eu/health/publications/infographic-organs-blood-tissues-and-cells-eu_en . Accessed July 2021.

[26] EDQM (2020) Newsletter Transplant: International figures on donation and transplantation 2019

[27] Unpublished. Collected as part of EMBT Activity Survey Data (2019). This covers the EU27 less Malta (EBMT indicates no known transplant programme in Malta).

[28] Additionally, 1,874 FMT procedures were performed in Europe in 2019 (1,095 in EU27).

[29] Baunwall et al. (2021). The use of FMT in Europe. The Lancet Regional Health – Europe. 2021. Available from: https://www.thelancet.com/action/showPdf?pii=S2666-7762%2821%2900158-7

[30] ICF analysis of Reference Compendia for the Application of a single European Coding System for Tissues and Cells. Annex 13.3

[31] European Commission (2020). DG SANTE infographic. Available from: https://ec.europa.eu/health/blood_tissues_organs/blood_en

[32] European Commission (2019). Commission Staff Working Document: Evaluation of the Union legislation on blood, tissues and cells {SWD(2019) 376 final}. Brussels. Available from: https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/swd_2019_376_en.pdf.

[33] Evidence suggests number of milk banks is increasing over time and there are 250 banks estimated for whole of Europe. *Source:* EFCNI (2021). Making Human Milk Matter - The need for regulation in the European Union. Available from: https://www.efcni.org/wp-content/uploads/2021/01/2021_01_21_EFCNI_MakingHumanMilkMatter_PolicyRecommendations_final-small.pdf.

authorities plus around 24 hospital-based FMT sites[34]. Establishments performing 'same surgical procedure' or 'not for transfusion' activities – which are currently exempt from the legislation – will also be affected.

Agility of the regulatory system to respond to avoidable risks for patients

A recognised problem with the current situation, expected to continue in the baseline scenario, is that the rules applied do not consistently reflect current scientific and technical knowledge (as rules in EU legislation are not up-to-date)[35]. If new information emerges about risks to patients, then it is desirable to be able to update these in the requirements applied by the sector to provide assured protection across the EU. The current arrangements to provide updates, which rely on the ability to amend legislation, are not fit for purpose.

This section considers the impacts of the options on this problem:

- Option 1 - theoretically provides a rapid mechanism for uptake of new advice into establishments' practices (in so far as establishments could use latest guidance from any source, including updates from national regulators or other jurisdictions). However, the failure of Option 1 to provide a mechanism to ensure that such updates are adopted consistently among different establishments across the EU means that it does not provide an assured solution to the problem and could potentially affect harmonisation of quality and safety requirements in the EU.
- Option 2 - the use of EU expert bodies (e.g., ECDC and EDQM) – is the strongest alternative. It offers a solution that combines quality with a flexibility that offers a more reliable mechanism for updating technical requirements than that provided by EU law. The expertise of the bodies and rigour of their process should mean that updated rules properly reflect the state of the science at the time of their review. The obligation on establishments to follow their guidance provides a standard that should help provide consistency of approach. This is supported by stakeholders consulted throughout this study (Annex 6 and Annex 7). Stakeholders suggest that use of EU expert bodies to develop technical requirements, combined with an obligation on BEs/TEs to follow those requirements when conducting their operations, is most likely to provide timely updates and ensure that the latest knowledge is used consistently across the BTC sector.
- Option 3 - codification in EU law – will require legislative action to update the rules. Unless the mechanism is changed, it could result in outcomes similar to the current legislation, under which it has not been able to provide timely updates of the quality and safety technical requirements that establishments need to follow.

Consultations with ECDC and EDQM suggest that current guidance review cycles last three to four years, from initial high-level planning through to publication of approved guidance. The appropriate frequency of review and, where necessary, update of BTC guidance would need to be determined by the Commission. Use of the proposed online platform to host the technical guidance would facilitate a quicker and more agile review and update process than the current model.

[34] There are 42 FMT centres within the European Council member states (24 in EU27). *Source*: Baunwall et al. (2021). The use of Faecal Microbiota Transplantation (FMT) in Europe. The Lancet Regional Health – Europe. 2021. Available from: https://www.thelancet.com/action/showPdf?pii=S2666-7762%2821%2900158-7

[35] Where technical requirements are codified in EU law, the envisaged review and update mechanisms is not agile enough to respond to the speed of innovation. If these are not up to date, there is the potential for patients to be subject to a higher level of avoidable risk.

The ability to respond quickly in emergencies is also important. The EU expert bodies have also demonstrated their capacity to react rapidly. For example, ECDC has a procedure for rapid risk assessments through which assessments can be conducted over periods from one week to several months[36].

The table below provides summary judgements on relevant 'agility indicators' based on a triangulation of available evidence (derived from the NCA and establishment surveys, stakeholder consultations including follow-up emails, and workshops). The level of protection provided to patients is expected to vary. Option 1 has the potential for rapid, but only partial adjustment without consistency or assured response whereas Option 3 offers a theoretical model of comprehensive protection but is comparatively slow and cumbersome, and not well equipped to respond rapidly to events.

Table 2 – Agility of the regulatory system to respond to avoidable risks

Indicator	Option			
	Baseline	1	2	3
Minimum time required to update/issue technical guidance in an emergency situation on quality and safety by the relevant experts in all Member States (months)	6-12	Not applicable*	1-6	6-12
Typical time required (end to end) to revise rules and bring them into force (months)[37]	Not yet achieved	Not applicable*	12**	48***
Ability to provide a dynamic regulatory system for BTC in which quality & safety requirements reflect current scientific and technical knowledge	=	-	+++	+

**In Option 1 there is no specific rule-setting process; establishments are free to make sure of whatever appropriate guidance is available at the time.*

***Consultations with ECDC and EDQM suggest guidance developed under a normal cycle takes 3 to 4 years from initial planning to publication. In the case of ECDC an accelerated process is available for use in emergencies. Estimation is therefore based on an average of the time taken by ECDC and EDQM to produce changes, taking into account possible future developments and process changes (e.g. use of online platform) which are expected to facilitate reductions in this timetable.*

****Estimation based on time required to develop rules plus time required for legislative process.*

Impact on equality of protection

This section considers the ability of options to provide a regulatory system for BTC in which all patients enjoy an equal level of protection. Current differences across the EU in regulatory approach and operating practices mean that patients are not presently assured a uniform level of protection across the EU – avoidable risks faced by some are higher than those faced by others. Stakeholders participating in consultations conducted for this study generally felt that, under the baseline scenario, there are no alternative methods to provide equality of protection to patients. . Independent action by Member States is not expected to deliver equality of protection and may increase divergences further.

Many of the measures in the proposed reforms could contribute directly or indirectly to improved consistency of protection. Objective 1 measures that are expected to make a particular contribution, for example, are the requirements for BEs/TEs to conduct risk assessments of their operations (measures M1.6-M1.8).

[36] ECDC communication to ICF. 6 July 2021

[37] Depends on the nature of update: more substantial changes would require multiple meetings and preparation. Possibly Member States would need to consult stakeholders / coordinate internally.

Option 1 is unlikely to deliver an assured equal level of protection because the establishments are entitled to base their risk assessments on guidance from a variety of sources, which may differ in their requirements and rigour. Variance in guidance is expected to be translated into variation in practices and thus unequal levels of patient protection. As such, this is expected to lead to a less favourable outcome (in terms of equality of protection) than Options 2 and 3, which establish a single set of EU rules that establishments need to follow. Option 3 is enshrined in law, but less nimble. Respondents to both of the surveys conducted for this study were more confident that Option 2 would resolve the baseline problem of inconsistent quality and safety rules than Option 3 and saw Option 1 having little or no impact (Figures 1 and 2 in Annex 7)[38].

Additional progress towards overall uniformity of protection (as compared to the baseline) is expected to be delivered by:

- The Objective 2 measures, which are intended to strengthen the consistency and quality of regulatory oversight, as regulators will operate to a common set of principles.
- The measure (M1.2) which extends the scope of the legislation, which will bring additional establishments under the controls applied by EU law and thus provide a level of assured protection to beneficiaries of for example breast milk banks, FMT recipients, etc.
- The measure (M4.1) that removes the exemption for same surgical procedures.
- The measures (M4.2-M4.4) that will support clarification of borderline issues.
- The measures (M4.10-M.12) which require risk assessments of novel BTC processes to be conducted.

The summary judgement on the impact of options on equality of protection is shown below.

Table 3 – Consistency of regulatory practice across the EU - geographical scope

Indicator	Option			
	Baseline	1	2	3
Consistency of regulatory practice across the EU - geographical scope*	=	-	+++	+++

**Number of Member States that follow the guidance in practice (either on a voluntary or a mandatory basis).*

Key: Baseline = consistency across some Member States; - possible inconsistency within countries; +++ consistency across all Member States. Note: Consistency of practice can mean different tests are performed based on a country's unique epidemiological situation (e.g. West Nile virus).

Quality of technical guidance - mobilising relevant scientific and technical knowledge in the BTC sectors

Option 1 will lead to an inconsistent access to expertise, across Member States and BEs/TEs depending on their size and available resources. Option 2 and Option 3 will ensure that high quality expertise is available to all Member States. Option 2 is, however, expected to allow mobilisation of expertise, due to procedures already in place, much more efficiently than Option 3. Therefore, Option 2 is considered to have a higher impact on this indicator.

[38] Minutes of the Workshop with Stakeholders and Blood, Tissue and Cell Competent Authorities Substances of Human Origin Expert Group (CASoHO E01718) of 6 May 2021, DG SANTE.

Table 4 – Mobilising relevant scientific and technical knowledge in the BTC sectors for the updates of guidance

Indicator	Option			
	Baseline	1	2	3
Mobilising relevant scientific and technical knowledge in the BTC sectors for the updates of guidance	=	-	+	+

Key: Baseline = Engagement of experts with the relevant expertise and resources for the updates/issuing technical guidance on quality and safety; - inconsistent (across Member States and BE/TEs depending on their size and available resources); + high quality expertise available to all Member States

Timeliness of reporting on adverse events

All options provide for more timely reporting on serious adverse events than is available in the baseline as measures relating to reporting are common to all three options. All options will ensure that consistent and structured data is available for all Member States, and there is a single reporting system.

Table 5 – Availability of timely information for risk management on serious adverse events for patients

Indicator	Option			
	Baseline	1	2	3
Availability of timely information for risk management on serious adverse events for patients	=	++	++	++

Key: = some information is available for risk management (BE/TE, clinicians, public health authorities, researchers) on certain high risk events; not consistent across Member States, no possibilities for advanced analytics; + data available for all Member States; + consistent, structured, single reporting & data available on high risk events allowing advanced analytics

Feasibility of implementation

The table below provides a commentary on the feasibility of specific measures. A summary of stakeholder views on feasibility is provided in Annex 8.

Table 6 – Feasibility of implementation of measures: Objective 1

Measure	Feasibility considerations
M1.1: EU legislation is amended to incorporate statement of principles relating to quality and safety	No major feasibility issues identified. Implementation would be affected by the detail of the principles.
M1.2: EU legislation amended to incorporate definitions ensuring that quality and safety provisions apply to all SoHO/BTC for which the Treaty give competence to the Union to legislate, including some that do not meet the current definitions that contribute to the definition of scope in the Directives	Number of additional establishments is expected to be comparatively small as a share of total establishment population so incremental load on NCAs is not expected to be excessive. The establishments brought into scope will need to adapt to the BTC regulatory system. The scale of the adjustment will be influenced by the risk categorisation and associated oversight applied by NCAs based on their activities and BTC used.
M1.3: EU law amended to require Member States to publish more stringent rules in an accessible format	NCA and BTC establishments responding to the ICF online inquiry were more sceptical about the implementation of this measures than most other measures (Annex 8). Implementation will be dependent on the requirements for publication of more stringent measures as laid down in the revised legislation. A challenge of this measure is the

Measure	Feasibility considerations
	reliability of monitoring whether NCAs are publishing more stringent rules in an accessible format.
M1.4: EU will develop the relevant component of the IT platform for quality & safety requirements	No major feasibility issues identified.
M1.5: EU legislation is amended to require competent authority inspectors to evaluate the BTC establishments' risk assessments to ensure that they have been conducted effectively and that the rules set adequately manage the identified risks	Option 1: this measure is perceived as potentially difficult to implement for competent authorities because of the extra challenges for inspectors created by establishments using a diversity of evidence sources to inform their risk assessment. This has implications for the capacity and authority of inspectors to make judgements, the skills required and associated training.
M1.6: EU legislation is amended to require BTC establishments to assess risks associated with their donor selection, testing, collection, storage, processing and supply procedures and to set technical rules for safety and quality compliant with the “high level principles” in EU legislation.	Option 1: some respondents to the establishment survey reported that this measure would create significant implementation problems, and therefore emphasised the need for clear instructions, mandatory testing, or joint inspections to ensure enforcement to mitigate this.
M1.7: EU legislation is amended to require establishments to take into account ECDC/EDQM rules on quality & safety requirements	Option 2: National requirements are already aligned with existing EU provisions in this way in some Member States. Implementation considerations include: the frequency of updates (which will require a trade-off between updating the guidelines against the cost for the sector to respond to these updates); the detailed process by which rules are determined, including the engagement with experts and the sector; the process by which the costs associated with rules are determined and balanced against safety improvements prior to rules being adopted; and the process by which the rules are accommodated into Member State regulatory processes.
M1.8: EU legislation is amended to incorporate quality & safety requirements directly. It contains a mechanism for regular updates to respond to changing risks and technologies under Comitology rules	Option 3. The principal implementation issue with this measure is potential uncertainty about legislative updates being feasible. There are also other features to consider in terms of process, e.g. consultation, benefit/cost appraisal and whether a full impact assessment would be required.

5.1.2. Increase protection of BTC donors, and children born from donated sperm, eggs or embryos, from specific risks (Objective 3)

A recognised shortcoming of the existing EU legislation is the limited degree of protection afforded to BTC donors, and offspring[39]. In both BTC basic acts, reporting of donor reactions is mandated, as part of vigilance, but only when the quality or safety of the donated substance itself has been compromised. The proposed legislative reforms provide for various measures that are intended to strengthen the protection provided to donors. The policy options and component measures can be found in Annex 2. Most of the measures proposed are common to all options, though the origin of the guidance and rules that would need to be used by establishments in preparation of detailed quality and safety measures to protect donors varies.

[39] European Commission (2019). Commission Staff Working Document: Evaluation of the Union legislation on blood, tissues and cells {SWD(2019) 376 final}. Brussels. Available from: https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/swd_2019_376_en.pdf.

Stakeholders affected by the measures

The target beneficiaries of these measures are the BTC donors and children born as a result of MAR. Illustrative estimates of the scale of the various donor populations and offspring are shown below. The number of potential beneficiaries is expected to be constant across all three options.

Table 7 – Illustrative data on donor numbers, per year, in the EU

	Illustrative data on number of people benefitting from measures that improve quality and safety each year	Source
Blood donors	Nearly 10.4 million donors	EU27 estimate calculated using data collected by EDQM[40] and Member State population data.
Cord blood donors	More than 75,000	Data supplied by Dr Frances Verter / Parent's Guide to Cord Blood Foundation (unpublished)[41].
Oocyte donors	More than 39,000[42] Number of cycles with oocyte donation: 26,645	Data collected by ESHRE[43]. Data supplied to ICF from ESHRE[44].
Hematopoietic stem cells donors	More than 30,000	Data available on Eurostat[45].
Sperm donors	More than 21,000 fresh cycles with sperm donation	Data supplied to ICF from ESHRE[46].
Children born as a result of MAR	Data suggest that there could be in excess of 125,000 children born as a result of MAR each year in the EU; the number has increased significantly over time.	Data supplied to ICF from ESHRE[47].

Though donors and children born as a result of MAR are the target beneficiaries, the direct incidence of measures is on establishments and regulators, both of which will acquire new legal obligations and will need to change aspects of their operating practices to a greater or lesser degree. Data on the distribution of the MAR establishments within the EU are provided in Annex 13.

[40] EDQM (2016). The collection, testing and use of blood and blood components in Europe – 2016 Report. Available from: https://www.edqm.eu/en/blood-transfusion-reports-70.html

[41] The information provided estimates around 75,000 donations in 17 EU countries (the 17 includes the largest Member States by population). Figures include private banking in family banks as well as public donation. See also https://parentsguidecordblood.org/en/news/percentage-births-banking-cord-blood-country

[42] Additional data collected by ESHRE for 2013 show that 39,000 egg donation treatments were performed in Europe from a total of almost 500,000 IVF cycles.

[43] ESHRE (2017). ESHRE fact sheets 3. Available from: https://www.eshre.eu/-/media/sitecore-files/Press-room/Resources/3-Egg-donation.pdf?la=en&hash=74DA05046D358DC2F763E175AAFC7864BCFF9169.

[44] ESHRE. Data supplied to ICF on 25 August 2021. Data related to 2017 and are likely to be an under-estimate due to incomplete reporting in some centres in certain Member States.

[45] EUROSTAT (n.d.). Stem Cell transplantation in the EU. Available from at https://ec.europa.eu/eurostat/web/products-eurostat-news/-/edn-20191011-1

[46] ESHRE. Data supplied to ICF 25 August 2021. Data related to 2017 and are likely to be an under-estimate due to incomplete reporting in some centres in certain Member States.

[47] These data refer to ART infants, meaning infants born after IVF and ICSI cycles, which includes fresh and frozen cycles, cycles after preimplantation genetic testing, and cycles with donated oocytes. The figure related to 2017. Source: ESHRE. Data supplied to ICF 25 August 2021.

Impacts and indicators

The measures aim to give greater protection through imposing additional obligations on establishments and regulators, with implications for operating practices and costs. The costs and benefits of Objective 3 measures will depend in part on the detail of the requirements for establishments and donors, as well as the requirements adopted by rule-setting bodies to reduce risk under Options 2 and 3.

The text below considers the impacts of the measures on recognised aspects of the current problem. In many respects the analysis mirrors that of the measures proposed to improve patient safety (Objective 1) in terms of performance against particular impact indicators.

Consistency of protection

The consistency of protection provided to donors is expected to vary across the options. Option 1 will extend aspects of the *status quo* (some Member States already require equivalent reporting). Options 2 and 3 offer EU-wide consistency.

Table 8 – Consistency of regulatory practice across the EU

Indicator	Option			
	Baseline	1	2	3
Consistency of regulatory practice across the EU - geographical scope*	=	=	+++	+++

** Number of Member States that follow the guidance in practice (either on a voluntary or a mandatory basis);*

Key: Baseline = consistency across some Member States; - possible inconsistency within countries +++ consistency across all Member States.

Availability of timely information for risk management

A key concern is that risk managers (establishments, clinicians, regulators, etc.) are equipped with the information they need in a timely manner. Serious adverse event reporting for donors is not currently undertaken by all Member States in the EU. The proposed measures, such as on reporting of adverse events for donors, offer improvements on the current model. All options will ensure that information is available to all Member States on all adverse events and that the information is presented in a comprehensive and consistent format.

Table 9 – Availability of timely information for risk management

Indicator	Option			
	Baseline	1	2	3
Availability of timely information for risk management, e.g., on issues with specific donors and with children born from donated gametes and embryos*	=	++	++	++

**Some information is available on certain high risk events for risk management (BE/TE, clinicians, public health authorities, researchers);*

Key: = not consistent across Member States, not comparable; + structured, comprehensive and consistent information is available on high risk events ; + information is consistently available across Member States ; + information is available on all adverse events

Mobilisation of expertise

A significant issue for the overall operation of the system is whether the BTC regulatory system's response to avoidable risks is informed by the highest quality and most relevant scientific and technical specialists.

Option 1 potentially leads to inconsistency, including circumstances where rather than following the relevant Member State guidance, establishments follow more diverse evidence.

Both Options 2 and 3 provide access to an EU-wide body of expertise that will be greater than that available to most Member States.

Table 10 – Ability of the regulatory system to respond to avoidable risks - mobilising relevant scientific and technical knowledge in the BTC sector

Indicator	Option			
	Baseline	1	2	3
Ability of the regulatory system to respond to avoidable risks - mobilising relevant scientific and technical knowledge in the BTC sectors	=	-	+	+

Key: = Engagement of experts with the relevant expertise and resources for the updates/issuing technical guidance on quality and safety ; - inconsistent; across Member States and BE/TEs depending on their size and available resources; + high quality expertise available to all Member States

Agility of response

A key issue is the ability of the regulatory system to consider and make use of new evidence on risks and their management. In considering this matter, there is a useful distinction between the rhythm of guidance or rule review and renewal on the one hand, and emergency response on the other. Experience, not least from the pandemic, suggests that the capacity to develop issues advice/or rules rapidly in an emergency is very important to being able effectively manage risk.

Table 11 – Agility of the regulatory system to respond to avoidable risks - time required for updates

Indicator	Option			
	Baseline	1	2	3
Typical time required (end to end) to revise rules and bring them into force (months)	Not achieved	Not applicable	12	48
Minimum time required to update/issue technical guidance on quality and safety by the relevant experts in all Member States (months) ["emergency response mode"]	6-12	Not applicable	1-6	6-12

Note: Option 2 provides greater agility than Option 3 – the latter requires time for the legislative process to be completed after the new rules have been researched and drafted. Where, in consultations, stakeholders had reservations about Option 2 these related to a concern that outputs from expert bodies may have less legal force. There were suggestions, in a workshop on protection of donors for non-reproductive tissues and cells,[48] that high level principles should be defined in legislation, with technical rules defined in the expert body guidance (in effect, an Option 2 – Option 3 hybrid model).

[48] The event was attended by 60 representatives from invited organisations including representatives from national competent authorities for tissues and cells, professional societies representing TEs and clinical users, donor associations, EDQM (Council of Europe) and DG SANTE. See Workshop Summary 4 in Annex 11.

Feasibility of implementation

The table below provides a commentary on implementation considerations for specific measures. In general, across all the measures considered, stakeholders were concerned that consultation processes for rule setting should be sufficient to enable relevant evidence to be submitted and the relevant issues discussed. A summary of stakeholder views on feasibility is provided in Annex 8.

Table 12 – Feasibility of implementation of measures: Objective 3

Measure	Feasibility considerations
M3.1 High level principles to protect BTC donors, including reporting measures (SARE/monitoring outcome)	No major feasibility issues identified. The role of donor registries in facilitating traceability was highlighted in consultations. There is not currently a consistent approach to regulation of donor registries across Member States.
M3.2 High level principles to protect offspring … including reporting (SARE/monitoring outcome).	Stakeholders (respondents to the survey and workshop participants) noted the issues of registries of children born as a result of MAR analogous to those for donors, and the need to integrate tracing and follow-up arrangements with paediatric care systems.
M3.3. New definitions	A NCA consulted as part of this study noted the challenges with genetic conditions transmitted from donors (in cases such as different forms of autism) (see Annex 8 for further information).
M3.4: The European Commission will develop the relevant component of an IT platform for quality and safety requirements	No major feasibility issues identified.
M3.5: BE/TEs required to define detailed quality & safety requirements to protect donors and children born as a result of MAR	Option 1. No major feasibility issues identified; however it has been noted that setting up these requirements could demand (specific scientific) expertise which is not feasible from every establishment.
M3.6: EU law is amended to require expert bodies to define detailed quality & safety requirements (as above) for donors and children born from donated gametes or embryos and to require BE/TE to 'take into account' the rules issued by the expert bodies	The process by which rules are developed and consulted upon in Option 2 is pertinent – i.e. engagement with experts and the sector; the process by which costs and benefits are balanced; and the overall rigour of this as compared to Option 3.
M3.7: EU law incorporates quality and safety requirements for donors and offspring of MAR, and a mechanism to update these as needed	Option 3. The principal implementation issue with this measure is potential uncertainty about legislative updates being feasible. There are also other features to consider in terms of process, e.g. consultation, benefit/cost appraisal and whether a full impact assessment would be required.

5.1.3. Quality of governance: strengthening and harmonisation of oversight among Member States (objective 2)

Stakeholders affected by measures intended to strengthen and harmonise oversight

The stakeholders directly affected by these measures are NCAs and their staff. There are expected to be indirect impacts on regulated BEs/Tes, and ultimately for patients, donors and children born from MAR. The institutional arrangements for BTC oversight vary at Member State level by reference to factors such as:

- Whether responsibility for (i) blood and (ii) tissues/cells are combined in one institution or allocated to different institutions.
- Whether those institutions also have oversight responsibilities under other regulatory frameworks.
- Whether there is a centralised structure based on national regulators, or a devolved structure based on regional authorities. For example, Spain and Germany devolve oversight to regional authorities, which are supported by one or more central coordinating bodies[49]. In Italy, while healthcare delivery is a regional competence, there are two NCAs, one for blood and one for tissues and cells (two separate entities, both departments of the Health Institute). Inspections are organised, and often carried out, in cooperation with the regional authorities, that identify which BTC establishments should be inspected.
- Aspects of their operating model, such as the conditions placed on inspectors on matters of, for instance, independence from the sector.

Data provided to ICF by the European Commission (unpublished) suggests that there are 50 national level BTC competent authorities (as shown in Annex A16.2) and 33 regional BTC authorities[50]. Some deal with only blood or only tissues and cells, or only MARs while others have responsibility for all sectors.

Impacts and indicators

The measures proposed to strengthen and harmonise oversight among Member States (as specified under Objective 2) are identical under all options (see Annex 2). As such the impacts (as compared to the baseline scenario) are expected to be the same for all options. The impact assessment thus makes a comparison of the proposed oversight 'package' with the baseline.

The measures are expected to have two types of impacts:

- Specific impacts at Member State level – i.e., adaptations needed by an individual country to strengthen oversight practices and ultimately lead to better patient / donor / child outcomes;
- Collective impacts realised at EU level – as measures build confidence and trust among Member State authorities and establishments in the oversight systems of others; this is expected to have indirect impacts such as greater exchange of BTC among Member States, faster uptake of new BTC applications recognised by other Member States. This will ultimately, benefit patients, donors and/or children born as a result of MAR.

There will be differences in impact of the oversight measures across the Member States because the baseline position varies by country in various aspects of regulatory oversight arrangements addressed by the proposals. Examples are:

- Whether the competent authority already complies with principles for NCA and for staff (as proposed in measure M2.1), or will need to reform its constitution, operating model, processes for selecting inspectors, etc.
- Whether the competent authority already applies a risk-based approach to its inspection regime, and thus whether it will need to modify its approach to comply with the requirement (M2.2) to apply a risk-based approach to inspection.

[49] In Spain, for instance, each of the 17 Autonomous Communities has a designated regional authority, and there are three national commissions, one for blood, one for non-reproductive tissues/cells, and one for MAR.

[50] From Spain and Germany

Impact on quality of inspections

The proposed oversight measures are expected to have a positive impact on the extent to which competent authority inspections are performed objectively and competently.

Table 13 – Impact on quality of inspections

Criterion	Baseline	Option 1	Option 2	Option 3
Stakeholder views on the extent to which measures will affect the quality of inspections*	=	++	+++	+++

*Note: Stakeholder perspectives shown in Annex 7, Figures 36 and 37. *The lack of common standards applicable across establishments in Option 1 was perceived to make it less likely that inspections would be raised to the same level as achievable under Options 2 and 3.*

Key: = no impact on quality of inspections; + partial impact on quality of inspection; ++ more than a partial impact on quality of inspections; +++ substantial impact on quality of inspections

Impact on the skills of inspectors

The measures include provision of inspection guidance, issued by the Commission. The proposed measures are expected to have a positive impact on the problem of inspectors not having the skills required to conduct inspections to the expected standard. This conclusion is supported by the views of stakeholders consulted in the present study.

Option 1 is expected to be more demanding of inspectors in terms of the skills required to carry out inspections because of the requirement to evaluate establishment risk assessments that may be based on a diversity of evidence sources. The organisation of training by the EU for BTC inspectors, which was not part of the package of measures consulted upon in Objective 2, has the potential to strengthen skills further.

Table 14 – Impact on the skills of inspectors

Criterion	Baseline	Option 1	Option 2	Option 3
Stakeholder views on the extent to which the measures will impact on the skills of inspectors	=	+	+++	+++

Note: Stakeholder perspectives provided in Annex 7, Figure 38.

Key: = no impact on skills of inspectors; + partial impact on skills of inspectors; ++ more than a partial impact on skills of inspectors; +++ substantial impact on skills of inspectors

Impact on trust/confidence among EU Member States

As set out earlier, the proposed measures are intended to resolve this problem of a lack of trust and confidence among EU Member States. Stakeholder consultations (summarised in Annex 7) suggest that Option 2 would have the strongest positive influence on mutual trust. However, stakeholder views may have overstated the difference between Option 2 and other options, given the number of measures common to all Options and the aggregated impact of the overall package of measures on this impact indicator[51].

[51] See Annex 7 for stakeholders' views supporting this (Workshop question: "Which Policy option is best suited to strengthening harmonisation, confidence and trust among Member States and thus facilitate the mutual exchange of BTC across borders?)

Table 15 – Impact on trust/confidence among EU Member States

Criterion	Baseline	Option 1	Option 2	Option 3
Extent to which the measures will build trust/confidence among Member States	=	++	++++	+++

Note: Stakeholder perspectives shown in Annex 7. Key: + borderline mechanisms resolve differences of interpretation; + publications of rules improve and EU audits improve transparency; + common EU 'rulebook', + stakeholder preference. A plus is awarded for each of these elements.

Feasibility of implementation

The table below provides an overview of the feasibility of implementation and consideration of specific measures to strengthen and harmonise oversight among Member States. Stakeholder views on feasibility are discussed further in Annex 8.

Table 16 – Feasibility of implementation of measures to strengthen and harmonise oversight

Measure	Feasibility considerations
M2.1: EU legislation is amended to incorporate oversight principles for the organisation and for staff in legislation	The list of principles established by the Commission which would be applied to NCAs and their staff will require varying degrees of change from institutions and their officers. For some NCAs there will be no impact because they already conform. A detailed mapping of the legal status and operating practices of each regulator against each of the proposed operational principles specified in the proposed measure would require further primary research.
M2.2: EU law is amended to obligate NCAs to base their inspection regimes on a risk-based approach	Current data (outlined in Section 4.1.7) suggests that 83% of BEs/Tes are already subject to risk-based inspections, and that this approach is applied in 20 EU Member States. Details on the assumptions used for this estimation are provided in Annex 5.1.5. The flexibility available to the authorities in adjusting the frequency of inspections is constrained by the EU legal requirement for establishments to be inspected at least once every two years. The two year requirement could be modified; lengthening the minimum period would provide more flexibility to regulators in deciding how to allocate resources (such as inspecting low risk establishments less frequently).
M2.3: The Commission will develop and maintain common guidance on oversight	No significant implementation issues were identified. The principle of new guidance was broadly welcomed in consultations.
M2.4: EU audits of national control systems; and M2.5 Member State joint inspections	Both models have been proven in other contexts; a period of learning and adjustment can be expected.

5.1.4. Access to BTC therapies – resilient supply in times of crisis (Objective 5)

There has been a long-standing concern about the resilience of the EU's BTC 'system' in the face of interruptions to supply. Among the factors contributing to this concern are barriers to transfer of BTC among Member States, arising in large part from differences in regulatory regimes within the EU and the EU's reliance on third countries' supplies, notably its dependency on plasma from the US.

The proposals include measures intended to help avoid shortages of critical BTC therapies (illustrated in Annex 13), improving overall resilience of the system through contingency

planning for supply shortages, improving decision-makers' access to data on shortages, and strengthening Member States' and the EU's ability to intervene to control and adjust supply, as necessary. More information can be found in Annex 2.

The measures to monitor BTC supply are common to all options so the assessment of impacts does not vary. The proposed arrangements for rules on contingency planning vary by Option and in those areas the analysis considers the relative merits of each option. More information can be found in Annex 2.

Stakeholders impacted by the proposals

The proposed measures have direct impact on establishments and EU/Member State regulators. Any impact on patients is indirect. For example, risks of postponement or cancellation of planned healthcare interventions may be mitigated by establishments and authorities being better able to maintain continuity of BTC supply. It is estimated that there are 1469 TEs with at least one authorisation in the EDQM 'critical BTC' categories. The distribution of these establishments by Member State is shown in Annex 13.3.

If the circa-1400 BEs are added (on the basis that most blood products are considered as critical) then the total number of establishments that would be obligated by the contingency planning new rules is around 2900, and a smaller number would be affected by the reporting obligations[52]. As discussed in the description of the baseline scenario, many establishments already have some form of supply risk planning and management arrangements.

Impacts and indicators

The proposed measures are expected to have a positive impact in reducing risks to public health and the health system through increasing transparency of the supply situation to regulators and improving the preparedness of actors within the system to deal with interruptions to supply. Insofar as most measures are common to all Options, and many establishments are already likely to have some form of contingency planning arrangements, the expected variance in performance of Options is less than in some other areas of this analysis.

The analysis here focuses on measures developed specifically to address the problem that the EU is vulnerable to interruptions in some BTC supply. Insofar as security of supply is undermined by barriers to exchange of BTC within the EU, the measures proposed in other parts of the reform package (specifically for Objective 2 and Objective 4) also have the potential to contribute to this objective. Harmonisation of rules across the EU and greater mutual trust of others' systems ought to help facilitate exchanges across Member States. The reform package does not directly address BTC supply and structural imbalances and, as such, does not seem likely to reduce some of the principal supply risks of concern (e.g. in relation to plasma). The specification and feasibility of other (e.g. supply-side) approaches to mitigating such risks was outside the defined scope of this study.

Impact on decision-makers' access to information to identify and manage supply risks and critical shortages

The measures proposed under Objective 5 give regulators certain information and powers to inform and enable decisions intended to mitigate the shortages of critical BTC if and when

[52] The scope of planning and reporting obligations would be on a sub-group of 'critical BTC', defined in Annex 14. Method for estimating number in scope for reporting is provided in Annex 5.

they arise. In turn, it is anticipated this will increase visibility of supply conditions and alert NCAs to critical shortages.

Details defined later will affect how supply risk monitoring would work in practice, for example the definition of 'shortage' conditions that would trigger the notification to competent authorities by establishments. The consulted stakeholders provided views supporting these points (Annex 7[53]).

Impact on availability of sufficiency data

The measures proposed will deliver sufficiency data in shortage situations and, by requiring routine collection of supply data by establishments, should improve NCAs' access to such information, helping them to build a clearer picture of the overall supply situation.

Comparable sufficiency data are likely to be delivered if the definitions are clear, standard units are available and the stated data requirements are calibrated to the capacity of establishments, as envisaged under Option 2 and 3 (Annex 7[54]). Work is ongoing, managed by EDQM, that could inform those data reporting protocols under Option 2. This is expected to help provide standard units for the various tissues and cells, in order to provide guidance/indicators to harmonise sufficiency data reporting[55].

The proposals do not require transmission of 'live' supply data for critical BTC to NCAs in order to provide a 'real time' view of the supply situation, as this would place very significant additional cost burdens on establishments and NCAs. In any case, it is likely that NCAs only need to be notified when there is a reduction in the supply situation.

Table 17 – Impacts on the EU's vulnerability to interruptions in some BTC supply

Criterion	Option			
	Baseline	1	2	3
Availability of information to predict and manage shortages/risks of interruption including emerging infectious health threats	=	++	+++	+++

Key: Baseline = information is available in some Member States, for certain BTCs; in a fragmented way; + structured, comprehensive and consistent information is available on critical BTCs allowing advanced analytics and self-reporting by donors; + information is consistently available across Member States; + timely availability of information

Impact on the EU's preparedness for future crises and public health emergencies

The main difference between options is the approach for specifying rules to be followed by establishments in developing contingency plans and guidance for sufficiency data reporting. Note, the proposed arrangements to supply data do not vary. In that context, there is comparatively little difference in the likely impact of options on overall preparedness and the EU's ability to manage future public health emergencies.

[53] Survey question: To what extent would the foreseen measures to monitor supply (including donations, exchanges between EU Member States, imports and exports, shortages) reduce the risk of critical shortages and help build strategic independence?

[54] Survey question: How confident are you that this option will provide sufficiency data that are comparable across the EU?

[55] See, for instance, EDQM, 2021. Harmonising activity data collection exercises in the field of tissues and cells in Europe. Conclusions and recommendations of the Working Group. Online at tissues_and_cells_conclusions_and_recommendations_harmonising_activity_data_collection_exercises.pdf (edqm.eu) . Accessed 12 August 2021.

The surveys and interviews conducted for this study suggest that supply risk management already features in many of the affected establishment's quality plans (88% has been assumed for the purposes of cost modelling, as detailed in Annex 5). The impact of the proposed measures will therefore also be influenced to a certain extent by any additional supply risk management requirements already imposed at a national level.

- Option 1 is likely to extend the existing model whereby the establishments are preparing contingency plans aligned to the requirements set by competent authorities, customers and other external bodies.
- Option 2 provides the benefit of a consistent approach and timeliness of update of guidance. It was best supported by feedback from the NCAs and respondents to the establishment survey[56].
- Option 3 is expected to provide consistency but lacks agility, although this consideration is less relevant for the problem of shortages compared to other problem areas, as rules in this area are expected to change less often.

Table 18 – Impacts on the EU's preparedness for future crises and public health emergencies

Criterion	Option			
	Baseline	1	2	3
Preparedness to implement effective and timely management of shortages/risks of interruption including emerging infectious health threats.	=	+	++	++

Key: = permanent cooperation allows Member States to coordinate crisis response; + Strengthened capacities in Member States to intervene to control and adjust supply, contingency plans are available but are not consistent across the EU; ++ Strengthened capacities in Member States to intervene to control and adjust supply, consistent, high quality contingency plans are available in all Member States for the BE/TEs, taking into consideration the strategic autonomy of EU supply; +++ above plus direct interventions to supply (either on the demand side e.g. export bans; or on the demand side increasing collections)

Impact on risk of interruptions of supply and shortages relating to third countries, and the EU's dependency on plasma imported from the US

The proposed measures address preparedness and market transparency rather than providing direct interventions or plans to strengthen EU domestic supply. As such there is not a clear mechanism by which they would reduce risk of interruption of supply and shortages relating to vis-à-vis third countries, and the EU's dependency on plasma imported from the US. This analysis is supported by feedback received via the surveys[57] and accompanying remarks (detailed in Annex 7) .

Greater knowledge about stocks and better coordination within Europe could help in tackling the problem over time. Nonetheless, a response based on monitoring and regulatory measures, while helpful, would not be sufficient. These conclusions are supported by views of the stakeholders consulted in the present study. A number of NCAs indicate that stronger supply-side measures would be needed if import dependency is to be reduced.

[56] Survey question: To what extent will each option improve the EU's preparedness for future crises and public health emergencies?

[57] Survey question: What impact will the proposed options have on the risk of interruptions of supply and shortages relating to vis-à-vis third countries, and the EU's dependency on plasma imported from the USA?

Impact on collection of critical BTC in the EU

As with the indicator above, the measures proposed are not expected to have a direct impact on collection of critical BTC. They focus more on avoiding and responding to crisis situations than in changing the wider, day-to-day challenges of matching supply to demand. Stakeholder inputs suggest scepticism that the measures proposed will have a positive impact on the collection of critical BTC[58].

Feasibility of implementation

A summary of the considerations relevant to each of the measures is given in the table below. These statements are supported by the views of stakeholders found in Annex 8. Importantly, there are some areas where the detailed specification and approach to implementation will shape the 'user experience' and feasibility, for example, the details of supply data reporting (thresholds/triggers, standard units).

Table 19 – Feasibility of implementation of measures to address shortages

Measure	Feasibility considerations
M5.1: EU law is amended to impose mandatory monitoring obligations on BEs/TEs	Monitoring and reporting obligations will need to be clearly defined to avoid disparities in implementation. Some ATMP manufacturers are required to hold a TE license to import and store BTC materials solely intended for ATMP manufacture. Additional reporting requirements should not apply in this case as this has the potential to create additional unnecessary burden and duplicate reporting requirements already existing in pharmaceutical legislation for reporting of shortages
M5.2: EU law is amended to require mandatory reporting and notification of sufficiency data for certain critical BTC in case of shortage/drop in supply	This measure is expected to be easier to implement than continuous data reporting. However, there is a need for clear definitions (e.g. 'shortage' and 'drop in supply') to ensure that the reporting properly reflects the reality in each country / BE/TEs. The configuration of the IT platform (the proposed reporting tool) will affect the ease with which establishments can report.
M5.3: EU law is amended to require mandatory measures for emergency supply responses	Supply risk contingency planning by establishments is already comparatively common. No major issues foreseen.
M5.5: EU law is amended to strengthen Member State ability to intervene to control and adjust supply, as necessary, under their national competence, and allow evidence-based support action at EU level.	No major issues foreseen.
M5.6: EU law is amended to obligate BE/TEs to develop monitoring and notification systems and contingency plans	Option 1 Some concerns were expressed by stakeholders about how supply risk contingency plans would integrate with existing quality plans/procedures. Requirements for ATMP manufacturers with tissue licences to report shortage risks under medicinal product/ATMP guidance may need to be explored to ensure alignment / avoid duplication.
M5.7: EU law is amended with references to guidance from expert bodies for rules on sufficiency data	Option 2 Incorporating engagement with stakeholders (professional societies, operators, patient organisations) into the process of developing guidance would help to ensure that issues such as

[58] Survey question: "To what extent will the options increase the collection of critical BTC in the EU?"

Measure	Feasibility considerations
reporting and on emergency preparedness / contingency.	administrative burdens and alignment to other quality processes are considered.
M5.8: EU law is amended to include rules on sufficiency data reporting and on emergency preparedness	Option 3 No major feasibility issues cited. Option 3 is expected to provide consistency but lacks agility, although this consideration is less relevant for the problem of shortages compared to other problem areas, as rules in this area are expected to change less often.

5.2. Economic impacts

This section covers the following categories of impact:

- Innovation and research
- Cost to regulators
- Cost to establishments
- Sustainability of public health budgets
- Competitiveness and trade
- Operation and conduct of small and medium enterprises (SMEs)

5.2.1. Innovation and research: facilitate innovation of safe BTC therapies (Objective 4)

Currently, there are two main barriers to innovation and research in the BTC sector:

- Without a clear or certain regulatory classification process or system for innovative products, so-called “borderline cases” can arise (examples of borderline cases are provided in Annex 9). Even at the earliest R&D stage, uncertainty in regulation can pose a barrier to investment in innovation due to anticipated product development and authorisation costs associated with different developmental pathways. It is also highly significant for the costs that healthcare systems incur when eventually providing a treatment (reimbursement costs) as well as patient access to, and the cost-benefit of, novel products or treatments.
- Additionally, as described in Section 4.1.9 (information about the baseline for handling of applications of novel applications of BTC), there are variations in preparation, classification and authorisation requirements and practices across the EU. This in turn has knock on consequences, including for equitable patient access to therapies across the EU (discussed in Section 5.1.1.).

Objective 4 measures are described in Annex 2.

Stakeholders affected by the measures intended to support innovation

The ultimate beneficiaries of measures in this area are patients who will benefit from the new and improved BTC-based products and treatments, both in the EU and worldwide. The stakeholders directly affected by the proposed measures will be those developing novel products and treatments in the BTC sector. There is no record of how large this group of stakeholders is, but information obtained for this study directly from the CAT, the main advisory body tasked with providing recommendations on the classification of ATMPs, provides an overview of those within and outside the BTC sector who may be affected by possible changes to the BTC legislation. This data suggests that applicants seeking advice on classifications on novel products/treatment (i.e. the first step in determining the appropriate development pathway) come from both the public and private sectors, and

include TEs, academic/research hospitals, pharmaceutical companies and small-medium enterprises.

Public/not-for-profit bodies developing and supplying new therapies: All BEs/TEs responsible for the procurement and processing of BTC used for novel treatments/products will be affected by any steps taken to strengthen preparation and authorisation processes in order to assess any risks associated with treatment with BTC prepared in innovative ways.

The scale of impact will be influenced by factors such as the national rules already in place and how they apply. University/research hospitals and stakeholders running clinical programmes working with SoHO brought into the scope of the revised legislation by measure M1.2 (such as faecal microbiota and breast milk) will also be affected (as this measure will improve clarity about which framework a substance belongs to).

Commercial/for-profit developers: SMEs and large pharmaceutical companies developing BTC-derived products and treatments will be impacted by changes to procurement and processing stages (which, as suggested by stakeholders consulted for the borderline case studies presented in Annex 9, may in turn impact the future pathway for commercialisation).

ATMP developers may be affected if BTC are used as starting materials for the manufacture of medicinal products/medical device (e.g. by new donor protection requirements). Data on commercial developers primarily focus on ATMP manufacturers but provide an indication of the size of the sector. A survey on challenges in ATMP development[59] identified 271 commercial developers active in ATMP development in 2017 in the EU (then the EU28)[60]. Data from the Alliance for Regenerative Medicine (ARM), dated 2020,[61,62] show the global ATMP sector is growing rapidly: there are 139 developers in the EU known to ARM[63].

The other main for-profit stakeholders that may be affected are stakeholders developing aesthetic/cosmetic treatments from BTC who are currently working outside the BTC legislation due to the “same surgical procedure” exemption (e.g. those using plasma rich platelets for beauty facial treatments or autologous adipocyte cells for cosmetic fillers). The literature evidences significant actual and projected growth in this field over the last few years[64].

Competent authorities: Another stakeholder group that will be affected is the competent authorities that will need to operate the new rules on authorisation of novel BTC applications. As set out earlier and in the evaluation, competent authorities vary in form and structure, with authorisation functions carried out in medicinal product authorities in most

[59] Ten Ham, R., Hoekman, J., Hövels, A. M., Broekmans, A. W., Leufkens, H., & Klungel, O. H. (2018). Challenges in Advanced Therapy Medicinal Product Development: A Survey among Companies in Europe. Molecular therapy. Methods & clinical development, 11, 121–130. https://doi.org/10.1016/j.omtm.2018.10.003

[60] This list includes active commercial developers involved in ATMP development for human use, established in or developing for at least 1 of the 28 EU member states.

[61] Alliance for Regenerative Medicine (2020a).Global Regenerative & Advanced Therapy Medicine Sector Report: H1 2020. Available from: https://alliancerm.org/sector-report/h1-2020-report/

[62] Alliance for Regenerative Medicine (2020b). European Regenerative & Advanced Therapy Medicine Sector Report: H1 2020. Available from: https://alliancerm.org/sector-data/h1-2020-report-europe/

[63] These data relate only to regenerative medicine and advanced therapy companies working in areas such as gene therapy, cell therapy and tissue engineering.

[64] European Commission (2019). Evaluation of the Union legislation on blood, tissues and cells. Staff working document. Available from: https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/swd_2019_376_en.pdf

Member States[65], BTC specialist authorities in others (e.g. EL, ES, LT and LU for blood[66]) , and even by national or regional health administrations[67].

EU bodies: The measures will potentially impact on the possible future interactions with advisory bodies in adjacent regulatory regimes. This includes the CAT, which operates in the ATMP field, and stakeholders responsible for regulation in the medical devices field (e.g. the BLCG subgroup which sits with the Medical Device Coordination Group).

Impacts and indicators

The measures defined to facilitate innovation of safe BTC therapies are intended to resolve established issues[68] and ensure a consistent, robust but proportionate approach to the assessment and use of novel substances and products. Most of the measures (shown in Annex 2) appear in all options – all the mechanisms proposed to address borderline issues, and rules on appraisal of novel BTC applications are applied in all cases. The options differ only in what rules the establishments are required to use when conducting their risk assessments for novel BTC preparation processes, and how those rules are developed.

Clarity on which regulatory framework applies

Four measures under Objective 4 (M4.1, M4.2, M4.3 and M4.4) and one measure under Objective 1 (M1.2) are provided to improve clarity about which framework a substance/product belongs to. These measures (described further in Annex 2) have the potential to provide the required clarity by:

- Bringing currently unregulated therapies (e.g. FMT, DHBM, SED) under the BTC legislation and ensuring all BTCs are covered by the regulatory framework.
- Earlier and easier resolution of borderline issues, such as those described in Annex 9. Note, there is no consensus on how many borderline issues are likely to occur among study stakeholders. A few experts working in the ATMP sector suggested there are very few 'true' borderline cases, whilst others attending the workshop on borderlines indicating that they expect to see increasing numbers of therapies being developed at the borderlines or crossing the borderlines.
- Enhanced harmonisation across Member States, leading to more opportunities for pan-EU R&D activities and cross-border exchange.
- A clearer regulatory pathway to follow across all adjacent frameworks (ATMP, medicinal products and medical devices).

All options are expected to have a positive impact and partially solve the current problem. A summary judgement on the impact on the 'clarity problem', based on evidence gathered for this study (as summarised in Annexes 7, 8 and 9), is provided below.

[65] According to the BTC implementation reports published in 2016, in 20 Member State the blood and/or tissue competent authority also has competence for medicinal products.

[66] European Commission (2016a). Commission Staff Working Document on the application of Directive 2002/98/EC on setting standards of quality and safety for the collection, testing, processing, storage and distribution of human Blood and Blood Components and amending Directive 2001/83/EC. Available from: https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/swd_2016_129_en.pdf.

[67] European Commission (2019). Evaluation of the Union legislation on blood, tissues and cells. SWD(2019) 376 final. Available from: https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/swd_2019_376_en.pdf

[68] European Commission (2019). Evaluation of the Union legislation on blood, tissues and cells. SWD(2019) 376 final. Available from: https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/swd_2019_376_en.pdf

Table 20 – Judgement on the extent to which policy delivers clarity on which regulatory framework applies

Indicator	Option			
	Baseline	1	2	3
The extent to which there is clarity as to which regulatory framework the substance/product belongs (including for products that move from one framework to the other)	=	++	++	++

Key: baseline = some BTCs are not regulated; for others, inconsistent application of the adjacent legal frameworks across Member States; + all BTCs are covered by a regulatory framework (incl. breast milk, FMT, other currently unregulated substances); + improved clarity and consistency of classification; + one single body issuing a single guidance / decision on the classification across the frameworks.

Consistent and comparable regulatory requirements for BTC, including coherence across adjacent legal frameworks

Several measures under Objective 4, provided under all options, aim to enhance the consistency and comparability of evidence demonstrating quality, safety and efficacy of novel BTC preparations (specifically M4.6, M4.7 and M4.9 as specified in Annex 2). This in turn can support harmonisation, mutual recognition, reinforcement of trust, increased availability of more novel products for patients and increased innovation. When substances move between regulatory frameworks (e.g. when BTC are the starting material for the manufacture of a medicine or a medical device), effective communication on traceability, vigilance, etc. between the relevant authorities is essential.

All options are expected to have a positive impact and partially solve the current problem of poor consistency/comparability in regulatory requirements for BTC, including coherence across legal frameworks. The main concern, which is common to all the options, relates to ensuring there is sufficient expertise supporting the development of consistent/comparable regulatory requirements. A summary judgement developed through this study is provided in the table below.

There was a repeated concern that Objective 4 measures related to advisory mechanism (M4.2, M4.3 and M4.4), provided under all options, will not go far enough because of existing provisions defined in the ATMP legislation. For example, the BTC reforms will not affect the criteria, currently defined in the ATMP legislation, which is used to differentiate between BTC and ATMP products.

Table 21 – Judgement on the extent to which option delivers consistent and comparable regulatory requirements for BTC

Indicator	Option			
	Baseline	1	2	3
The extent to which there is consistent/comparable regulatory requirements for BTC, including coherence across legal frameworks	=	++	++	++

Key: baseline = the regulatory requirements for demonstrating quality, safety and efficacy are substantially different depending on the framework; + comparability/consistency in the level of evidence required for demonstrating quality, safety and efficacy for products of similar risk/benefit profiles; + clinical evidence generated under the different frameworks is more accessible and comparable and can be exchanged (interoperability and standards facilitate seamless mutual exchange); + consistent guidelines defining the level of required evidence across legal frameworks, and all clinical data generated, is shared.

Facilitation of research and development (R&D)

All measures being considered under Objective 4 are expected to have a positive impact, partially resolving issues that impede R&D in the BTC sector. There is potential for the

measures to: foster public-private partnerships; enhance transparency of research (circulation of data, research results or researchers); and enhance transparency of R&D costs. Improved circulation of data and research results may lead to greater R&D in the sector (e.g. through the promotion and development of certain techniques or processes) with downstream benefits to patient access (e.g. as a result of more products being developed and approved for use).

Triangulation of evidence from different sources (workshops, interviews and the borderline case studies) suggests enhanced regulatory coordination (facilitated by the advisory mechanisms proposed under M4.2, M4.3 and M4.4) and exchange of clinical and authorisation data (M4.8 and M4.9) between developers would enhance transparency, mutual trust and confidence in the BTC sector (more information on measures provided in Annex 2). This in turn could encourage growth in the research environment, including more cross-border research activity (e.g. multi-centre trials, supply of starting materials). Potential limiting factors are data protection barriers and management of confidential and propriety information.

The need for proportionality was emphasised when implementing Objective 4 measures to strengthen preparation processes (specifically requests for proportional evidence generation under the authorisation procedure supported through measures M4.5, M4.6 and M4.7 as specified in Annex 2) – with recognition for the size of the patient population being treated as well as the clinical indication. Without this, fewer entities (and, disproportionally, public sector entities reliant on public funding) may be able to fund R&D activities. The requirement for clinical evaluation for high risk applications (M4.7) could result in less private sector interest, particularly where there are few participants to recruit and therefore trials need to run for longer (with accompanying costs).

Future investment into the development of novel products may be impacted if the upfront costs/risks cannot be calculated. Measures that improve the definition of regulatory pathways and generate more rigorous authorisation/clinical data should help to encourage investment. The predictability of upfront costs will become increasingly important as therapies become ever more personalised (i.e. treatments for single patient-use).

Table 22 – Facilitation of R&D

Indicator	Option			
	Baseline	1	2	3
Extent to which measure facilitates R&D (fostering partnerships across the public and private sector; transparency of research: circulation of data, research results or researchers; transparency of R&D costs)	+	++	++	++

Key: = a number of successful innovation partnerships exist; however in general there are limited capacities of public sector, academia as well as SMEs, to participate in a balanced cooperation; + incentives remain for the private sector to benefit from their investment capacities; + level playing field for public sector innovation (e.g. improved process authorisation; clear regulatory pathway, proportionate requirements for evidence generation), which also supports more balanced public private partnerships.

Stakeholders were more confident that Option 2 would best deliver an outcome-driven authorisation process than the other options. In Option 2 establishments are required to conduct risk assessments on novel processes in compliance with technical guidance from expert bodies as referred to in EU legislation. That would provide a more agile regulatory model than Option 3, which could evolve in response to changes in science and technology.

Table 23 – Outcome-based preparation process authorisation[69]

Indicator	Option			
	Baseline	1	2	3
Stakeholder confidence that the proposed measures would result in a strengthened and consistent preparation process authorisation system that is outcome based.	=	+	+++	++

Key: baseline = no impact; + partially solve; ++ more than partially solve; +++ substantially solve

Public sector innovation

Manufacturers of ATMPs or medical devices, when using BTC as starting material, follow the ATMP requirements for the manufacturing which are more stringent (e.g. maintaining GMP-certified facilities, obtaining marketing authorisation etc.)[70]. Public sector innovators unable to meet the higher costs associated with these requirements may be driven out of the sector. There are several 'borderline' examples (see Annex 9) where the reclassification of a BTC product to an ATMP (e.g. cultured limbal cells, cultured keratinocytes and isolated hepatocytes) has affected hospitals' ability to continue delivering their treatments. Reclassification into ATMP framework has a disproportionate impact on hospitals (which have previously been delivering the therapies) as they cannot offer these therapies any more due to high costs and the introduction of additional ATMP requirements. This then has an impact on access to these therapies through BTC establishments[71].

Objective 4 measures are expected to have a positive impact on public sector innovation, and partially solve the existing problems. Improved interactions between adjacent sectors (facilitated through the mechanisms specified in M4.2, M4.3 and M4.4) will help to raise public sector stakeholders' awareness of likely costs (before production/development) and regulatory requirements. This should support the development of innovative products.

A recurrent finding from interviews with public sector stakeholders (in the borderline case studies) was that a heavy regulatory burden created by the authorisation procedures applied to innovative preparation processes (e.g. M4.5-M4.7) could decrease innovation in the public sector. Additional regulatory burdens could be offset by the sharing of authorisation data (M4.8) given that long approval processes are often a limiting factor on the pace of innovation in the public sector. However, this will be highly dependent on the type and level of information that Member States or developers are willing to share (as discussed further in the following section).

Impacts are expected to be experienced first and foremost by academic researchers and hospitals (who often pioneer innovative therapies), particularly those involved in tissue engineering processes which can fall at the borderline of the BTC and ATMP legislation.

Table 24 – Public sector innovation

Indicator	Option			
	Baseline	1	2	3

[69] More information on this indicator – which refers to measures under Objective 4 – can be found in Annex 2

[70] Pirnay, J. P., Vanderkelen, A., De Vos, D., Draye, J. P., Rose, T., Ceulemans, C., Ectors, N., Huys, I., Jennes, S., & Verbeken, G. (2013). Business oriented EU human cell and tissue product legislation will adversely impact Member States' health care systems. Cell and tissue banking, 14(4), 525–560. https://doi.org/10.1007/s10561-013-9397-6

[71] Although the hospital exemption pathway is a possible additional route under the ATMP framework, implementation diverges across Member States.

Public sector innovation	=	++	++	++

Key: baseline = certain innovative substances public sector entities are unable to develop/provide. Innovations started by public sector/academia are often brought to market by industry, that can take the costs and risks of authorisation/market entry (single, for-profit entity - monopolistic situation); + level playing field for public entities and academia to complete the development of an idea into an innovation and supply it; + improved research environment where the technical specifications of innovations are shared; + open innovation model (e.g. clinical societies sharing studies).

Member States sharing data on national preparation process authorisations

The proposed IT platform (M4.8), common to all options, is intended to bring efficiencies and to encourage more consistent preparation process authorisations by increasing the number of Member States sharing data on national authorisations. This is supported by measures (M4.5-M4.7) to enhance the rigour and quality of data for authorisations of novel BTC preparation processes. The main impact of this measure will be to encourage harmonisation across Member States. In turn, this may lead to greater cross-border exchange. The implementation of the IT platform could offset costs created by more stringent preparation process authorisations (introduced under M4.5-M4.7) by providing shareable validation data. This would speed up preparation processes authorisation and encourage trust and mutual recognition not only between countries but also within countries with regional authorisation bodies.

Under each option, it is expected a similar number of Member States will share data on national authorisations (over 20, but not all Member States). This is highly dependent on the information that Member States are willing or able to share[72], and there is a risk that confidentiality clauses for proprietary data and information, and the need for data protection, may significantly reduce the impact this measure might have.

Table 25 – Number of Member States sharing data on national authorisations

Indicator	Option			
	0	1	2	3
More consistent and better improved national process authorisations: number of Member States sharing data on national authorisations	=	++	++	++

Key: = under 10 Member States ; + over 10 but under 20 Member States; ++ over 20, but not all Member States; +++ all Member States

Patient access

A key objective of all the measures under Objective 4 (as defined in Annex 2) is to provide a robust but agile regulatory framework which supports innovation by providing developers with consistent and coherent advice on regulatory pathways, access to clear, up-to-date technical rules and efficient, proportionate preparation process authorisation procedures that are applied consistently across Member States. All options are expected to have a positive impact on accessibility.

There was some stakeholder concern (expressed by those consulted in the development of borderline case studies, described in Annex 9) about the costs associated with the evidence required to support preparation process authorisation and whether public sector actors will be able to mobilise the necessary resources.

[72] It is currently unclear to what extent Member States / developers will be willing to share information on new, innovative processes on a voluntary basis.

Table 26 – Impact on patients' access to novel therapies with proven added value

Indicator	Option			
	Baseline	1	2	3
Impact on patients' access to novel therapies with proven added value	=	+	+	+

Key: baseline = certain public sector entities are not able to develop/provide innovative preparation processes, there is a single, for-profit entity (monopolistic situation which tends to increase prices and restrict access); + possibility for multiple developers/providers (including public entities) to develop and supply innovative treatments which improves access and reduces prices (no longer a monopolistic supplier)

Feasibility of implementation

Issues relating to feasibility of implementation are summarised here, with stakeholder perspectives discussed in Annex 8.

Table 27 – Feasibility of implementation of measures to increase innovation

Measure	Feasibility considerations
Removal of same surgical procedure exemption (M4.1)	The principal implementation concern related to scope and definition of 'proportionate' requirements for point-of-care preparations brought into scope. Importantly, this will be affected also by the amendment of the scope of blood legislation (M1.2) which will bring same-surgical/bedside treatments such as PRP for clinical and cosmetic purposes and autologous SEDs fully under the scope of the legislation. Introducing mandatory registration of point-of-care processes (such as activity data and vigilance reporting obligations, along with desk-based preparation process authorisation) was considered as a way to yield further benefits.
Advisory mechanisms within BTC and with other frameworks (M4.2, M4.3, M4.4)	The impact of these measures is potentially constrained by the advisory status of the recommendations provided by the proposed mechanisms (committees). Stakeholders made suggestions for enhanced monitoring and follow-up processes to track the implementation of recommendations, plus greater communication and exchange of information between authorities. Advisory mechanisms need to be agile and not procedurally burdensome, so developers receive timely answers to questions. Implementation would need to prevent duplicative activities and divergence from, or competition with, existing classification advice or mechanisms (established under ATMP and Medical Devices legal frameworks). Stakeholders called for good communication and coordination with bodies in (AT)MP, Pharma and medical device sectors from the outset.
Authorisation of preparation process for novel applications (M4.5, M4.6)	The main implementation concern for the authorisation procedures relate to costs and resource implications for developers, as these could increase barriers to entry and slow innovation. A second, allied, issue is the expertise required to assess preparation processes authorisation requests by staff in competent authorities. Clear roles and responsibilities for BTC manufacturers and for oversight bodies should be defined. There was also a view that common international standards should be applied as much as possible, with efforts made not to diverge from rules used in major third country jurisdictions (e.g. US) where possible.
Clinical trial required for high risk applications (M4.7)	The concern for this measure was that further clinical evaluation requirements should be proportional and limited to high-risk products where sufficient data could be collected. There was a lot of support among participants for clinical outcome registries to play a role in the collection of clinical data, as well as for the (anonymised) exchange of clinical data between Member States and between competent authorities.
IT platform (M4.8)	Risks that confidentiality clauses and the need for data protection will significantly reduce the impact of this measure.

5.2.2. Costs to regulators

The proposed measures will have implications for the expenditure of the regulators operating the BTC oversight system, both within Member States and at European level (EU/Member State regulators' enforcement costs). There will be costs associated with transition to the new operating model specified by the revised EU legislation where that does not match the baseline condition in a given Member State (adjustment costs). There will then be changes to recurrent expenditure in various areas (enforcement costs).

Determination of the net change in costs versus baseline is made more complex by:

- The ***potential for additional costs to be counted but not cost savings***. The long-term operational cost savings arising from less regulatory divergence and increasing harmonisation are less easily quantified than servicing the requirements specified in the proposed legislative reforms;
- ***The variety of oversight models, institutional structures and BTC regulatory procedures in Member States;***
- ***Lack of reference data on 'adjustment costs'.*** There are instances where measures proposed in the EU reforms are already operational in specific Member States. However, estimates of costs incurred in implementing these measures were not provided by stakeholders consulted as part of this study. This reduces the accuracy by which it has been possible to estimate any future adjustments costs.

Additionally, there are instances where the current proposals establish new oversight mechanisms but, as the actual ***future costs to competent authorities will only become apparent when the detail is specified, it is not possible to provide estimates*** (examples being thresholds for shortage reporting by BEs/TEs in Objective 5, or the detail of follow-up requirements for children born as a result of MAR).

To accommodate these issues the discussion below provides cost estimates as ranges and provides explanatory narrative to aid interpretation. A full description of the costing methodology is provided in Annex 5. The estimates are informed by desk research, surveys and interviews with relevant stakeholders. Estimates are in present value terms. The ten year figures are projected from the given date on which the legislation comes into effect. Unit labour cost figures are taken either from data provided by stakeholders or from Eurostat sources.

Table 28 shows the estimated incremental costs of the measures considered under the different objectives for NCAs and EU institutions compared to the baseline.

Table 28 – Estimated impacts of the proposed reforms on enforcement costs and adjustment costs for NCAs and EU institutions over ten years[73] (EUR thousand)

Indicator	Option 1		Option 2		Option 3	
	Lower boundary	Upper boundary	Lower boundary	Upper boundary	Lower boundary	Upper boundary
Estimated change in annual enforcement costs to competent authorities	19,732	21,587	18,728	20,590	18,728	20,590

[73] EU institutions here means European Commission and EU expert bodies. One such expert body, EDQM, is not an institution of the European Union but is a Directorate of the Council of Europe. Incremental EDQM costs associated with the proposals that the European Commission agrees to fund will be financed by the EU budget and so are classified as EU costs for the purposes of the current analysis.

Estimated one-off adjustment costs to competent authorities	2,406	3,199	2,788	3,708	2,597	3,453
Estimated change in annual enforcement costs to EU institutions	1,499	1,721	7,294	7,516	8,591	8,813
Estimated one-off adjustment costs to EU institutions	6,071	6,071	6,071	6,071	6,071	6,071

Table 29 shows the estimated changes in costs (both enforcement and adjustment costs) of the measures considered under the different objectives for NCAs and EU institutions, compared to the baseline.

Table 29 – Estimated impacts of the proposed reforms on costs for competent authorities and EU institutions (EUR thousand) over ten years[74]

Objective	Cost category and incidence	Option 1		Option 2		Option 3	
		Lower boundary	Lower boundary	Upper boundary	Upper boundary	Lower boundary	Upper boundary
Objective 1 – Increase patient protection from all avoidable risks	Estimated change in costs to competent authorities over ten years	9,819	9,819	6,957	6,957	6,871	6,871
	Estimated change in costs to EU institutions over ten years	4,001	4,001	10,040	10,040	13,405	13,405
Objective 2 – Strengthen and harmonise oversight among Member States	Estimated change in costs to competent authorities over ten years	232,811	308,128	232,811	308,128	232,811	308,128
	Estimated change in costs to EU institutions over ten years	6,309	8,010	6,309	8,010	6,309	8,010
Objective 3 – Increase protection of BTC donors, and children born from donated sperm, eggs or embryos, from specific risks	Estimated change in costs to competent authorities over ten years	34,142	34,220	31,542	31,693	31,323	31,439
	Estimated change in costs to EU institutions over ten years	N/A	N/A	5,415	5,415	5,415	5,415
Objective 4 – Facilitate innovation of safe BTC therapies	Estimated change in costs to competent authorities over ten years	19,419	42,527	19,901	43,491	19,633	42,954
	Estimated change in costs to EU institutions over ten years	17,748	17,748	18,806	18,806	18,086	18,086
Objective 5 – Avoid shortages of critical BTC therapies	Estimated change in costs to competent authorities over ten years	4,915	5,077	3,779	4,068	3,588	3,813
	Estimated change in costs to EU institutions over ten years	N/A	N/A	N/A	N/A	6	6

Note: Some costs for EU institutions are the same under Objectives 1, 3, 4 and 5. In particular, the costs for the IT platform are the same for Objectives 1, 3 and 5, while EDQM costs are shared between Objectives 1, 3, 4 and 5. In this table they are presented only once, under the first Objective for which they incur, to avoid double counting.

[74] The full list of measures considered per each Objective is provided in Annex 2

The text below discusses enforcement cost impacts on NCAs and EU institutions by reference to each of the five objectives.

The costs to regulators of measures intended to increase patient protection from avoidable risks (Objective 1)

Costs for NCAs: These will be influenced by: the broadening of the scope of EU legislation (M1.2); the requirement for Member States to publish more stringent rules (M1.3, for Options 2 and 3 only); and the requirement for authorities to evaluate risk assessments prepared by establishments (M1.5, Option 1). Table 30 provides an overview of the cost impacts for NCAs of the measures under consideration. Option 1 is expected to impose the highest additional costs.

Table 30 – Costs of increased patient protection from avoidable risks for NCAs (EUR thousands)

	Option 1	Option 2	Option 3
Costs for NCAs (over ten years)	9,819	6,957	6,871

Note: More information on the costings can be found in Annex 5.

Source: NCA survey (Annex 6)

Extending the scope of EU legislation (M1.2) will increase the number of establishments that NCAs oversee, bringing into scope establishments working with substances such as breast milk and FMT, and cosmetics used for non-therapeutic uses and currently unregulated stem cell treatments. It will have implications for NCAs' workloads. A conservative estimate (covering milk banks and FMT establishments) puts the increase at about 7% of the BTC establishments already regulated. The actual number is likely to be higher but there is uncertainty about the size of the sector providing cosmetic treatments for non-therapeutic use (see Annex 5) and other bedside procedures treatments that fall under the same surgical exemption (which involves removing cells, treating them and re-administrating to patients).

NCAs may incur costs in defining the obligations that will apply to newly regulated establishments and in adapting procedures and rules. The new establishments (on which NCAs currently have little or no information) will have to be authorised, added to inspection plans and given the appropriate risk profile (risk criteria may need to be adapted to the activities of the new establishments). NCAs may need to bring in external expertise and spend money on staff training. There will be higher ongoing enforcement costs for NCAs.

Many NCA costs cannot be directly attributed to oversight of individual establishments, so it is not possible to accurately calculate an 'average oversight cost per establishment' and apply the figure to the number of additional establishments.

The incremental costs for inspections of new establishments illustrate the additional NCA workload, which will be combined with the new risk-based inspection regime to be introduced as part of Objective 2.

The requirement for NCAs to publish more stringent rules in an accessible format (M1.3) will generate costs for NCAs proportionate to: the number of new, more stringent rules adopted each year; and the frequency of update of such documents. The cost is expected to be modest but will be affected by the details specified in the EU law, such as any requirement to translate the documents into a standard set of EU languages[75].

[75] For the purposes of cost estimation, it has been assumed that the revised, clearer framework for the BTC sector will lead to the publication of only two documents per year per NCA.

Measure M1.5, which applies only under Option 1, obliges inspectors to evaluate establishments' risk assessments, including for the new SoHO establishments under the scope of the EU legislation (e.g. establishments working with substances such as breast milk and FMT). It is expected to increase NCA workload (although evidence collected suggested that a majority of Member States already have a similar measure for establishments already in the scope of the legislation[76]). Under Option 1, inspectors will potentially have to familiarise themselves with a possibly different risk assessment framework at every inspection/evaluation. The added complexity will be demanding for inspectors and create challenges in achieving economies of scale and standardisation of process. This is likely to require training and an inspection system that can accommodate a variety of sources and rules.

This measure will, however, be combined with the new, risk-based inspection regime introduced under Objective 2, which should prompt a more efficient and effective schedule of inspection activities. Therefore, the final impact of this measure on NCAs is considered to be limited, as the more efficient risk-based inspection regime will partly offset the additional costs.

Option 3 has the potential to create additional workload for Member State legislative bodies or government authorities if the update of the rules in EU law has to be codified in national or regional law before it has effect. If the EU legal instrument used comes into effect in all Member States without transposition, then this impact is avoided. A GAPP project survey[77] suggests that regulatory processes for a significant share of Member States are codified in law rather than guidance. Costs of national legislative processes have not been estimated.

Costs for EU institutions: will be determined by the broadening of the scope (M1.2); the IT platform (M1.4); and mechanisms for setting the rules for BTC establishments to take account of EU rules on quality and safety (M1.7 or M1.8) (described further in Annex 2).

Table 31 – Costs of increased patient protection from avoidable risks for EU institutions (EUR thousands)

	Option 1	Option 2	Option 3
Costs for EU institution (over ten years)	4,001	10,040	13,405

Note: Estimates come from interviews with EU institutions' services. The costs of some of the Objective 1 measures are shared with Objective 3, 4 and 5 measures

The expansion of scope of the legislation (M1.2) is expected to have minimal impact on EU costs (a very small extension to the scope of audits, accounted for in the estimation of cost impacts for Objective 2). The IT platform (M1.4), funded and supported by the Commission, will enable exchange of information on quality and safety requirements. It will also facilitate distribution of timely updates in case of emergency and sharing of information on the national and regional differences. The same platform will be used to support measures under Objectives 1, 3 and 5. The costs provided for this measure relate to the design and maintenance of the platform.

The specification of quality and safety requirements (M1.7 and M1.8) will see EU institutions incur costs relating to: funding by the Commission of EU expert subgroups meetings,

[76] The assessment commonly follows the guidance issued by the NCA, which is often based on scientific evidence and documentation from EU (ECDC and EDQM), international and national expert bodies. NCA inspectors typically evaluate the risk assessment as part of the inspection; an ad hoc procedure specifically focused on the risk assessment is rare.

[77] GAPP WP5 Survey. This has 24 responses, of which 23 were national competent authorities and 1 regional authority.

supporting the work of experts and the translation in all EU official languages of guidelines[78]. The funding of expert bodies (e.g. EDQM) will be maintained, as already considered in the definition of the baseline[79]. Under Option 2 (M1.7), the same activities will be carried out, but with the Commission (DG SANTE) co-funding the subgroup meetings and expert activities, together with the European expert bodies (EDQM); translation costs will remain. For Option 3 (M1.8), the definition and update of rules will include the time spent by EU officials steering the requirements into EU legislation, and the time for the legislative process of adopting the implementing act (about 15-20 weeks each time after the European expert bodies have defined the requirements)[80]; and the costs of yearly meetings of the expert groups.

The total cost of Option 2 and 3 is influenced by the frequency of updates. Under Option 2, updates are expected to happen more frequently than under Option 3. The flexibility of the update process envisaged under Option 2 is likely to offset the costs of more frequent updates. However, under Option 3, there will be additional work (and therefore costs) required to manage each round of update via the legislative process. The costs to EU institutions are also expected to be higher for Option 3, due to a greater need for coordination at EU level. These costs will be incremental to the activities already ongoing or planned to be implemented in the future (e.g. improvement for patients SARE reporting, or ongoing work on rapid alerts (RAB/RATC)).

The costs of measures intended to strengthen and harmonise oversight among Member States (Objective 2)

The costs of the enhanced oversight measures are expected to be identical under all options as the measures are the same in each case.

Costs for NCAs: These will be influenced by the mandating of risk-based inspections (M2.2); Commission audits of national control systems (M2.4), and joint inspections of BTC establishments (M2.5). Table 32 provides an overview.

Table 32 – Costs of stronger, harmonised oversight for NCAs (EUR thousands)

	Across NCAs (1 year)		Across NCAs (over ten years)	
	Adjustment costs	**Enforcement costs**	**Adjustment costs**	**Enforcement costs[81]**
M2.2 Risk-based inspections	147 – 196	M2.2 Scenario 1: 13,895 M2.2 Scenario 2: 9,120	139 – 185	M2.2 Scenario 1: 107,187 (+1,156 with respect to the baseline) M2.2 Scenario 2: 69,900 (-36,130 with respect to the baseline)
M2.4 EU audits	Negligible	118 – 174	Negligible	981 – 1,131

[78] The funding will cover all the EDQM activities related to setting up and revision of requirements for protection of patients.

[79] Details are provided in Annex 5

[80] As per the Better Regulation Guidelines, such 'hassle costs' are not monetised. However, they are expected to influence the efficiency and agility of the measure (more details in Annex 5).

[81] Both scenarios include the changes in number of establishments to be inspected over time.

M2.5 Joint Member State inspections	300 – 450	52 – 56	283 – 424	399 – 426

Note: Estimates in M2.4, M2.5 are based on interviews with relevant stakeholders for NCAs (from the Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction and Transplantation – Joint Action (VISTART) project) and EU services. For M2.2 Scenario 1 assumes the existing 2 year maximum gap between inspections is retained. Scenario 2 is described below and models a more flexible inspection regime.

The requirement to adopt a risk-based (M2.2) approach to the allocation of inspection effort will modify the criteria used for inspection planning in some Member States. At least 14 Member States (and an estimated 20 in total, covering 82% of all BTC establishments in the EU[82]) already use risk parameters to allocate inspection effort – combining fixed-frequency inspections (every two years) with more frequent controls for certain establishments. The incremental cost of this measure will depend on the criteria set in EU legislation for defining risk profiles and the intensity and frequency of the controls for each risk profile. It is also affected by whether the requirement to inspect at least every two years is retained.

While most of the incremental costs are expected to fall on those NCAs that do not currently have a risk-based element to their inspection regime, the others will also incur some additional costs, the scale of which will depend on the size of the gap between the new risk-based regime and their existing model.

If the recommendations from the Commission's Operational Manual on inspections of BTC establishments[83] are followed in the revised framework, the transition to the new system may lead to more radical changes in use of the inspectors' time – decreasing the frequency of controls for low-risk establishments and increasing it for high-risk ones. Such a system could make it possible for competent authorities to transition to the new risk-based inspection regime, while maximising the use of available resources to ensure proper follow-up to the most complex, high-risk situations. Depending on the frequency of inspections in each establishment risk category, and distribution of establishments according to risk, a more flexible inspection regime could result in a more efficient allocation of resources, which would allow inclusion of the new SoHO establishments in inspection plans (as per Objective 1) without a requirement for significant additional resources.

Given existing inspection patterns, if the two-year rule is retained (Scenario 1 in Table 32), the requirement for a risk-based approach will lead to more inspections per year compared to the baseline situation – there will be a larger pool of BTC establishments that are subject to more frequent inspections (an estimated 18% of BTC establishments currently under the standard inspection regime).

A change in the inspection regime consistent with the recommendations in the Operational Manual is captured in Scenario 2 in Table 32. It would require a lower level of resources compared to the baseline (-34%), while Scenario 1 would require a slight increase in resources to complete the inspection schedule (+1.5% compared to the baseline). In many cases, *in situ* inspections (which are more resource intensive) are scheduled more frequently for 'high risk' establishments while desk-based inspections are more common for 'low risk' establishments and for follow-up cases. The transition to a risk-based inspection regime may provide opportunity for a broader re-design of inspections, for instance on the

[82] More details in Annex 5.

[83] It recommends that a general system-oriented inspection covering all areas of activity should be performed at least every four years. *Source:* DG SANTE, (2015), Inspection of Tissue and Cell Procurement and Tissues Establishments – Operational Manual for Competent Authorities, European Commission. Available online: https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/manual_11_en.pdf. The assessment is based on four categories of risk, each of which characterised by different levels of complexity and of risk (i.e. negligible risk, inspected every four years on average, low risk, inspected every two years, moderate risk, inspected every year, and high-risk, inspected twice a year). More details are provided in Annex 5.

use (and combination) of on-site inspections with desk-based and 'virtual' (online) inspections.

The models used to assess an establishment's risk, and the frequency with which the assessment is refreshed, will have an impact on costs and risk management procedures. Differences in approach across Member States could lead to differences in risk assessment and management. As such, continued cross-EU engagement on best practice in conducting risk-based inspections would help to ensure that this measure supports the aim of a consistent, high quality oversight BTC regime for the EU as a whole.

European Commission audits of national control systems (M2.4) will have a modest cost impact on NCAs, defined by the days (and related salary costs) spent by inspectors accompanying the Commission's auditors and in preparation and follow-up. The small number of audits per year (up to six to seven across the EU as a whole, on average) will mean that there is not a major diversion of resources from inspections, and a very low risk of the audits inadvertently undermining an NCAs inspection system/schedule.

The implementation of joint inspections (M2.5) is expected to improve consistency of inspections arrangements across the EU, facilitate the dissemination of best practices and help build confidence in other Member States' inspection systems. This measure will have some cost implications for NCAs, both those receiving the inspectors from another Member State, and those sending staff to another country. These costs will comprise salary costs for inspectors (both in the posting and in the receiving countries), travel costs (for posting countries) and translation costs (for receiving countries)[84]. Travel and accommodation costs are expected to be funded by the EU budget. Estimates, based on recent Joint Actions[85] and NCA interviews, suggest 10 joint inspections per year, most likely targeted at high-risk establishments where the added value of access to specialised knowledge and transferring know-how between countries is greater.

Joint inspections may lead to a reduction in costs for NCAs over time, as an effect of the learning benefits (possibly substituting for official training) and reducing the need for external experts with specific expertise. Such savings are, however, not yet quantifiable. The adjustment costs incurred setting up the system will depend on the extent to which it is based on existing pilots and practices from other domains. They are not expected to be significant.

EU institutions: The proposals for stronger, harmonised oversight will have some costs implications for EU institutions, notably in relation to common guidance on oversight (M2.3) the proposed audits (M2.4) and the IT platform (M2.6). Table 33 provides an overview.

Table 3 3– Costs of stronger, harmonised oversight for EU institutions (EUR thousands)

	EU Institutions (1 year)		EU Institutions (over ten years)	
	Adjustment costs	**Enforcement costs**	**Adjustment costs**	**Enforcement costs**
M2.1 Oversight principles for NCA and staff	Limited	Limited	Limited	Limited
M2.3 Commission guidance on oversight	Limited	124	Limited	950

[84] The salary cost element is an opportunity cost of the alternative use of the time – it is not expected that additional staff will be hired to service joint inspections.

[85] VISTART project, see: https://vistart-ja.eu/

M2.4 EU audits of national control systems	Limited	231 - 453	Limited	1,774 – 3,475
M2.5 Joint Member State inspections	-	114	-	874
M2.6 IT Platform - oversight	836	251	788	1,923

The development and maintenance of common oversight guidance (M2.3) includes costs for expert sub-group meetings and experts, that will support the definition of common EU approaches and practices on oversight.

Commission audits of national control systems (M2.4) will have a limited cost impact on EU institutions, defined essentially by the days (and related salaries) of the auditors, to be accompanied by national inspectors during the process, and travel and accommodation costs. The adjustment costs (one-off) of setting up the system will depend on the extent to which the system is modelled on existing pilots and practices from other domains, but are unlikely to be significant. Similarly, the joint inspections (M2.5) will impact to some extent on the EU budget, which will fund the travel, accommodation costs for inspectors visiting other Member States.

The IT platform (M2.6) supporting this objective will support the implementation of the oversight measures. The costs related to this option concern the design and maintenance of the platform.

The costs to regulators of measures intended to reduce avoidable risks for BTC donors and for children born from donated eggs, sperm or embryos (Objective 3)

Costs for NCAs: NCA costs will include the need to check that establishments are following the new rules implemented for the safety of donors and children born from donated gametes/embryos, as well as associated activities (e.g. receiving notifications about adverse effects on donors/offspring). NCA costs will also depend on the baseline in each Member State at the time of implementation. Table 34 provides an overview.

Table 34 – Costs of increased protection of donors and children born as a result of MAR for NCAs (EUR thousands)

	Option 1	Option 2	Option 3
Costs for NCAs (over ten years)	34,142 – 34,220	31,542 – 32,693	31,323 – 31,439

The increased protection of donors and of children born as a result of MAR (Objective 3, M3.5-M3.7 as defined in Annex 2) is expected to generate costs for NCAs related to implementation of quality and safety requirements in those countries where they are not in place. The adjustment costs for implementing such measures at EU level in a harmonised manner will be contained, as only a minority of countries (eight Member States, based on ICF estimates) will have to design and then implement the set of rules. It is also possible that NCAs that already have similar measures will face some adjustment costs, depending on the extent of the amendments to the system necessary to be aligned with the new set of EU rules.

M3.2 (defined in Annex 2) also introduces a long-term monitoring obligation for high-risk subgroups only, which is expected to have an impact on the costs for inspections of the establishments targeted by the measure. M3.2 is expected to generate costs for competent authorities related to the investigation of adverse events or reactions and to follow-up on possible corrective actions generated by the investigations. In research conducted for this

study, some competent authorities reported experience of investigation of adverse events or reactions (six out of 15 authorities), both for donors and for children born from donated eggs, sperm or embryos and the follow-up on possible corrective actions generated by the investigation. The reported volume of the investigation activities (number of cases investigated) varies across the countries, from fewer than one per year to up to 15, depending on the size of the country and of the BTC sector.

The investigation is usually triggered by the monitoring system, which includes registries of donors and of children born from donated eggs, sperm or embryos. Such registries are not necessarily fully automated, or combined into one national registry for all donors. It is not uncommon to have different registries for related and unrelated donors, and for different types of cells and tissues. The follow-up periods vary depending on the substance donated, ranging from one year to 10 (e.g., for bone marrow). The information available does not support reliable quantification of the time and costs of such investigations, nor of the likely impact of the measures on the volume of such investigations. However, should a centralised, automated registry be needed for systematic monitoring and investigation, the costs would be substantial.

Depending on the implementation system chosen for the definition of the rules for quality and safety requirements, the expected workload for NCAs is likely to change. Option 1 is likely to create cost and difficulty for NCAs as inspectors will have to familiarise themselves with a different set of procedures at every inspection. This approach is also likely to require additional training and an inspection system that can accommodate this variety of sources and rules.

Costs for EU institutions: Additional costs will be incurred in setting up an IT platform, and defined EU rules on donor/child safety. Table 35 provides an overview.

Table 35 – Costs of increased protection of donors and children born from donated eggs, sperm or embryos for EU institutions (EUR thousands)

	Option 1	Option 2	Option 3
Costs for EU institution (over ten years)	21	5,415	6,273

Note: Estimates come from interviews with EU institutions' services. The costs of some measures are shared with measures under objectives 1, 3, 4 and 5 (see text).

The costs for the EU institutions will vary by option. They include: the costs of funding the EU expert bodies[86]; the costs of defining and updating rules for quality and safety requirements (which, under Option 3, as well as the costs of supporting the work of the expert groups (including meetings), will include the costs of the efforts from EU officers to include the requirements into EU legislation and the time needed for the legislative process (15-20 weeks for each update)[87]); and the costs of supporting the work of the expert group.

The cost to regulators of measures intended to facilitate innovation of safe BTC therapies (Objective 4)

Member State competent authorities and EU institutions will incur additional costs if the proposed measures for facilitating innovation of safe BTC therapies are adopted. The table below provides a summary of those costs. The scope for NCAs to recover costs for reviewing authorisation applications via charges to the applicants and levies varies by Member States (see Section 5.2.4 on financial sustainability impacts). Where cost recovery

[86] The funding will cover all the EDQM activities related to setting up and revision of requirements for protection of donors.

[87] As per the Better Regulation Guidelines, such 'hassle costs' are not monetised. However, they are expected to influence the efficiency and agility of the measure.

mechanisms are in place (or would be provided in the future) then the incidence of some of the costs indicated below would be transferred from NCAs to the applicants.

Table 36 – Costs of measures to increase the scale and pace of innovation - NCAs (EUR thousand)

	Option 1	Option 2	Option 3
Costs for NCAs (over ten years)	19,419 – 42,527	19,901 – 43,491	19,633 – 42,954

Competent authorities: Measures with cost impacts on authorities are: the removal of the same surgical procedure exemption; the strengthened preparation process authorisation for novel BTC applications; and the requirement for risk assessment of novel BTC preparation processes.

The removal of the same surgical procedure is expected to increase the number of activities regulated, with consequences for oversight. Most NCAs consulted for this study (Annex 7) expressed concern about the potential impacts of this measure on their volume of work. One area of uncertainty is the precise definition of 'same surgical procedure', and thus the scope of the measure. Its implementation may require discrete descriptions of specific procedures which should be included/excluded. The scope could potentially encompass plastic surgery (including private cosmetic surgery), and general surgery. Dentistry is assumed to be excluded.

The impact on Member State authorities will vary depending on: how close the national definition of 'same surgical procedure' (which varies across Member States) is to the new EU one and the regulatory approach required – e.g. on the spectrum from light touch regulation that might require a simple registration process for preparation of PRP through to a full establishment authorisation on the standard model[88]; the number of establishments / clinicians etc. falling within scope. Given the current exception regime, same surgical procedures are not monitored or accounted for. The number of establishments performing same surgical procedures is also unknown.

For the purpose of cost calculation and based on the information provided by the Commission, it was estimated that this measure will apply to hospitals[89]. It is expected that most of the same surgical procedures will follow a 'simple' or 'light' pathway, which would require NCAs to process the registrations and to verify (e.g. on a yearly basis, or within inspections, when applicable) the notifications submitted by the hospitals. NCAs will have to set up a process for registration of hospitals performing same surgical procedures (and process such registrations), and for notifying about the procedure (and then process/verify the notifications). While the volume of documentation to be revised could be considerable (as it is intended that the provision will apply to hospitals), the actual complexity of the work (and the related effort) for NCAs is likely to be low.

The measures relating to assessment and authorisation of novel BTC preparation processes are meant to provide greater clarity on what rules to apply and what approach is

[88] Following a study workshop on Regulating Point-of-Care BTC Processing (bed-side and same surgical procedure) on 12 May 2021, the following requirements were envisaged by the Commission for the oversight of "same surgical procedure" or bedside procedures: (1) Required registration of the activity with the NCA. Light – a 'notification' with details of the process and procedure and a declaration of compliance with certain provisions including activity data reporting and vigilance. (2) Preparation process authorisation – desk based – an application, assessment and authorisation. Given that many of these procedures are medical device based (so will be standardised – e.g., PRP preparation) an authorisation can be applied to multiple sites. (3) NCAs will have the power to inspect if considered necessary and to require a clinical study depending on the degree of novelty/risk. More information on the workshop can be found in Annex 11.

[89] For the purposes of cost estimation one registration has been assumed for each EU hospital. in reality, not all hospitals are performing such procedures and other entities could also be affected.

required to evaluate novel BTC preparation processes. These are expected to generate costs for NCAs that will vary according to the scale of such activity within their jurisdiction, whether they already have a formal system for assessing novel BTC preparation processes, and the gap between that existing system and the new requirements.

The available evidence (including the baseline data supplied by the GAPP project and data collected for this the study via surveys, email follow-ups and interviews) suggests many Member States (14 of 24 respondents)[90] already have a system to manage the authorisation of novel BTC applications. Eleven of the 15 that provided data for ICF's cost inquiry indicated that they already had such a system.

The majority of Member States (19 based on the estimates described in Annex 5) have implemented systems to manage the authorisation of novel BTC preparation processes, while clinical investigations are rarely covered. For many national systems, minor or incremental innovation require simpler evidence but BTCs with higher degree of novelty usually require more documentation, up to clinical trials for those considered as 'high-risk'.

The proposed regime will set up a system for authorisation of novel BTC applications with requirements (and corresponding costs) linked to the level of risk attributed to the novel BTC, following - to some extent - work done by GAPP. The cost of the measure for NCAs will be determined by the level of risk attributed to the novel BTC preparation processes , as well as by the volume of the activity (i.e., the number of authorisations per category of risk). Novel BTC preparation processes with negligible and low risk (estimated to be respectively 50% and 25% of the total) are likely to require a limited effort from NCAs (around EUR 2,000-4,000 and EUR 6,000-10,000 respectively in internal effort for processing and for assessing the evidence). Conversely, those with 'moderate risk' (about 20% of the total), requiring clinical investigations, and those with 'high-risk' (about 5% of the total), requiring clinical trials, are expected to be the more complex and costly, requiring between EUR 12,000-20,000 and EUR 20,000-45,000 in internal effort for processing and evaluating the evidence produced.

There is very limited evidence on the volume of clinical investigations assessed currently by NCAs. Information available suggest about 15 per year in France and 35 per year in Germany (Germany has a particularly high number of BTC establishments). These figures have been used to derive a rough estimate of the number of authorisations for novel BTC preparation processes at EU level for the different category of risk, assessed to be between 1,800 and 2,500 per year on average.[91] The extent of this activity among NCAs will vary by reference to the volume of 'innovation activity' of the BTC sector in the country, and of the scale of the BTC sector in the country.

The impact of the reforms on each Member State will be determined by the 'gap' between the existing national system and the new set of rules defined at EU level. Member States with an established system will experience smaller impacts. For those Member States that need to set up a system for managing authorisation of new BTC processes, costs are likely to be in the range of EUR 10,000-20,000 in internal effort. Additional external costs such as experts' fees are also possible, but hard to quantify.

Additional costs may be offset by the potential benefits of the wider reform package (e.g. increased harmonisation and trust, more effective information sharing, etc) leading to NCAs having better visibility of what has been approved elsewhere and being more willing to take this into account when considering applications made under their own system. This dynamic ought to deliver cost savings in the future by reducing duplication of NCA authorisation effort. These potential savings are not currently quantifiable.

In addition, a clearer, more harmonised system for authorisation of novel BTC preparation processes is expected to increase the level of innovation across the EU. It is not possible

[90] NCA survey data supplied by GAPP. Survey was conducted in 2019.

[91] More information are provided in Annex 5

to estimate to what extent this would be reflected in the number of authorisations for novel BTC preparation processes processed by year (across the different level of risks).

Other governance measures are likely to have minor costs implications for NCAs. The availability of standard EU guidance for risk assessments of preparation process under Options 2 and 3 ought to reduce the overall effort required to maintain up to 27 sets of national guidance across the EU. Authorities, however, might incur some initial adaptation costs, if the national framework is not fully aligned with the guidance provided.

EU institutions: EU institutions are expected to incur costs for: the introduction of new advisory mechanism at EU level; the definition of rules for strengthened novel preparation process authorisations (including clinical trials/investigations), and the shared EU IT platform. The table below provides an overview of the principal costs.

Table 37 - Costs of facilitating innovation of safe BTC therapies - EU Institutions (EUR thousands)

	Option 1	Option 2	Option 3
Costs for EU institutions (over ten years)	17,748	18,806	18,086

Note: Estimates come from interviews with officials at relevant European institutions. The costs of some measures are shared with measures under Objectives 1, 3 and 5

The following measures are expected to address borderline problems in a more coordinated and harmonised way: an EU-level advisory mechanism established to recommend/advise Member State on when/what BTC requirements should be applied in part or in full (M4.2), a mechanism to prompt regulators of 'adjacent' legal frameworks (SoHO/Pharma/Medical Devices) to better coordinate their rules, especially in respect of substances that are regulated under more than one legal framework (M4.3), and an EU level advisory mechanism which will advise where other frameworks (in particular medical devices and medicinal products) might be applied for particular novel BTC (M4.4).

EU institutions will incur costs supporting and funding the expert subgroups, large scale meetings with authorities and the related preparatory work to maintain the advisory mechanisms. The EU level advisory mechanisms will need participation from NCA officials and experts. As such, the main cost items will relate to travel costs and daily allowances for participants, and the coordination of events and processes.

The actions of the EU level advisory mechanisms are expected to benefit both NCAs and BTC establishments. This effect is expected even if the decisions issued are recommendations rather than legally binding judgements. The operational efficiencies for regulators arising from the harmonisation of advice are not quantifiable.

Measures defining rules for strengthened novel process authorisations and clinical trials/investigations will set up a clearer, more harmonised framework for novel BTC processes. The incremental costs for the EU institutions relate to the costs of:

- Funding EDQM to define and revisit the requirements for risk assessment of novel preparation processes (in Option 2);
- Translating documentation and requirements produced by EDQM (in Option 2);
- Defining and updating rules for novel preparation process authorisation in EU legislation, which will include, in addition to the costs of supporting the work of a dedicated expert group, the costs of EU officers' time for the legislative process (Option 3) and the time needed for the legislative process of adopting the act; and
- Any additional meetings of the Member State expert groups convened in support of these measures.

The costs for implementing Option 1 are expected to be slightly lower than for Options 2 and 3 over ten years (due to the translation of the EDQM documentation and of the funding of the dedicated expert group respectively, whose costs would not be incurred under Option 1). The IT platform developed under Option 4 (based on the work from GAPP) will allow NCAs to exchange information on novel BTC preparation process authorisations and will be used for acceptance of authorisations across Member States on a voluntary basis[92].

The cost to regulators of measures proposed to reduce the risk of shortages due to insufficient or unreliable BTC supply (Objective 5)

The measures reducing the EU's vulnerability to shortages in supply of critical BTCs will impose some costs on NCAs and EU institutions.

Competent authorities: NCAs are expected to see changes in costs as a result of the proposals targeted at reducing supply risk, specifically from notification of sufficiency data and emergencies for critical BTC supplies, and monitoring and notification systems and contingency plans. Table 38 provides an overview. Some Member States have cost recovery mechanisms through which specified regulator costs are recovered from the sector. To the extent that those would apply to the costs identified below (e.g. for inspection of contingency plans) then the incidence of the costs shown would be transferred to the BTC sector.

Table 38 - Costs of better protection against risk of shortages in BTC supply for NCAs (EUR thousand)

	Option 1	Option 2	Option 3
Costs for NCAs (over ten years)	4,915 – 5,077	3,779 – 4,068	3,588 – 3,813

M5.2 introduces a mandatory notification of sufficiency data for certain critical BTC in case of shortage/drop in supply, and M5.5 provides additional powers for Member States to manage supply within their competences. This is expected to have cost impacts for NCAs.

In many Member States (14, based on estimates), NCAs are notified by establishments about the level of BTC supply on a regular basis, ranging from yearly to monthly (or weekly in rare circumstances) communications. In a few cases, communication only happens in case of shortages/supply issues. Additional data on the supply levels are captured during inspections, as part of the normal verification of the establishments' activities. The notification systems are not necessarily fully centralised and automated, although there are examples of IT platforms where establishments upload data on supply at pre-defined frequencies.

Mandatory measures are proposed for emergency supply responses, requiring establishments treating 'critical' BTC supplies to notify NCAs of sudden drops in critical BTC supplies. This measure will require NCAs to process notifications received from establishments[93] via an automated system based on a central IT platform provided by the Commission (M5.4) that allows standardised notification of BE/TE to their NCA. The evidence collected suggests overall limited enforcement costs for competent authorities for managing a notification system for supply of critical BTC, which is expected to remain low thanks to the automated design. The number of reporting BTC establishments is estimated in approximately 2,500, including all BEs/TEs establishments dealing with critical BTC[94].

[92] Details on the costing for this platform are in Annex 5.

[93] The cost implications for this measure do not include the handling of the cases notified, which are beyond this proposal.

[94] Based on list provided in Annex 14.

The measures obliging for NCA inspectors to evaluate BTC establishments' contingency plans are expected to increase NCA workload. While few Member States appear to have implemented obligations for establishments to have supply risk contingency plans, some prepare them as part of their risk and quality assurance procedures. In those cases, contingency plans are assessed by NCAs at inspection. As a result of the combination of national obligations and industry practices, it is estimated that about 50% of BTC establishments have contingency plans. The contingency plans tend to follow the general guidance issued by NCAs, often based on available scientific evidence and documentation from European (EDQM), international and national expert bodies. In addition, NCAs will be required to create (and maintain/update) a national contingency plan for critical BTC supplies.

The NCA workload will vary depending on the implementation system chosen for the definition of the contingency plan rules. If rules are based on a devolved approach (Option 1), costs are likely to be higher for NCAs, as their inspectors will need to assess the adequacy of each establishment plan without reference to a single standard. If contingency plans have to be based on rules developed by EU expert bodies (Option 2) or set in EU law (Option 3), NCAs inspectors will have a clear reference text against which to assess plans. This should reduce workload. The preparation/update (for establishments) and verification (for NCAs) of the contingency plans for critical BTC supplies will take place during inspections of establishments. The combination of this measure with the implementation of risk-based inspection regime (as per Objective 2) is expected to reduce the burden of this new measure for both establishments and inspectors.

EU institutions: EU institutions will incur costs for the IT platform (M5.4) and developing rules to be followed by establishments on contingency plans (M5.7). Table 39 provides an overview.

Table 39 - Costs of better protection against risk of shortages in BTC supply for EU institutions (EUR thousands)

	Option 1	Option 2	Option 3
Costs for EU institution (over ten years)	N/A	N/A	2.427

Note: Estimates come from interviews with EU institutions' services. The costs of some measures are shared with measures under Objectives 1, 3,4 and 5 (see text).

The same IT platform will be used to support measures under Objectives 1, 3 and 5. It will enable sharing of information on quality and safety requirements, as well as on the national and regional differences. It will also allow timely updates in case of emergency and sharing information (M5.4). In addition, a central IT-module in the IT platform will allow standardised notification of NCAs by establishments treating critical BTC (M5.2). Measures defining the rules for contingency plans will be set by EU expert bodies (Option 2) or included in EU legislation (Option 3).

The costs for EU institutions will vary to some extent by option, and will consist of the additional funding needed by EU expert bodies (beyond what is envisaged in the baseline) to support the work required on Option 2; and the costs of defining and updating rules for contingency plans of establishments in EU legislation; the costs of any additional meetings of the Member State expert groups convened in support of these measures.

The costs to EU institutions for these measures are in addition to the many activities already ongoing or planned to be implemented, such as the work on rapid alerts (i.e. the Rapid Alert System for human Blood and Blood Components (RAB) and Rapid Alert System for human Tissues and Cells (RATC)) and existing support for the activities of EDQM and ECDC.

5.2.3. Costs to establishments

The options are expected to have implications for the 'enforcement costs'[95] incurred by BTC establishments, namely: adjustment costs, which encompass those investments and expenses incurred as establishments adjust their activity to the requirements contained in a legal rule; costs associated with activities directly linked to the implementation of the revised legislation, such as operating systems required by regulators for compliance purposes and accommodating inspections; and the indirect operational consequences of the revised legislation, such as the costs of operating to a more demanding safety standard.

Key issues relevant to estimation of this category of impacts are:

- The ***complexity of the baseline*** situation – there is significant variation in the regulatory baseline across (and in some cases within) Member States on parameters relevant to the impacts of the options. Effort has been made to establish national baseline conditions (see Section 4.1), with a particular emphasis on Member States that host a larger share of regulated entities.
- The ***regulatory baseline gives an imperfect estimation of establishments' current organisational*** practice. Establishments may be conducting an activity proposed in the legislative reforms (e.g. preparation of contingency plans for supply interruptions) even when the national regulation does not require it, to meet requirements of customers or other stakeholders, or as part of the organisation's approach to risk and quality management.
- ***There is a lack of source data on adjustment costs in some areas*** – stakeholders were generally unable to estimate the resource implications of executing a change from the current state to the proposed future state or recall the costs of similar transitions executed in the past.
- The legislative reforms propose new mechanisms for rule-setting but, for a number of measures, the future ***direct and indirect costs for regulated entities will be determined by what rules are specified at a later date***, including (in Option 2) after the adoption of the legislation.

If the proposals are successful in achieving greater harmonisation, then in the future there will be greater consistency of regulatory requirements and fewer Member States adopting more stringent measures. Establishments, especially those working across jurisdictions, should spent less time and resources navigating that complexity.

There is, however, the potential for asymmetrical bias in the estimation of cost savings versus cost increases: the options include specific proposals for changes in regulatory requirements whose costs can be estimated using standard approaches, but ***the benefits of future simplification of the regulatory landscape and the burdens avoided as a result of there being fewer unique national rules are hard to estimate*** - the direct and indirect costs of current complexity are not well documented.

The ***regulated entities vary significantly in organisational type*** (e.g. from functional units in public hospital to substantial non-profit institutions) and ***activities regulated by the legislation are also diverse*** (e.g. from blood banks to large multi TEs as well as MAR services), with concomitant variation in processes, cost factors, etc.

Table 40 shows incremental costs of the measures considered under the different objectives for BTC establishments.

[95] As per the Better Regulation Guidelines, enforcement costs are a component of the direct compliance costs

Table 40 - Impacts of the reforms on costs for establishments over ten years (EUR thousand)[96]

Indicator	Option 1		Option 2		Option 3	
	Lower boundary	Upper boundary	Lower boundary	Upper boundary	Lower boundary	Upper boundary
Estimated change in annual enforcement costs	71,268	84,091	63,570	84,091	68,393	84,091
One-off adjustment costs	170,298	248,382	124,372	190,254	124,372	190,254

The costs to establishments of measures intended to increase patient protection from all avoidable risks (Objective 1)

The costs to establishments of efforts to increase patient protection from avoidable risks will be determined by the combined effect of several measures and are expected to vary by policy option. Table 41 provides an overview[97].

Table 41 – Costs of increased patient protection from avoidable risks for establishments (EUR thousand)

	Option 1	Option 2	Option 3
Costs for establishments (ten years)	62,136 – 63,930	46,127 – 50,163	42,781 – 45,771

The extension of the scope of EU legislation (M1.2) will increase the number of entities regulated, covering establishments working with substances such as breast milk and FMT, and cosmetics used for non-therapeutic uses. This will generate adjustment and enforcement costs for the affected organisations, starting with the obligation to be authorised. There are no consolidated sources providing indications on the number (and size) of these establishments. A conservative estimate puts the figure at about 7% of the current BTC establishments[98]. The incremental cost to these entities will depend on the extent to which they already have processes and procedures consistent with the legislative framework. They will incur adjustment costs identifying the obligations that apply to them, and updating and adapting procedures and rules. They are likely to need to prepare to receive inspections. They may need to invest in external expertise and training to help them with the adjustment.

Under Option 1, there is a requirement for all establishments to assess the risks associated with their procedures, which is then evaluated by the relevant NCA (M1.6). This might be expected to have significant cost implications. However, the evidence collected suggests that the majority of establishments across the EU already implement a similar process – either because of a specific national regulatory obligation or because it is part of their risk and quality assurance procedures (and potentially a requirement of the supply chain in which they operate). Establishments' risk assessment and risk management approaches

[96] The full list of measures considered per each Objective is in Annex 2

[97] Costs associated with authorisation of preparation processes, and costs of clinical investigations/trials are covered in the costing of 'innovation' measures.

[98] Details of the estimation are in Annex 5.

are frequently required to follow guidance issued by the relevant NCA and evaluated during the NCA's standard inspection.

The risk assessment is expected to be prepared and verified during the inspection. The move to the mandatory risk-based inspection regime (per Objective 2) is expected to minimise the burden of this measure for establishments.

Under Option 1, each establishment will need to determine the basis on which to prepare its risk assessment. If support is not available it will need the capability to research and interrogate available evidence autonomously, which is likely to generate problems especially for the smaller ones, less likely to have the resources and skills in-house.

The costs to establishments of measures intended to strengthen and harmonise oversight among Member States (Objective 2)

Most of the measures proposed under Objective 2 have a direct effect only on NCAs but the measure (M2.2) requiring competent authorities to operate a risk-based inspection regime will change costs for some establishments. The impacts are expected to be the same under all options since a single package of measures has been developed for this oversight objective. The table below provides an overview.

Table 42 – Costs of stronger, harmonised oversight for establishments (EUR thousands)

	1 year		Over ten years	
	Adjustment costs	**Enforcement costs**	**Adjustment costs**	**Enforcement costs**
M2.2 Risk-based inspection	11,679-15,622	M2.2 Scenario 1: 38,767 M2.2 Scenario 2: 24,455	11,088 - 14,725	M2.2 Scenario 1: 297,120 M2.2 Scenario 2: -218,086

For M2.2, Scenario 1 is where the existing 2 year maximum gap between inspections is retained. Scenario 2 is described in Section 5.2.2 and models a more flexible inspection regime (based on the Commission's recommendation).

As set out already in the description of costs of stronger, harmonised oversight for regulators (Section 5.2.2), a system combining fixed-frequency inspections with more frequent controls whose schedule is determined based on a set of risk parameters is already in place in at least 14 Member States, covering an estimated 82% of BTC establishments The actual costs of this measure for establishments will depend on the detail of the specification as adopted into EU law and the intensity and frequency of the controls for each risk profile.

While establishments active in countries that do not currently have a risk-based inspection regime are expected to bear the majority of the additional costs, there will be some impact on others, depending on similarities between the new risk-based regime and the existing model. If the new risk-based regime maintains the same regime for inspections of the existing one (e.g. two year maximum gap between inspections), the enforcement costs for establishments subject to such system may increase, depending on the level of risk attributed. If a more flexible regime is applied (Scenario 2), it may lead to a reduction in enforcement (compliance) costs for establishments.

A more flexible system – relaxing the frequency of controls for low-risk establishments and increasing it for high-risk ones – could result in less frequent inspections for low-risk establishments, with wider gaps than the current two years, and thus lower enforcement costs. This is illustrated by the modelling of the inspection regime (with results shown as Scenario 2 of Table 42, which would lead to a 9% decrease in enforcement costs for establishments compared to the baseline).

The costs to establishments of measures intended to reduce avoidable risks for BTC donors and for children born from donated eggs, sperm or embryos (Objective 3)

Of the measures proposed to protect BTC donors, and children born from donated sperm, eggs or embryos, from specific risks, the regulatory burdens on BTC establishments are expected to be most influenced by: the adoption of principles on donor safety and protection of MAR offspring, including reporting of adverse events and additional SARE monitoring of donors for high-risk groups (M3.1); and the requirement for establishments to set detailed quality and safety requirements for donors and for MAR offspring (M3.5-M3.7). Table 43 provides an overview of the costs that can be estimated.

Table 43 – Costs of increased protection of donors and children born from donated eggs, sperm or embryos for establishments (EUR thousands)

	Option 1	Option 2	Option 3
Costs for establishments (over ten years)	139,977	148,690	143,849

As the implementation model varies across the options there is variation in cost impact on establishments. Option 1 is expected to result in the largest initial costs in order to develop rules according to the new requirements (further information is presented in Annex 5). The change in ongoing operating costs will be determined by details of the future rules (e.g. on testing).

The increased protection of donors and of children born from donated gametes or embryos provided under measures (M3.1 and M3.2) is likely to generate costs for establishments related to the monitoring and reporting of adverse events. Most establishments are already subject to monitoring provisions and reporting of adverse events. The adjustment and enforcement costs for implementing such measures at EU level in a harmonised manner could be comparatively low, as relatively few establishments (an estimated 460 / 16% of BTC establishments[99]) will have to comply with an entirely new set of rules. Establishments that already operate to similar principles will have to face some adjustment costs, depending on the extent of the amendments to the system necessary to be aligned with the new set of EU rules.

The measure also introduces a long-term monitoring obligation for high-risk subgroups only, which is expected to have a non-negligible impact on the costs for establishments in scope[100] (about 800 establishments), which is expected to have an impact on the costs for setting up and complying with the additional requirements, and during inspections of the establishments targeted (albeit very limited).

M3.1 and M3.2 are likely to generate costs for establishments related to the investigation of adverse events or reactions reported and to the follow-up on possible corrective actions generate by the investigation. Few establishments provided information on investigations. The evidence collected suggests variation in national approaches to the follow-up and investigations of adverse events, ranging from investigations being limited to serious adverse events only to the systematic follow-up of any incident. Such divergent approaches translate into very different numbers of investigations for establishments in each country, ranging from about 1 per year to up to 400, depending on the type of BTC and the size and volume of activities of the establishment. It is likely that measures enhancing protection of donors and children born from donated eggs, sperm or embryos will increase reporting requirements, with possible repercussions on the number of investigations. This is an area where further research, referenced to detailed specification of the legal proposal and its fit

[99] Details on estimation are in Annex 5.

[100] The measure is estimated to impact approximately 800 establishments, either for donor reporting BEs (plasma) HSC (family donors) and MAR establishments (sperm/oocyte banks and those with own donors). More details in Annex 5.

to Member State practice, may be required to address the uncertainty about implementation costs.

The measures requiring implementation of quality and safety requirements enhancing protection of donors and of children born from donated gametes or embryos (M3.5-M3.7) have the potential to increase costs for establishments. The evidence collected shows that the majority (21) of Member States have a similar measure and 90% (based on ICF estimates[101]) of establishments will be operating to those requirements. From the evidence collected, quality and safety requirements are updated on a regular basis (approximately every 2-5 years).

The effort requirement by establishments to develop the rules is likely to be higher under Option 1 as they will have to understand and elaborate available scientific evidence autonomously, which is likely to generate problems especially for the smaller ones, less likely to have the resources and skills in-house. Option 2 and 3 are simpler to operate. Costs will depend on the gap between their current system and the EU rules. Establishments having to comply with an entirely new set of requirements will incur higher costs.

The costs to establishments of measures intended to facilitate innovation of safe BTC therapies (Objective 4)

Measures proposed under Objective 4 that are expected to influence costs to establishments are: the removal of the same surgical procedure exemption (M4.1); Measures requiring establishments to conduct risk assessments on novel preparation processes (M4.10-M4.12); and the requirement for establishments to perform clinical trial/investigation for high risk applications (M4.7).

Table 44 provides an overview. These represent the largest cost estimates of the overall package of measures. A key determinant of actual costs is the number of medium and high risk innovative processes for which authorisation is requested – about which there is significant uncertainty. The assumptions used in the modelling are described below.

Table 44 – Costs of measures to facilitate innovation of safe BTC therapies– establishments (EUR thousand)

	Option 1	Option 2	Option 3
Costs for establishments (over ten years)	165,661 – 465,300	244,435 – 604,229	200,672 – 527,046

The removal of the same surgical procedure exemption (M4.1) will introduce new requirements to ensure quality and safety for such preparations. Establishments and representative organisations consulted during the study (via the survey) expressed concern about the potential impact of this measure on the costs for their establishments, e.g. need to hire personnel and the additional administrative procedures. Concerns included the potential scope of the measure (potentially as broad as to include regular surgical operations, plastic surgery- including private cosmetic surgery, and dentistry), and the complexity of the procedure to be followed. The measure involves a 'light' regulatory approach. It is intended that the measure will apply to hospitals (other establishments, e.g. dentistry practices, are excluded for costing purposes).

[101] Details on estimation are provided in Annex 5.

It is expected that most of the same surgical procedures will follow a 'simple' registration process, which would require establishments to register their activity with NCAs, and to apply for a (desk-based) preparation process authorisation. Applications submitted will be verified by NCAs (e.g. on a yearly basis, or within inspections, when applicable), and followed-up when necessary. BTC establishments will have to define a procedure for registration[102] and for preparing the notification. Both the registration and the notification are expected to require a limited amount of information from hospitals; the notification especially is expected to be desk-based only. Including such measure in the national frameworks is expected to require effort for establishments, which is likely to vary depending on how close the national definition of 'same surgical procedure', which vary across Member States, will be close to the one defined in the revised legislation. Overall, the actual complexity of the work (and the related effort) from establishments is likely to be low, in consideration of the limited set of information requested.

The measures relating to assessment and authorisation of novel BTC applications (M4.5 and M4.6) are intended to provide greater clarity on what rules to apply and what approach is required to evaluate novel BTC applications.

The impact of the requirement to conduct risk assessments on novel BTC processes (M4.10-M4.12) on individual establishments will vary depending on whether they develop novel processes, the scale of such activity, whether they already operate a system for assessing novel BTC preparation process, and the difference between the national system and the new EU requirements. As already previously stated in Section 5.2.2, the higher the degree of novelty or innovation, the greater need for evidence, particularly for processes/substances considered 'high-risk'.

Only a minority of Member States (six, based on estimates) required BTC establishments to perform a systematic risk assessment of novel BTC procedures, even if some establishments may perform such activities as part of their risk and quality assurance system. It is thus considered that about 90% of the establishments will incur into costs for setting up and maintaining a risk assessment system for novel BTC processes. However, while very large establishments could implement sophisticated internal procedures, estimates suggest that on average the costs for setting up and maintaining such systems are comparatively limited. It is also considered that these measures would impact (at least potentially) all BTC establishments, which would need to assess the risks of (novel) BTC preparation processes.

The costs incurred by establishments for managing authorisation of a novel BTC process will depend on the difference between the national system and the new set of rules defined at EU level, which are not currently specified. A process that includes engagement with experts and the sector when the detail of these requirements are specified would help to avoid unforeseen disproportionate costs that could reduce innovation in the sector. Future change to EU rules (under Option 2, 3 review processes) could trigger further incremental costs.

The proposals will set up a system for authorisation of novel BTC applications with requirements (and corresponding costs) that depend on the level of risk attributed to the novel BTC. The cost of the measure for establishments will be determined by the level of risk attributed to the novel BTC application, and the volume of the innovation activity (i.e., the number of authorisations per category of risk required). While it is likely that large and/or more dynamic establishments will be more heavily impacted by these measures (as they are more likely to pursuit innovation), many BTC establishments could potentially be affected (if only for occasional, negligible-risk applications).

[102] For the purposes of cost estimation one registration has been assumed for each EU hospital.

The impact of novel BTC applications with negligible and low risk (estimated to be 50% and 25% of the total respectively) are likely to require a limited effort from establishments (requiring around EUR 1,000-7,000 in internal effort for the application and for producing the evidence). Costs can be much higher for establishments requesting authorisations for novel BTC preparation processes with 'moderate risk' (about 20% of the total), and with 'high-risk (about 5% of the total). There will be wider variation depending on the evidence requested (i.e., the number of patients and the costs per patient to be involved in clinical investigations and in clinical trials). 'Moderate risk' novel BTC preparation processes will require clinical investigations, which may generate costs for EUR 1,000-60,000, depending on these parameters. The variations in possible costs are much broader for 'high-risk' novel BTC preparation processes, which may range from EUR 60,000-600,000. It is very likely that BTC establishments will incur in costs for clinical investigations and clinical trials closer to the lower (or middle) boundary of such ranges. However, in absence of data on the distribution of those costs for BTC establishments, it is not possible to provide a more precise indications on costs.

Offsetting these additional costs are the potential benefits of the wider reform package (e.g. the increased harmonisation and trust, more effective information sharing, etc.) leading to establishments having better visibility of what has been approved elsewhere and of the evidence available to prove the quality and safety of novel BTC preparation processes. This dynamic ought to deliver cost savings in the future by reducing duplication of authorisation efforts and of generating evidence. These potential savings are not currently quantifiable.

A clearer, more harmonised system for authorisation of novel BTC preparation processes is expected to increase the level of innovation across the EU. It is not possible to estimate to what extent this would reflect in the number of authorisations for novel BTC preparation processes processed by year (across the different level of risks).

The cost to establishments of measures proposed to reduce the risk of shortages due to insufficient or unreliable BTC supply (Objective 5)

Of the measures proposed to reduce EU vulnerability to shortages in supply of critical BTCs the items affecting establishment costs are provisions for: monitoring and notification of sufficiency data [M5.1-M5.2]; emergency measures for critical BTC supplies [M5.3]; and monitoring and notification systems and contingency plans [M5.6-M5.8]. Table 45 provides an overview.

Table 45 - Costs of better protection against risk of shortages in BTC supply for establishments (EUR thousands)

	Option 1	Option 2	Option 3
Costs for establishments (ten years)	147,408 – 162,087	150,651 – 169,849	132,580 – 147,259

Overall, the introduction of measures requiring internal monitoring of BTC supply (as distinct from reporting the data) is not expected to generate costs for establishments as most already have in place similar measures. It is estimated that 90% of establishments[103] already perform this task, either because of legal requirements or in the context of supply chain management. Measures introducing mandatory notification of sufficiency data for critical BTC in case of shortage/drop in supply and providing Member States additional power to manage supply within their competences are expected to have cost impacts for

[103] Details on estimations are in Annex 5.

establishments (M5.2). Notifications will be made via an automated system using a central module in the IT platform that allows standardised notification from establishments to their NCAs. The number of BTC establishments to be connected is estimated at 2,500[104].

Consultations and survey responses suggest many establishments (~ 50%) are already subject to notification obligations for critical BTC supplies which necessitate some form of reporting to competent authorities, on a frequency that ranges from yearly to monthly to (in rare circumstances) weekly. BTC supplies are managed and monitored as part of the normal establishments' supply chain activities, and information is reported in the establishments' documentation of the activity. Additional data on the supply levels are captured during inspections, as part of the normal verification of the establishments' activities. Existing systems will be substituted by the automated procedure managed via the IT platform.

Mandatory or automated emergency notifications of shortages/supply issues are not common. Establishments often communicate possible supply issues to competent authorities through existing channels. The future cost of a notification system for establishments, will depend on the details of the reporting rules and technical aspects of any system established to facilitate reporting, e.g. the level of automation of the reporting system, and its links with the proposed EU IT platform. The functionalities of the IT platform to be designed and maintained by the EU at central level could have major repercussions for BTC establishments. If the new EU system will require establishments to report supply data and/or notify authorities via the EU IT platform, the adaptation costs are expected to be substantial. However, the use of an automated system has the potential to reduce ongoing reporting costs. Costs are expected to vary across individual establishments and Member States based on factors that include:

- Whether the establishment already has an automated monitoring and/or notification system (e.g. reporting to the relevant competent authority);
- Whether the practices adopted for monitoring critical BTC supplies are already in line with the EU set of rules (e.g. concerning scope and levels of supply triggering the notification and alarm systems, the units used);
- Whether the standards used by information system currently adopted are compatible with the standards of the EU IT platform; and
- How often the reporting requirements for the EU system change.

The measures requiring establishments to prepare contingency plans (M5.5-M5.8) are expected to increase costs to the sector. Survey responses suggest that few establishments are subject to the legal obligation to have contingency plans for supply risks (only in six Member States). Consultations also suggest that such contingency plans are often prepared as part of their risk and quality assurance procedures, and/or to meet supply chain requirements.

For the purposes of this analysis it is estimated that about 50% of the establishments already have some form of supply risk contingency plan. These are likely to incur in minor costs related to the implementation of this measure, depending on how close the framework they implement is to the set of rules defined by the new EU system. Establishments that need to comply with an entirely new set of requirements are expected to incur higher costs. The analysis assumes a close alignment of existing practices on contingency plans to the requirements of the new EU system.

The implementation system chosen for the definition of the rules for the contingency plan is another factor determining the costs of the measure for establishments. Initial costs are likely to be higher under Option 1 because establishments will have to navigate the process

[104] Ibid.

of determining the evidence and approach without recourse to standard guidance. This is likely to generate problems especially for the smaller organisations that have fewer resources and in-house skills. In Option 2 and 3 there will be a single reference document to guide preparation of the plans.

Coupling the preparation (and update) of the contingency plans with the risk-based inspection regime is expected to minimise the costs of the measures for many establishments, i.e. Those in the negligible and low risk categories, required to prepare the contingency every few years[105].

5.2.4. Sustainability of public health budgets

Efficiency of oversight

The proposals include a measure (M2.2), provided under all options, that would mandate risk-based inspections. The theory underpinning the introduction of risk-based inspection is that it provides alignment of investment of inspection made in an individual establishment to the risk posed by that establishment.

As discussed in the section on costs, the cost and efficiency impacts of this measure are influenced by whether the EU legal requirement for all establishments to be inspected at least once every two year is changed. The efficiency benefits of this measure are increased if a longer period is provided, on the understanding that such an extension is neutral with regard to risk management (i.e. NCAs are as effective in managing the risks posed by establishments whatever the maximum duration). It is understood that the risk-based inspection model proposed would be flexible – i.e. potentially subject to change based on information such as compliance history and evidence of effective risk assessment and management processes.

In Option 1, the efficiency of oversight is reduced by the complexity imposed on competent authorities as a result of the lack of a common set of rules. This complexity is expected to have a cost to NCAs. Since in the baseline situation many countries already have a risk-based approach, the incremental impact across all options is moderate for such countries.

Impacts on oversight efficiency are expected to be experienced by competent authorities, which will see a change in the scale and distribution of their oversight effort and associated costs. They are also expected to be experienced by regulated establishments, which may see a change in the:

- Frequency of inspections and thus in the scale/distribution of associated costs incurred preparing for and responding to the inspection and its findings; and
- Competent authority fees that they incur, in those cases where NCAs recover their inspection costs via charges on the regulated entities.

Table 46 - Efficiency of oversight

Indicator	Option			
	Baseline	1	2	3
Extent to which the inspections are proportionate to the risks of activities*	=	+	++	++
Number of Member States using a risk-based inspection model	12	27	27	27

[105] More details on the risk categories and related inspection schedule are provided in Annex 5.

**Assumes maximum period between inspections is extended. Key: = unchanged; + some positive impact.*

Efficiency of authorisation

The measures proposed under Objective 4 relating to authorisation of novel BTC preparation processes (M4.5, M4.6) will help to harmonise the approach taken to risk management of such processes across the EU. As already discussed in the discussion of Objective 4 measures, a standardisation of the evidence submitted by establishments will harmonise the evaluative processes performed by competent authorities (including appraisal of the risk of each novel application).

The proposal to use an IT platform to share information among competent authorities about authorisations of novel BTC preparation processes (M4.8) should also help to improve the overall efficiency of authorisation activity, avoid duplication of evidence generation and administrative effort for both applicants and authorities.

The efficiency of Option 1 is expected to be slightly lower than the efficiency of Options 2 and 3. This is because of an expected variability in risk assessment processes derived from establishments' freedom to make use of a variety of evidence when conducting their risk assessments. It is anticipated that this will add some process complexity for competent authorities.

Table 47 – Efficiency of authorisation

Indicator	Option			
	Baseline	1	2	3
Extent to which the authorisations are proportionate to the risks of activities	=	=	+++	+++

Key: = unchanged; + some positive impact

Impact on financial sustainability of competent authorities

The measures proposed to strengthen oversight are expected, overall, to increase costs for competent authorities. A potential risk is that competent authorities subject to new requirements to change their institutional and governance structures, models for appointing inspectors, and their approach to inspection, are not able to mobilise the financial resources required to fund the transition to the new operating model. Some comments in the authorities' oversight workshop (Annex 11.6) referenced lack of resources as a potential barrier to the policy objectives being achieved.

Based on NCA survey responses and follow-up verification, it has been assumed that half the Member State authorities operate a fee or levy system that would enable them to recover certain additional costs from BTC establishments. It has not been possible to establish where costs associated with organisational reforms would be recoverable via these mechanisms in each case based on the detail of the legislation in each country. The impact on financial sustainability is thus uncertain but expected to be similar under all Options (the analysis of costs to NCAs shows comparatively little variation in costs across the options). This risk is a parameter to be managed during implementation by Member States and monitored at EU level.

The remainder of this section considers the ways in which proposed measures may impact on health budgets. Examples are:

- Better visibility across establishments (via the IT platform) of BTC preparation processes for therapies and treatments to address different health problems;

- Better availability of affordable BTC therapies through proposed mechanisms e.g. to resolve borderline issues so that more BTC applications are available via public healthcare systems;
- More consistent rules on testing of BTC, informed by evidence on efficacy;
- BTC processes being approved based on a more consistent set of standards for proof of efficacy (so that public budgets are not spent on ineffective treatments); and
- Improved supply of BTC, which give more options to healthcare providers.

Overall, the difference that the options would make to overall public health expenditure is not feasible to determine given the scale and complexity of the systems, contexts and variety of possible results (i.e. more authorised BTC applications means more spending on BTC, but more spending BTC could result in savings on alternative treatments that would otherwise be applied), and the backdrop of long term increases in demand for healthcare from an ageing population.

It is, however, possible to form a judgement on the impact of options on availability of evidence. All options are expected to have a positive impact on this indicator as a result of the transparency measures proposed (the IT platform being particularly important in this context); and standards of evidence for novel processes, etc.

Table 48 – Sustainability of health budgets

Indicator	Option			
	Baseline	1	2	3
Availability of evidence to inform national/local decisions for the effective use of healthcare budget	=	++	++	++

Key: Baseline = inconsistent/ limited evidence is available on the efficacy of treatments for local and national decision-making decision for the effective use of healthcare budget (i.e. identifying the cost-effective BTC); + technical requirements for testing and processing reflect the best available evidence; no outdated tests/procedures required nor ones of unproven value; + for high risk/highly innovative substances/treatments evidence is available to assess their efficiency/effectiveness for national decisions for effective use of the healthcare budget; + evidence is available on all BTC to assess their efficiency/effectiveness

5.2.5. Competitiveness, trade and investment

Competitiveness

The measures proposed under Objective 4 to support innovation have the potential to address concerns about EU competitiveness in the development of innovative BTC applications. The consensus view on Options 2 and 3 is that they will increase the level of harmonisation within the EU for BTC, both through rule-setting and through new mechanisms that advise on (i) borderline issues between BTC and other regulatory frameworks, and (ii) matters of interpretation relating to issues internal to the BTC legislative framework. As such there is expected to be a positive impact on the EU's competitiveness as a location for innovation in BTC. The innovation measures are expected to benefit public and private sector.

Trade

The analysis of the impact of the proposed legislative measures on sustainability of supply suggests a consensus that, whilst helpful in other respects, they are unlikely to have a major impact on plasma dependency, and that other actions will be required to tackle that specific issue. No material difference between options in trade impacts is expected.

The primary external trade flow of interest to the analysis is the EU's dependency on imports of plasma from the US. Analysis is impeded by lack of up-to-date trade data. The PPTA, an organisation that represents private sector manufacturers of plasma protein therapies and

collectors of source estimated, before to the UK's exit from the EU, that around 35% of the plasma for medicines needed by about 300,000 Europeans with chronic diseases comes from the US[106]. The dependency of the EU27 is understood to be significant, though no quantitative estimate has been identified.

Investment

Investment was not a major point of discussion with stakeholders consulted for this study but can be viewed as linked to the innovation agenda. Measures that result in increased innovation, authorisation and use of BTC are expected to be positive for investment in the sector. The measures proposed to address the interface between BTC and other regulatory frameworks are also potentially relevant. The borderline case studies (provided in Annex 9) shed light on levels of commercial interest in different substances and therapies, and the impact on investment when heavy regulatory burdens are posed.

Summary

A summary judgement on the impacts on competitiveness, trade and investment flows is provided in the table below. This was developed by the study team based on the evidence synthesis.

Table 49 – Impact on competitiveness, trade & investment flows

Indicator	Option			
	Baseline	1	2	3
Improvement in competitiveness, trade and investment flows as compared to baseline	=	+	++	++

Key: = no change, + some improvement expected, but with uncertainties; ++ strong likelihood of a positive impact on barriers to trade / investment and addressing factors that impede competitiveness.

5.2.6. Operation and conduct of SMEs

As already stated, the EU's BEs/TEs are diverse in their organisational type, scale and size. As such, conventional categories for SMEs are not easy to apply. Data on the distribution of entities by size (whether measured by financial turnover, number of patients or procedures) are not available.

Consultations with establishments did surface some concerns that the additional costs associated with the reforms would be more difficult for smaller establishments to absorb and that there would be some further consolidation of the sector. As noted above, some of these effects will be internalised within public healthcare systems.

5.3. Digital impacts

The options are not expected to lead to developments in healthcare technologies or other technologies that will contribute to the EU's digital economy. The primary innovation impact foreseen is in BTC treatments and products.

The options include an investment in the use of digital technology to support information flow among regulators and between regulators and blood/TEs. This is expected to be implemented via database solutions. In particular, by connecting isolated systems, and

[106] *Europe wants to make its own drugs, but it needs American blood plasma.* https://www.reuters.com/article/us-health-coronavirus-eu-plasma-analysis-idUSKBN23F1F7

facilitating reporting (including standardised notifications), efficiencies are expected for competent authorities and blood/tissues establishments.

The European Commission has commissioned a parallel study which focuses on the future implementation of an EU-wide data system in the SoHO sector.

5.4. Impacts on fundamental rights

This section considers the implications of the proposed legislative reforms for fundamental rights. Relevant elements include the measures addressing:

- Donor protection;
- Updating and harmonisation of BTC quality and safety rules;
- Protection of children born from donated gametes/embryos;
- Equity of access to innovative BTCs; and
- Measures in support of a sustainable BTC supply.

A summary judgement on the impact on fundamental rights is provided below, referencing the impacts expected on:

- Health protection for children born as a result of MAR, such as through changes to the donor testing requirements;
- Tackling discrimination, such as through greater harmonisation of donor rules;
- Data protection; and
- Donor's rights.

As shown in the table below, it is anticipated that the proposed measures will have a small positive effect in each of those areas. It was therefore judged that all policy options could have an equal impact on indicators shown.

Table 50 – Fundamental rights impacts

Indicator	Option			
	Baseline	1	2	3
Improving the level of human health protection (Charter of Human Rights, Article 35) for children born from donated sperm, eggs or embryos	=	+	+	+
Reducing discrimination (Charter of Human Rights, Article 21) (e.g. consistency in the term 'partner'; deferral from donation must be proportional to risks)	=	+	+	+
Consistent application of privacy provisions (Charter of Human Rights, Article 5) for personal data	=	+	+	+
Strengthening the fundamental rights of donors. Strengthening informed consent (Charter of Human Rights, Article 3) by a follow-up on the use of donated BTC. processes, excluding personal health data)	=	+	+	+

Key: = no change, + some positive impact

5.5. Environmental impacts

Research and consultations did not yield any information suggesting that the options would result in any specific and significant changes to natural resource use or environmental impacts, either within the public health system or at a wider system level. To the extent the reforms lead to greater use of BTC products/treatments, a detailed systems analysis would

need to consider issues such as the resource use (such as consumption of medical supplies) and environmental impacts of BTC products/treatments versus any available alternatives, and any differences in impacts arising from changes in health outcomes achieved.

6. Comparison of options

This section considers how the options compare in their effectiveness, efficiency and coherence. There are three defined policy options and the baseline scenario. There is a set of measures common to all options, and then a number of areas where the different options codify alternative approaches to the determination of rules that will need to be followed by BEs/TEs. This analysis is preliminary, as the final comparison of the options will be carried out by DG SANTE, via a multi-criteria decision analysis, and based on the criteria described in the previous section.

6.1. Effectiveness

Effectiveness is measured by the extent to which options are expected to achieve the target objectives.

6.1.1. Objective 1: to increase patient protection from all avoidable risks

Objective 1 captures the ambition to provide patients with an assured high level of protection from avoidable risks wherever they are being treated with in the EU, with establishments operating according to rules that reflect current scientific knowledge.

Progress towards Objective 1 is also supported by the measures discussed under:

- Objective 2, insofar as stronger oversight should reduce risks to patients;
- Objective 3, which will strengthen rules for protection of donors and children born as a result of MAR;
- Objective 4, through removal of the same surgical procedure exemption, and the risk-based authorisation of novel BTC preparation processes; and
- Objective 5, which should reduce the risk that patient welfare is harmed as a consequence of BTC supply shortages.

The current lack of consistency of protection of patients is expected to persist in the baseline scenario. There is no indication that updating rules via existing legislative mechanisms will be any more effective than they have been since 2004.

A summary judgement on the options' effectiveness is provided below. Only Option 2 offers both consistency of the rules and agility in rule-setting. Option 3 offers consistency of rules but a more cumbersome updating process for the rules that establishments need to follow when preparing operational risk assessments. Option 1 could potentially result in less consistency of protection than in the baseline (because establishments may follow diverse sources of guidance when developing risk assessments).

There are some potential risks and implementation challenges that could prevent the full potential of the Objective 1 measures being achieved. An example is the risk that the requirement for Member States to publish more stringent rules will either not be applied as intended (e.g. because the definition of 'more stringent' is circumvented) or will not induce greater harmonisation (i.e. making these rules more visible does not induce changes in Member State rule-setting behaviours).

A summary judgement on the performance of the options against the aim of the Objective 1 is provided below.

Table 51 – Summary judgement on the effectiveness of options in achieving Objective 1 (increasing patient protection)

Indicator	Option			
	Baseline	1	2	3
Effectiveness in increasing patient protection from all avoidable risks above that foreseen in the baseline	=	+	++++	+++

Key: = status quo; + modest change in direction of Objective 1; +++ substantial progress towards Objective 1 expected, ++++ Objective 1 very likely to be achieved

6.1.2. Objective 2: to strengthen and harmonise oversight

Member States have deployed a variety of organisational models, operating principles and inspection practices in their oversight systems for BTC. The research conducted for this study found no expectation of a cross-EU harmonising force acting on regulatory practices that would resolve the divergences in the absence of EU legislative action. As such, in the baseline scenario the level of harmonisation of oversight practice is not expected to increase. Indeed, practices may well diverge further as innovations in BTC are regulated in different ways across the EU.

A single package of measures, identical in all options, is proposed specifically to strengthen and harmonise oversight among Member States. The evidence gathered suggests that the policy measures, if implemented as envisaged, are expected to be substantively effective in strengthening and harmonising oversight. The performance of all options in achieving this objective, based on those measures alone, is expected to be equal.

There is, however, the potential for progress towards the oversight objective to be influenced by other measures that are proposed primarily to address other policy objectives. Specifically, in Option 1, the possibility for different rules being applied by establishments (i.e. rules for risk assessments, protection of donors and children born as a result of MAR and for contingency plans) means that the harmonisation of oversight practice is likely to be less than under the alternative Options, even in the context of strengthened oversight institutions, as authorities work to regulate establishments that can make use of a wide diversity of evidence.

The measures imply changes to institutional governance arrangements, processes for appointing inspectors and inspection regimes for some competent authorities. The principal risk to the measures not performing as expected is that authorities will lack the resources to implement required changes. Whilst some competent authorities are reliant on government subventions for their income, others rely on mechanisms that recover costs from regulated entities. The legislation will need to provide sufficient time for authorities to implement the reforms; the period required is likely to vary by measure – adjustments to the scope and timing of inspections are likely to be more easily implemented than changes to organisational set-up. A summary judgement on the performance of these options against the aim of the Objective 2 is provided below.

Table 52 – Summary judgement on the expected effectiveness of options in achieving Objective 2 (strengthening and harmonisation of oversight)

Indicator	Option			
	Baseline	1	2	3
Effectiveness in strengthening and harmonisation of oversight above that foreseen in the baseline	=	++	+++	+++

Key: = status quo; ++ some positive change in direction of Objective 2 expected; +++ substantial progress towards Objective 2 expected.

6.1.3. Objective 3: to increase protection of BTC donors, and children born from donated sperm, eggs or embryos, from specific risks

Option 2 is judged to have the highest likelihood of increasing protection for BTC donors and children born as a result of MAR. The obligation for all establishments to follow a single set of rules that are set by EU expert bodies will result in uniform rules and the prospect of a reliable mechanism for updating those rules if and as appropriate (a mechanism that can also work quickly in emergencies). Option 3 provides consistency of rules but has a more cumbersome process for updating them where necessary. Option 1 has a decentralised model which introduces greater uncertainty about control of avoidable risks. There is some uncertainty about requirements and likely outcomes in relation to obligations for follow-up.

A summary judgement on the performance of these options against the aim of Objective 3 is provided below. Option 2 appears to be more effective at achieving this Objective as it provides a standard yet flexible set of requirements, rooted in current scientific and technical knowledge, that will help to achieve a consistent level of protection across the EU.

Table 53 – Judgement on the options' expected performance in protecting donors from avoidable risks

Indicator	Option			
	Baseline	1	2	3
Effectiveness in protecting donors and children born from donated sperm, eggs or embryos, from avoidable risks	=	++	++++	+++

Key: = status quo; ++ some change in direction of Objective 3 expected; +++ substantial progress towards Objective 3 expected, ++++ Objective 3 very likely to be achieved.

6.1.4. Objective 4: to facilitate innovation of safe BTC therapies

Innovation may involve new risks. Whilst innovation in the BTC sector has benefited from significant scientific, medical and technological developments over the last two decades, the existing regulatory framework has failed to manage associated risks - including those created by the exclusion of a growing number of BTC-derived treatments delivered under the same surgical procedure, the development of 'out of scope' therapies (PRP, FMT and DHBM) and developments of novel products at borderlines with other frameworks. A recognised issue with this has been the rigidity of the current legislation which fails to keep pace with innovation.

Taken as a package, there was general agreement that the proposed measures would provide an improved regulatory framework, which will be more effective for facilitating innovation of safe BTC therapies and products. Specifically:

- Enhanced coordination and communication (achieved by M4.2, M4.3 and M4.3) can effectively reduce any borderline issues between BTC, medical devices and/or ATMPs earlier in the development process. Genuine collaboration across regulatory frameworks will enhance the effectiveness of these measures.
- Measures to strengthen the preparation process authorisation will lead to the development of a common approach (under Options 2 and 3) to assess and to authorise preparation processes for novel products, ensuring the safety and effectiveness of these treatments. This will be both facilitated and enhanced by the exchange of national preparation process authorisation data (M4.8) which aims to not only reduce barriers to authorisations across the EU, but also provide greater assurance of safe and effective products that can be exchanged across borders.

- Clinical data/studies will more effectively support the authorisation of higher risk BTC preparation processes in some circumstances – though there is a clear need for proportionality (to the risk or degree of innovation involved) to prevent barriers to entry.

A summary judgement on the performance of the policy options against Objective 4 is provided below. Both Options 2 and 3 would support a more harmonised implementation of M4.5 and M4.6 (and in particular the implementation of a risk assessment process) compared to Option 1. Option 3 is less preferred as a regulatory model compared to Option 2; the latter was commonly agreed to be more dynamic and flexible.

The principal challenge is to balance increased regulatory burdens with the benefits of a rigorous, consistent approach to authorisation of innovative BTC. If the costs of providing the required evidence are too high, in a context where many establishments operate in resource-constrained public health systems, the anticipated flow of innovations will be constrained.

Table 54 – Summary judgement on the expected effectiveness of options in achieving Objective 4 (facilitating innovation of safe BTC therapies)

Indicator	Option			
	Baseline	1	2	3
Effectiveness in facilitating innovation of safe BTC therapies above that foreseen in the baseline	=	++	++++	+++

Key: = status quo; ++ some change in direction of Objective 4 expected; +++ substantial progress towards Objective 4 expected, ++++ Objective 4 very likely to be achieved

6.1.5. Objective 5: to reduce the risk of shortages due to insufficient or unreliable BTC supply

The proposed measures are expected to be effective in meeting Objective 5 by: (i) improving overall supply risk management in the system; (i) increasing regulators access to data on supply conditions, and more timely and consistent information about supply status in the event of shortages for risk management purposes; and (ii) improving overall levels of preparedness among BTC establishments by prompting development of supply risk contingency planning for critical BTC.

The various measures that contribute to harmonisation of rules for BTC across the EU have the potential to reduce barriers to movement of BTC within the EU in ways that could help to reduce supply risks in specific operational contexts. The proposed measures are not, however, expected to change structural supply-side imbalances (such as the EU's dependency on supplies of plasma from the US). Risks associated with such dependencies are thus not fully mitigated.

A summary judgement on the performance of the policy options against Objective 5 is provided below, focusing on preparedness and response aspects of the problem. As noted above, there are structured supply-side issues which seem less likely to be resolved by the proposed measures.

Both Options 2 and 3 are likely to be more effective in avoiding shortages of critical BTC therapies compared to Option 1 due to the increase in consistency expected by taking an EU-wide approach. This contrasts with Option 1, under which it is expected establishments will prepare contingency plans aligned to the requirements set by competent authorities, customers and other external bodies.

Table 55 – Summary judgement on the expected effectiveness of options in achieving Objective 5 (avoiding shortages of critical BTC therapies)

	Option			
	Baseline	1	2	3
Effectiveness in avoiding shortages of critical BTC therapies as compared to what is foreseen in the baseline	=	++	+++	+++

Key: = status quo; ++ some positive change in direction of Objective 5 expected; +++ substantial progress towards Objective 5 expected.

6.2. Efficiency

Assessment of efficiency requires weighting of impact against the overall costs (considering the resource implications for both regulated entities and regulators). Details of anticipated costs for regulators are specified in Section 5.2.2 and for establishments in Section 5.2.3.

The appraisal of comparative efficiency faces a number of challenges:

- There is a lack of quantitative comparative outcome metrics (so that options cannot be compared on the basis of, for instance, cost per QALY saved).
- The costs saved by improving harmonisation are not quantified.
- The need for an assumption that guidance and rule-setting mechanisms established under the Options would themselves take account of efficiency concerns when setting guidance and rules in the future (i.e. they will balance costs and benefits of achieving changes).

A further feature of the reform package is that several measures are common to all options, so a comparative appraisal of efficiency is in practice considering trade-off between the difference in costs of the three governance models and the differences in expected outcomes of those approaches.

A dynamic perspective is also required – there being a positive value attached to the standards being up-to-date. If the Options 2 and 3 are seen as equally likely to change establishment quality and safety standards, and quality of supply risk management, then the greater agility of the Option 2 approach suggests the potential for greater efficiency.

Overall efficiency is influenced by results in a few areas, notably the cost of evidence required to support for authorisation of innovative BTC preparation processes, where assumptions on the number, scale and cost of clinical trials has a substantial impact on overall costs.

The table below provides a summary judgement of the overall relative efficiency of the Options as compared to the baseline. This suggests that Option 2 is the preferred model by which efficiency can be achieved.

Table 56 – Summary judgement on overall relative efficiency of the options

Indicator	Option			
	Baseline	1	2	3
Efficiency of the options as compared to baseline	-	+	+++	++

Key: = status quo; ++ some positive change in direction of Objectives is expected; +++ substantial progress towards Objectives is expected.

6.3. Coherence

All policy options contain measures intended to support and/or clarify the regulatory arrangements currently in place under the baseline. All are expected to contribute – to varying degrees – to improvements in coherence, specifically:

- Coherence with adjacent EU and national legislative frameworks, including those for medical devices, pharmaceuticals, medicinal products and ATMPs.
- Coherence between Member State practices and regulatory frameworks.

All Options will all have a positive impact on EU regulatory/policy coherence (compared to the existing situation) by clarifying the scope of the BTC regulatory framework, resolving (through the various advisory mechanisms) difficulties at the interface of different regulatory frameworks, and deploying complementary sets of communication and trust-building measures to increase the level of harmonisation across the EU.

The decentralisation of rule-setting to establishments under Option 1 reduces harmonisation at operational level among establishments, increases complexity for competent authorities and could create harmonisation (and therefore coherence) issues.

Option 2 and 3 will drive adoption of common rules across Member States which will help to streamline regulatory pathways. Adoption of rules into EU law (Option 3) would provide reassurance that uniform/equivalent practices and standards for quality and safety were being applied across the EU. However, legally binding requirements were considered by most stakeholders to not be flexible enough to respond to changes in adjacent fields, and take too long to update, thereby eroding coherence in the longer term. In contrast, fewer borderline cases are expected in the future in Option 2 due to more responsive, flexible and coordinated advice/guidance being provided.

In summary, whilst all options are expected to have positive impacts on coherence, Option 2 seems most likely to enhance coherence between Member States and with other EU legislation and would better guarantee a future-proof approach.

Table 57 – Summary judgement on the expected coherence of the options

Indicator	Option			
	Baseline	1	2	3
Coherence with other EU policy objectives and interventions	-	++	++++	+++

Key: - negative impact on coherence; ++ some change to coherence; +++ substantial progress towards coherence; ++++ coherence is very likely to be achieved.

6.4. Preferred option

Overall, the balance of evidence appears to favour the delivery model provided by Option 2. It offers a combination of agility and pan-EU consistency that is not presented by the alternative governance models provided by Option 1 or 3. There are, however, conditions attached to that result. The rule-setting process would need to provide for appropriate engagement and consultation with experts and BTC stakeholders, and consideration of the costs versus improvements in target outcomes (such as improved safety).

7. Monitoring and evaluation

This section, alongside Annex 10, provides suggestions for the monitoring and evaluation framework.

Once the revised legislation has been adopted, the Commission and other stakeholders will need access to evidence that provides insights on the impact of the changes and the status of the problems that the revision intended to address. Regardless of the framework or the policy option that is implemented, there needs to be more focus on the implementation of the legislation by the Member States. This section considers the monitoring arrangements that would be needed to achieve this objective.

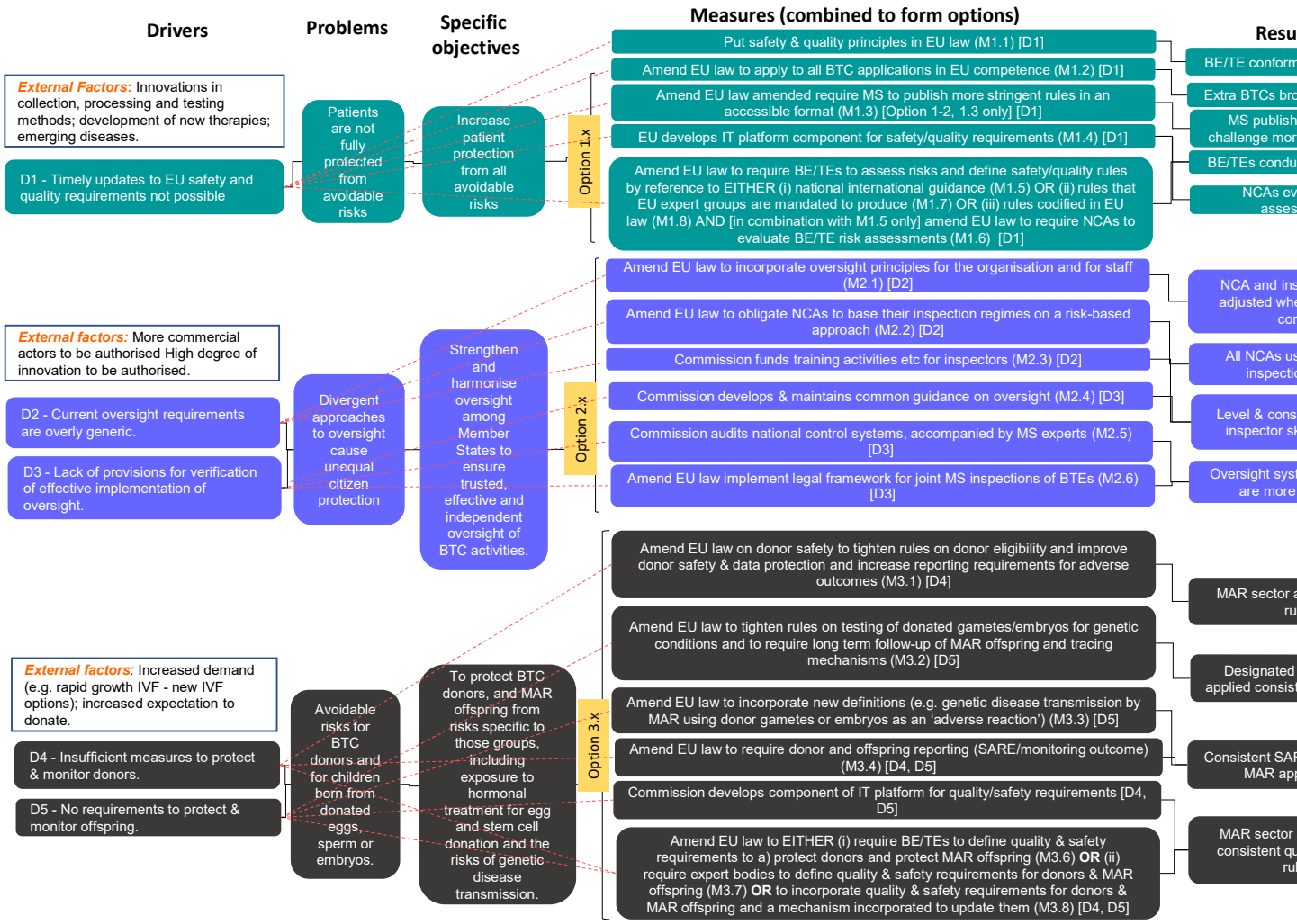
In the cases where the baseline situation already varies across Member States, and where countries have already adopted some of the measures being proposed, it may be possible through cross-country comparisons to isolate the effects of the legislative reforms from other changes.

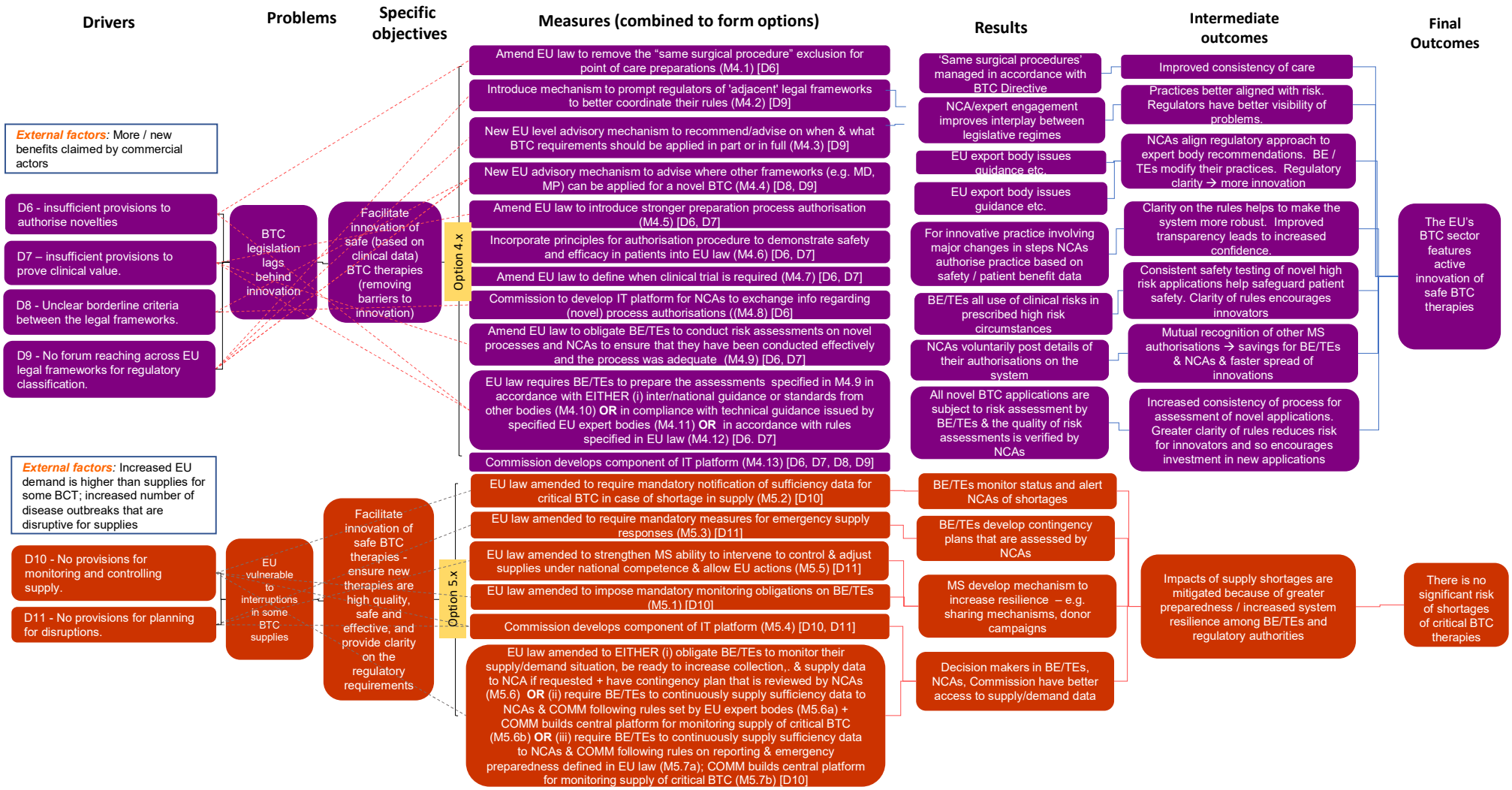
Annex 10 identifies indicators suitable for tracking progress towards each specific objective. It shows who would be responsible for collecting the data, and the method/process that might be used. Ideally surveys and other monitoring activity would be repeated (e.g. annually, biennially) to track change over time.

A common issue is that the changes in costs experienced by stakeholders as they adjust to new obligations in the immediate aftermath of the legislation being adopted are not measured at the time during which they are incurred, and evaluations commissioned years later are unable to estimate the values. Furthermore, changes in ongoing costs become incorporated in ‘business as usual’ operating models and cannot be identified. Targeted research that is timed to coincide with the adjustment process is generally required if these costs are to be accurately estimated. Ideally the research would span the period from adoption of the legislation (to provide baseline data) to two years after the new requirements have come into force to allow for adjustments in NCAs and BE/TEs. Research would need to provide for cross-country comparisons that reflect diversity of Member State baseline conditions (oversight structures, distribution of BE/TEs, etc). Such research would provide evidence that could inform future impact assessments.

ANNEXES

Annex 1: Intervention logic




Drivers
Problems
Specific objectives
Measures (combined to form options)
Results
Intermediate outcomes
Final Outcomes
External factors: More / new benefits claimed by commercial actors
D6 - insufficient provisions to authorise novelties
D7 – insufficient provisions to prove clinical value.
D8 - Unclear borderline criteria between the legal frameworks.
D9 - No forum reaching across EU legal frameworks for regulatory classification.
BTC legislation lags behind innovation
Facilitate innovation of safe (based on clinical data) BTC therapies (removing barriers to innovation)
Option 4.x
Amend EU law to remove the "same surgical procedure" exclusion for point of care preparations (M4.1) [D6]
Introduce mechanism to prompt regulators of 'adjacent' legal frameworks to better coordinate their rules (M4.2) [D9]
New EU level advisory mechanism to recommend/advise on when & what BTC requirements should be applied in part or in full (M4.3) [D9]
New EU advisory mechanism to advise where other frameworks (e.g. MD, MP) can be applied for a novel BTC (M4.4) [D8, D9]
Amend EU law to introduce stronger preparation process authorisation (M4.5) [D6, D7]
Incorporate principles for authorisation procedure to demonstrate safety and efficacy in patients into EU law (M4.6) [D6, D7]
Amend EU law to define when clinical trial is required (M4.7) [D6, D7]
Commission to develop IT platform for NCAs to exchange info regarding (novel) process authorisations ((M4.8) [D6]
Amend EU law to obligate BE/TEs to conduct risk assessments on novel processes and NCAs to ensure that they have been conducted effectively and the process was adequate (M4.9) [D6, D7]
EU law requires BE/TEs to prepare the assessments specified in M4.9 in accordance with EITHER (i) inter/national guidance or standards from other bodies (M4.10) OR in compliance with technical guidance issued by specified EU expert bodies (M4.11) OR in accordance with rules specified in EU law (M4.12) [D6. D7]
Commission develops component of IT platform (M4.13) [D6, D7, D8, D9]
'Same surgical procedures' managed in accordance with BTC Directive
NCA/expert engagement improves interplay between legislative regimes
EU export body issues guidance etc.
EU export body issues guidance etc.
For innovative practice involving major changes in steps NCAs authorise practice based on safety / patient benefit data
BE/TEs all use of clinical risks in prescribed high risk circumstances
NCAs voluntarily post details of their authorisations on the system
All novel BTC applications are subject to risk assessment by BE/TEs & the quality of risk assessments is verified by NCAs
Improved consistency of care
Practices better aligned with risk. Regulators have better visibility of problems.
NCAs align regulatory approach to expert body recommendations. BE / TEs modify their practices. Regulatory clarity → more innovation
Clarity on the rules helps to make the system more robust. Improved transparency leads to increased confidence.
Consistent safety testing of novel high risk applications help safeguard patient safety. Clarity of rules encourages innovators
Mutual recognition of other MS authorisations → savings for BE/TEs & NCAs & faster spread of innovations
Increased consistency of process for assessment of novel applications. Greater clarity of rules reduces risk for innovators and so encourages investment in new applications
The EU's BTC sector features active innovation of safe BTC therapies
External factors: Increased EU demand is higher than supplies for some BCT; increased number of disease outbreaks that are disruptive for supplies
D10 - No provisions for monitoring and controlling supply.
D11 - No provisions for planning for disruptions.
EU vulnerable to interruptions in some BTC supplies
Facilitate innovation of safe BTC therapies - ensure new therapies are high quality, safe and effective, and provide clarity on the regulatory requirements
Option 5.x
EU law amended to require mandatory notification of sufficiency data for critical BTC in case of shortage in supply (M5.2) [D10]
EU law amended to require mandatory measures for emergency supply responses (M5.3) [D11]
EU law amended to strengthen MS ability to intervene to control & adjust supplies under national competence & allow EU actions (M5.5) [D11]
EU law amended to impose mandatory monitoring obligations on BE/TEs (M5.1) [D10]
Commission develops component of IT platform (M5.4) [D10, D11]
EU law amended to EITHER (i) obligate BE/TEs to monitor their supply/demand situation, be ready to increase collection,. & supply data to NCA if requested + have contingency plan that is reviewed by NCAs (M5.6) OR (ii) require BE/TEs to continuously supply sufficiency data to NCAs & COMM following rules set by EU expert bodes (M5.6a) + COMM builds central platform for monitoring supply of critical BTC (M5.6b) OR (iii) require BE/TEs to continuously supply sufficiency data to NCAs & COMM following rules on reporting & emergency preparedness defined in EU law (M5.7a); COMM builds central platform for monitoring supply of critical BTC (M5.7b) [D10]
BE/TEs monitor status and alert NCAs of shortages
BE/TEs develop contingency plans that are assessed by NCAs
MS develop mechanism to increase resilience – e.g. sharing mechanisms, donor campaigns
Decision makers in BE/TEs, NCAs, Commission have better access to supply/demand data
Impacts of supply shortages are mitigated because of greater preparedness / increased system resilience among BE/TEs and regulatory authorities
There is no significant risk of shortages of critical BTC therapies
Assumptions: NCAs have the financial resources and skills to implement the additional tasks assigned to them. BE/TEs are able to access the finances and skills to discharge the obligations and make any operational adjustments required. There are no external events or other 'shocks' that affect public trust in the system

Annex 2: Option definitions and narrative theory of change

A2.1. Option definition

Table 1 – Composition of the policy options: increasing patient protection from avoidable risks

Problem 1: Patients are not fully protected from avoidable risks				
The measures proposed under Objective 1 aim to increase patient protection from avoidable risks, by keeping technical rules for safety and quality up to date. The options share many of the same components but differ in where the rules (which BEs and TEs need to follow when preparing their risk assessments) are defined. The scope of European law on BTC is extended to cover additional types of BTC. Quality and safety principles are built into the new law. Depending on the option, establishments must either follow rules written into EU law, guidance provided by EU expert bodies (Option 2), or use the freedom provided to use available guidance from a much wider range of sources. Under all Options, the Commission will build an IT platform to share safety/quality information. Under Option 2 and 3, Member States are required to publish more stringent national rules in an accessible format.				
Option component ("measure")		**Option 1.1**	**Option 1.2**	**Option 1.3**
M1.1	Principles for safety and quality principles in EU law.	✓	✓	✓
M1.2	EU law is changed so that all SoHO/BTC for which the EU has legal competence are covered by EU safety and quality rules (bringing breast milk, faecal microbial transplants, etc. under EU law).	✓	✓	✓
M1.3	Member States are required to publish more stringent BTC rules in an accessible format.		✓	✓
M1.4	The European Commission builds an IT platform that provides information on quality and safety requirements.	✓	✓	✓
M1.5	National competent authority inspectors have to evaluate BE/TEs' risk assessments to ensure that they have been conducted effectively and that the rules set adequately manage the identified risks.	✓		
M1.6	BE/TEs are required to assess the risks associated with their procedures, and to set technical rules for safety and quality, compliant with the principles defined in EU law. They must base the rules on risk assessment and scientific evidence, and update whenever the need arises. They can follow inter/national guidance or standards from other bodies in setting their rules.	✓		
M1.7	BE/TEs are required to take into account ECDC/EDQM rules on quality & safety requirements. EDQM/ECDC update their guidance as required; Member State expert group participates in the EDQM drafting and review process.		✓	
M1.8	BE/TEs are required to take into account of quality and safety requirements that are defined in EU law. There is a mechanism to provide regular updates in response to changing risks and technologies (using Comitology rules).			✓

Table 2 – Composition of the policy options: tackling the problem of divergent approaches to oversight

Problem 2: Divergent approaches to oversight cause unequal citizen protection and barriers to the exchange of BTC across EU

There is a single package, built up from six distinct measures that are together intended to tackle the problem of divergent approaches to oversight. These measures are expected to lead to the strengthening and harmonisation of oversight among Member States and ensure trusted, effective and independent oversight of BTC activities. They should help to secure equal protection of citizens, and facilitate exchange of BTC among Member States.

Option component ("measure")		Option 2.1	Option 2.2	Option 2.3
M2.1	EU law incorporates oversight principles for the NCA and for staff.	✓		
M2.2	EU law requires competent authorities to base their inspection regimes on a risk-based approach.	✓		
M2.3	The European Commission will develop and maintain common guidance on oversight.	✓		
M2.4	Commission audits of national control systems, accompanied by Member State experts.	✓		
M2.5	EU law is amended to implement a legal framework for Joint Member State inspections of blood and tissue establishments.	✓		
M2.6	The European Commission will develop the relevant component of the IT platform for oversight.	✓		

Table 3 – Composition of the policy options: reducing the avoidable risks for BTC donors and for children born from donated eggs, sperm or embryos

Problem 3: Avoidable risks for BTC donors and for children born from donated eggs, sperm or embryos

The measures proposed under Objective 3 are intended to reduce the avoidable risks for BTC donors and for children born from donated eggs, sperm or embryos. The intended outcome is they are protected from the risks that are specific to those groups, including exposure to hormonal treatment for egg and stem cell donation and the risks of genetic disease transmission to children born from assisted reproduction.

Option component ("measure")		Option 3.1	Option 3.2	Option 3.3
M3.1	EU law incorporates high level principles to protect BTC donors, including reporting measures (SARE/monitoring outcome).	ü	ü	ü
M3.2	EU law incorporates high level principles to protect offspring born from donated gametes/embryos, including reporting measures (SARE/monitoring outcome).	ü	ü	ü
M3.3	EU law incorporates new definitions (e.g. to include genetic disease transmission by MAR using donor gametes or embryos as an 'adverse reaction').	ü	ü	ü
M3.4	The European Commission will develop the relevant component of an IT platform for quality and safety requirements.	ü	ü	ü

M3.5	EU law requires establishments to define detailed quality & safety requirements to protect donors and protect children born from donated gametes or embryos.	ü		
M3.6	BE/TEs are required to follow ECDC/EDQM technical rules on quality & safety requirements. EDQM/ECDC update their guidance as required; Member State expert group participates in the EDQM drafting and review process.		ü	
M3.7	EU law incorporates quality and safety requirements for donors and offspring of MAR, and a mechanism to update these as needed.			ü

Table 4 – Composition of the policy options: tackle the problem of insufficient scale and pace of innovation in the BTC sector

Problem 4: BTC legislation lags behind innovation

The measures proposed under Objective 4 intend to tackle the problem that the scale and pace of innovation in the BTC sector is reduced by features of the existing framework, including insufficient provision for authorisation of novel BTC, insufficient provisions for proof of clinical value of BTC, and unclear borderlines between the BTC framework and those for medicinal products, medical devices, etc. There is no forum that can classify BTC-based therapies and technologies at the interface of other EU legal frameworks. The aim is to facilitate innovation of safe BTC therapies. Most of the Objective 4 measures appear in all options. The options differ in what rules the establishments are required to use when conducting their risk assessments.

Option component ("measure")		Option 4.1	Option 4.2	Option 4.3
M4.1	The "same surgical procedure" exclusion for point of care preparations is refined/removed.	ü	ü	ü
M4.2	An EU level advisory mechanism is established to recommend/advise Member States on when/what BTC requirements should be applied in part or in full .	ü	ü	ü
M4.3	A mechanism is introduced to prompt regulators of 'adjacent' legal frameworks (SoHO/Pharma/Medical Devices) to better coordinate their rules, especially in respect of substances that are regulated under more than one legal framework.	ü	ü	ü
M4.4	An EU level advisory mechanism will advise where other frameworks (in particular medical devices and medicinal products) might be applied for particular novel BTC. Implementation might involve exchange/mutual consultation with advisory bodies for medicinal products (EMA, EMA Innovation Taskforce and the CAT) and medical devices (BLCG).	ü	ü	ü
M4.5	EU law sets principles for authorisation procedure (good practice for authorisation procedures including validation of facilities, equipment and processing and clinical data requirement according to level of risk and novelty) to demonstrate safety and efficacy in patients.	ü	ü	ü
M4.6	EU law requires that, for major changes in the steps of collection, processing and use of BTC, competent authorities have to grant prior authorisation based on data demonstrating safety and benefit for patients that justifies any risks associated with treatment with BTC prepared in innovative ways.	ü	ü	ü
M4.7	EU law sets rules for implementing a clinical trial for BTC (if high level of risks).	ü	ü	ü
M4.8	The European Commission will develop an exchange (IT) platform for competent authorities to exchange info regarding (novel) process authorisations (the platform would be used for (voluntary) acceptance of authorisations among Member States). This includes clinical evidence collected by clinicians with the support of learned societies.	ü	ü	ü

M4.9	EU law requires establishments to conduct risk assessments on novel processes. These are evaluated by the competent authority inspectors.	ü	ü	ü
M4.10	EU law requires establishments to design the risk assessments on novel processes. Establishments could follow inter/national or standards from other bodies.	ü		
M4.11	EU law requires establishments to conduct risk assessments on novel processes in compliance with technical guidance from expert bodies as referred to in EU legislation.		ü	
M4.12	EU law requires establishments to conduct risk assessments on novel processes in compliance with technical rules set in EU legislation.			ü

Table 5 – Composition of the policy options: reducing the risk of shortages due to insufficient or unreliable BTC supply

Problem 5: EU vulnerable to interruptions in some BTC supply

These measures are intended to reduce the risk of shortages due to insufficient or unreliable BTC supply by establishing a system to monitor donations and supply and to support pre-emptive and/or corrective action in case of disruptive epidemiological outbreaks, or similar events. There are eight measures, most are common to all options. The options differ in what rules the establishments are required to use for supply monitoring and preparing emergency plans.

Option component ("measure")		Option 5.1	Option 5.2	Option 5.3
M5.1	EU law is amended to impose mandatory monitoring obligations on BEs/TEs.	ü	ü	ü
M5.2	EU law is amended to require mandatory notification of sufficiency data for all critical BTC in case of shortage/drop in supply (rapid notifications).	ü	ü	ü
M5.3	EU law is amended to require mandatory emergency plans from establishments and NCAs.	ü	ü	ü
M5.4	The European Commission will develop the relevant component of the IT platform for exchange of information on supply and activity.	ü	ü	ü
M5.5	EU law is amended to strengthen Member States' ability to intervene to control and adjust supply, as necessary, under their national competence, and allow evidence-based support action at EU level.	ü	ü	ü
M5.6	EU law is amended to obligate BE/TEs to develop monitoring and notification systems and contingency plans. These will be reviewed for adequacy by the authority during inspection.	ü		
M5.7	EU law is amended with references to guidance from expert bodies for rules on sufficiency data reporting (including monitoring and notifications) and on emergency preparedness/contingency.		ü	
M5.8	EU law is amended to include rules on sufficiency data reporting (including monitoring and notifications) and on emergency preparedness.			ü

A2.2. Problem 1: Patients are not fully protected from avoidable risks

Drivers

The current regulatory structures mean that it is not possible to update EU safety and quality requirements in a timely manner.

Relevant external factors

The European BTC sector is seeing ongoing change. Features include innovations in collection, processing and testing methods, and the development of new therapies. At the same time Europe faces challenges from emerging diseases.

Actions

To protect patients from avoidable risks the following actions are planned (described below). Two measures (M1.1, M1.2, M1.3) are base measures that form part of all options. Alternative ways of implementing enhanced quality and risk management measures are codified in alternative measures (M14 + M1.5, M1.6, M1.7) that, when combined with the base measures, define options that are differentiated by whether the risk assessment requirements are defined in EU law, by an EU expert group, or by blood/TEs based on available guidance.

M1.1 – EU legislation is amended to incorporate statement of principles relating to safety and quality

This measure is implemented through a change in EU law. It will have some direct effects on the sector, by removing outdated terms from the legislation, but it will primarily have an indirect effect through other accompanying measures.

M1.2 – EU legislation amended to incorporate definitions ensuring that safety and quality provisions apply to all SoHO/BTC for which the Treaty give competence to the Union to legislate, including some that do not meet the current definitions that contribute to the definition of scope in the Directives.

This measure will clarify and extend the scope of the EU's legislation. This will have a set of direct effects on the sector by leading establishments working with substances such as breast milk and FMT, and cosmetics used for non-therapeutic uses to comply with the requirements of the BTC legislation. It will also bring new activities such as donor registries for bone marrow into the scope of the legislation. It is expected that this will result in some changes in administrative burdens placed on the sector and, in turn, some adjustments to working practices that may change operating costs. It will also have some impact on the scope of regulators' obligations. The change in scope is expected to ultimately help to ensure that assured high standards of protection are provided and the risks to health are reduced.

M1.3 – EU law amended to require Member States to publish more stringent rules in an accessible format

This measure, implemented via EU law, will obligate Member State authorities to make available, in an accessible format, the details of any rules adopted at national level which go beyond EU rules. Member States already have the freedom to adopt more stringent measures. Theory of this measure is that the enhanced transparency will enable BTC regulators and establishments across Europe to scrutinise the rule-making actions of other Member States more easily and contribute to sharing of expertise and good practices . This will help Member States to scrutinise rules made by other countries and, for instance, may prompt challenges of rules that have a disruptive effect on the movement of BTC or on other operational aspects in other Member States. In so doing it should lead to improved

circulation of BTC in the EU, and this should help to secure consistently positive health outcomes.

This measure applies to Options 1-2 and 1-3 only.

M1.4 – EU will develop the relevant component of the IT platform for quality & safety requirements

This is a non-legal measure. A shared IT platform funded and supported by the Commission will enable sharing openly information on the quality and safety requirements – the process will vary according to the options). It also allows timely updates in case of emergency. The platform shall also allow sharing of information on national and regional differences, in particular if more stringent national measures are applied.

M1.5 – EU legislation is amended to require competent authority inspectors to evaluate the BTC establishments' risk assessments to ensure that they have been conducted effectively and that the rules set adequately manage the identified risks.

This measure is implemented via EU law. It provides a mechanism that assures the quality of the risk assessments prepared by BEs/TEs and helps to ensure that the obligations imposed by M1.5 have meaningful effect. The NCA's assessment relates to whether adequate rules are applied based on the risk assessment.

For this measure to have the intended effect, it is necessary that competent authorities are able to secure the resources (financial, human) needed to conduct the evaluations.

When combined with M1.1, M1.2, M1.3, M1.4, and M1.6 it defines Option 1-1.

M1.6 – EU legislation is amended to require BTC establishments to assess risks associated with their donor selection, testing, collection, storage, processing and supply procedures and to set technical rules for safety and quality compliant with the "high level principles" in EU legislation. They must base the rules on documented risk assessment and scientific evidence, and update whenever the need arises. BE/TEs can follow national or international guidance or standards from other bodies in setting their technical rules for safety and quality.

This measure is implemented through a change in EU law. The BEs/TEs are expected to assess risks and develop rules in accordance with available guidance. They must base those rules on documented risk assessment and scientific evidence, and update whenever the need arises. This will require a one-time familiarisation and adjustment, at some additional cost.

This option will allow for rapid changes of rules if needed, possibly tailored according to the local epidemiological situation.

When combined with M1.1, M1.2, M1.3, M1.4 and M1.5, it defines Option 1-1.

M1.7 – EU legislation is amended to require establishments to take into account ECDC/EDQM rules on quality & safety requirements ("dynamic" reference, meaning it always refers to the "ongoing" version of the guidance documents). Member State expert group participates in the EDQM drafting and review process. EU legislation is amended to require BE/TE to 'take into account' the rules issued by the expert bodies.

This measure effects change by obligating BEs/TEs to 'take into account' (i.e. to operate in accordance with) and thus, where required, modify their working practices in ways that help to assure consistently high levels of protection for patients. Alongside the legislative element which imposes that obligation, this measure includes administrative action by the Commission to prompt (and where necessary fund) the relevant EU expert bodies to prepare and issue rules that the BEs/TEs will then refer to. The rule-setting activity could be on a rolling basis; periodic or on Commission request.

The combination of M1.1, M1.2, M1.3 and M1.4 it defines Option 1-2.

M1.8 – EU legislation is amended to incorporate quality & safety requirements directly. It contains a mechanism for regular updates to respond to changing risks and technologies under Comitology rules.

This measure is intended to improve the management of risks in the BTC by ensuring that quality and safety requirements applied to BEs/TEs are kept up to date. In this case, however, the requirements themselves are written into EU law. This means that revision of the quality and safety rules will require amendment of EU law. Various implementation routes are being considered for development of updates (role of a scientific committee). As with alternative equivalent measures it may cause BE/TEs to, where required, modify their working practices in ways that help to assure consistently high levels of protection for patients.

When combined with M1.1, M1.2, M1.3 and M1.4 this measure defines Option 1-3.

Outcome

Collectively these measures are expected to lead to consistent protection of patients from all avoidable risks, across the EU.

A2.3. Problem 2 The divergent approaches to oversight cause unequal citizen protection and barriers to the exchange of BTC across EU

Drivers

Current oversight requirements at EU level are overly generic. There is a lack of provisions for verification of effective implementation of national oversight functions relating to vigilance, inspections and authorisations.

Relevant external factors

There are more commercial actors to be authorised. There is a high degree of innovation to be authorised.

Action

M2.1 – EU legislation is amended to incorporate oversight principles for the organisation and for staff in legislation.

This measure establishes common principles for the status and power of regulators in a context where there are differences among Member States in the institutional status of BTC competent authorities. The principles will cover: independence of the authority and the inspectorate (if different) from the sector and from the political level; conflicts of interest; transparency; national co-ordination; qualifications of inspectors; and enforcement powers of inspectors. For example:

- The authority (and inspectorate) shall be fully independent of the BTC sector.
- The authority (and inspectorate) shall have operational independence and be free to take decisions on application of the prevailing BTC law free of outside interference or influence.
- The authority shall maintain robust procedures to manage the risk of conflicts of interest.
- The authority shall have mechanisms to ensure transparency in its decisions on regulatory matters.
- There will be effective national coordination among competent authorities within the same country.

- The authority shall ensure that its staff have the skills and qualifications required for them to competency discharge their assigned functions.
- The authority's inspectors shall be provided with powers under national law sufficient for their decisions on matters relating to regulation of BEs/TEs to be enforceable..

The measure will, in those Member States where the current set-up deviates from the prescribed oversight principles, prompt change in regulatory structures / powers / operating principles etc.

M2.2 – EU law is amended to obligate NCAs to base their inspection regimes on a risk-based approach

This measure will obligate NCAs to target inspection effort on the basis of risk rather than on a fixed frequency or other parameter. The legislation will propose for an implementation model in which the risk rating assigned to each establishment by the NCA is influenced by that establishment's risk management performance (e.g. as reflected by volume of activity, compliance history, quality of risk management procedures, etc.).

The measure will prompt NCAs to develop and deploy new risk-based inspection regimes if they do not already have such practices. The change should ultimately enable the regulators to be more efficient (in terms of matching inspection investment to potential for risk reduction).

This measure is expected to have indirect impacts on establishments. Depending on the strategic response by the NCAs (i.e. whether NCAs reallocate the same resource or just reduce the inspection effort allocated to low risk establishments), the measure may reduce the inspection burdens on low risk establishments and/or increase the administrative burden on high risk establishments. It provides scope for 'earned recognition', lowering inspection burdens for well-run establishments. The risk-based approach to inspection may in turn lead to a reduction in actual risk to patients in higher risk establishments, and so ultimately to improve health and safety outcomes.

M2.3 – The Commission will develop and maintain common guidance on oversight

This measure is intended to improve the consistency of oversight across the EU through development and dissemination of guidance to be applied in all Member States. It will result in direct costs to the Commission to fund development and maintenance of the guidance, and some ongoing costs to NCAs to review new guidance and integrate it into their own inspection guidance, training and practices. The guidance is expected to contribute to harmonisation of inspection practices and thus lead to more consistent, high quality inspection and ultimately to better health and safety outcomes. It should contribute to increasing trust among Member States and thus facilitate exchange of BTC.

M2.4 – The European Commission conducts audits of national control systems (inspection, authorisation, vigilance), issuing recommendations and action plans for improvement when necessary. The Commission auditors are accompanied by Member State experts (usually inspectors).

Audits by the Commission, accompanied by Member State experts, and the resultant recommendations are expected to help improve the consistency of inspection arrangements around the EU. The conduct of the audits, and opportunity they provide for Member State experts to see practices in other Member States are expected to help build confidence in other Member States' inspection systems. Such changes are expected to help support the exchange of BTC within Europe.

M2.5 – EU law is amended to implement a legal framework for Joint Member State inspections of BEs/TEs -

Under this measure EU law provides for joint Member State inspections of BEs/TEs. As with alternative measures it is intended to have direct effects on the quality and consistency of systems, and indirect effects on the Member States' confidence in the systems of other countries. The joint inspections can also help with pooling expertise of inspectors in certain

techniques. Such changes are expected to help support the exchange of BTC within Europe.

M2.6 – The European Commission will develop the relevant component of the IT platform for oversight

This is a non-legal measure. A shared IT platform, funded and supported by the Commission, will enable sharing information on oversight, vigilance and other activities. The platform can also provide additional features (e.g. direct SARE reporting). This will apply to all options.

Outcome

The Objective 2 measures are expected to lead to the strengthening and harmonisation of oversight among Member States and ensure trusted, effective and independent oversight of BTC activities. They should help to secure equal protection of citizens, and facilitation of exchange of BTC among Member States.

A2.4. Problem 3: Avoidable risks for BTC donors and for children born from donated eggs, sperm or embryos.

Drivers

There are insufficient measures to protect and monitor donors and no requirements to protect and monitor offspring.

Relevant external factors

There is increased demand (e.g. rapid growth IVF, new IVF options) and increased expectation to donate.

Actions

M3.1 – EU legislation on donor safety amended to prevent donations by donors that should not donate due to their own health condition or medical history; prevent donor health being compromised by an act of donation or by over-frequent donation, even if they are fully eligible; avoid any risk to donor privacy by protecting their personal data; ensure that adverse outcomes caused by donation are reported and investigated and that these are collated and published at EU level

This measure will tighten up the rules on who can donate at the same time as increasing protection of those who do donate. This measure is expected to change the donor supply conditions for BE/TEs, and potentially change the costs of access to BTC. It should also help to reduce risk to donors and thus help, ultimately, to improve health and safety outcomes. It should help to build trust in the system for donors, patients, etc.

M3.2 – EU legislation is amended to: incorporate high level principles in legislation protecting offspring born from donated gametes/embryos; ensure that children born from donated gametes or embryos do not have genetic conditions that were reasonably avoidable through donor selection and testing; ensure that, where children are born with genetic conditions transmitted by a gamete or embryo donor(s) that these are reported to authorities, and possible other affected families, and actions are taken to prevent further use of the donated gametes or embryos as appropriate.

This measure will tighten up the rules on testing of donated gametes/embryos for genetic conditions. It will also require follow-up of offspring from MAR (tracking health status) and tracing mechanisms. These are collectively intended to reduce the risk of harm to offspring. The reporting and follow-up obligation for offspring is assumed to last for two years from birth.

In case of reporting of genetic conditions transmission, NCAs will take measures to locate the MAR establishment (which may be in another jurisdiction, which then requires involvement of another NCA) and instigate tracing of embryos/gametes/offspring associated with the same donor(s). The investigation would establish whether other children were born from that donor and whether they might have been similarly affected. Also, sperm (and increasingly eggs) will already have been distributed and will be in storage in Member State MAR centres for future use. Those should be blocked from further use (or in some cases, for those wishing to use them because they already have children from that donor, information should be given on risk and the family should decide whether to use them).

M3.3 – EU legislation amended to incorporate new definitions (e.g. To include genetic disease transmission by MAR using donor gametes or embryos as an 'adverse reaction')

This measure would, in combination with M3.4, increase the scope and power of monitoring of child conditions and the level of reporting by clinics to competent authorities, and by competent authorities to the European Commission.

M3.4 – The European Commission will develop the relevant component of an IT platform for quality & safety requirements

This is a non-legal measure. A shared IT platform, funded and supported by the Commission, will enable sharing information on the quality and safety requirements for donor and children born from MAR (the process will vary according to the options). It also allows timely updates in case of emergency.

The platform shall also allow sharing of information on national and regional differences under Option 3-1.

M3.5 – EU law is amended to require BE/TEs to define detailed quality & safety requirements to a) protect donors (age and medical history eligibility rules, donation frequency rules, donation health monitoring rules, adverse reaction reporting rules etc.) and b) protect children born from donated gametes or embryos (donor genetic testing rules, new born health monitoring rules, adverse outcome reporting rules etc.)

This measure is intended to enhance the protection provided to donors and offspring by requiring establishments to develop quality and safety rules. It provides a 'devolved' model by which BE/TEs can 'set their own rules'. NCAs will be responsible for checking how BE/TEs have defined the rules and established their risk assessments. Theory is that the process of developing, setting and following the requirements will engender better practice among the BE/TEs concerned. The measure will apply to all BTC donors and the children born from donated gametes or embryos.

In combination with measures M3.1, M3.2, M3.3 and M3.4, this measure defines Option 3-1. It is an alternative to M3.6 and M3.7.

M3.6 – EU law is amended to require expert bodies to define detailed quality & safety requirements (as above) for donors and children born from donated gametes or embryos and to require BE/TE to 'take into account' the rules issued by the expert bodies

This measure is intended to enhance the protection provided to donors and offspring by developing and maintaining common EU quality and safety requirements for BTC donors and children born from donated gametes or embryos. The requirements would be developed by an EU expert body at the request of the European Commission. The expert group would maintain/update the requirements as needed.

BE/TEs will be obligated to apply the rules specified by the expert bodies. NCAs will check their compliance.

In combination with measures M3.1, M3.2, M3.3 and M3.4 this measure defines Option 3-2. It is an alternative to M3.5 and M3.7.

M3.7 – EU law is amended to incorporate detailed quality & safety requirements (as above) for donors and children born from donated gametes or embryos; and a mechanism incorporated to update these as needed

This measure is intended to enhance the protection provided to donors and offspring by specifying EU quality and safety requirements for donors and children born from donated gametes or embryos. The requirements would be incorporated into EU law.

BE/TEs will be obligated to apply the rules specified in the EU legislation. NCAs will check their compliance.

In combination with measures M3.1, M3.2, M3.3, and M3.4, this measure defines Option 3-3. It is an alternative to M3.5 and M3.6.

Outcome

The target outcome for the Objective 3 options is for BTC donors, and children born from donated sperm, eggs or embryos, to be protected from risks specific to those groups, including exposure to hormonal treatment for egg and stem cell donation and the risks of genetic disease transmission to children born from assisted reproduction.

A2.5. Problem 4 BTC legislation lags behind innovation

Drivers

The problem drivers are that there are insufficient provisions to authorise novelties [D6], there are insufficient provisions to prove clinical value [D7] and unclear borderline criteria between the legal frameworks of BTC medicinal products, medical devices, etc. [D8].

Additionally, there is no forum empowered to determine a comprehensive classification of BTC-based therapies and technologies at the interface of different EU legal frameworks (BTC, (AT)MP, MD) [D9].

External factors

More/new benefits are claimed by commercial actors.

Actions

M4.1 – Point of care preparations: The "same surgical procedure" exclusion currently provided in the tissue and cell Directive for point of care preparations is refined/removed[107]

This measure will remove the exception that is currently applied to point of care preparations used in the same surgical procedure. The purpose of this is to remove any ambiguity about the legal treatment of such point of care preparations and subject them to the same safety standards as other BTC practices. This should increase the consistency of approach.

The enhanced safety will help to reduce risks to patients and help facilitate innovation. This will require adding proportionate requirements to ensure safety and quality for such point of care preparations.

This measure will enhance/support the changes intended under M1.2.

[107] All public and private hospitals would be affected by a change to the same surgical procedure exemption (when there is processing of the BTC). The change in exemption being considered is from the full exemption that currently exists to just exempting those BTC which are unprocessed, immediately reused and provided to the patient. It will require a registration of the hospital, and an authorisation of the preparation process, with requirements proportionate to the risks. Such preparation process authorisation should also prevent the use of unproven therapies, and this will be a strength of the revised framework.

M4.2 – Classification advice: internal BTC: Establishment of a new EU level advisory mechanism to make recommendations to/advise Member States on when and what BTC requirements should be applied in part (donation, collection and testing) or in full (all steps from donation to supply for clinical use)

This measure will address the borderline problems by establishing an advisory mechanism (a new EU level committee) to provide advice on matters of interpretation relating to issues internal to the BTC legislative framework.

The committee composition is to be finalised at a later date but may, for instance, comprise representatives of NCAs, scientific experts, the Commission and representatives of doctors and patients. The Commission would provide the secretariat.

It is understood that the recommendations provided by the committee would be advisory in nature rather than having legal force. The effect would come through the clarification embodied in its advice. Competent authorities are assumed to change their regulatory approach to align to recommendations from the committee. Innovators (in BE/TEs or elsewhere) would benefit from the clarifications – ambiguity about how their innovative therapy/technology will be regulated will be addressed. The barriers to innovation that stem from lack of clarity about how the legislation would is to be applied in particular circumstances would be lowered, leading to more innovation in the sector and a larger number of BTC applications that provide benefit to patients becoming available.

M4.3 – Interplay SoHO/Pharma/Medical Devices: A mechanism is introduced to strengthen interplay with 'adjacent' legal frameworks (SoHO/Pharma/Medical Devices) by better coordination of rules and oversight in different frameworks, especially in respect of substances that are regulated under more than one legal framework.

This measure is intended to help address borderline issues that exist at the interface of BTC legislation and other legal frameworks. The current situation can lead to practices that are not taking into account the final application of the donated substance. Vigilance systems do not always connect with each other effectively.

The ‘mechanism’ and the means of implementation (e.g. a change to EU law) is not defined by the measure as currently stated. However an approach similar to GMP Annex 14 (for plasma that becomes starting materials for plasma derived medicinal products) can be explored.

Two potential legal requirements that have been mentioned are (i) when the ultimate use is a product regulated under another law then the regulator is required to consult the designated regulator for that other regime and (ii) for starting materials, consultation between regulators is needed to ensure traceability and vigilance.

M4.4 – Classification advice: advice related to other legal frameworks. EU level advisory mechanism will advise where other frameworks (in particular medical devices and medicinal products) might be applied for particular novel BTC. Implementation might involve exchange/mutual consultation with advisory bodies for medicinal products (EMA innovation task force, EMA the CAT) and medical device frameworks (Borderlines and Classification Working Party).

This measure will address the borderline problems by establish an advisory mechanism to provide advice on matters of interpretation relating to issues at the interface of the EU’s BTC legislative framework and other adjacent legislative frameworks (e.g. pharmaceuticals, medical devices).

A potential implementation model is for the committee defined at M4.2 to be given a mandate to engage with parallel committees (from other legislative framework) to resolve borderline issues.

It is understood that the recommendations provided by the committee would be advisory in nature rather than having legal force. The effect would come through the clarification

embodied in its advice. Competent authorities are assumed to change their regulatory approach to align to recommendations from the committee. BE/TEs would then modify their practices based on changes to NCA approach. The barriers to innovation that stem from lack of clarity about how the legislation would is to be applied in particular circumstances would be lowered, leading to more innovation in the sector and a larger number of BTC applications that provide benefit to patients becoming available.

M4.5 – The EU legislation will set principles for authorisation procedure (good practice for authorisation procedures including validation of facilities, equipment and processing and clinical data requirement according to level of risk and novelty) to demonstrate safety and efficacy in patients.

This legal measure works in concert with M4.5 (above). M4.6 defines the principles whereas M4.5 imposes an obligation on competent authorities. The alternative implementation mechanisms are then specified by M4.10 – M4.12 (these differentiate the M4 options, providing alternative approaches to preparation process authorisation).

The M4.5/M4.6 measures provide greater clarity on what rules apply and what approach is required. This will help make the regulatory system more robust and so protect patients. The increased clarity of the regulatory requirements should increase stakeholder confidence in the system.

M4.6 – Strengthened preparation process authorisation: EU law modified so that, for major changes in the steps of collection, processing and use of BTC, competent authorities will have to grant prior authorisation based on an upfront risk assessment and, then, a proportionate set of data demonstrating safety and benefit for patients that justifies any risks associated with treatment with BTC prepared in innovative ways.

This measure works in concert with M4.5 (above). The M4.5/M4.6 measures provide greater clarity on what rules apply and what approach is required. This will help make the regulatory system more robust and so protect patients. The increased clarity of the regulatory requirements should increase stakeholder confidence in the system. The "novelty" relates to the demonstration of efficacy/benefit for patients

M4.7 – The EU legislation will set rules for implementing a clinical trial for BTC (if high level of risks)

This legal measure works together with M4.5 and M4.6. It will define when a clinical trial is required to assess the safety of a novel BTC application. Rather than set a new set of requirements for clinical trials it will refer to existing rules on clinical trials.

By providing clarity on when proof of safety/efficacy need to be demonstrated in a clinical trial this measure will provide increased consistency of regulatory practice and safety across the EU (clinical trials are already applied in some Member States). It will also help to provide greater clarity for innovators on the circumstances in which a trial is required.

M4.8 – EU will develop an exchange (IT) platform for NCAs to exchange info regarding (novel) process authorisations (the platform would be used for (voluntary) acceptance of authorisations among Member States). This includes clinical evidence collected by clinicians with the support of learned societies.

This is a non-legal measure. A shared IT platform, funded and supported by the Commission, will facilitate efficient sharing of information among Member States about their authorisations of novel BTC applications. Theory is that Member States will be more likely (and/or quicker) to authorise a novel BTC application if they see, via the platform, that the same application has been authorised by another Member State and would have access/reference to the data used for the authorisation. Despite its voluntary basis, this measure would lead to an alignment in the way Member States organise such authorisations. To have the desired effect competent authorities will need to register their own authorisations on the platform. The platform would also give access to, as well as

support the collection and analysis of of clinical evidence collected by clinicians with the support of learned societies.

M4.9 – EU law is modified to obligate BE/TEs to conduct risk assessments on novel processes. These risk assessments will be evaluated by the competent authority inspectors to ensure that they have been conducted effectively and the preparation process authorisation was adequate.

This measure is intended to strengthen the quality and consistency of the risk assessments applied to novel BTCs. It will require BE/Tes to acquire the competence to carry out the risk assessment (or retain a third party to conduct the assessment on their behalf).

The precise details of the risk assessment procedure are defined in an accompanying measure – M4.10, M4.11 or M4.12, depending on the option.

The quality assurance mechanism introduced via the obligation placed on competent authority inspectors will extend the scope of work for competent authorities. Depending on the option (Option 4.1, 4.2 or 4.3), the inspectors will need to assess the risk assessments' conformity with a diversity of guidance and standards (M4.10), guidance issued by an EU expert group (M4.11) or the requirements specified in EU law (M4.12).

M4.10 – EU law is modified to obligate BE/Tes to design the risk assessments on novel processes and decide on the nature and extent of laboratory and/clinical studies needed to demonstrate safety and quality. The BE/Tes could follow national or international guidance or standards from other bodies in conducting their risk assessments.

This measure places an obligation on BE/Tes to develop risk assessment protocols for novel processes. It gives them the freedom to use a variety of sources of guidance and standards in doing so.

This measure works in concert with M4.9. When combined with M4.1-M4.9 it defines Option 4-1. It is an alternative to M4.11 and M4.12.

M4.11 – EU law is modified to obligate BE/Tes to conduct risk assessments on novel processes in compliance with technical guidance on the conduct of RA and studies (from expert bodies) referred to in EU legislation (dynamic references)

This measure places an obligation on BE/Tes to conduct risk assessment protocols for novel processes in accordance with guidance prepared by nominated EU expert bodies. This measure works in concert with M4.9. When combined with M4.1-M4.9 it defines Option 4-2. It is an alternative to M4.10 and M4.12.

To give effect to this measure it is also necessary for the Commission to task relevant expert body/bodies with the development and maintenance of the technical guidance, and for this guidance to be made available for use.

M4.12 – EU law is modified to obligate BE/Tes to conduct risk assessments on novel processes in compliance with technical rules on the conduct of RA and studies needed set in EU legislation.

This measure places an obligation on BE/Tes to conduct risk assessment protocols for novel processes in accordance with rules specified in EU law. This measure works in concert with M4.9. When combined with M4.1-M4.9 it defines Option 4-3. It is an alternative to M4.10 and M4.11.

Updates to the rules would require modification of EU law.

Outcome

The target outcome is to facilitate innovation of safe (based on clinical data) BTC therapies (so removing barriers to innovations).

A2.6. Problem 5: EU vulnerable to interruptions in some BTC supply

Drivers

There are currently no provisions for monitoring and controlling supply [D10], and no provisions for planning for disruptions [D11].

External factors

EU demand is higher than supplies for some BTC. There is an increased number of disease outbreaks that are disruptive for BTC supplies.

Actions

M5.1 – EU law is amended to impose mandatory monitoring obligations on BEs/Tes

This measure requires BE/TE to monitor supply and demand situation, for some defined (critical) BTC. The scope of this monitoring obligation is derived from EDQM recommendations.

The measure does not in itself have an impact beyond imposing an obligation to collect/store relevant data. Its effect on 'the supply problem' comes when used in combination with other Objective 5 measures.

M5.2 – EU law is amended to require mandatory reporting and notification of sufficiency data for certain critical BTC in case of shortage/drop in supply (rapid notifications)

This measure imposes an obligation on BE/Tes to notify competent authorities about shortages/supply issues in certain circumstances, for a sub-set of critical BTC (i.e. a more restricted set of BTC than the scope of M5.1) . The BE/Tes will take the initiative to report when a shortage becomes apparent.

M5.3 – EU law is amended to require mandatory measures for emergency supply responses

This measure will impose an obligation on BE/Tes to develop and adopt contingency plans that show how they will handle supply shortages. The requirement for contingency plans will apply to a sub-set of critical BTC only (the same scope of BTC as M5.2).

M5.4 – The European Commission will develop the relevant component of the (IT) platform for exchange of information on supply and activity

This is a non-legal measure. A shared IT platform, funded and supported by the Commission, will facilitate efficient sharing of information among BE/Tes / Member States and expert bodies on activities and supply. It will ensure timely access to data for coordinated action for crisis management. This measure will apply to all options.

M5.5 – EU law is amended to strengthen Member States' ability to intervene to control and adjust supply, as necessary, under their national competence, and allow evidence-based support action at EU level.

This measure, codified in EU law, will give Member States additional power to manage supply within their competence and powers to the EU to act.

This is a strategic risk management measure that has an 'enabling' function. The precise conditions under which such powers would be available are not currently defined. The focus of this measure is on 'critical BTC' as defined in M5.1 above.

M5.6 – EU law is amended to obligate BE/TEs to develop monitoring and notification systems and contingency plans. These will be reviewed for adequacy by the authority during inspection.

This measure introduces a 'decentralised' model of supply risk management. It would apply to critical BTC only, as defined in M5.1. It would give effect to M5.2 and M5.3.

Individual establishments monitor their own situation. Data must be supplied to the competent authority only if there is a request from the authority. The measure does not oblige the competent authority to share those data with the European Commission.

Under this measure no standard or guidance is provided for the contingency plans that individual establishments are obligated to prepare under M5.3. The quality of those contingency plans must be assessed by the relevant competent authority (extending the scope of work of the NCAs). The NCAs will need to develop their own approach to dealing with the variability of the contingency plans.

This measure is used in combination with M5.1 to M5.5, and as an alternative to M5.7 and M5.8. As such, it defines Option 5-1.

M5.7 – EU law is amended with references to guidance from expert bodies for rules on sufficiency data reporting (including monitoring and notifications) and on emergency preparedness/contingency.

This measure sets up a continuous, EU-wide system for collection and monitoring of sufficiency data for critical BTC. This would cover reporting of donations, distribution, import, export and use by BTC establishments to national authorities and to the Commission. The rules on data reporting are specified by EU expert bodies. In this measure the contingency plans that BE/TEs will produce are expected to conform to guidance prepared and maintained by a designed EU expert body.

This measure would require establishments to continually collect and submit the prescribed data in the required format at the required frequency. The proposed IT system, and other aspects of this system, are being examined in a study procured by the Commission. NCAs will oversee compliance.

This measure is used in combination with M5.1 to M5.5, and as an alternative to M5.6 and M5.8. As such, it defines Option 5-2.

M5.8 – EU law is amended to include rules on sufficiency data reporting (including monitoring and notifications) and on emergency preparedness

This measure is identical to M5.7 except that the rules on data reporting and emergency preparedness are defined in EU law rather than by EU expert bodies.

This measure is used in combination with M5.1 to M5.5, and as an alternative to M5.6 and M5.7. As such, it defines Option 5-3.

Outcome

Reduced the risk of shortages due to insufficient or unreliable BTC supply as a result of the systems established to monitor donations and supply and to support pre-emptive and/or corrective action in case of disruptive epidemiological outbreaks, or similar events.

Annex 3: Problem definition – supplementary analysis

This annex provides additional detail that supports the summary analysis of the problem definition text for: (i) the impacts of the COVID-19 pandemic, and (ii) borderline issues.

A3.1 The impact of the COVID-19 pandemic on the sector

The COVID-19 pandemic has highlighted the importance of EU cooperation in the BTC sector. Cooperation between EU institutions and Member States allowed several non-legislative actions to be undertaken in response to the pandemic:

- the ECDC provided rapid non-binding guidance on donor testing and deferral;
- the European Commission published a guidance document on the use of convalescent plasma, set up a database to collect evidence on convalescent plasma as a treatment for COVID-19, and published a clarification that SoHO are considered to be essential goods/services for which free circulation within the EU is crucial.
- the European Commission, through the Emergency Support Instrument, committed €36 million to 24 projects throughout the EU and the UK to support and increase the collection of COVID Convalescent Plasma.

The pandemic also highlighted some of the legislation's shortcomings. Respondents to both the establishment survey and the NCA survey conducted for this study identified the greatest weaknesses of the legislation in the context of the pandemic response to be: the lack of a legally binding requirement that ECDC donor selection and COVID testing guidance be followed[108]; a lack of a provision for monitoring of the supply situation[109]; and a lack of proportionate approach to the quick assessment of novel therapies (i.e. CCP)[110]; followed by a lack of provision for export bans[111].

A3.1.1 The impacts on safety and quality of substances, supply sufficiency and oversight

There has been at least one case of COVID-19 transmission via a lung transplant[112], however no cases of transmission via transfusion of blood and tissue grafts have been reported. The possibility of COVID-19 transmission by transfusion/transplantation in the future cannot be completely excluded and mitigation measures needed to be implemented. As with other infectious disease outbreaks, the legislative provisions on donor selection and testing in the BTC legislation could not be updated rapidly enough to address this risk and instead non-binding guidance was prepared by the ECDC in March 2020. Measures to mitigate the risk of COVID-19 transmission including the implementation of stricter donor selection criteria and donor deferral criteria, donor testing for COVID-19 and the use of viral inactivation techniques were outlined.

While most stakeholders who responded to the stakeholder surveys did not believe there was a major impact on the quality and safety of SoHO, they confirmed concerns raised regarding the lack of a legally binding requirement that ECDC donor selection and COVID testing guidance be followed as this might have resulted in the circulation of SoHO that did not comply with this guidance as Member States could not insist on these requirements

[108] Establishment survey respondents: 34.2%; NCA survey respondents: 58.3%. Note respondents could select more than one option.

[109] Establishment survey respondents: 27.8%; NCA survey respondents: 33.3%

[110] Establishment survey respondents: 21.5%; NCA survey respondents: 29.2%

[111] Establishment survey respondents: 12.7%; NCA survey respondents: 16.7%.

[112] Kaul, D.R., Valesano, A.L., Petrie, J.G., et al. 2021. Donor to recipient transmission of SARS-CoV-2 by lung transplantation despite negative donor upper respiratory tract testing. Am J Transplant. 21(8). doi: 10.1111/ajt.16532.

being mandatory. In addition, stakeholders felt it would be beneficial to publish guidance by the ECDC in real time, as this would allow quicker implementation of mitigation measures.

In response to the establishments survey, a healthcare provider of the clinical application of tissues or cells (transplantation) highlighted that the mandatory requirement to perform nasopharyngeal swabs on the donors and to obtain a confirmed negative result for SARS-CoV-2 before the tissue is released for transplantation has reduced the probability of inadvertent distribution of corneas from asymptomatic donors, which has emerged as a significant feature of COVID-19. However, it is not known whether these requirements were mandatory in all countries (with subsequent impact on quality and safety if BTC substances were distributed cross-border).

An additional concern raised by stakeholders in relation to the impact of the COVID-19 pandemic on the quality and safety of SoHO related to the need to cryopreserve HSC in situations where they would not have previously needed to do so. They cited an increased risk of unpredictable logistical difficulties at transplant centres, or a donor or patient becoming unavailable at the time of planned transplantation, due to community-acquired COVID-19, being a close contact or travel restrictions. The impact of cryopreservation on cell viability was noted.

One of the 24 NCAs who responded to the Commission's consultation indicated that difficulties at the beginning of the pandemic with the movement of goods caused concern regarding the availability and supply of test kits, reagents and materials such as blood bags and also of personal protection equipment necessary to ensure the safe continuation of transfusion and transplantation services and that this also had the potential to impact the quality and safety of BTC during the pandemic.

A3.1.2 Sufficiency and Safety of Supply of SoHO

COVID-19 poses a risk to the sufficiency and sustainability of SoHO supply by reducing donor availability, lowering the capacity of the collection establishment to accommodate donors due to distancing measures, affecting the availability of staff at SoHO facilities, changing demand for SoHO products, and limiting the provision or distribution of critical materials, equipment, and SoHO products. Several respondents (including NGOs) to the Public Consultation launched by DG SANTE noted that the COVID-19 pandemic demonstrated that the SoHO supply chain is not adequately prepared for epidemiological emergencies and crisis.

According to data from the European Blood Alliance, 15 European national and regional blood services reported a 9% (median, range 1-27%) decrease in blood and blood components collected in March and April 2020 compared to the same period in 2019, while the decline in blood components distributed to hospitals was 12% (median, range 1-18%)[113]. The reduction in elective procedures in hospitals and the low requirement for transfusion in COVID-19 patients has counterbalanced the reduction in blood component availability to some extent.

During the first wave of the pandemic, the EMA reported no shortages in the supply of PDMPs although the donations of plasma for fractionation had dropped. Plasma collectors experienced significant declines in collections due, in part, to the impact of physical distancing measures and other mobility restrictions caused by the COVID-19 pandemic. Given that the complex manufacturing of plasma-derived therapies can take 7-12 months, any decline in plasma donations could potentially affect patients' ability to access life-saving therapies. PDMP availability in the EU is highly dependent on imported supplies, mainly from the US, and the current status may therefore reflect the status of plasma collection in

[113] ECDC (2020). Coronavirus disease 2019 (COVID-19) and supply of substances of human origin in the EU/EEA - second update. 10 December 2020. Available online: https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-supply-substances-human-origin-second-update.pdf

the US. In a position paper, the European Plasma Alliance reported that COVID-19 has amplified the need to collect more plasma and noted that there have been significant declines in collections during the pandemic. In response to the establishment survey, a representative organisation representing manufacturers reported that with the importance of US BTC exports in mind, there were serious concerns that the US administration would invoke the Defence Procurement Act for blood and plasma exports as well, similarly to what they did with personal protective equipment and ventilators. Manufacturers were reportedly striving to implement effective contingency measures to mitigate such supply chain disruptions.

COVID-19 also poses a risk to the supply and transplantation of tissues and cells, not only by decreasing the donations and modifying demand, but also by extending waiting lists and prolonging waiting times for transplantation. Several examples of the reduction in donation and transplantation of tissues and cells have been documented in the ECDC Guidance updated in December 2020. For example, 64 eye banks, covering 95% of the European corneal donation activity, reported a mean decrease in the number of corneas procured of 38%, 68% and 41%, respectively, in March, April and May 2020 against the mean for the previous two years. Meanwhile corneal transplants decreased by 28%, 68% and 56% respectively, corresponding to 3 866 untreated patients in three months. In the UK, the number of deceased donors decreased by 66% and the number of deceased donor transplants decreased by 68% during the COVID-19 lockdown period from 23 March to 10 May 2020, compared to the same period in 2019.

As COVID-19 transmission cannot be excluded because of the uncertain effects of infection in assisted reproduction technologies and pregnancy, the ESHRE suggested postponing assisted reproduction treatments as a precaution to avoid unnecessary risk, with, the exception of the necessary cryopreservation of gametes, embryos or tissue in cases requiring urgent fertility preservation in oncology patients. This had a significant impact on provision of such treatments.

Most respondents to the establishment survey indicated they believed the pandemic resulted in a decrease in the donation and collection of SoHO. A stakeholder commented that, as far as blood and blood components are concerned, the COVID-19 pandemic has had, and is still having, a significant impact on the sufficiency of supply of blood components for transfusion. This has made it more difficult for supply to be maintained and significant organisational changes have been required to guarantee safe access of donors to collection sites. In addition, they noted the pandemic has had, and is still having, a very significant negative impact on the collection of plasma for fractionation.

In response to the establishments survey, a representative organisation for of patients treated products manufactured from BTC (PDMPs) commented that many of European patient organisations had seen tensions or shortages in their countries during the pandemic and provided the following statistics: 7 out of 13 countries have experienced and continue to experience shortages either at national or at hospital level. This means for patients with primary immunodeficiencies: 35% have had to change brands; 6% had to change route; 12% experienced an increased duration between treatments and 12% had their dosage decreased; no new patients are accepted for Ig treatment (6%); and new patients can't have their treatment (12%)[114].

Figure 1 demonstrates the impact of immunoglobulin shortages on patient treatments during the pandemic.

[114] The response did not provide further information about the source of this data.

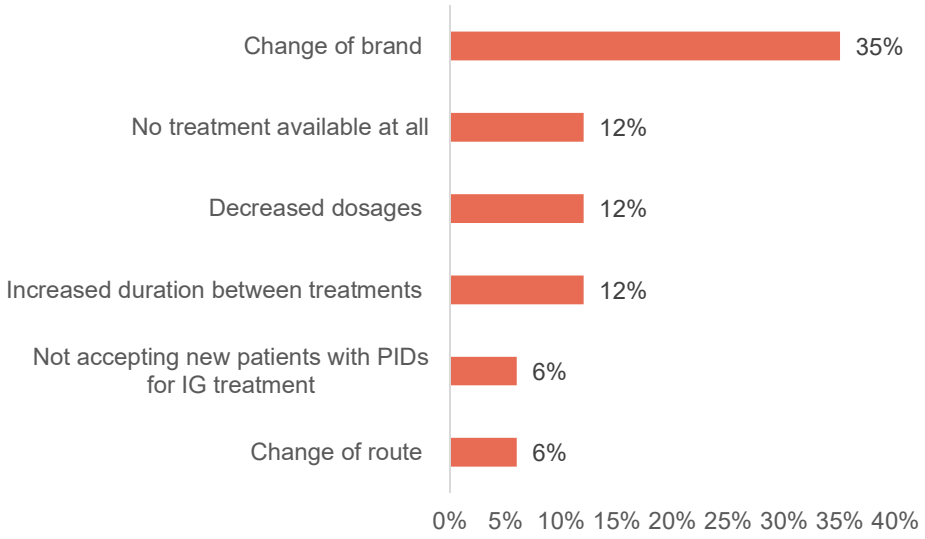


Figure 1. Impact of immunoglobulins (IG) shortages during the COVID-19 pandemic on patients' treatment

Source: Stakeholder commentary on the IPOPI IG shortage survey

A blood establishment noted that there have been difficulties in collecting and forecasting needs for labile blood components after the first lockdown, particularly concerning the management of "peaks and troughs" influenced by the health measures and restrictions in place (for donor attendance). There is a difficulty in returning to the level of pre-COVID stocks. There is also a problem concerning the collection of certain tissues, which is decreasing due to the constraints linked to the pandemic (donor qualification). The same establishment reported complications with the arrival of grafts from abroad (e.g. due to the disparity in legislation concerning tests and donor selection criteria, there has been a need to freeze, particularly allogeneic HSC).

A national eye bank commented that the pandemic had a negative impact on the rate of donation and distribution of corneal tissues (i.e., tissues collection and harvesting), their distribution to the ophthalmology wards and usage for surgical purposes. It reported a reduction of nearly 60% of the overall corneal transplant activity as compared to the same period in 2019 due to the reorganisation of the national health service needed to manage the pandemic (e.g. conversion of operating theatres into intensive care unit wards, cancellation of elective surgery unless urgent cases). Up to 421 corneas available for transplantation were discarded during the lockdown in this Member State because they were not used before their expiry date. This was a significant waste of resources.

While no direct evidence was put forward, most NCAs responding to the NCA survey believed there was some reduction in the sufficiency of SoHO supply during the pandemic. In the Public Consultation organised by DG SANTE, an NGO stakeholder noted that COVID-19 has exposed the scarcity of suitable donors, facilities and personnel for blood collection, which increases the risk of shortages in the near future, especially of plasma medicines such as immunoglobulins, for which Europe already relies heavily on American plasma. Other Public Consultation respondents (companies / business associations) reported a lack of consistent approach across Member States during the pandemic. For example, donor collection and material processing for FMT was reportedly paused in some countries but allowed to continue in others, and in some countries, there was a shortage of supply which likely resulted in patients unable to access FMT (which may have resulted in adverse outcomes). Another company / business association stakeholder reported different determinations of whether semen could contain COVID-19 or if the semen quality could be affected by an infection.

An NGO responding to the Public Consultation reported that shortages of blood products, such as occurred early in the COVID-19 pandemic, increase the consequences of discriminatory practices in acceptance of donations.

A3.1.3 Oversight of BTC Activities

The majority of respondents to the establishment survey and NCAs responding to the NCA survey launched for this study indicated that they did believe that oversight of BTC activities was affected by the COVID-19 pandemic. It was not possible to do onsite inspections during the height of the pandemic; desk-based or remote inspections (sometimes with a virtual component) were undertaken instead. One representative organisation for donors of BTC noted that, '*in many European countries the pandemic has had a negative impact on the oversight of blood activities which appears to have been significantly slowed down and/or "reduced to essentials" (e.g. desktop inspections/audits replacing on site visits). In addition, it has probably heightened the already existing lack of homogeneity of oversight activities between Member States'*.

A3.1.4 Lessons learnt about the resilience and functioning of the BTC sector during the COVID-19 crisis

Respondents to the stakeholder surveys for the present study, as well as respondents to the Commission's Public Consultation, commented on the lessons to be learnt about the resilience and functioning of the BTC sector during the COVID-19 crisis. A theme across the responses was that COVID-19 has demonstrated that previous procedures and requirements can be adapted and past routine practices can and should be replaced.

Stakeholders noted that it is currently not possible to use plasma from centres that are not yet approved as part of the Plasma Master File (PMF) even when compliant with EU guidelines. Some stakeholders (companies/business organisations) reported that there had been use of convalescent plasma outside the PMF. These claims have not been verified by ICF.

In the Public Consultation, a public authority recommended flexibility for interpretation of regulations in a pandemic, including flexibility to open up for recruitment of donors with a broader age spectrum or more flexible donor eligibility than are given in the regulation (e.g. in connection with a need for blood or other emergency needs for transfusion and transplantation). Other stakeholders responding to the Public Consultation (company/business organisation; public authority) noted that the pandemic had highlighted the need for flexible rules regarding inspections. As an example, they allow for virtual or remote inspections when needed and appropriate. Another business association reported that COVID-19 has shown that modification of GMP inspection procedures is needed, including provisional certification of new manufacturing facilities, re-certification of existing manufacturing facilities, modification of GMP inspections to include remote or paper audits for the duration of COVID-19. The stakeholder called for update and flexibility of inspection procedures, and operational support to national authorities which currently are not able to apply flexibility, such as remote GMP inspections.

In the Commission's Public Consultation stakeholders reported there is a need for authorities to support awareness of plasma donations, and there is an urgent need for collaboration between the private and public sectors to collect more plasma in Europe. If more plasma is collected in "normal" times, this could create more resilience in times of crisis.

A Public Consultation respondent suggested that COVID-19 has underscored the urgent need for the development, evaluation, and implementation of innovative approaches to optimise transfusion use and blood management in chronic diseases. The role of a national blood system, and blood and blood components as essential medicines, was reportedly not sufficiently considered in national pandemic preparedness plans. A public authority reported

that COVID-19 stressed the capacity to respond to an infectious disease outbreak, and exposed the need to be equipped with standardised and homogeneous risk assessment tools at national and international level to increase the necessity to build-up blood components collection programmes in emergency situations. Several business associations reported that more comprehensive guidance on patient blood management will be required to address blood shortages and blood service disruptions.

In the establishments survey, a healthcare provider of the clinical application of tissues or cells (transplantation) reflected that the pandemic has highlighted the unpredictability in the SoHO supply and demand, and the need for close monitoring of the epidemiological situation and public health interventions specific to SoHO in order to maintain balance in SoHO supply and demand. An NCA reported that some SoHO could withstand the temporary setback in collection, whereas for others with known shortages, such as plasma, difficulties with the collection were encountered. Difficulties with plasma collection are discussed above in the subsection on Sufficiency and Safety of Supply of SoHO.

Finally, a few stakeholders in the both the NCA and the establishment survey (including NCAs, a representative organisation for of patients treated with BTC or products manufactured from them, and a representative organisation representing manufacturers) reported that it is crucial that emergency work plans or an EU-level emergency and contingency plan in the BTC sector is accepted and implemented to minimize future critical shortages and to protect staff and donors.

A3.2 Borderlines

The lack of clarity about which regulatory framework certain emerging novel BTC therapies fall under has become an increasingly pressing problem for all stakeholders in the sector. The BTC legislation provides both a complete regulatory framework for treatments using BTC, and a partial framework for the regulation of starting materials for medicinal products/ATMPS as well as for BTC used in medical devices which include, as an integral part, non-viable tissues or cells or their derivatives (that have an additional function to that of the device). The BTC legislation therefore provides a starting point from which several regulatory pathways are possible.

A key issue that has emerged that some terms and definitions used in the BTC legislation that were intended to create clear demarcations between legislative borders and to direct users to the correct regulatory pathway have, in fact, had an inverse effect - raising questions about interpretation and definition rather than providing clarity and legal certainty.

Evidence examined for the present study, discussed in more detail below, suggests that the lack of clarity on the regulatory status of emerging novel therapies has led to a number of negative impacts for the sector as a whole and, that it may be a contributing factor to inequities in terms of patient access to novel therapies. In 2015, a study on the Economic Landscape for Tissues and Cells[115] noted that legal uncertainty and borderline issues posed problems for developers and other stakeholders. This finding was confirmed by the 'Evaluation of the Union legislation on blood, tissues and cells' carried out in 2018/19 ('the Evaluation'). As the Evaluation report notes, both the Council of Europe (EDQM[116]) and the CoReSoHO[117] refer to inconsistencies and ambiguities in the scope and regulatory borderlines that lead to confusion and hamper oversight and patient access. As summarised by a regulatory stakeholder, poor understanding on the classification of borderline products,

[115] Rathenau Instituut (2015). Economic landscapes of human tissues and cells for clinical application in the EU. Final Report. Available from: https://ec.europa.eu/health//sites/health/files/blood_tissues_organs/docs/economiclandscapes_humantissuescells_en.pdf (Accessed 6 September 2021]

[116] Submission to the PUBLIC CONSULTATION by Council of Europe/EDQM with file title CoE-EDQM.pdf and its annex.

[117] Submission to the PUBLIC CONSULTATION by the Common Representation for Substances of Human Origin (CoReSoHO).

and the resulting applicable regulatory frameworks, may result in hospitals/academia developing medicines or novel BTC that may not meet quality, safety or efficacy requirements to obtain necessary positive pre-approval assessment outcomes (i.e. no/delayed market access).

The Public Consultation and Targeted Public Consultation conducted by the Commission in preparation of the impact assessment of the revision of the BTC legislation included questions on this issue. The present study has also prepared 15 case studies of BTC products that are considered to be borderline to aid the analysis of the problem (Annx 9). These have been informed by interviews with experts working in the relevant fields. In examining the borderline problem three sets of questions have been asked:

- What is the extent of the problem posed for/by therapies/technologies falling in the borderline zone between BTC framework and other frameworks (in particular, medical devices, medicinal products/ATMP), in terms of patient access, affordability and sustainability? What are the dynamics of innovation, including ownership of the technology? What is their overall economic value and how is it expected to evolve in the future?
- What are the impacts of divergent classifications for public health (including access and possible exposure of/to inefficacious/unsafe products) and the economic impacts (including patient access, affordability, and sustainability?
- To what degree are these issues on coherence caused by following definitions laid down in the different legal frameworks: industrial processing, placing on the market (medicinal products legislation), substantial manipulation, non-homologous use (ATMP regulation), extracted derivatives (medical device regulation), same surgical use (blood and tissue and cells directives), or other provisions laid down in these different EU legal frameworks?

The extent of the problem was explored as part of the Targeted Public Consultation with the following question, 'From your experience, how easy have the following aspects been when developing therapies that are at the borderlines with other EU regulatory frameworks? The responses, summarised in Figure 2, suggest that stakeholders have significant difficulties in understanding the precise scope of the relevant legislation and in obtaining advice or confirmation on the status of a product, either at the national level or the EU level. Divergent Member State classifications have made the paradigm of 'mutual recognition' between Member States challenging in practice, causing potential barriers to the free movement of BTC among Member States, as well as presenting significant problems to innovators seeking to develop novel products that may involve pan-European clinical trials.

To date, the CAT have played a significant role in helping to clarify the regulatory pathway and provide recommendations on whether a product should be classified as an ATMP. As indicated by the growing number of applications to the CAT, this provision has enabled manufacturers and developers to seek expert guidance at an early stage. However, a known issue is that the CAT are limited in that they can only classify a product as an ATMP or not an ATMP, and they cannot go a further step to advise if a product should be developed as a medicinal product or a tissue/cell. This can lead to the situation where developers struggle with fragmented advice or knowing where to go. This suggests an opportunity for more joined-up working and interplay with adjacent legal frameworks. Additionally, the CAT are not legally obliged to (systematically) follow-up on products once their classification decision has been made. This also means that there is not a concrete mechanism for understanding how many Member States (and therefore establishments) have accepted the scientific recommendation made by the CAT.

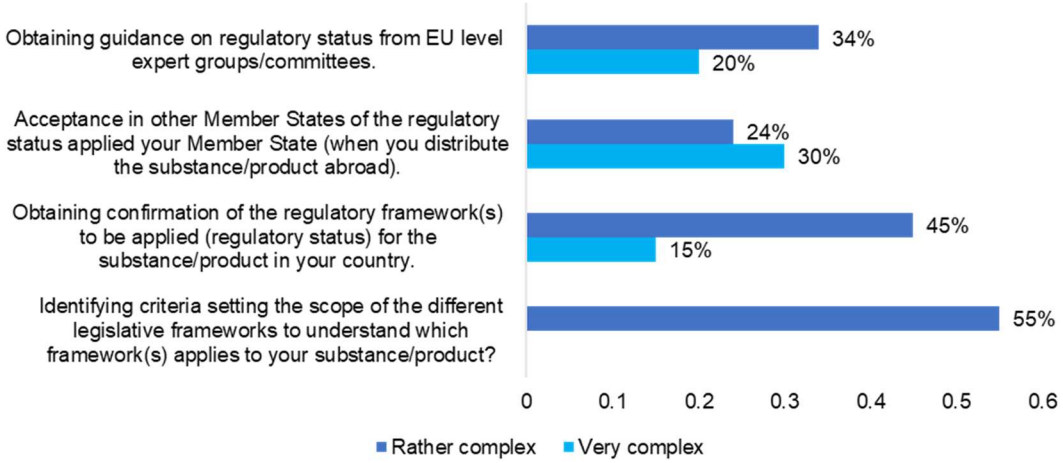


Figure 2. Headlines from Targeted Public Consultation responses to the question 'From your experience, how easy have the following aspects been when developing therapies that are at the borderlines with other EU regulatory frameworks?

Further evidence of the extent of the access problem is provided by several borderline case studies (see the relevant case studies in Annex 9).

One key recurrent issue in the borderline case studies was that Member States regulate the products of interest in non-harmonised ways. For example, lack of harmonisation was documented for autologous adipocyte cells, decellularised dermis, decellularised heart valves, demineralised bone, FMT, DHBM, isolated hepatocytes, PRP, and SEDs. As set out in the underlying rationale of the ARISE trial (a project working on a clinical study to determine the feasibility, safety and efficacy of regenerative heart valves for aortic valve replacement), translating research in regenerative medicine "from bench to bedside is frequently hampered by lengthy and complex regulatory procedures"[118], particularly when regulatory paths at national level are unclear and products are intended to be available across Europe, given the lack of harmonised procedures[119]. There is also the potential risk that applicants could select the countries/bodies where the outcome may be the most favourable for them ('pick & choose'; preference for less stringent requirements or oversight).

A source of confusion or lack of harmonisation has been that some of the borderline cases have changed their classification over time, which increases confusion, for example cultured limbal cells provide an example of a therapy that was developed by TEs under the tissue and cells legislation, but is now considered (under the recommendation of the CAT) an ATMP. Similarly, cultured keratinocytes have gone from unregulated and prepared in research/hospital settings, to being regulated under the tissues and cells legislation, to the current situation where the product is regulated as an ATMP (under the recommendation of the CAT).

Interplays, or borderlines, with the EU Medical Device Regulation (Regulation 2017/145) have also been the source of some borderline issues. For example demineralised bone contains non-viable cells (therefore potentially "derivatives"), and the combination of demineralised bone with scaffolds adds an additional element as primary versus ancillary action determines classification in the medical devices regulation. Similarly, PRP may represent a combination of a blood product and a medical device. The BTC evaluation study

[118] ARISE (n.d.). About Arise: Concept / Funding. Article. Available from: http://www.arise-clinicaltrial.eu/about-espoir0.html

[119] European Commission (2019). Competent Authorities on Substances of Human Origin Expert Group (CASoHO E01718). Meeting of the Competent Authorities for Tissues and Cells. 13 and 14 May 2019. Available from: https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/ev_20190513_sr_en.pdf

noted that for bedside devices which manipulate blood, it is not clear whether the use of these devices is subject to the EU blood legislation and/or the medical device regulation, as Directive 2002/98/EC only defines standards for collection and testing, whatever the intended purpose[120].

Another barrier to determining which framework a product falls under is that the classification of different products varies (as illustrated in the PRP case study). Classification of medical devices is based on intended use, Pharma is based on method of action, ATMP is also based on method of action, where it is used, and the function. Stakeholders reported that classification methods for BTC are not clear.

Some borderline issues are also caused in part by the scope of the current blood legislation. The scope has caused some issues related to PRP, as it may be too strict. The blood legislation only includes blood intended for transfusion, and excludes procedures which are part of the same surgical procedure. PRP is produced in hospitals or medical settings using a medical device, but there is legal uncertainty about which legislation should apply. Similarly, the Commission has stated that SEDs manufactured from whole blood could fall under the Directive as it applies to "the collection and testing of human blood and blood components, whatever their intended use …". As described in the minutes of the meeting[121] at which this was discussed, the Commission noted that it may be difficult to ensure that these procedures comply with the provisions of EU blood legislation, and that changes (to Article II of Directive 2002/98/EC) could be considered during a future revision of the legislation. According to a group of stakeholders interviewed as part of this study, who provide SED treatments in the UK, there has been continued uncertainty since this discussion – EU law has not been modified to put SEDs within the scope of the BTC legislation and Member States continue to have diverging practices.

Divergent approaches and/or uncertainty about a product's regulatory status may push certain products 'under the regulatory radar'. In some Member States there are borderline products that are currently not falling into any regulatory framework. Examples are FMT, DHBM, and autologous adipocytes administered in the same surgical procedure. This situation raises significant concerns about patient safety and creates a regulatory vacuum in which patients could be offered unsafe and unproven treatments.

In examining the root causes of borderline issues, it is necessary to examine the legislative provisions and to consider the extent to which the definitions contribute to the borderline problem. The evaluation identified that there were several definitions or terms used in the BTC legislation that lacked clarity, resulting in divergent interpretations and classifications of BTC products. This finding has been further validated through the consultation process undertaken as part of this current study. The definitions or terms most frequently cited as lacking clarity are those that were intended to provide a clear demarcation between where the scope of the BTC legislation ends, and where the scope of adjoining legislation begins. The evidence clearly demonstrates that unclear definitions or terms used in the legislation have been a contributing factor to the divergent approaches taken by Member States when considering the regulatory status of new BTC products. For example, a stakeholder consulted in the present study stated that the borderline related to autologous adipocyte cells centres around two qualifiers for classifying an ATMP: "substantial manipulation" and "non-homologous use".

During an interview with stakeholders from the CAT, it was agreed that the definitions of substantial and homologous use have previously led to many questions from stakeholders

[120] European Commission (2017). Meeting of the Component Authorities on Blood and Blood Components. 1-2 December 2016. Summary Minutes. (Accessed 24 June 2021). Available from: https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/ev_20161201_mi_en.pdf

[121] European Commission (2013). Meeting of the Competent Authorities on Blood and Blood Components. 17 and 18 April 2013. Summary Report. Available from: https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/blood_mi_20130417_en.pdf (Accessed 20 June 2017]

on what is and is not covered by the ATMP regulations, which is why the CAT produced a reflection paper to shed light on this in a guiding way. As the paper makes clear, the scientific complexity of novel products and processing techniques means that although a body of classification precedents may provide guiding principles as to the likely classification of a product, classification in this evolving area of science is an iterative process and there can be no 'one-size-fits-all' classification of new products.

Other definitions that are considered to be contributors to the borderline problem are found in the adjoining legislation of the medical device regulation and medicinal framework: "placing on the market"; "substantial manipulation"; non-homologous" use; and "derivative". These terms are used by NCAs, and advisory bodies such as the CAT, as a basis for making classification recommendations on when a BTC product ceases to be a BTC product and enters the scope of the medical device regulation or medicinal regulations or ATMP.

The remainder of this section discusses the current impacts of these borderline issues, including impacts on quality and safety, patient access, innovation, and cost.

Divergent classifications and unresolved borderline cases have impacted public health and quality and safety. Examples of this are given below:

- The case study on SEDs indicates a direct correlation between the regulatory approach (classification of a product) taken by a Member State and the ability of patients to access SEDs that conform to a standardised set quality and safety procedures, potentially resulting in geographical inequity in terms of access to products that meet uniform high standards of safety and quality.
- An article in Medical Device Network[122] reported that inconsistent regulation and a lack of access to FMT has caused some patients to undergo dangerous at-home procedures using a family member's faeces and a blender to mimic FMT. This is dangerous as it does not involve screening donor faeces, and the colon or rectum can be damaged during self-administration of an enema.
- One stakeholder reported that whenever it is unclear which regulations apply (as in the case of autologous adipocyte cells), loopholes will put patients at risk of harm as opportunists can exploit the system to create unsafe or non-efficacious products. Another stakeholder reported that businesses on the market are providing what they call "advanced therapies" while circumventing regulatory authorities.
- Diverging interpretations of the legislation across Member States can impact the quality and safety of SED treatments due to differences in preparation standards. Due to the uncertainty in interpreting the legislation for SED treatments, a good manufacturing practice (GMP) approach is not taken uniformly across the EU – and the processing largely depends on the experience of single blood centres according to national or regional BEs[123]. A survey of international production methods used to produce serum eye drops organised by the Biomedical Excellence for Safer Transfusion collaborative highlighted a lack of consensus globally on the technical details (e.g. maximal storage time, dilution of the serum, and temperatures) that influence the quality and characteristics of the final dispensed product[124]. A stakeholder described how they tried to previously set up the option of autologous SED treatments for their patients but had to discontinue this service because – under existing national legislation – the serum had to be processed in a blood

[122] Nawrat, A. (2021). Exploring the challenges of regulating faecal microbiota transplants. Medical Device Network. (Accessed 06 July 2021). Available from: https://www.medicaldevice-network.com/features/exploring-the-challenges-of-regulating-faecal-microbiota-transplants/

[123] Bernabei F, Roda M, Buzzi M, Pellegrini M, Giannaccare G, Versura P. (2019). Blood-based treatments for severe dry eye disease: The need of a consensus. J Clin Med. 2019;8(9):1478. doi:10.3390/jcm8091478

[124] Marks DC, van der Meer PF; Biomedical Excellence for Safer Transfusion (BEST) Collaborative. Serum eye drops: a survey of international production methods. Vox Sang. 2017 May;112(4):310-317. doi: 10.1111/vox.12502. Epub 2017 Mar 23. PMID: 28332214.

transfusion centre, rather than the eye bank itself. The stakeholder explained this affected the quality of the product; despite training transfusionists to produce eye drops, they were still not produced in the same way the eye bank would have. The stakeholder described the impact on patient access where such an arrangement between an eye bank and transfusion centre is required: a patient with severe medical issues seeing an ophthalmologist would have to make several appointments at a transfusion centre for the donation and collection of the eye drops, each costing the patient time/money.

- The classification of pancreatic islets is important given the impacts this has on quality, safety, access and cost. A survey of isolation facilities conducted in 2018 found that every islet isolation centre has its own procedures and processes situated within its unique framework of regulatory issues, donor organ availability and quality, local processing facility requirements, and financial considerations – with implications for the control of the source material, isolation process, quality of the islets obtained and ultimately the graft outcomes[125].

Patient access is negatively impacted by borderline cases and the absence of harmonised regulation of borderline products. Regulatory uncertainty and complexity go hand-in-hand with the problem of borderline products. It is well documented (in journals and in the consultation process undertaken as part of this study), that regulatory uncertainty and complexity create an environment inimical to innovation and creates barriers to the free movement of products across the EU. This, in turn, affects patient access. Stakeholders reported Member States' different quality and safety standards for DHBM impact on cross-border exchange of milk and therefore access. Further examples from specific borderline case studies are given below:

- The FMT case study found that inconsistencies in how FMT is regulated may have negatively impacted R&D of FMT, and potentially resulted in restrictions on access to the treatment[126] where overly stringent regulatory requirements have been put in place. There is a particular issue where a Member State has classified FMT as a medicinal product as the hospitals providing the treatment are unable to comply with, or resource, the regulatory requirements of that legislation.
- A lack of harmonisation can also impact early stage research and development and therefore patient access to novel therapies. For example, to implement a cross-border, multi-centre trial, the ESPOIR consortium[127] spent almost three years obtaining approval for the decellularised heart valve and the set-up of the study from the relevant regulatory authorities and European Network of Centres for Pharmacoepidemiology and Pharmacovigilance.
- The 'unlicensed' status of SEDs reportedly severely restricts how the service can be promoted, affecting patients' access to the SED treatment[128]. A paper by Rauz et al (2017) reported that in the UK (and probably in EU Member States), under existing regulation the absence of robust systems for recording outcomes or implementing

[125] Nano, R., Kerr-Conte, J. A., Scholz, H., Engelse, M., Karlsson, M., Saudek, F., Bosco, D., Antonioli, B., Bertuzzi, F., Johnson, P., Ludwing, B., Ling, Z., De Paep, D. L., Keymeulen, B., Pattou, F., Berney, T., Korsgren, O., de Koning, E., & Piemonti, L. (2020). Heterogeneity of Human Pancreatic Islet Isolation Around Europe: Results of a Survey Study. Transplantation, 104(1), 190–196. https://doi.org/10.1097/TP.0000000000002777

[126] Verbeke, F., Janssens, Y., Wynendaele, E., & De Spiegeleer, B. (2017). Faecal microbiota transplantation: a regulatory hurdle?. *BMC Gastroenterology*. 17. https://doi.org/10.1186/s12876-017-0687-5.

[127] The ESPOIR consortium brought together seven leading European clinics for paediatric cardiac surgery (London, Leiden, Padua, Zürich, Leuven, Chisinau and Hannover), four tissue banks (European Homograft Bank, Deutsche Gesellschaft für Gewebetransplantation, Fondazione Banca dei Tessuti di Treviso and Euro Heart Valve Bank), and an innovative bio-tech company, Corlife oHG.

[128] Chandrasekar, A. (2015). Bringing tears to your eyes: serum eyedrops. Presentation. Available from: https://www.bbts.org.uk/downloads/bbts2016/presentations/akila_chandrasekar_bbts_se_2016.pdf/

withdrawal/stopping strategies, has led to variation in practice and geographical inequity in access to treatment.

- Despite isolated hepatocyte transplantations being considered safer, less invasive, and more cost effective than transplanting a whole organ, confusion of the regulatory pathway prevents their use as an alternative treatment for liver disease. A stakeholder from Sweden agreed the decision to treat isolated hepatocytes as an ATMP has an impact on patient access**.** The main issue is that university hospitals using public funding, and not even considering going into larger processing, do not have the means to meet the requirements for ATMPs (e.g. funding for, and patient recruitment to, clinical studies) and this has led to a standstill of the hepatocyte programme. Linked to this, there may be additional issues around affordability as commercial products.

In addition to borderline issues leading to access restrictions for products, there can also be issues where access to treatments is not restricted enough. For example, many stakeholders in the sector believe patients have too easy an access to unsafe/unproven therapies, e.g. using adipocytes and PRP.

The borderline problem also extends to the operation of the market in terms of innovation, affordability, and the economic viability of the sector. Operators working in this area, when asked in the establishment survey how concerned they were about borderline issues on these areas, expressed significant concerns; 73% stated that they were slightly/very concerned about its effect on innovation, 80% were concerned about the consequences for the economic viability of the sector and 84% were concerned about the implications for costs and affordability. Several respondents noted that overly-restrictive regulation hampers innovation and that in classifying borderline products, it is important to get the right balance between managing risk appropriately and incentivising innovation through proportionate regulation. As reported in the keratinocytes case study, stakeholders argued that although the use of cultured keratinocytes was a well-established process in many TEs, the classification as an ATMP came with significant cost implications associated with achieving marketing authorisation as a medicine.

According to Pirnay (2012) the higher costs of having to comply with the medicinal products legislation put the preparation of these tissue and cell products outside the capability of many TEs, which potentially restricted access to novel tissue and cell therapies that were not of significant commercial interest[129]. Such centrally authorised keratinocyte preparation has not yet reached the market, while the ATMP classification has required TEs to stop their preparation for a duration of several years. A stakeholder consulted for the PRP case study reported that continuation of the current regulatory status could lead to companies exiting the European market as it is too difficult and complex to navigate.

Many of the borderline cases are of limited clinical applicability and therefore of limited interest for commercial companies/entities that see limited scope for return on investment. A high regulatory burden on TEs risks limiting patient access due to affordability issues.

Feedback collected during the consultations frequently referred to that fact that an environment of regulatory uncertainty and complexity is likely to negatively affect investment in R&D and therefore limit innovation in Europe. Innovation in SEDs may be hampered if regulatory issues in this area are not resolved. For example, one stakeholder noted how currently it would be easier to regulate SED treatments if they were paired with a medical device (e.g. a contact lens or gel as a carrier for the SEDs). Although the stakeholder understood that this would depend on whether the device plays a primary/ancillary role or alters the active properties of the substance, it was argued that this could be open to

[129] Pirnay JP, Vanderkelen A, De Vos D, et al. Business oriented EU human cell and tissue product legislation will adversely impact Member States' health care systems. Cell and Tissue Banking

interpretation by some competent authorities if the fundamental and existing regulatory issues were not resolved.

The intrinsic nature of 'novelty' is its uniqueness and as complex novel products emerge there will inevitably be some which, because of the level of novelty, do not clearly fall into one framework or another. Therefore, even with improved definitions and terms in place, some level of regulatory uncertainty is likely to persist as the sector innovates and for innovation to flourish there needs to be sufficient flexibility in the system to accommodate it. The challenge in addressing the borderline problem in the revised legislation will be to get the right balance between safety, certainty and flexibility. Legal texts cannot anticipate every possible eventuality; the problem analysis suggests a role for mechanisms that debate and resolve issues as they arise.

Annex 4: Methodology

This section describes the research methodology. The research agenda was driven by the research questions set by the study specification and the data requirements emerging from the preliminary impact mapping.

This study collected and utilised quantitative and qualitative information from both, primary and secondary sources. Desk research and field work (online targeted consultations and interviews) was used to collect data on prospective impacts and costs (Task 2). The research plan benefited from online participatory workshops (Task 3) and case studies on borderlines (Task 4).

The following sub-sections detail the research undertaken. The data collection primarily focused on closing information gaps and complementing what had already been gathered by the Commission, with the aim of avoiding duplication of effort and minimising respondent fatigue.

A4.1. Desk research – Task 2.1

Task 2.1 collected information and data on the impacts of policy from secondary sources. The desk research involved review of existing documents, analyses and data against the options appraisal framework, including:

- Assembly of data and documentation.
- Data mapping to review and analyse the documentation and data that has already been compiled. This helped to identify the strength and limitation of the existing evidence and confirm the extent of potential evidence gaps and strategies to find alternative evidence or proxies.
- A targeted desk research strategy identified and reviewed additional documentation of relevance to the baseline scenario, policy options and the key indicators described in the research plan.

ICF has mapped the documentation and data assembled during the inception phase of the study and explored the strengths and limitations of using information from these as evidence for the impact assessment. This involved:

- Examining the type of evidence source to understand the strength of evidence available.
- Extracting information on the ‘problem’ and how this relates to the objectives under consideration (to understand the documents relevance).
- Review of each document to identify if there is useful evidence relating to the indicators we have set out, so as to understand what impacts may result under each objective/option/measure.

The mapping found that studies provided rich insight into drivers for change. As expected, few data were available on current and projected administrative burdens and direct/indirect costs. By definition, the desk research could be used to provide results for the criteria that require solicitation of stakeholder opinions on the relative performance of options – these required direct consultation. The desk research was, however, expected to provide information on specific aspects of the measures and their deployment.

In addition to information collected by DG SANTE as part of the targeted consultations, and the information that is already available from the previous evaluation study, the desk research has been particularly relevant to support the development of the baseline.

In total, the study team identified >200 secondary sources (in addition to responses to the DG SANTE public consultations and Terms of Reference) which provide contextually

relevant information, specifically focusing on future priorities and needs (see Annex 12 for a 'snapshot' of the document log). There are few data that project how things might change over the next ten years. This information, however, has been captured through the consultation activities.

Additional secondary data sources include: the results of the Commission's public and targeted consultations that were distributed earlier in 2021 and outputs from a parallel study commissioned by DG SANTE on an IT system proposed in the reform package. Data from ESI funding and EUCCP are expected to be useful in assessing impacts of COVID (e.g. increased plasmapheresis capacity by Member State, evolution of plasma collection). Other relevant data sources include the Tissue and Cell Establishment Compendium, and position papers provided by stakeholders for the project workshops.

The desk research strategy also involved identification of additional source material through engagement with stakeholders. A meeting was held with DG SANTE on 16 July to review gaps in evidence and plan follow up actions. Email exchanges were used to solicit information from various stakeholders on specific measures and data gaps

Sources were logged, interrogated, coded against problems/measures/questions, a summary statement of the contents drafted, and relevant information extracted and stored in a structured spreadsheet to support its incorporation into the analysis.

A4.2. Online targeted questionnaire – Task 2.2

The questionnaires and data requests prepared and distributed under Task 2.2 collected stakeholder views on the different options relevant to the research questions, and gathered data required to develop quantitative estimates of impacts. The research instruments (questionnaires, data requests) were shared with Commission in advance of despatch.

The analysis conducted during the inception phase (specification of data requirements, desk research mapping, etc.) confirmed that the consultations were an important data source for many of the option appraisal criteria – collecting carefully specified primary data on stakeholder opinions' views on the performance of the options, on the cost impacts of the measures, and the expected evolution of current problems over the coming ten years (the baseline scenario). Specific questions were closely focused on the absolute and comparative performance of the policy options, addressing issues not addressed by previous consultations and which could not be answered through review of secondary sources. To mitigate burdens on stakeholders the approach involved:

- Focusing on the essential requirements – keeping the number of questions (and expected response time) within manageable bounds;
- Using different research instruments for different target audients / stakeholder groups, so that the content can be tuned to the issues pertinent to each group;
- Smart design of research instruments – e.g. in the online questionnaire presenting questions on a randomised subset of objectives to avoid high drop-out rates leading to few responses on questions further down the survey questionnaire;
- Where data protection consents allow, inviting responses from engaged stakeholders that have already demonstrated an interest through responses to previous consultations; and
- Using active intermediaries, such as representative organisations to promote / distribution / support consultations.

The table below summarises the strategy. The selection of online survey vs. offline tool was based on prior experience with similar studies. General experience is that NCAs tend to have a preference for offline documents that can be emailed within the organisation and the response built up over time as the institution's position on each point is developed and then approved. Such documents need to be configured to be resilience to attempts to change structure and configuration.

Table 1 – Summary of the online consultation strategy

Stakeholder group	Proposed sampling strategy	Research instrument	Areas of enquiry
Member State competent authorities for BTC Member State Ministries of Health and other relevant regulatory bodies	Direct distribution to all Member State NCAs via Commission's list of NCA contact points	Offline document containing data request + Online survey	Responses on qualitative indicators (health, innovation, fundamental rights) Input factors for the quantification of cost impacts / indicators (focusing on costs to national regulators) Other quantitative data (e.g. scale of inspection activity & BTCs overseen) Financial sustainability questions (fee-raising powers etc). Baseline scenario definition Impact of Covid Other (relevant) research questions
BTC establishments Professionals working in BTC donation and supply and their professional associations Healthcare professionals using BTC in their clinical practice and their professional associations	Distribution via representative organisations, for onward transmission to their membership (e.g. European Association of Tissues and Cell Banking, European Blood Alliance)	Online survey	Responses on qualitative indicators (health, innovation) Input factors for the quantification of cost impacts / indicators (focusing on costs to BTC establishments) Baseline scenario definition Impact of Covid Other (relevant) research questions
EU institutions & other entities specified in the measures (e.g. EDQM)	Direct approach to designated contacts	Online survey	Input factors for the quantification of cost impacts / indicators (focusing on costs to EU entities) Impact of Covid Baseline scenario definition
Other stakeholders: Patients and donors and their associations; manufacturers; upstream / downstream service and equipment suppliers and users; ethics bodies; research organisations/ associations and academia	Distribution to stakeholders that have responded to previous consultations (where consents permit). 'Snowballing' distribution via sector interests and intermediaries.	Online survey	Impact of Covid Baseline scenario definition Appraisal criteria (focus on health, innovation, fundamental rights)
Relevant international organisations Third country regulators Third country representative sector organisations	Direct approach to designated contacts	Online survey	Interface between the proposed options and the interests/mandates of the organisation concerned

The survey for BTC establishments was disseminated via representative organisations. Individual establishments were also able to respond via the open 'wider stakeholder' survey if not affiliated to a representative organisation. This strand of the research was combined with interviews/engagement with selected organisations.

The survey instrument for the wider stakeholder consultation included a question that invites respondents to identify their stakeholder category. The research instruments included a field capturing the respondent organisation's name to facilitate, for instance, cross-check against workshop attendance lists. The survey instrument for the wider stakeholder consultation included a question that invited respondents to identify their stakeholder category.

Respondents to prior Commission consultations for whom the data protection consents provide allow re-contact were sent information about the survey.

The surveys were available for 4 weeks, launched on 28 June and closed on 24 July.

A4.3. Targeted interviews – Task 2.3

Task 2.3 gathered more granular evidence from stakeholders. The overall approach was less structured compared with the online questionnaires, and the interview guides were drafted to enable further follow-up to the consultation and opportunities for more detailed feedback.

A total of nine semi-structured qualitative interviews were conducted. These were used mainly:

- For very specific data requests and related queries (e.g. on funding of measures undertaken at EU level);
- To fill gaps left by the target consultations.

The following stakeholder groups were interviewed:

- A sample of NCAs selecting a diversity of countries and BTC contexts, with the interviews providing an opportunity to explore the impacts on NCAs in more depth. Six interviews with NCAs were organised.
- Five interviews with key EU representative organisations for the BTC sector after agreement with the Commission.
- Interviews/ email exchanges with other impacted organisations.

More information can be found in Annex 6.

A4.4. Participatory workshops – Task 3

The aim of Task 3 was to assist the European Commission to set up and moderate 11 online workshops on specific topics (one more than the 10 required by the project specification). The workshop topics and the invitees were selected by the Commission. The workshops were delivered with the support of the Steering Committee.

The workshops involved Member State authorities, BEs/TEs, health professionals and other stakeholders. They were used to gather input on the IA questions, the baseline, and key elements of the policy analysis and work towards a consensus on key elements.

Evidence from the workshops, including sli.do poll results, verbal contributions from stakeholders and material from papers associated with the workshops formed part of the evidence base used in triangulation of evidence on impacts of options.

Workshop topics and timetable: The workshops took take place between the 27th of April and the 10th of June 2021. The topics of the workshops and dates were agreed with DG SANTE (as outlined in Table 2 below).

Table 2 – Workshops' topics and dates

Workshop topic	Date
Authorising Novel BTC	27 April (morning)
Regulating Point-of-Care BTC Processing (bed-side and same surgical procedure)	12 May (morning)
Strengthening Blood and Plasma Donor Protection	17 May (morning)
Better Protection of Donors for Non-Reproductive Tissues and Cells	17 May (afternoon)
Better Protection of MAR Donors and Children Born from MAR	18 May (morning)
Strengthening Oversight (Inspection, Authorisation, and Vigilance) – Authorities	25 May (morning)
Strengthening Oversight (Inspection, Authorisation, and Vigilance) – Operators	26 May (morning)
Key Definitions - Improvements and Additions	1 June (morning)
Refining the Scope of the BTC Legislation	2 June (morning)
Ethical Principles (Voluntary Unpaid Donation, Prohibition of Profit from the Human Body and BTC Allocation)	8 June (morning)
Borderlines with Other Regulated Frameworks: Classification Advice and Interplay	9 June (morning)

There is a finite number of topics that can be covered within the time available in each workshop agenda. There were trade-offs to be made in setting the agenda, such as discussing impacts or detailed issues of scope and specification on the other. There was also a breadth vs. depth trade-off to consider.

The workshop agendas were developed with these issues in mind, to include

- discussion of the options and solicitation of participants' opinions on the extent to which they expect individual options to address the target problems.
- discussion of topics relevant to the detailed specification of options and their implementation.

The workshop template developed during the inception phase is specified below. Table 3 shows the distribution of roles and activities in Task 3 according to the terms of reference.

Table 3 – Distribution of responsibilities

Organisation	Responsibility
SANTE / HADEA	Agree on the design, agenda and target audience Prepare the list of stakeholders to invite for each workshop Review key documents
Steering Committee	Inputs to design, advice to participants on preparation required and identification of documents to be shared with participants Liaise with the Commission on design and participant briefings Participate, facilitate and co-chair the meetings with the Commission Draft the conclusions (in the summary notes) and validate findings

Organisation	Responsibility
ICF Team	Prepare landing page (registration website), for each meeting Send list of registered participants to DG SANTE, for approval Send confirmation email to confirmed participants (with final agenda, link to the meeting) Send email informing 'rejected' participants who cannot attend Provide the logistics and the organisational support Support the Steering Committee in its tasks Drafting the workshop note.

ICF's three-stage process for workshop organisation was applied, as summarised below.

Stage 1: Planning and organisation before the workshops

Identifying stakeholders

During the Inception phase, DG SANTE provided ICF with a list of stakeholders. The stakeholders contacts indicated in that list were used to select the participants for each workshop and invite them.

Inviting stakeholders

An invitation letter was prepared together with a practical information sheet, containing details such as how to connect to the online workshop. The invitation letter and draft agenda were approved by DG SANTE before distribution. These products followed the template set by the texts agreed for the first workshop, adjusted to accommodate learning points from the first event.

Providing information before the workshop helped ensure that attendees had the opportunity to engage with the material prior to the event and facilitated a more productive meeting. The links to relevant material for preparation were sent to the invitees within the invite.

The study team managed participant invitations through a dedicated tracking system using a study mailbox and live, Excel-based participants' database (this collected registrants' details, such as name, contact details, and organisation). Data were processed in accordance with GDPR requirements).

To ensure an active participation and interactive discussions, the number of participants was limited to maximum two participants per organisation.

Preparing the agenda and key questions for discussion

The Steering Committee, with ICF support, developed the content and format of the workshops in consultation with the Commission, including the preparation of a draft agenda for the workshops and key questions for discussion. ICF advised and supported on questions that addressed the appraisal criteria.

The workshop agenda included presentations and allowed as much time as possible for interaction and critical debate. When specific topics had to be discussed in more detail, sub-groups of participants (to attend breakout sessions) were created. The subgroups composition was defined by the Steering Committee in agreement with DG SANTE.

A standardised agenda structure was used, using the template developed for the first workshop. The questions varied for each workshop but the general structure, timings and approach to break-out groups management was standardised.

Organising logistics for the online workshops

The workshops were organised online and delivered using Microsoft Teams. During the event, an online voting facility (Sli.do) was used to get feedback on specific questions will have to asked to the participants during the workshop.

Preparing a facilitation plan

For the facilitators, ICF and the Steering Committee prepared a facilitation plan to ensure effective facilitation and chairing. The facilitation plan was finalised and circulated in advance of the workshop. The template developed for the first workshop was used in subsequent events.

Stage 2: Running the workshops

During the workshops, the following activities helped ensure successful delivery: overall coordination; support to presentations, chairing and facilitation (Steering Committee); engaging participants; ensuring note-taking and documentation. The events were recorded and Teams transcription tool used to capture the discussions.

Stage 3: Follow-up after the workshops

The notes from the workshops were written up as a report of up to three pages structured according to the workshops programme and acting as a record of the main points discussed and overall conclusions. Steering Committee members reviewed the notes, drafted conclusions and validated the workshop reports. Summaries of the workshop reports are provided in Annex 11.

A4.6. Borderline case studies – Task 4

The evaluation of the blood, tissues and cells directives identified instances of uncertainty relating to the classification and regulation of some borderline substances and products. In looking at the borderline issues, regulatory coherence is to be sought with legislation governing advanced therapy medicinal products[130], medical devices[131], the pharmaceutical legislation[132] and the on-going Pharmaceutical Strategy for Europe process[133].

In Task 4, ICF developed case studies of substances/products with perceived borderline issues. The purpose of this task was to:

- Gather views and evidence on the regulatory history and issues surrounding a range of products and substances, thereby providing insight into the problems/challenges of the current regulatory framework and processes.

[130] Regulation (EC) No 1394/2007 provides the overall framework on ATMPs. The Regulation established the Committee for Advanced Therapies (the CAT) as a multidisciplinary committee, whose primary responsibility is to assess the quality, safety and efficacy of ATMPs, and to follow scientific developments in the field. As of June 2009, the CAT issues scientific recommendations on ATMPs classification.

[131] Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC, and Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU.

[132] References to the 'pharmaceutical legislation' are to Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use and Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency.

[133] Adopted on 25 November 2020, the Pharmaceutical Strategy for Europe aims at creating a future proof regulatory framework and at supporting industry in promoting research and technologies that actually reach patients in order to fulfil their therapeutic needs while addressing market failures. The Communication on a Pharmaceutical Strategy for Europe includes a set of actions which will notably see a proposal for revision of pharmaceutical legislation in 2022. More information can be found online: https://ec.europa.eu/health/human-use/strategy_en

- Explore possible impacts of changes to the existing regulatory framework on resolving existing problems/challenges, and examine the impact of these on outcomes regarding safety/quality, innovation, cost and access. This mainly focused on the Objective 4 measures described in this report.

The case studies also informed the overall impact assessment.

Case studies were selected based on Commission and expert input and discussions. The definition of the core regulatory issue was informed by early inputs from the Steering Committee, DG SANTE and the CAT, and explored and expanded upon as part of the desk research phase, as set out in the table below.

Table 4 – Borderline case studies

Case	Study justification
Human breast milk	Unregulated at EU level and very different across Member States (no regulation, tissue and cell, Medicinal products). Substance can be prepared in a spectrum of ways from minimal processing (pasteurisation) to complex processing (pooling to manufacture fortifiers for addition to DHBM). Also a source of stem cells, and there is a high level of interest from hospitals and from industry (fortifiers). Mode of action nutritional but also therapeutic . Increasing use – for preterm infants. Stakeholders ready with proposals.
Faecal microbiota	Unregulated at EU level and very different across Member States (no regulation, tissue and cell, Medicinal products). Substance can be prepared in a spectrum of ways from minimal conservation through complex processing (enrichment) to genetic manipulation. High level of interest from academia and from industry. Autologous and allogeneic. Increasing use – particularly for Clostridium difficile infection and for bone marrow transplant patients. Stakeholders ready with proposals
Autologous adipocyte cells	Prepared in hospitals and high level of interest from hospitals. Unregulated at EU level unless substantially manipulated (- source of stem cells – ATMP). If adipose cells are not substantially manipulated, then a generic classification cannot currently be decided: this will depend on the intended use of the cells. Can be perceived as excluded from BTC by same surgical procedure exclusion. There are case of non-cultured products that are used in non-essential function. Mode of action mechanical but also regenerative, used in different anatomical locations. Increasing use – thousands in Italy each year. Stakeholders ready with proposals. A lot of use in the commercial sector.
Cultured keratinocytes	Long history of safe and effective use as tissue. Previously regulated at BTC before 2009 – now ATMP (the CAT recommendation accepted in Member States due to the culturing process). Mode of action important: if the keratinocytes were claimed to have a pharmacological, immunological or metabolic action, they were regulated under the pharma legislation before the ATMP Regulation. Of note, these were the type of products that the Commission wanted to get included in the ATMP framework via the 'grandfathering procedure' (transitional period: art 29 of Regulation 1394/2007); this possibility was not used by the manufacturers of cultured keratinocytes. No commercial interest – never been an application for marketing authorisation. Skin banks ready to supply as tissue if allowed.
Cultured limbal cells	Therapy developed in TEs, and evidence of safety and efficacy from work done in TEs. Previously regulated at BTC before 2009 – now ATMP (the CAT recommendation accepted in Member States due to the culturing process). The CAT has authorised a product based on cultured limbal cells (Holoclar) but very low level of access due to cost. The CAT also reviewed one more marketing authorisation application of such type of products (application withdrawn by the applicant before approval). Eye banks ready to supply as tissue if allowed. Mode of action relevant to the intended indication is important: if the limbal cells were claimed to have a pharmacological, immunological or metabolic action, they were regulated under pharma before the ATMP Regulation.
Demineralised bone (with or without the addition of gel or putty)	Large volumes produced for wide range of indications. Discussion at the MDCG subgroup Borderline and Classification on whether tissues from which cells have been removed (or rendered nonviable) should be considered as 'derivatives' and should therefore fall under the new Medical Device Legislation. If the tissues or cells or their derivatives is principal and not ancillary to that of the device and the product is not governed by Regulation No 1394/2007, the product shall be governed by Directive 2004/23/EC. Commission Survey in 20019 indicated that 11 Member States regulate as tissue and cell, 1 as MD and 1 as MP. Produced on Commercial Scale (not by public sector TEs). Many are marketed as medical devices. May be supplied imported directly

Case	Study justification
	to hospitals / dentists without knowledge of NCA or requirement to fulfil the tissues and cells legislation.
Decellularised dermis	Used for a range of skin replacement treatments, including burns and for aesthetic surgery. Discussion at the MDCG subgroup Borderline and Classification on whether tissues from which cells have been removed (or rendered nonviable) should be considered as 'derivatives' and should therefore fall under the new Medical Device legislation. A Commission survey of EU tissue and cell competent authorities indicates the following current situation: 13 regulate under the tissues and cells legislation 7 have no current regulation or do not have therapy.
Decellularised heart valves	Very different across Member States (tissue and cell, Medicinal products, arguments for medical device (– no viable cells – derived from tissue)). Valves are prepared by enzymatic digestion of human tissue (potentially considered substantial manipulation?). Interest from academia and from industry. Industry funded by H20:20 in DE where it is classified as medicine – public sector see it unfair competition. Stakeholders ready with proposals
Platelet rich plasma (and related products e.g. fibrin)	Unregulated at EU level, prepared in hospitals and used in different anatomical locations. Excluded from tissue and cell legislation by same surgical procedure exclusion and from blood legislation as 'not used for transfusion'. Very wide usage across EU. Mode of action mechanical but also healing/clotting. Is the device authorisation enough? Can be combined to create a point of care device.
Serum eye drops	Prepared for patients with dry eye syndrome – usually stored and applied at home by the patient. Significant benefits for patients in comparison to commercial eye drops. Potentially could fall under the scope blood directive as it applies "to the collection and testing of human blood and blood components, whatever their intended use …" as defined in Article 2 of Directive 2002/98/EC. Many BEs and some TEs collect prepare and supply the product. A Commission survey of EU tissue and cell authorities in 2019 indicated that 7 Member States regulate under the blood legislation 3 apply tissue and cell requirements 3 regulate as a medicinal product (non-ATMP) 8 Member States do not regulate. Originally autologous product, more recently allogenic. UK, Germany and IE regulate under 'Specials' Licence and 'Exempt Medicinal Product' – Both require a Manufacturing Authorisation – restricts availability as BEs need to obtain BE Authorisation and MA. Regulatory requirements need to be proportionate.
Isolated Hepatocytes	To assist liver transplant patients – acts as a 'bridge' until transplant. Affects a specific group of patients. Hepatocytes have been considered ATMPS as enzymatic digestion results in single cell dispersion and this treatment is known to change the cells characteristics (surface markets, genome expression profile). The CAT has reviewed a marketing authorisation application for Hepatocytes (Heparesc), for the treatment of urea cycle defects. This product was previously classified as an ATMP based on substantial manipulation of the cells: the extensive enzymatic digestion is resulting in the generation of a cell suspension (dissociation to the single-cell level), which has been reported in scientific literature as resulting in substantial changes to the characteristics of cells (cell markers, etc). This is the scientific rationale to consider extensive enzymatic digestion (to release single cells) as a substantial manipulation.
Pancreatic islet cells	Used as an alternative to pancreas transplantation in patients with type 1 diabetes. The CAT considers that these fall within tissue and cell Directive as they are only undergoing a mild enzymatic digestion, aiming to release the islets from the surrounding tissue. As the islets are maintain their functional characteristics as a tissue after enzymatic digestion, this treatment is not considered a substantial manipulation: Pancreatic islets as such are therefore not considered ATMP, provided they do not undergo additional manipulations (e.g. to isolate the beta cells from the islets, and incorporate these in structural/semi-permeable scaffolds). Question if ruling on enzymatic digestion without expansion is consistently applied across sector. Also falls within 'same surgical procedure' discussion – pancreas may be removed to laboratory for processing. No commercial interest. Prepared in hospitals only.
Chondrocytes	Chondrocyte containing products have always been ATMP due to the culturing process. Only before 2009, they might have been classified differently. Of note, these were the type of products that the Commission wanted to get included in the ATMP framework via the 'grandfathering procedure" (transitional period: art 29 of Regulation 1394/2007); this possibility was used by some of the manufacturers. In the meanwhile, the CAT has approved 3 chondrocytes containing product. But also included in EDQM Guide, and numerous Articles refer to classification of this chondroselect as ATMP being too restrictive and costly and resulted in withdrawal of MAA in 2016. Could this product be more effectively regulated under a revised tissue and cell framework?

Case	Study justification
Extra-cellular vesicles (EVs)	Complex, novel products whose use as new therapeutic modalities are only now being explored - there is no existing regulatory approach. The CAT interpretation is that if there is a therapeutic claim, they would be medicinal products. There have been cases of EVs from genetically modified cells and this has been classified as gene therapy because they were considered the vehicle for the recombinant nucleic acid.
Consolidated case study examining the ATMP classification process	This case study covers five products in detail. Two of the products of interest (Autologous bone marrow cell aspirate, concentrated and Banked leukocytes with cancer killing activity) have been classified as an ATMP by the CAT, but the other three (Human allogeneic amniotic membrane, sterile, cryomilled and lyophilised; MA-Omental Film; and Modulated immune cells) have not. Note: The final case study was originally intended to cover all five products separately, but following discussions with the CAT and DG SANTE it was agreed this would form one consolidated case study to examine the ATMP classification process in greater detail.

Work on the case studies was phased over time and began with a period of piloting to confirm the methodology and final reporting.

Scoping research

The Commission and Steering Committee helped to: (1) define the parameters of the issue being considered; (2) develop the team's understanding of the regulatory issue (both broadly and in reference to the specific substances being considered); and, (3) inform the data collection approach (e.g. by suggesting stakeholder to interview and identifying relevant literature).

Data collection

This consisted of:

- **A rapid desk review** to provide further information on the regulatory issue. A targeted approach was taken, with priority given to the most relevant literature. Further information and data was also obtained from ad-hoc exchange with stakeholders by email.
- **Semi-structured interviews** conducted with experts who had a comprehensive understanding of the regulatory issue and with whom we could explore in depth how each problem might change or evolve considering the range of policy options. To reduce respondent fatigue, some interviews were grouped to cover a range of borderline substances/products based on the experts' knowledge and expertise. The final list of interviewees was confirmed with the Commission. All interviews were conducted remotely; stakeholders were invited to take part via email.

All interviewees were sent a descriptive list of measures to hypothesise the possible impact of these with specific consideration to the borderline product/substances under consideration. In addition to asking for more information on the regulatory problem, the main questions to be investigated during the interviews were:

- Compared to the baseline ('doing nothing'), how do you think the measures might support resolution of the borderline issue in question? Are there any measures which could be improved or are redundant (not needed)?
- Which policy option model works best for resolving this/similar borderline issues when combined with the measures? Why?
- Compared to the baseline ('doing nothing'), how might the options/package of measures impact on the following issues? Quality and safety (for patients and donors), affordability, patient access, transparency, innovation, self-sufficiency and sustainability.

- How much would costs increase or under each of the different measures compared to the baseline ('do nothing')? (e.g. direct compliance costs, administrative burdens, costs to regulators to implement the rules, other costs).

Case study development (analysis and writing)

Analysis: The first step was to qualitatively assess the impacts of the policy options on the borderline issues. The second step was to estimate the potential improvement that could be made in each case based on the data collected. Interpretative synthesis of the different data sources provided the basis for the analysis of each case study.

Reporting: The case studies were written up using a common template in a style which that supported the analysis and offer interesting information for readers. The template was intended to help focus on (i) the specific problem and (ii) the benefits of resolving it. Information available from the case studies was also analysed to provide answers to the relevant study questions in the research plan (primarily under Objective 4). This activity was undertaken by in close consultation with the case study researchers. The case studies were checked by the Steering Committee prior to submission.

A4.7. Analysis and synthesis

Overall, diverse data sets were accessed and evaluated in the study. These ranged from data on BTC establishments and scale of use of BTCs, to indicators of health status, and cost information and survey data through to qualitative information gathered from interviews and workshops.

Data sets were subject to appropriate methods of analysis. Examples are:

- Structured analysis of Tissue Compendium data to develop a profile of the tissues sector by Member States, BTC authorised, etc.;
- Structure analysis of comments provided by stakeholders in open text responses within the surveys;
- Interview evidence gathered for the borderline case studies;
- Review of qualitative data collected from workshop discussions; and
- Scrutiny of cost data supplied by companies and NCAs to provide figures for input factors to the costing analysis.

The individual blocks of analysis were subject to internal review and cross-check.

The outputs of the various research tasks were then brought together in the synthesis stage. This informed descriptions of the comparative performance of the different options (as compared to baseline) and considered their efficiency, effectiveness, coherence etc.

The sources of evidence used in development of answers to each of the impact assessment questions have been specified. For most of the option appraisal criteria, multiple statistically significant data sets are not available. Source data used in the development of answers was provided to the Commission at the end of the study (anonymised where necessary to comply with consents). Statements of impact have been developed for each option based on evidence gathered during the research phase.

The methodology used in the costing of impacts is description in Annex 5. This includes description of the input factors (such as the assumed unit cost of labour), or the amount of time required to complete a task that would be required under the reformed legislation, and where the information used came from (its derivation). This provides the transparency needed for stakeholders to understand how the overall cost calculations have been developed, and reproduce them if necessary.

Cost calculations have been built up on a measure-by-measure basis. The data requests in the targeted consultations were designed to elicit the necessary information, complemented by results from the desk research as needed.

The calculations are expressed as change versus the baseline. Where the research has determined that there is significant uncertainty about significant input factors that influence cost then we will ranges have been used to appropriately capture the uncertainty.

Costs have been expressed in real terms (2021 €).

The Better Regulation Guidance's discount rate has been applied and costs projected for a ten year period from adoption of the legislation.

Baseline scenario

A baseline scenario was elaborated, looking forward over the coming ten years. This has been described in narrative form, by reference to the problem drivers and key issues, with quantitative data provided where relevant and available. Examples of topics of interest are expected trends in innovation, expectations for market demand for different BTC applications and cross-border exchanges. The research findings on the impacts of COVID-19 on the BTC sector formed a contribution to the baseline. Baseline estimates for certain quantitative criteria were specified based on research outputs.

Assessment framework

The figure below provides a schematic high-level representation of the assessment framework.

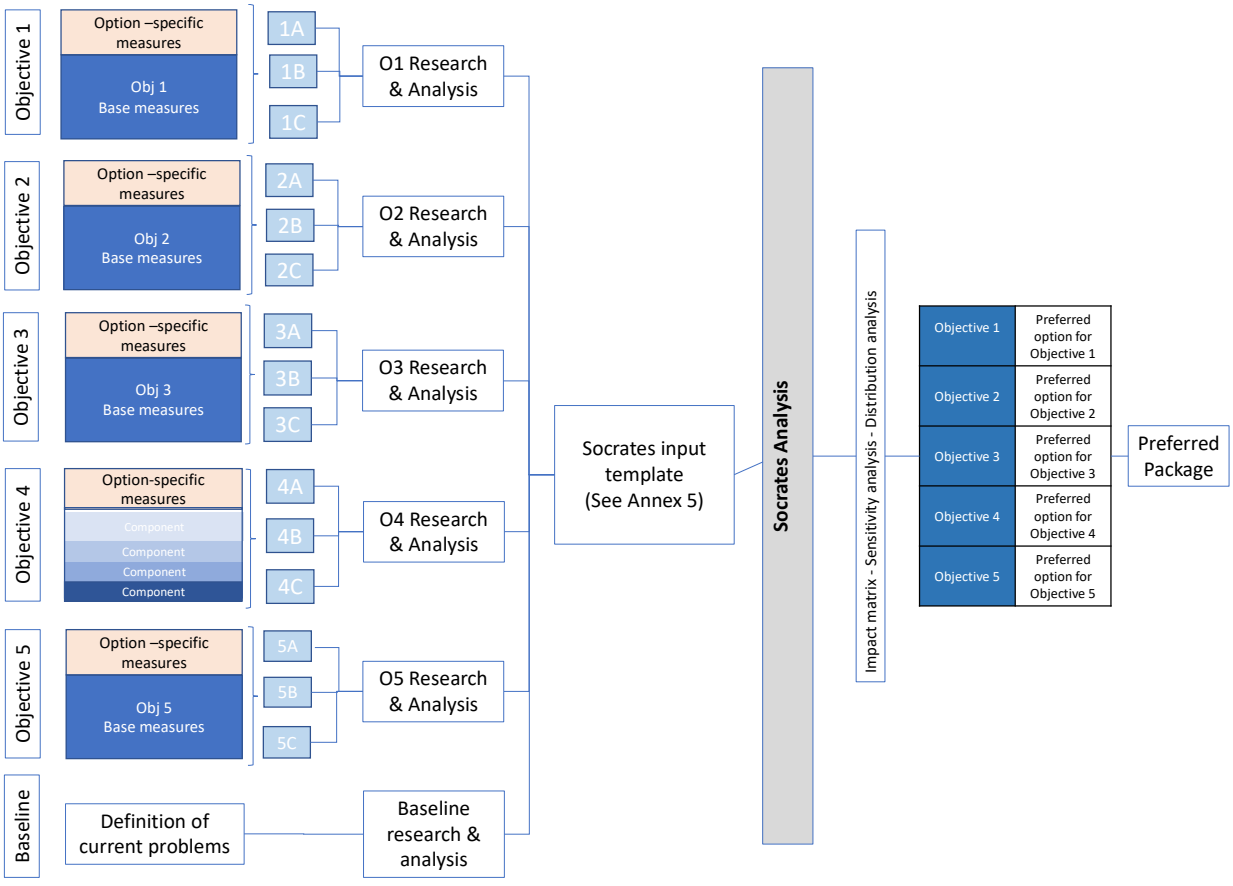


Figure 1: Schematic representation of the assessment framework

The study specification stated that the multi-criteria assessment would be managed within the Joint Research Centre's SOCRATES[134] software tool. The contractor was required to provide the input matrix which specifies the impact (value) for each of the criteria. Criteria are related to policy measures, and fall under the policy options (including the baseline). Significant effort was invested in the development of these criteria, and to considering how to structure the analysis.

The agreed criteria for SOCRATES input template were developed on a co-production basis with the Commission through an iterative process informed by the intervention logic and discussions about the different aspects of the problems/problem drivers that the options would be seeking to address.

The matrix was further developed after submission of the first and second draft interim report (July 2021 and September 2021 respectively), benefitting from inputs from the Steering Committee.

In brief:

- Measures were packaged into options. For each objective there was at least one option. Objective-level options were assessed as complete packages (for example, 3A vs 3B vs 3C).
- There was a distinct set of criteria for each specific objective, tuned to fit the problem being targeted defined in each case.
- The SOCRATES tool was intended to be used to identify the optimal composite policy option that addresses all objectives. While this was processed as a single appraisal, the process was set up to provide the 'best option for each objective, not simply an 'Option 1 vs. 2 vs. 3' appraisal in which an option in which (for instance) a decentralised solution to achieving all objectives is compared with a centralised approach to or all objectives. Results of the analysis showed the performance of the objective-based policy options by criteria. This allowed determination of the best response (decentralised regulation, joint regulation, or centralised regulation) for each objective and thus definition of the preferred overall composite option.

The outputs of the multi-criteria analysis could thus provide advice on the best overall policy option from the initial set, and suggest improvements on that option by including elements from the others where they performed better on a specific criterion. This optimal, mixed policy package would indicate which strategic approach is preferred to achieve each measure.

Following submission of the draft interim report, the Commission explored the potential of a best 'composite' policy option with the aid of SOCRATES through simultaneous appraisal of the decentralised, joint and centralised regulation options identified for Objectives 1 to 5 (with impacts assessed versus the baseline). This appraisal concluded that there was no mix of decentralised / joint / centralised regulation for the different Objectives that yielded outcomes better than the original options. As a result – on the instruction of the Commission - a fourth option was not subject to further elaboration.

Monitoring and evaluation indicators

The contractor was required to provide advice on the monitoring and evaluation (M&E) framework for the legislative reforms. This is framework is described in the main text of the report and presented in Annex 10. The *ex post* indicators follow the overall structure of objectives/measures and their description also include the data source.

[134] SOcial multi-CRiteria AssessmenT of European policieS

The M&E framework can be set up to collect data on outcome indicators that are important measures of the efficacy of the reforms but cannot be quantified with data available to the current study.

Reporting

Interim and final reports are prepared as specified in ICF's offer of services. Content plans were circulated in advance to help provide clarity on the structure and content before drafting of the documents.

Data handover

Data and documentation gathered during the study was transferred to the Commission on completion of the work, anonymised where required for consistency with research consents.

Annex 5: Costing methodology

This annex sets out the methodology and sources used to estimate the costs presented in the main report.

A5.1. General Approach

A5.1.1. Sources

The assessment of the costs was carried out using multiple sources and triangulating data when possible. The main sources used have been:

- **Desk research:** This included analysis of data from the European Commission's Public Consultation surveys; and data from the Reference Compendia for the Application of a single European Coding System for Tissues and Cells.
- **Cost inquiry for Establishments:** The online inquiry targeted at representative organisations and establishments included a set of questions on the costs incurred by establishments for complying with the current regulations. The survey received 40 (partial) replies from organisations from 14 countries[135].

- Approximately half of the replies came from establishments only handling tissues (20). Only a few responses were from establishments only handling blood (3) or establishments handling both blood and tissues (6).
- The remaining replies came from human breast milk banks (5) and other organisations (other SoHO banks and professional associations).
- Replies to the cost enquiry included public and non-for-profit organisations (14 and 10, respectively). Replies from commercial organisations (16) mostly concerned MAR establishments (e.g. fertility clinics).
- Replies were received from micro and small organisations (11 and 10 respectively), medium-sized (12) and, to a lesser extent, large organisations (7).

- **Cost inquiry for Regulators:** A cost inquiry targeted at regulators (NCAs) was designed to collect information on the status of implementation of measures (i.e. The extent to which measures proposed are already implemented) and on potential costs incurred by new proposals. This provided (partial) replies from regulators in 12 Member States[136].
- **Follow-up activities with Regulators:** Following receipt of information from the surveys and cost inquiries, interviews were conducted with NCAs in four Member States (Austria, Italy, the Netherlands and Spain) to gather additional details and complement information provided via the cost enquiry.

  Additionally, emails were sent to 23 NCAs to confirm the status of implementation of key measures (i.e. the extent to which measures proposed are already implemented). 15 replies were received, which enabled clarification of information

[135] These include 11 EU Member States, namely Austria, Belgium, Denmark, France, Germany, Greece, Italy, the Netherlands, Poland, Portugal, Spain, and non-EU countries: UK, Turkey and US. More information is available in Annex 6.

[136] These include Austria, Bulgaria, Denmark, Estonia, France, Germany, Ireland, Italy, Netherlands, Slovenia, Spain, Sweden.

and collection of information from additional Member States, thus improving the accuracy of the assessment of the baseline[137].

- **Stakeholder consultations:** The exercise also benefited from information collated from other stakeholder consultations carried out as part of the study, in particular from workshops.

A5.1.2 General assumptions

Dimension of the BTC sector

The desk research (Annex 12 and Annex 13.1 provide an overview of the main documents and data analysed) and the analysis of the Compendium data (Annex 13.3) gave a baseline estimate of the current numbers of establishments operating in the BTC sector. It was estimated that there are currently approximatively **4658 regulated BTC establishments**.

- Based on the analysis of the Compendium data, the current total number of establishments operating in the tissue and cell sector is 3258. Amongst those, 1716 are specifically authorised for MAR activities. 63% of all TEs are based in four Member States (France, Germany, Italy, Spain). The 37% remaining establishments are based in the other 23 Member States.
- Based on literature research, it was estimated that there are currently 1400 establishments operating in the blood sector. In the absence of specific data, the same geographical distribution was assumed as for TEs.

The estimation of the number of BTC/SoHO establishments that might be impacted by the extension of the EU legislation (relevant to measures under Objective 1) is subject to a degree of uncertainty. Based on literature research, our estimates suggest that there are currently about 300 additional establishments which will be impacted (approximately 6% of the total BTC sector), covering breast milk and FMT. However, no sources were identified to evidence the number of establishments utilising SoHO for non-therapeutic use (e.g. the use of PRP for cosmetic purposes). Therefore, the estimates for these measures are quite conservative.

The study also estimated that there are 50[138] NCAs responsible for oversight of BTC establishments in the EU. In some countries, regional authorities are also directly involved in the implementation of the BTC regulatory framework. For the purposes of this study, regional authorities were excluded from the cost estimations because they are not directly responsible for the transposition of EU legislation in the BTC sector, nor for the design of national measures necessary for its implementation.

Labour costs

The cost inquiry exercise requested NCAs and BTC establishments to provide average salary costs of staff who might be involved in the implementation of the new measures.

The ratio of the annual salary costs of relevant staff on the real GDP per capita[139] was then calculated for each Member State that provided sufficient data. The average of the percentage difference between annual salary costs of relevant staff and real Gross

[137] Follow-up emails were sent to officers in NCAs of several Member States, that had been contacted for the survey and for other tasks of the study, namely: Belgium, Bulgaria, Croatia, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Lithuania, Netherlands, Slovenia, Spain, and Sweden. Replies were provided by: Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Italy, Lithuania, Netherlands, Poland, Spain, Sweden (answers for Austria and Italy were confirmed via interviews).

[138] The full list is provided in Annex 13.2.

[139] Available from: https://ec.europa.eu/eurostat/databrowser/view/sdg_08_10/default/table?lang=en

Domestic Product (GDP) per capita was then calculated for those Member States in which data from establishments and NCAs were made available.

In those Member States in which NCAs and establishments failed to provide data, the above percentage differences were used as a factor to derive estimated annual salary costs for relevant staffs from the real GDP per capita data.

Using the average estimated salary costs of relevant staff across all Member States, daily labour costs were then derived from:

- Applying an assumption of 220 working days per year
- Applying an uplift of 100% to cover non-salary employer costs (pensions, benefits) and overheads.

Daily labour cost are thus: (relevant staff annual salary/220) x 2. The uplift factor is not specified in Better Regulation Guidance (no guidance on unit time cost build-up, allowing for overheads, is provided) but has been accepted when used by ICF in previous impact assessment support studies. The table below provides an overview of the key data points for labour costs used throughout the cost estimation.

Table 1 – Labour cost factors – applied to all relevant measures

Cost factor	Salary	Daily cost factors inclusive of non-salary employment costs and overheads*	Source
NCA - Inspector	62,000	347	NCA survey and Eurostat
NCA – other	28,045	255	NCA survey and Eurostat
Establishments	46,218	420	Establishment survey and Eurostat
EU institutions	152,000	691	DG Budget

*Note: *2x multiplier applied to salary costs, 220 working days assumed*

A5.1.3 Other costs of implementation

Respondents to the NCAs and establishments cost inquiries were asked for information on any additional costs related to the measures, such as travel and training costs. When such information was provided (by at least three respondents from different Member States), they were included in the relevant estimations.

It was assumed that the additional costs apply in half of the relevant cases (i.e. half of the NCAs and half of the establishments impacted by the measure).

While this parameter is not specified in Better Regulation Guidance (no guidance on additional costs is provided), it has been used previously by ICF in impact assessments support studies and accepted.

Cost factors used to cost certain measures for EU institutions, discussed and agreed upon with EU services are:

- Expert subgroup meetings: EUR 22,000 each;
- Expert group meetings: EUR 28,000 each;
- Expert fees (for preparatory work): EUR 400 per person/day.

A5.1.4 Ten year projections

The study is looking at the impact of the various measures over a ten year period. Based on the information gathered from consultation and other evidence compiled, it was assumed that the structure of the BTC sector in Europe will remain the same for the next ten years.

Alongside the desk research, the stakeholder consultations (specifically the ICF online inquiries, workshops and Commission Public and Targeted Consultations) informed the study to varying extents, providing assumptions about the growth of the BTC sector itself over the next ten years.

The main projections identified are described below:

- Consulted stakeholders were generally of the view that the blood sector will remain relatively stable. To estimate the number of BEs in ten years, we looked at the population growth projection[140] in each Member State and applied the same growth factor to the number of establishments.
- Consulted stakeholders were generally of the view that the tissue and cell sector will grow in the coming decade. This is particularly the case for the MAR sector. To estimate the number of TEs in ten years (excluding establishments operating in MAR activities), we applied the same logic as above, adding a factor of 1% on top of the projected population growth percentage. To estimate the number of MAR establishments in ten years, we applied again the same logic, adding a factor of 2% on top of the projected population growth percentage.
- In addition, based on discussions with the Commission, it is estimated that as an effect of the provisions introduced, about 750 TEs will lose their 'establishment' status and instead become 'entities' that are subject to different (less strict) requirements. This change (impacting about 600 establishments in tissue and cells sector and 150 in MAR) has been reflected into the projections over time.
- It was assumed that the overall geographical distribution of all establishments would remain the same: 63% of all BTC establishments are based in the four largest Member States (Germany, France, Spain, Italy); the 37% remaining establishments being based in the other 23 Member States.

The table below provides an overview of the key data points for labour costs used throughout the cost estimation. The figures take into account the expected impact of the proposed measures.

Table 2 – BTC sector – Current population and projections over ten years

Type of establishments	Current population	Population in ten years (projection)	Average over ten years
BEs	1,400	1,420	1,410
TEs	3,258 (excl. MAR 1,542)	3,047 (excl. MAR 2,236)	3,153 (excl. MAR 1,889)
MAR establishments	1,716	1,022	1,369
Other SoHO establishments	300	304	304
NCAs	50	50	50

[140] https://ec.europa.eu/eurostat/databrowser/view/tps00002/default/table?lang=en

In accordance with the revised version of the Better Regulation Guidelines and in agreement with DG SANTE, a 3% **social discount rate** was applied.

A5.1.5 Baseline scenario and costs of measures

The baseline scenario defines the expected evolution of the BTC system (and the problems of concern within it) in the absence of additional EU intervention.

For each of the five identified gaps, a baseline scenario was determined to understand which Member States already implement what is proposed under each of the main areas covered by the proposed EU reform and to which extent these Member States have already put in place these provisions. This analysis allows for the identification of those countries for which the EU proposals will require incremental spending.

As a first step, we conducted a mapping exercise. Based on the information collected via the cost enquiries and the follow-up activities, we obtained a mapping of the *status quo* for the key measures in 15 Member States. For the remaining Member States, we assumed that half of them already implement the measure under consideration in some form. This basic assumption was then applied to define the baseline and the incremental costs incurred by NCAs and establishments for the proposed measures under consideration. To assess the number of NCAs already implementing the measure (and thus, by difference, the ones least impacted by the provision), a simple proportion was applied to the overall number of NCAs identified (50)[141]. For establishments, we combined the results of the mapping exercise with data on the geographical distribution of BTC establishments.

For each of the five Objectives covered by the study, we collected the following data points:

From NCAs:

- on the current volume of activity (e.g., number of BTC establishments regulated by NCAs, number of inspections, number of inspectors)
- the costs related (e.g. salary costs for inspectors and other relevant staff, any indirect major costs related to the activity, such as equipment or IT) and;
- financial resources available (to have a basis for assessing the financial viability and sustainability of the system).

From establishments:

- current type of activities (e.g., processing of one or several BTC products, Member State(s) where the establishment is located)
- structure of costs, e.g., number of FTEs and related salary costs, other operating costs, such as equipment or IT.
- efforts and costs related to the current inspection regime, e.g., person-days necessary to prepare for, receive and follow-up inspections (to be combined with the data on salaries), other costs related to the current BTC inspection regime (such as equipment or IT).

For each of the five Objectives, the baseline costs were estimated based on the following general formula:

- **Establishments:** {(Level of Effort (in person days) * Labour cost) + additional costs in half of the cases} * estimated number of establishments already having the provision in place

[141] See full list in Annex 13.2

- **NCAs:** {(Level of Effort (in person days) * Labour cost) + additional costs – in half of the cases} * estimated number of Member State already having the provision in place

The labour cost input factor used incorporates a provision for non-salary employment costs and an allowance for overheads, as described above.

Table 3 – Baseline costs per objective (over ten years)

Objective	Stakeholder	Cost of the baseline (EUR thousand)	Source
Objective 1 – Patient protection	NCAs	10,245	NCAs survey, follow-up emails and interviews
	EU institutions	9,197	Interviews with EU services
	Establishments	36,770	Establishments survey, follow-up emails and interviews
Objective 2 – Oversight	NCAs	106,030	NCAs survey, follow-up emails and interviews
	EU institutions	6,154	Interviews with EU services
	Establishments	239,049	Establishments survey, follow-up emails and interviews
Objective 3 – Donor protection	NCAs	30,686	NCAs survey, follow-up emails and interviews
	EU institutions	13 (many activities included in Obj. 1 already)	Interviews with EU services
	Establishments	531,260	Establishments survey, follow-up emails and interviews
Objective 4 – Innovation	NCAs	62,177	NCAs survey, follow-up emails and interviews
	EU institutions	333	Interviews with EU services
	Establishments	451,136	Establishments survey, follow-up emails and interviews
Objective 5 – Supply monitoring	NCAs	3,382	NCAs survey, follow-up emails and interviews
	EU institutions	(activities included in Obj. 1 already)	Interviews with EU services
	Establishments	58,689	Establishments survey, follow-up emails and interviews

A5.1.6 Costs estimations of measures

Cost types included in the estimation

As agreed with DG SANTE, the cost estimation exercise focused on the **direct costs of regulation**, and in particular on:

- Direct compliance costs, i.e. costs that need to be borne to comply with the provisions of the regulation. Within this category, it was agreed to focus on the adjustment costs, which encompass those investments and expenses that businesses, citizens, or public authorities have to bear in order to adjust their activity to the requirements contained in a legal rule; and on

- Enforcement costs, i.e. costs associated with activities linked to the implementation of an initiative such as monitoring, inspections and adjudication/litigation (which are thus recurring costs).

It was agreed that the monitoring/reporting costs related to the measures considered (e.g. monitoring adverse events for MAR/ follow-up for children under Objective 3, activities related to oversight under Objective 2 and activities related to supply monitoring under Objective 5) should be placed under this category, as opposed to administrative costs[142].

When 'hassle costs' are incurred (e.g. resulting from unnecessary waiting time, delays, redundant legal provisions, corruption), these are not monetised, as per the Better Regulation Guidelines.

The costs that the policy measures and related options are expected to trigger have been calculated for three stakeholder groups, namely 1) EU institutions, 2) NCAs, and 3) BTC establishments.

Estimations of costs for EU institutions

Costs for the EU institutions include costs incurred by the EU Commission and by EU agencies (ECDC and EDQM) in the baseline scenario and under the measures under consideration.

These costs include the labour costs, costs for organising meetings and coordinating activities, costs for IT platform, funding (from the EU Commission to the expert bodies).

The costs for EU institutions were collected via exchanges and interviews with DG SANTE and relevant agencies (e.g. ECDC).

The costs for the IT platform were supplied by the SoHO-X Feasibility Study[143] prepared for DG SANTE. Consistent with the SoHO-X Feasibility Study, we assumed that the maintenance costs represent 30% of the development costs for the IT platform.

The same IT platform is to be developed for Objectives 1, 3 and 5, therefore the related costs are presented only once (under Objective 1), to avoid double counting. As discussed with DG SANTE, the costs for this IT platform correspond to the costs of the platform defined as 'New single system' by the SoHO-X Feasibility Study, while those for the IT platform under Objective 2 correspond to the platform defined as 'Upgrade and connect'. Finally, the costs for the IT platform under Objective 4 were estimated by the GAPP project.

Estimation of costs for NCAs

Where quantification was possible, estimates of specific costs are based on data (number of activities, frequency, salary and other costs) provided by Member States that already have measures similar to those proposed in the EU legislative reforms. The identification of the number of Member States (and NCAs) impacted by the measures followed the approach described above. For example, the costs incurred in Member States that require contingency plans provide a basis for estimation of the costs of implementation of contingency plans in Member States that do not.

The calculation of **adjustments costs** for NCAs was based on the following general formula: *{(Level of Effort (in person days) * Labour cost) + additional costs in half of the instances} * number of NCAs affected*

[142] Administrative costs are those costs borne by businesses, citizens, civil society organisations and public authorities as a result of administrative activities performed to comply with administrative obligations included in legal rules.

[143] European Parliament, DG DIGIT, DG SANTE, 'Feasibility study on the implementation of a SoHO-X data system', Unpublished

It was assumed that the adjustments costs would be incurred by NCAs during a three-year period. Adjustments costs were therefore distributed over three years and discounted.

The calculation of **enforcement costs** for NCAs were based on a general formula: *{(Level of Effort (in person days) * Labour cost) + additional costs in half of the instances} * number of NCAs affected*

It was assumed that enforcement costs would occur during the ten years period considered by the impact assessment. This approach has been used by ICF in other studies accompanying impact assessments and accepted.

Estimation of costs for establishment

Where quantification was possible, estimates of specific costs are based on data (number of activities, frequency, salary and other costs) provided by establishments operating in Member States that already have measures similar to those proposed in the EU's legislative reforms. The identification of the number of establishments impacted by the measures followed the same approach described above. For example, the costs incurred by establishments in Member States that require contingency plans provide a basis for estimation of the costs of contingency plans in Member States that do not.

The calculations of **adjustments costs** for establishments were based on the following general formula: *{(Level of Effort (in person days) * Labour cost) + additional costs} * number of establishments affected*

It was assumed that the adjustments costs would be incurred by establishments during a three-year period. Adjustments costs were therefore distributed over three years and discounted.

The calculations of **enforcement costs** for establishments were based on a general formula: *{(Level of Effort (in person days) * Labour cost) + additional costs} * number of establishments affected*

It was assumed that enforcement costs would occur during the ten year period considered by the impact assessment. This approach has been used by ICF in other studies accompanying impact assessments and accepted.

A5.1.7 Costs estimations of Options

The assessment of the different options under each objective have been calculated similarly following a consistent and relevant general approach.

For each of the five Objectives, the study considered three Options which define the different ways the measures would be implemented:

- Rules based on a decentralised approach, which corresponds to Option 1;
- Rules established (and updated) by an EU expert body, which corresponds to Option 2; and
- Rules included in EU legislation, which corresponds to Option 3.

The results from the cost inquiries and the stakeholders' consultations show that when proposed measures are already in place in Member States, they are generally provided in national legislation and/or from NCAs and informed by the best available scientific evidence and publications from EU expert bodies such as the ECDC/EDQM.

This evidence is therefore the best proxy to understand and estimate what would happen under the implementation rules of Option 2.

Based on the data available and the stakeholders' consultation, a set of parameters were chosen to reflect the different implementation of measures in Option 1 and Option 3, relative to Option 2 (as the current situation is a closer proxy for Option 2).

Cost Estimation for Option x.1

EU institutions

Adjustment costs are mainly represented by the costs for the IT platform.

Enforcement costs are expected to remain unchanged compared to the baseline. In the case of Objective 3, it is expected that Option 1 will generate a slight increase in the effort (and thus costs) for elaborating guidelines. The enforcement costs for the maintenance of the IT platform are expected to be the same under Options 1, 2 and 3.

NCAs

Adjustment costs are assumed to be the same under all options for NCAs. It is likely that, under Option 3, especially, NCAs will have to implement legislative action to include the EU rules in the national legislative framework (e.g. designing the framework). However, these are likely to depend to a large extent on the form chosen for the EU rules and on the legislative process in each Member State, so it was not possible to define costs at the moment.

Enforcement costs incurred by NCAs are factored by 1.5 in Option 1 compared to Option 2. This is based on the evidence that under Option 1, establishments are responsible for setting their own rules. It is expected that this will increase the variability in establishment's rules and therefore NCAs will incur higher enforcement costs, having to familiarise themselves with different frameworks (potentially, each establishment inspected/regulated may have a slightly different interpretation of the scientific evidence available).

Establishments

Adjustment costs are assumed to be higher under Option 1 compared to Option 2 for establishments. A 1.2 factor applies to reflect the fact that under this Options implementation, establishments would need to interpret the scientific evidence available and define their reference framework. Information collected via cost enquiries and interviews pointed out that this option may prove problematic for small establishments, which do not have the internal resources to perform such activities nor to hire external experts to provide support.

Enforcement costs are assumed to be the same as under Option 2. While it can be argued that in a devolved approach, BTC establishments may tend to set rules at a less demanding level compared to what is set in legislation (either at national or at EU level). However, it was agreed with DG SANTE that the general objective of guaranteeing high levels of quality and safety would be maintained under Option 1, as well.

Cost Estimation for Option x.2

EU institutions

Adjustment costs are mainly represented by the costs for the IT platform, assumed to be the same under all policy options.

Enforcement costs are incremental compared to the baseline (and to Option 1). They include additional activities such as translation of guidelines, additional meetings and additional funding for EU expert bodies (EDQM).

Enforcement costs for the maintenance of the IT platform are expected to be the same under Options 1, 2 and 3. Based on information provided by EDQM, it is assumed that guidance rules will be revised three times over the ten years period (on average[144]).

NCAs

In absence of data from the cost enquiry, adjustment costs are assumed to amount to two to three times the enforcement costs (as measured by the effort of the staff). This assumption was used in other impact assessment support studies and accepted. Other costs are applied (when available) as per the general assumptions. Based on information provided by EDQM, it is assumed that guidance rules are revised, on average, three times over the ten years period. It is assumed that the update will not change the framework entirely, but still require some adjustment from NCAs to comply with the revised rules.

Enforcement costs are derived using the baseline as proxy, as described above.

Establishments

In absence of data from the cost inquiry, adjustment costs are assumed to amount to two to three times the enforcement costs (as measured by the effort of the staff). This assumption was used in other impact assessment support studies and accepted. Other costs are applied (when available) as per the general assumptions. Based on information provided by EDQM, it is assumed that guidance rules are revised, on average, three times over the ten years period. It is assumed that the update will not change the framework entirely, but still will require some adjustments to comply with the revised rules by establishments.

Enforcement costs are derived using the baseline as proxy, as described above.

Cost Estimations of Options x.3:

EU institutions

Enforcement costs include the setting up of expert groups as part of the Commission's activities, which includes the costs of general coordination and secretariat, the costs of meetings and the elaboration, publication and inclusion in EU legislation of BTC quality and safety requirements. The legislative process (i.e., the 'conversion' of the guidance elaborated into EU legislative acts, such as implementing acts) is expected to generate costs as well as require additional time to become operational, compared to Option 2. While this 'hassle cost' is not monetised per se (as per the BRGs), the longer updated process is reflected in the assumption on the frequency of update of the framework. Based on information provided by EDQM and ECDC, it is assumed that technical requirements are revised twice over the ten years period (on average).

Adjustment costs are incremental compared to the baseline (and to Option 1). Additional activities (such as translation of guidelines, additional meetings and additional funding for EU expert bodies (EDQM). Enforcement costs for the maintenance of the IT platform are expected to be the same under Option 1, 2 and 3. In addition, this option includes savings for the EU Commission in the form of reduction of the funding provided to the expert bodies.

NCAs

In absence of data from the cost enquiry, adjustment costs are assumed to be two to three times the enforcement costs (as measured by the effort of the staff). This assumption was used in other impact assessment support studies and accepted. Other costs are applied (when available) as per the general assumptions. It is assumed that guidance rules are revised twice over the ten year period. It is assumed that the update will not change the

[144] In practice – and depending on the final format and structure of the guidance – updates may happen more quickly to particular sections or requirements in response to changing situations.

framework entirely, but still require some adjustment from NCAs to comply with the revised rules. Enforcement costs are assumed to be the same as under Option 2.

Establishments

In absence of data from the cost enquiry, adjustment costs are assumed to be two to three times the enforcement costs (as measured by the effort of the staff). This assumption was used in other impact assessment support studies and accepted. Other costs are applied (when available) as per the general assumptions. It is assumed that guidance rules are revised twice over the ten year period. It is assumed that the update will not change the framework entirely, but still will require some adjustments to comply with the revised rules by establishments. Enforcement costs are assumed to be the same as under Option 2.

A5.1.6 Cost estimations per objective

Measures under Objective 1, Objective 3 and Objective 5

The assessment of costs of measures under Objectives 1, 3 and 5 follows the process and assumptions described above. The tables below provide an overview of the key assumptions used for the more important measures under those objectives.

The full list of measures can be found in Annex 2.

Table 4 –Key assumptions adopted for measures under Objective 1

Measure	Assumption	Comments
M1.2 (Change in scope of law)	• Number of additional SoHO establishments in scope: 304 • Number of Member States impacted: all • Adjustment costs for SoHO establishments: registration (20 person/days) • Enforcement costs for SoHO establishments: applying safety and quality provisions (inspections – 19/person-days, and reporting • Inspecting SoHO establishments (as per inspection schedule)	
M1.3 (Publication of more stringent rules)	• Number of NCAs impacted: 26 (13 Member States) • Number of documents: 2 per year • Average effort: 15 days policy officers + 10 days other staff (baseline); 0.5 person/day per document using IT platform when new provisions are in place	
M1.5 (NCA inspections)	• Number of Member States impacted: all • Impact for NCAs: 1 extra person-day per inspection (based on risk-based inspection schedule, as per Objective 2) • Number of establishments inspected on a given year: as per inspection schedule (2,282 using average frequency for risk-based inspection regime) • Costs only apply to Policy Option 1	
M1.6 – M1.7 (Risk assessment and rules on quality and safety requirement)	• Adjustment costs (Policy Option 2&3): setting up a risk assessment system (10-15 person-days) – apply to 18% of the sector • Enforcement costs: carry out the risk assessment (frequency as per risk-based inspection schedule): 3 person-days (Policy Option 2&3), 5 person-days (Policy Option 1) • Number of establishments inspected on a given year: as per inspection schedule	Costs of options estimated as per section A5.1

Table 5 – Key assumptions adopted for measures under Objective 3

Measure	Assumption	Comments
M3.1 (SARE reporting)	**SARE Reporting:** • Number of Member States impacted as a new measure: 8 (13 NCAs) • Number of establishments impacted: 3,250 (all BEs, sperm/oocyte banks (50), HSC (900)), • MAR establishments for offspring reporting (1,772) • Average effort for establishments impacted: 5 person-days (10 for adjustment costs) • Adjustment costs for NCAs: 30person-days • Enforcement costs for NCAs: 45.25 person-days (including extra time for inspections) • Enforcement costs for establishments: medium-complexity report (EUR 2,200) **Long-term high risk SARE Reporting:** • Number of Member States impacted as a new measure: 25 • Number of establishments impacted: 800 in impacted Member States (BEs (plasma), sperm/oocyte banks HSC (family donors) MAR establishments sperm/oocyte banks, own donors) • Enforcement costs for NCAs: 0.5 person-days (monitoring) • Enforcement costs for establishments: 10 person-days	
M3.5-M3.7 (Detailed quality and safety requirements to protect donors or children born from MAR)	**Evaluation of rules for safety and quality for donors and offspring** • Number of Member States impacted as a new measure: 7 (13 NCAs) • Number of establishments impacted: • Adjustment costs for NCAs: setting up the monitoring and evaluation system: 30 person-days • Enforcement costs for NCAs: evaluating safety and quality for donors and offspring: 5.5 – 15.5 person/days (including risk-based inspections as per Objective 2) (Option 1); effort .25 to 15.25 (options 2&3). • Number of inspections in a given year: as per inspection schedule (2,282 using average frequency for risk-based inspection regime) • Number of establishments impacted: all • Adjustment costs for establishments: setting up safety and quality system: 30 person-days (Option 2&3) • Enforcement costs for establishments: revising/updating safety and quality system: 20 person-days	Costs of options estimated as per section A5.1

Table 6 – Key assumptions adopted for measures under Objective 5

Measure	Assumption	Comments
M5.1 (Mandatory monitoring obligations of critical BTC supplies)	• Number of Member States impacted (implementing new measure): 13 (24 NCAs), • Number of BTC establishments impacted: all (new measures for 571 establishments, as many already monitor supplies because of industry practices) • Average effort for NCAs: 5-15 person-days (and EUR 3,000 for additional costs) • Average effort for establishments: 2-5 person days (and EUR 2,500 for additional costs)	
M5.2 (Mandatory notification of shortages in critical BTC supplies)	• Number of Member States impacted (implementing new measure): 27 (50 NCAs), new system based on EU platform; • Number of BTC establishments impacted: 2,500 • Costs for EU institutions: EUR 500,00 for design of module in IT platform (30% enforcement costs for maintenance);	

Measure	Assumption	Comments
	• Adjustment costs for establishments: 2 person-days (+ EUR 15,000 for consultancy fees under PO1) • Enforcement costs for establishments: 1 person-day per notification (100 notifications per year on average)	
M5.6-M5.6 (Critical BTC supplies contingency plans)	• Number of Member States impacted (implementing new measure): 21 (39 NCAs), new system based on EU platform; • Adjustment costs for NCAs: 12 person-days ; • Enforcement costs for NCAs: 0.5 person-days per NCA per year (Policy Option 1), 0.125 person-days per NCA per year (policy Option 2 and 3); • Adjustment costs for establishments: 20 person-day; • Enforcement costs for establishments: 12 person-day per revision/update of plan (PO1, 6 person-days for PO2 and PO3) • Number of establishments inspected in a given year: as per inspection schedule	Costs of options estimated as per section A5.1

Measures under Objective 2

This Objective focuses on oversight measures and does not include the Options which define the different ways the measures would be implemented . Therefore, the estimations and options described in above do not apply.

The table below provide an overview of the key assumptions used for the more important measures under this objective.

Table 7 – Key assumptions adopted for measures under Objective 2

Measure	Assumption	Comments
M2.2 (Risk-based inspection)	• Number of Member States impacted: 7 Member States (13 NCAs) implementing new measure. • Number of establishments impacted: all (including SoHO establishments not current regulated as per Objective 1). • Adjustment costs for NCAs: 20-40 person-days; • Adjustment costs for establishments: 14-21 person-days. **Scenario 1** • High risk category: 10% of establishments (456) , inspected twice per year, average effort 14 person-days; • Medium-risk category: 30% of establishments (1,369) , inspected every year, average effort 9.5 person-days; • Low risk category: 60% of establishments (2,378), inspected twice per year, average effort 14 person-days; • Number of establishments inspected in a given year: 3,879. **Scenario 2** • High risk category: 10% of establishments (456), inspected twice per year average effort 14 person-days; • Medium-risk category: 30% of establishments (1,369) inspected every two years , average effort 9.5 person-days; • Low risk category: 60% of establishments (2,378), inspected every year, average effort 6 person-days • Number of establishments inspected in a given year: 2,282	
M2.4 (Commission's audits)	• Number of audits per year: 6 to 7 audits per year; • Costs for DG SANTE: 2 auditors , travel and accommodation costs (EUR 2,200 per person), translation costs (EUR 6,000); • Costs for NCA: 2 experts accompanying DG SANTE's auditors per each audit; audit	

Measure	Assumption	Comments
	• Effort: 35 person-days per audit (including preparation, fieldwork and follow-up);	
M2.5 (Joint inspections)	• Number of joint inspections per year: 10 per year; • Costs for dispatching NCAs: 1 inspector per 8 days per audit; • Costs for receiving NCAs: 2 inspectors, 6-7 person-days per audit; • Costs for EU: travel and accommodation costs for dispatching administration (EUR 5,400), translation costs (EUR 6,000).	

Measures under Objective 4

Measures under this Objective are intended to support innovation in the BTC sector. It was not possible to apply the general approach described above to some of the measures considered, due to the lack of relevant input from the cost enquiries (both to NCAs and to establishments). Therefore, in cooperation with DG SANTE, a set of assumptions was developed for use in development of cost estimations.

Below we describe the key assumptions elaborated per each group of measures under consideration.

Measure 4.1 – Removal of 'same surgical procedure' exclusion

Note: This is not the only amendment to scope which will result in an increase of establishments requiring regulation. Under M1.2. – the amendment of the blood legislation to remove the 'not for transfusion' clause in the scope – other products and therefore other establishments will also fall under the umbrella of the new BTC framework.

EU institutions

This measure, which will mean that there are some additional documents to review and assess during audits of national control systems, is expected to generate negligible additional costs for EU institutions.

NCAs

Scope of the measure: Member States do not apply a similar measure currently, therefore it is assumed that all NCAs would incur in both adjustment and enforcement costs.

- Adjustment costs: in agreement with DG SANTE, it was assumed that these would be limited in scale, as most procedures and materials can be derived from similar procedures implemented in similar areas.
- Enforcement costs: in agreement with DG SANTE, it was assumed that these would be very small in scale, as the amount of information related to the same surgical procedure to be verified would be quite limited[145].

Establishments

Scope of the measure: For the purposes of the cost calculation, DG SANTE has advised that the measure would apply to hospitals rather than to BTC establishments. The number of hospitals has been derived from secondary sources[146]. It is assumed that clinics would not be impacted. However, given the number of establishments currently benefitting from such exemption (e.g. in sectors such as cosmetics), this is likely an underestimation.

[145] In practice, this is not necessarily the case if processing is undertaken.

[146] Available from: https://gateway.euro.who.int/en/indicators/hfa_471-5011-number-of-hospitals/

- **Adjustment costs:** in agreement with DG SANTE it was assumed that these would be very limited, corresponding to the simple registration process. For simplicity, it was assumed that there will be one registration per hospital, excluding thus multiple registrations for different departments of the same hospital. Estimated: 2 hours per registration, 1 registration per hospital.
- **Enforcement costs:** in agreement with DG SANTE, it was assumed that these would be an annual report of information already collected by the hospital. These costs are monetised using the costing for 'moderate complexity' reports under the SoHO-X Feasibility Study[147]. Estimated: 'easy' reporting cost (automated process): EUR 374 per year per hospital
- **Number of establishments impacted:** 11,000 hospitals

Measures M4.2 to M4.4 – Advisory mechanisms

Most of the additional costs triggered by these measures would be incurred by EU institutions. They are estimated using the general approach and assumption described above.

Measures M4.5 to M4.7 – Strengthened Preparation Process Authorisation

EU institutions

Costs for EU institutions are estimated using the general approach and assumption described above.

NCAs

Scope of the measure: based on the mapping exercise and on information provided by the GAPP project (and the general assumptions used for the cost estimation exercise), it is assumed that 19 Member States implement some form of authorisation for novel BTC processes, including the four Member States with the higher concentration of BTC establishments. The share of NCAs that would need to implement such measures entirely is estimated using the general assumptions described above.

The adjustment costs for NCAs are assumed to apply to the setting up of the system for strengthened preparation process authorisation as a whole, and not to each type of authorisation.

Enforcement costs are estimated to include both the effort to process of the authorisation request submitted by the establishments and the effort to examine the evidence produced. Such costs are estimated to increase with the level of risk of the novel BTC process. The information obtained via the cost enquiry for the high-risk novel BTC procedures provided the basis for the estimation.

Establishments

Scope of the measure: as the measures focus on authorisations, we have used those to estimate the costs. Therefore, the enforcement costs for establishments are expressed per authorisation, not per establishment. It is extremely likely that a limited number of (large) establishments would pursue innovation, especially that assessed as 'moderate' and 'high-risk'. However, it was not possible to correlate the number and type of authorisation requested with the number of establishments (e.g., the number of establishments requesting authorisations and the type of authorisation requested).

Adjustment costs are expressed per establishment, estimated using the general assumptions described above. Given the uncertain correlation between authorisations and

[147] Ibid.

establishments, it was assumed that these costs would apply to all establishments identified.

Enforcement costs include both the effort for preparing the authorisation and for generating the evidence required and are expressed as costs per authorisation. The costs for preparing the authorisation are estimated to increase with the level of risk of the novel BTC process. The information obtained via the cost enquiry for the high-risk novel BTC procedures provided the basis for the estimation.

The costs for generating the evidence are also assumed to increase with the level of risk of the novel BTC process. They are assessed using available literature and in agreement with DG SANTE. The broad ranges used for the estimation reflect the wide ranges of costs for generating evidence, and the uncertainties in estimating a more precise distribution of such costs.

Other key parameters

A key parameter for the estimation of these measures is the quantification of the likely number of strengthened preparation process authorisations requested, by level of risk of the novel BTC processes.

Levels of risk of the novel BTC processes: in agreement with DG SANTE and following discussions with the GAPP process, we have identified four categories of risk for novel BTC processed and the distribution, namely:

- Negligible risk, representing about 40% of the total number of authorisations, and requiring a 'complex reporting' (monetised using the costing for 'high complexity' reports under the SoHO-X Feasibility Study[148]);
- Low risk, representing about 25% of the total number of authorisations, and requiring a clinical evaluation;
- Moderate risk, representing about 20% of the total number of authorisations, and requiring a clinical investigation; and
- High risk, representing about 5% of the total number of authorisations, and requiring a clinical trial.

Number of authorisations: the total number of authorisations was extrapolated from the figures available on the number of clinical trials for high-risk novel BTC processes carried out in France and Germany, applying the general assumptions described above. A lower boundary was build changing the assumption of linearity for the extrapolation and considering that establishments in France and Germany pursue proportionally more innovation than establishments in the remaining Member States.

Measure M4.8 – IT platform

Costs for EU institutions to design and maintain the IT platform are estimated using the general approach and assumption described above.

Measures M4.9 to M4.12 – Strengthened Preparation Process Authorisation

Costs for EU institutions, NCAs and establishments for these measures were estimated using the general approach and assumption described above.

The table below provide an overview of the key assumptions used for the more important measures under this objective.

[148] Ibid.

Table 8 – Key assumptions adopted for measures under Objective 4

Measure	Assumption
M4.1 (Removal of same surgical procedure exemption)	• Number of Member States impacted: 27 (50 NCAs); • Number of establishments impacted: 11,000 hospitals; • Adjustment costs for NCAs: 10 person-days; • Enforcement costs for NCAs: 2 hours per hospital per year; • Adjustment costs for hospitals: 2 hours for registration, 1 registration per hospital • Enforcement costs for hospitals: 'easy' reporting cost (automated process, from SoHO-X Feasibility Study): EUR 375 per year per hospital.

M4.5 – M4.7 (Strengthening outcome-based process preparation)	• Number Member States impacted: 8 (15 NCAs);
	• Number of novel BTC processes per level of risk:
	  ○ Negligible risk: (Complex reporting): 50% (909 – 1,271)
	  ○ Low risk (Clinical evaluation): 25% (455 - 653);
	  ○ Moderate risk (Clinical investigation): - 20% (364 - 508);
	  ○ High risk (Clinical trials): 5% (91 - 127).
	• Adjustment costs for NCAs: setting up the system 30 -60 person-days;
	• Enforcement costs for NCAs (assessing request):
	  ○ Negligible risk: 1-2 person-days;
	  ○ Low risk: 4-8 person-days;
	  ○ Moderate risk: 10-20 person-days;
	  ○ High risk: 30-45 person-days;
	• Enforcement costs for NCAs (assessing clinical evidence):
	  ○ Negligible risk: 5-10 person-days;
	  ○ Low risk: 15-20 person-days;
	  ○ Moderate risk: 25-40 person-days;
	  ○ High risk: 30-90 person-days;
	• Adjustments costs for establishments: 40-80 person-days;
	• Authorisations can be re-used (conservative estimation 25%_
	• Enforcement costs for establishments (submitting request):
	  ○ Negligible risk: 2 person-days;
	  ○ Low risk: 5-10 person-days;
	  ○ Moderate risk: 15-25 person-days;
	  ○ High risk: 30-45 person-days;
	• Enforcement costs for establishments (collecting clinical evidence – function of number of patients requested and cost per patients):
	  ○ Negligible risk: not applicable;
	  ○ Low risk: number of patients: 15-20, costs per patients EUR 20 – EUR 1,200;
	  ○ Moderate risk: number of patients: 50, costs per patients EUR 20– EUR 1,200;
	  ○ High risk: number of patients: 50-100, costs per patients EUR 1,200 – EUR 6,000.

A5.1.7 Measures not quantified

Some of the measures under consideration for the different Objectives were not quantified, either because they do not generate direct compliance costs per se (e.g., they only do in combination with other measures), or because the data collected via through the different sources was not sufficient to overcome the uncertainties and provide reliable estimates.

The measures (described in full in Annex 2) **not quantified** are the following:

- M1.1: not feasible to estimate the possible indirect savings for establishments generated by abolishing out-of-date requirements that could currently impose costs on the sector, without knowing more about what requirements will be removed;
- M1.5: costs for NCAs assessed in conjunction with measures M1.6-M1.8 (i.e., per each option);
- M2.1 : assessed only in a qualitative way, as data collected too unreliable to provide robust estimations;
- M3.2; the costs of this measure are assessed in conjunction with measure 3.1;
- M3.3: not feasible to estimate without knowing more about the content of the new definitions incorporated in EU legislation;
- M3.4: the costs of this measure are assessed in conjunction with measures M3.5 to M3.7 (i.e., per each option)
- M4.5: Costs assessed in conjunction with measure M4.6;
- M4.9: costs for NCAs assessed in conjunction with measures M4.10-M4.12 (i.e., per each option);
- M5.3: costs of this measures are assessed in conjunction with measures M5.6-M5.8 (i.e. per each option); and
- M5.5: not feasible to estimate without knowing more about the content of the measure.

A5.2 Cost tables

The table below provides an overview of all direct costs (€) expected to be incurred either on a one-off basis or recurrently over a ten year period as a result of the implementation of the proposed measures. The detailed list of measures can be found in Annex 2.

	II. Overview of costs – all measures					
	EU institutions		NCAs		Establishments	
	One-off	Recurrent	One-off	Recurrent	One-off	Recurrent
M1.1						
M1.2			298,572 €	3,234,143 €	2,404,970 €	11,651,634 €
M1.3				133,096 €		
M1.4	1,163,352 €	2,837,735 €				
M1.5 (option1)						
M1.6 (option1)			85,829 €	6,067,572 €	4,015,463 € - 5,809,606 €	44,064,210 €
M1.7 (option2)		6,038,904 €	257,486 €	3,033,786 €	10,038,658 € - 14,524,015 €	22,032,105 €
M1.8 (option3)		9,403,473 €	171,657 €	3,033,786 €	6,692,438 € - 9,682,677 €	22,032,105 €
M2.1						
M2.2			138,551 € - 184,970 €	69,899,947 € - 107,186,707 €	11,008,170 € - 14,725,007 €	218,086,434 € - 297,120,260 €
M2.3		950,357 €				
M2.4		1,773,628 €		981,282 € - 1,331,164 €		
M2.5		873,715 €	282,858 € - 424,287 €	399,287 € - 425,907 €		

	II. Overview of costs – all measures					
	EU institutions		NCAs		Establishments	
	One-off	Recurrent	One-off	Recurrent	One-off	Recurrent
M2.6	788,387 €	1,923,093 €				
M3.1 (SARE reporting donors +offspring)	19,537 €	3,126,980 €	106,096 € - 148,534 €	16,458,628 €	8,876,328 €	80,830,055 €
M3.1 (SARE reporting – high risk)			88,393 €	8,160,549 €		25,751,602 €
M3.2						
M3.3						
M3.4						
M3.5 (option1)			218,255 € - 254,631 €	9,109,743 €	5,808,704 €	18,710,286 € - 19,934,774 €
M3.6 (option2)		2,268,594 €	654,764 € - 763,892 €	6,073,162 €	14,521,760 €	18,710,286 € - 19,934,774 €
M3.7 (option3)		3,126,980 €	436,509 € - 509,261 €	6,073,162 €	9,681,174 €	18,710,286 € - 19,934,774 €
M4.1			163,540 €	3,656,766 €	3,364,078 €	40,048,544 €
M4.2		947,291 €				
M4.3		1,981,954 €				
M4.4		1,851,663 €				
M4.5						
M4.6			147,186 € - 294,373 €	12,481,358 € - 29,565,985 €	41,120,039 € - 82,240,078 €	10,055,163 € - 98,738,570 €

	II. Overview of costs – all measures					
	EU institutions		NCAs		Establishments	
	One-off	Recurrent	One-off	Recurrent	One-off	Recurrent
M4.7			Included in M4.6	2,538,581 € - 7,982,816 €	Included in M4.6	11,213,592 € - 133,601,445 €
M4.8	3,770,384 €	9,197,001 €				
M4.9	Included in M4.10-M4.12		Included in M4.10-M4.12		Included in M4.10-M4.12	
M4.10 (Option 1)			268,206 € - 536,412 €	163,557 € - 327,114 €	52,516,005 € - 92,619,137 €	7,344,035 € - 14,688,070 €
M4.11 (Option 2)		1,057,655 €	804,619 € - 1,609,237 €	109,038 € - 218,076 €	131,290,013 € - 231,547,841 €	7,344,035 € - 14,688,070 €
M4.12 (Option 3)		337,223 €	536,412 € - 1,072,825 €	109,038 € - 218,076 €	87,526,675 € - 154,365,228 €	7,344,035 € - 14,688,070 €
M5.1			369,288 € - 374,734 €	620,939 € - 713,193 €	10,525,432 € - 16,169,092 €	18,496,146 € - 42,647,787 €
M5.2			32,708 €	664,867 €	37,326,798 €	8,047,376 €
M5.3						
M5.4						
M5.5						
M5.6 (Option 1)			190,973 € - 254,631 €	3,036,581 €	50,971,181 € - 60,006,977 €	22,040,787 €
M5.7 (Option 2)			572,919 € - 763,892 €	1,518,290 €	54,214,776 € - 67,768,470 €	22,040,787 €
M5.8 (Option 3)		2,427,184 €	381,946 € - 509,261 €	1,518,290 €	36,143,184 € - 45,178,980 €	22,040,787 €

Annex 6: Stakeholders consulted

A6.1. Surveys

The objective of the stakeholder surveys was to collect views on the different options as relevant to the research questions, and gather data required to develop quantitative estimates of impacts.

Two targeted surveys were distributed to: NCAs; and BTC establishments and other relevant stakeholder groups that included: EU institutions, healthcare providers, manufacturers, academia, ethics bodies, donors, patients and other stakeholders relevant to this consultation.

The surveys were conducted between June 2021 and July 2021. BTC establishments, NCAs and other stakeholder groups received an online impacts survey containing questions intended to gather opinion on a set of policy options and their impacts on targeted problems. Blood / TEs also received an online version of a costs inquiry to assess the costs of each policy option. NCAs received an off-line cost inquiry.

Findings are available from:

- An online impacts survey sent to organisations: 82 responses from organisations across 15 Member States (all except Bulgaria, Croatia, Estonia, Finland, Hungary, Latvia, Lithuania, Luxembourg, Malta, Romania, Slovakia and Slovenia). A small number of responses from outside the EU were set aside.
- An online impacts survey sent to NCAs: 24 responses from NCAs across 20 Member States (all except Austria, Cyprus, Greece, Malta, Romania and Slovakia).
- A costs survey sent to establishments and NCAs : 56 responses (40 Establishments, 16 NCAs).

Table 1 show the responses to the surveys by type of stakeholder.

Table 1 – Stakeholder survey responses

Stakeholder group		Online impact survey responses	Online costs survey responses	Offline costs survey responses
BTC establishments		34	40	x
Other relevant stakeholder groups	Healthcare provider	7	x	x
	Standards setting body	2	x	x
	Manufacturers	11	x	x
	Academia	7	x	x
	Donors	2	x	x
	Patients	6	x	x
	Other sector relevant to this consultation[149]	14	x	x
NCAs	Blood	3	x	1
	Tissues and Cells	6	x	3
	Both	15	x	12
	Total	106	40	15

[149] Respondents in this category included: an adjacent regulatory body, a non-governmental organisation; consultant; representative organisation representing the interests of preterm, sick, and low birthweight infants and their families; milk bank; health ingredient supplier (including probiotics as potential LBPs); ATMP product developer; international network of national haemovigilance agencies; health professionals (physicians); Association of Reproductive and Clinical Scientists.

Table 2 – Stakeholder impact survey responses by country

Country	Organisations	NCAs
Austria	3	0
Belgium	18[150]	1
Bulgaria	0	2
Croatia	0	1
Cyprus	1	0
Czechia	0	1
Denmark	5	1
Estonia	0	1
Finland	0	1
France	5[151]	1
Germany	9[152]	2
Greece	3	1
Ireland	1	1
Italy	5	1
Latvia	0	1
Lithuania	0	1
Luxembourg	0	1
Netherlands	7	1
Poland	2	1
Portugal	3	1
Slovenia	0	1
Spain	3	1
Sweden	2	2
Switzerland	3	0
UK	7	0
Other	6	0
Grand Total	82	24

Table 3 – Stakeholder cost survey responses by country

Country	Blood or tissue establishment (Online survey)	NCAs (Offline survey)
Austria	2	1
Belgium	4	1
Bulgaria	0	1
Denmark	5	1

[150] Includes one late response from PPTA and one late response from EMA

[151] Includes one late response from PRI

[152] Includes one late response from VITA

Country	Blood or tissue establishment (Online survey)	NCAs (Offline survey)
Estonia	0	1
France	4	2
Germany	2	2
Greece	1	0
Ireland	0	1
Italy	5	1
Netherlands	3	2
Poland	2	0
Portugal	3	0
Slovenia	0	1
Spain	3	1
Sweden	0	1
UK	4	0
Other	2	0
Total	40	16

Table 4 – List of impact survey respondents (Organisations)[153]

Country	Organisation	Stakeholder category
Austria	NextClinic IVF Center	Blood or tissue establishment
Austria	Red Cross Blood Transfusion Service of Upper Austria	Blood or tissue establishment
Austria	United European Gastroenterology (UEG)	Healthcare provider
Belgium	ILGA-Europe	Other sector relevant to this consultation
Belgium	Plasma Protein Therapeutics Association (PPTA) (2 Responses)	Blood or tissue establishment
Belgium	Université libre de Bruxelles (ULB)	Blood or tissue establishment
Belgium	The European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) (2 responses)	Manufacturers
Belgium	European Association of Hospital Pharmacists (EAHP)	Healthcare provider
Belgium	European Medicines Agency (EMA)	Other sector relevant to this consultation
Belgium	European Federation of Pharmaceutical Industries and Association (EFPIA)	Manufacturers
Belgium	Alliance for Regenerative Medicine	Other sector relevant to this consultation
Belgium	Fertility Europe	Patients
Belgium	Blood Transfusion Association	Manufacturers
Belgium	European Alliance for Vision Research and Ophthalmology	Healthcare provider

[153] The size of BTC establishments responding to the survey varied. There were responses from four micro organisations (1 to 9 employees), 12 small organisations (10 to 49 employees), ten medium organisations (50 to 249 employees), and seven large organisations (250 or more employees). One establishment did not provide an answer.

Country	Organisation	Stakeholder category
Belgium	Cord Blood Bank UZ Gent	Manufacturers
Belgium	European Haemophilia Consortium (EHC)	Patients
Belgium	AZ Sint-Jan Brugge-Oostende	Blood or tissue establishment
Belgium	UZ Brussels - University Hospital Free University Brussels (VUB)	Blood or tissue establishment
Belgium	HPTP-UZ Leuven	Blood or tissue establishment
Cyprus	Thalassaemia International Federation	Patients
Denmark	Cryos International Sperm and Egg Bank	Blood or tissue establishment
Denmark	Freya Biosciences Aps	Manufacturers
Denmark	Hvidovre Hospital	Other sector relevant to this consultation
Denmark	European Sperm Bank	Blood or tissue establishment
Denmark	South Danish Transfusion Service & Tissue Center	Blood or tissue establishment
France	Institut national de la recherche agronomique (INRAE)	Academia
France	Pharmabiotic Research Institute (PRI_	Academia
France	Etablissement Français du Sang	Blood or tissue establishment
France	MaaT Pharma	Manufacturers
France	European Patient Organisation for Dysimmune and Inflammatory Neuropathies (EPODIN)	Patients
Germany	European Foundation for the Care of Newborn Infants	Other sector relevant to this consultation
Germany	Vita 34 AG	Blood or tissue establishment
Germany	German Society for Tissue Transplantation (DGFG) gGmbH	Blood or tissue establishment
Germany	German Institute for Cell and Tissue Replacement (DIZG gGmbH)	Blood or tissue establishment
Germany	Hornhautbank Muenchen gGmbH	Blood or tissue establishment
Germany	German Medical Association	Other sector relevant to this consultation
Germany	pbm Academy Stiftung	Other sector relevant to this consultation (please specify)
Germany	Profertilita	Blood or tissue establishment
Germany	Univeryity Tissue Bank Charité	Blood or tissue establishment
Greece	Maternity Hospital Helena Venizelou	Healthcare provider
Greece	Hospital Children Agia Sofia Athens Greece	Healthcare provider
Greece	Hellenic Cord Blood Bank	Blood or tissue establishment
Ireland	Irish Blood Transfusion Service	Blood or tissue establishment
Italy	Transfusion Medicine Department ULSS 8 Berica - Vicenza	Blood or tissue establishment
Italy	Siena Skin bank - Italy	Blood or tissue establishment
Italy	Società Italiana Studi di Medicina della Riproduzione Via Giuseppe Mazzini (S.I.S.Me.R)	Blood or tissue establishment

Country	Organisation	Stakeholder category
Italy	PMA Uslsudest toscana	Healthcare provider
Italy	San Giovanni Battista Hospital	Patients
Netherlands	Bone Marrow Donors Worldwide	Standards setting body
Netherlands	Matched unrelated donors for (stem)cel donation (Matchis)	Academia
Netherlands	Erasmus MC	Academia
Netherlands	International Haemovigilance Network	Other sector relevant to this consultation
Netherlands	Academic organisation and European Haematology Association	Academia
Netherlands	Caelus Health	Manufacturers
Netherlands	Sint Antonius Ziekenhuis	Healthcare provider
Other	FIODS/IFBDO - International Federation of Blood Donor Organisations	Donors
Other	IFF	Other sector relevant to this consultation
Other	Seres Therapeutics Inc. / Serestherapeutis Netherlands BV	Manufacturers
Other	International Federation of Blood Donor Organisations (IFBDO/FIODS)	Donors
Other	Geocord Farmax Ltd	Blood or tissue establishment
Other	MDA public cord blood bank	Blood or tissue establishment
Poland	Polski Bank Komórek Macierzystych (FamiCord Group)	Blood or tissue establishment
Poland	Polski Bank Komórek Macierzystych S.A.	Blood or tissue establishment
Portugal	BEBEVIDA	Blood or tissue establishment
Portugal	Stemlab, SA	Blood or tissue establishment
Portugal	AVA Clinic	Blood or tissue establishment
Spain	EuroGTP II Management Committee	Standards setting body
Spain	IVI Fertility Clinic Madrid	Blood or tissue establishment
Spain	IVI Fertility Clinic Sevilla	Blood or tissue establishment
Sweden	UEG Stool Bank Working Group, under United European Gastroenterology	Academia
Sweden	Swedish Blood Alliance & Akademiska sjukhuset	Blood or tissue establishment
Switzerland	University of Zurich	Academia
Switzerland	PharmaBiome AG	Manufacturers
Switzerland	SSCB - Swiss Stem Cells Biotech SA	Blood or tissue establishment
UK	Consulting on Advanced Biologicals	Other sector relevant to this consultation
UK	NHS Blood and Transplant	Blood or tissue establishment
UK	International Patient Organisation for Primary Immunodeficiencies (IPOPI)	Patients
UK	Cells4Life Group LLP	Blood or tissue establishment
UK	The Human Milk Foundation	Other sector relevant to this consultation
UK	Association of Reproductive and Clinical Scientists	Other sector relevant to this consultation
UK	Hearts Milk Bank	Other sector relevant to this consultation

Table 5 – List of impact survey respondents (NCAs)

Country	NCA
Belgium	Federal Agency for Medicines and Health Products
Bulgaria	Executive Agency Medical Supervision
Bulgaria	Bulgarian Drug Agency - Department Control of Blood transfusion system
Croatia	Ministry of Health Republic of Croatia
Czechia	Ministry of Health of the Czech Republic
Denmark	Danish Patient Safety Authority
Estonia	State Agency of Medicines
Finland	Finnish Medicines Agency
France	Agence de la biomédecine
Germany	Paul-Ehrlich-Institut and German Ministry of Health
Germany	Paul-Ehrlich-Institut
Hungary	Hungarian national Blood transfusion Service
Ireland	Health Products Regulation Authority
Italy	Centro Nazionale Trapianti
Latvia	State Agency of Medicines
Lithuania	National transplant bureau under the Ministry of health
Luxembourg	National Health Directorate Luxembourg
Netherlands	Ministry of Health, Welfare and Sport
Poland	National Blood Centre
Portugal	Portuguese Institute for Blood and Transplantation (IPST)
Slovenia	Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP)
Spain	Sub-directorate General for Health Benefit Basket of the National Health System and Clearing Funds.
Sweden	National Board of Health and Welfare
Sweden	Inspektionen för vård och omsorg, IVO

Table 6 – List of cost survey respondents (Blood or TEs)

Country	Establishment	Stakeholder category
Austria	NextClinic IVF Center	Tissue or cell donation or banking for assisted reproduction
Austria	Red Cross Blood Transfusion Service of Upper Austria	Other stakeholder category
Belgium	Université libre de Bruxelles (ULB)	Blood (component) collection and/or blood (component) banking
Belgium	ZOL St Jan Genk IVF lab	TEs
Belgium	Fertility Europe	Other stakeholder category
Belgium	European Network of TEs (eNOTE)	TEs
Denmark	Cryos International	Tissue or cell donation or banking for transplantation
Denmark	Freya Biosciences	Tissue or cell donation or banking for transplantation
Denmark	Hvidovre Hospital	Milk collection or banking

Country	Establishment	Stakeholder category
Denmark	The Danish Cornea Bank	Tissue or cell donation or banking for transplantation
Denmark	European Sperm Bank	Tissue or cell donation or banking for assisted reproduction
France	BIOBANK	Tissue or cell donation or banking for transplantation
France	Etablissement Français du Sang	Blood (component) collection and/or blood (component) banking
France	MaaT Pharma	Tissue or cell donation or banking for transplantation
France	Hopital de la Pitié salpetriere	Other stakeholder category
Germany	German Society for Tissue Transplantation (DGFG) gGmbH	TEs
Germany	Fertility Center - Gynaekologicum	Other stakeholder category
Greece	Maternity Hospital Helena Venizelou	Other stakeholder category
Italy	Human Milk Bank - Città della Salute e della Scienza, Torino (Italy)	Milk collection or banking
Italy	Pma Usl toscana sudest	TEs
Italy	Transfusion Medicine Department ULSS 8 Berica Vicenza	Both BEs/TEs
Italy	Milano Cord Blood Bank	Tissue or cell donation or banking for transplantation
Italy	Ausl-Irccs Reggio Emilia	TEs
Netherlands	Bone Marrow Donors Worldwide	Other stakeholder category
Netherlands	Sanquin Blood Bank	Blood (component) collection and/or blood (component) banking
Netherlands	netherlands donor feces bank	Other stakeholder category
Other	Tran & T1cb Ankara University School Of Medicine Unrelated Blood And Marrow Donor Registry	Both BEs/TEs
United States	Seres Therapeutics Inc.	Tissue or cell donation or banking for transplantation
Poland	Polski Bank Komórek Macierzystych S.A.	Both BEs/TEs
Poland	PBKM	Tissue or cell donation or banking for transplantation
Portugal	Stemlab, SA	Tissue or cell donation or banking for transplantation
Portugal	AVA Clinic	Tissue or cell donation or banking for assisted reproduction
Portugal	BEBEVIDA	Both BEs/TEs
Spain	UR International Group	Tissue or cell donation or banking for assisted reproduction
Spain	IVI Madrid	Tissue or cell donation or banking for assisted reproduction
Spain	IVI Sevilla	Tissue or cell donation or banking for assisted reproduction
UK	NHS Blood and Transplant	Both BEs/TEs
UK	Hearts Milk Bank	Milk collection or banking
UK	The Human Milk Foundation	Milk collection or banking

Table 7 – List of cost survey respondents (NCAs)

Country	NCA	Type of establishment: blood, tissues or both
Austria	BASG/AGES MEA	Both
Belgium	FAMHP	Both
Bulgaria	Bulgarian Drug Agency	Blood
Denmark	Danish Patient Safety Authority	Both
Estonia	State Agency of Medicines	Both
France	Agence de la Biomédecine	Tissues and cells
Germany	Paul-Ehrlich-Institut	Both
Germany	MoH and federal states	Both
Ireland	HPRA	Both
Italy	Italian National Transplant Centre	Tissues and cells
Netherlands	Further rapporteurs of the IES	Both
Netherlands	Dutch Health Care Inspectorate	Both
Slovenia	JAZMP	Both
Spain	Organización Nacional de Trasplantes	Both
Sweden	Inspektionen för vård och omsorg, IVO	Both

A6.2. Interviews

Two sets of interviews have been conducted for this study:

- Interviews conducted for the borderline case studies. In total, 44 stakeholders across 25 organisations have been consulted.
- The second set of interviews focused on further follow-up to the consultation and allow for more detailed feedback. In total, 6 semi-structured qualitative interviews were conducted. Tables below provide a complete list of stakeholders that were consulted.

Names of individuals have been withheld for privacy/data protection purposes.

Table 8 – Organisations consulted for the borderline case studies

Organisation
Akademiska sjukhuset
Alliance for Regenerative Medicine (ARM)
Andalusian Transplant Coordination
Barcelona Tissue Bank
the CAT
Complejo Hospitalario Universitario A Coruña (Hospital Teresa Herrera)
Department of Hepatology and Gastroenterology, Aarhus University Hospital; UEG stool bank working group; Centre for Faecal Microbiota Transplantation (CEFTA) at Aarhus University Hospital; general expert on FMT
Department of Transplantation surgery at Karolinska University Hospital, Sweden
EDQM
EMA Innovation Taskforce
German Competent Authority
International human milk banking consultant and expert in human milk banking and breastfeeding

UK Association for Milk Banking
European Milk Bank Association
International Society for Extracellular Vesicles
NHSBT
Pharmacobiotics Institute
Queen Astrid Military Hospital
Royal Orthopaedic Hospital NHS Trust
Servei Català de la Salut (CatSalut), part of Organització Catalana de Trasplantaments (OCATT)
Socialstyrelsen
Terumo
United European Gastroenterology (UEG); Netherlands donor feces bank
Veneto Eye Bank Foundation

Table 9 –Stakeholders interviewed in follow-up interviews

Organisation
European Society for Blood and Marrow Transplantation
European Association of Tissues and Cell Banking
European Society of Human Reproduction and Embryology
Cord Blood Association - European Section & Membership
European Breast Milk Bank Association

Table 10 – NCAs interviewed

Country
Austria
Italy
Netherlands
Spain
Germany
France

Table 11 – Other groups interviewed

Others
Vigilance Expert Subgroup
GAPP
VISTART

Table 12 – Follow up emails with NCAs

Follow up emails
Austria
Belgium
Bulgaria
Czech Republic

Follow up emails
Denmark
Estonia
Finland
France
Germany
Italy
Lithuania
Netherlands
Poland
Spain
Sweden

A6.3 Workshops attendee list (by organisation)

Workshop summaries can be found in Annex 11.

Table 13 – Authorising Novel BTC (27 April 2021)

Organisation name	Type of stakeholder
Agence de la biomedicine	Public Administration
Agence nationale de sécurité du médicament et des produits de santé (ANSM)	Public Administration
Austrian Agency for Health and Food Safety (AGES)	Public Administration
Bulgarian Drug Agency	Public Administration
Danish Patient Safety Authorisation	Public Administration
Deloitte	Other (Feasibility Study)
Department for Health Regulation	Public Administration
Department of Hepatology and Gastroenterology - Aarhus University Hospital	Healthcare Provision
Directorate-General of Health	Public Administration
Establecimiento de Tejidos, Fundacion Clinica San Francisco	BE/TE
EuroGTP II Management Committee	Standards setting body
European Association of Tissue Banks	BE/TE
European Commission - DG SANTE	Commission / EU Bodies
European Directorate for the Quality of Medicines (EDQM)	International Organisation
European Hospital and Healthcare Federation (HOPE)	Healthcare Provision
European Society for Blood & Marrow Transplantation	BE/TE
European Society of Human Reproduction and Embryology (ESHRE)	BE/TE
Federal Ministry of Health, Germany	Public Administration
Federation of European Academies of Medicines	Academia
Finnish Medicines Agency (FIMEA)	Public Administration
French Blood Establishment (EFS)	BE/TE
Health Products Regulatory Authority (HPRA)	Public Administration

Organisation name	Type of stakeholder
Inspektionen för vård och omsorg (IVO)	Public Administration
Italian National Blood Centre	Public Administration
Malta Medicines Authority	Public Administration
Ministry of Health of Portugal - Instituto Português do Sangue e da Transplantação, IP	Public Administration
Ministry of Health of the Republic of Croatia	Public Administration
Ministry of Health, Welfare and Sports	Public Administration
National Blood Transfusion Service	BE/TE
National Board of Health and Welfare	Public Administration
NHS Blood and Transplant	BE/TE
Norwegian Directorate of Health	Public Administration
Organización Nacional de Trasplantes	Public Administration
Ottawa Centre for Attachment and Trauma Therapy (OCATT)	Public Administration
Paul-Ehrlich-Institut	Public Administration
Pharmabiotic Research Institute - PRI	Manufacturers
Red Cross Flanders	BE/TE
Sanquin Blood Supply	BE/TE
State Agency of Medicines - Estonia	Public Administration
The European Society for Blood and Marrow Transplantation (EBMT)	BE/TE
Unaffiliated individual [name redacted]	Public Administration

Table 14 – Regulating Point-of-Care BTC Processing (bed-side and same surgical procedure) (12 May 2021)

Organisation name	Type of stakeholder
Agence nationale de sécurité du médicament et des produits de santé (ANSM)	Public Administration
Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP)	Public Administration
Austrian Agency for Health and Food Safety (AGES)	Public Administration
Biomedicine Service, Sektor Za Transplantaciju	Public Administration
Bulgarian Drug Agency	Public Administration
Centro Nazionale Trapianti - Ministero della Salute	Public Administration
Committee for Advanced Therapies	Commission / EU Bodies
Danish Medicines Agency	Public Administration
Danish Patient Safety Authority	Public Administration
European Association of Tissue and Cell Banking	BE/TE
European Commission	Commission / EU Bodies
European Commission - DG SANTE	Commission / EU Bodies
European Directorate for the Quality of Medicines (EDQM)	International Organisation
European Hospital and Healthcare Federation (HOPE)	Healthcare Provision
European Medicines Agency	Commission / EU Bodies
Federal Minsitry of Health, Germany	Public Administration

Organisation name	Type of stakeholder
Finnish Medicines Agency (FIMEA)	Public Administration
General-Directorate of Health	Public Administration
Health Products Regulatory Authority (HPRA)	Public Administration
Italian National Transplant Center	Public Administration
Krajowe Centrum Bankowania Tkanek i Komórek (National Centre for Tissue and Cell Banking)	Public Administration
Leitat Technological Center	Manufacturers
Ministerio de Sanidad, Consumo y Bienestar Social	Public Administration
Ministry of Health	Public Administration
Ministry of Health of the Republic of Croatia	Public Administration
Ministry of Health, Welfare and Sports	Public Administration
National Board of Health and Welfare	Public Administration
NHS Blood and Transplant	BE/TE
Paul-Ehrlich-Institute	Public Administration
Servizio di Medicina Trasfusionale	BE/TE
Spanish Agency for Medicines and Medical Devices (AEMPS)	Public Administration
State Agency of Medicines of the Republic of Latvia	Public Administration
TBF Génie Tissulaire (TBF)	BE/TE
Temuro	Manufacturers
Turkish Republic Ministry of Health	Public Administration
UZ Brussel	BE/TE

Table 15 – Strengthening Blood and Plasma Donor Protection (17 May 2021)

Organisation name	Type of stakeholder
Austrian Federal Office for Safety in Health Care	Public Administration
Bulgarian Drug Agency - Competent Authority for Blood	Public Administration
Directorate-General of Health	Public Administration
Etablissement Français Du Sang	BE/TE
European Blood Alliance (EBA)	BE/TE
European Commission - DG SANTE	Commission / EU Bodies
European Directorate for the Quality of Medicines (EDQM)	International Organisation
European Haemophilia Consortium (EHC)	Patients
European Medicines Agency	Commission / EU Bodies
French Ministry of Health	Public Administration
General-Directorate of Health	Public Administration
German Ministry of Health	Public Administration
Health Products Regulatory Authority (HPRA)	Public Administration
International Plasma Fractionation Association (IPFA)	Manufacturers
ISBT WP Donors and Donations	Donors
Italian National Blood Center	Public Administration
Italian National Blood Centre (CNS) - Centro Nazionale Sangue	Public Administration

Organisation name	Type of stakeholder
Ministerio de Sanidad	Public Administration
Ministry of Health, Welfare and Sports	Public Administration
Ministry of Helath of the Republic of Czechia	Public Administration
Ministry of Social Affairs, Health, Care and Consumer Protection	Public Administration
National Board of Health and Welfare	Public Administration
Narodowe Centrum Krwi	Public Administration
Norwegian Directorate of Health	Public Administration
Paul-Ehrlich-Institute	Public Administration
PPTA (Plasma Protein Therapeutics Association)	Manufacturers
Sanquin	BE/TE
Spanish National Transplant Organisation	Public Administration
State Agency of Medicines	Public Administration
State Institute for Drug Control (competent authority of the Czech Republic)	Public Administration
The International Federation of Blood Donor Organizations (IFBDO/FIODS)	Donors
Vigilance Expert Subgroup	Standards Setting

Table 16 – Better Protection of Donors for Non-Reproductive Tissues and Cells (17 May 2021)

Organisation name	Type of stakeholder
Agence de la biomedicine	Public Administration
Bone Marrow Donors Worldwide	Donors
Catholic University of Rome, Gastroenterology Unit	Academia
Centro Nazionale Trapianti	Public Administration
Cord Blood Association	BE/TE
Cord Blood Association (CBA)	BE/TE
Danish Patient Safety Authority	Public Administration
Direcao Geral da Saude	Public Administration
Directorate-General of Health	Public Administration
European Association of Tissue Banks	BE/TE
European Commission - DG SANTE	Commission / EU Bodies
European Directorate for the Quality of Medicines (EDQM)	International Organisation
European Society for Blood and Marrow Transplantation (EBMT)	BE/TE
Federal Office for Safety in Health Care	Public Administration
Frauenmilchbank-Initiative e.V. (FMBI) (Human Milk Bank Initiative)	Healthcare Provision
French Ministry of Health	Public Administration
German Ministry of Health	Public Administration
Health Products Regulatory Authority	Public Administration
Health Products Regulatory Authority (HPRA)	Public Administration
Human Milk Foundation	Healthcare Provision
International Haemovigilance Network	Standard Settings
Italian National Transplant Centre	Public Administration

Organisation name	Type of stakeholder
Krajowe Centrum Bankowania Tkanek i Komórek (KCBTiK)	Public Administration
Leitat Technological Center	Manufacturers
Matchis Foundation	Donors
Ministry of Health of Portugal - Instituto Português do Sangue e da Transplantação, IP	Public Administration
Ministry of Health of the Republic of Croatia	Public Administration
Ministry of Health, Welfare and Sport	Public Administration
Ministry of Helath of Croatia	Public Administration
Ministry of Social Affairs, Health, Care and Consumer Protection	Public Administration
National Blood Service - Ospedale Policlinico San Martino di Genova	BE/TE
National Transplant Agency	Public Administration
National Transplant Organisation	Public Administration
Paul-Ehrlich-Institut	Public Administration
Pharmabiotic Research Institute (PRI)	Manufacturers
Prolacta BioScience	Healthcare Provision
Sanquin, International Society of Blood Transfusion	BE/TE
Santos	Public Administration
State Agency of Medicines	Public Administration
UEG Stool Bank Working Group	Healthcare Provision
Vigilance Expert Subgroup	Standards Setting

Table 17 – Better Protection of MAR Donors and Children Born from MAR (18 May 2021)

Organisation name	Type of stakeholder
Agence de la biomedecine	Public Administration
Cryos International	BE/TE
Danish Patient Safety Authority	Public Administration
DG SANTE	Commission / Eu Bodies
European Commission	Commission / Eu Bodies
European Directorate for the Quality of Medicines (EDQM)	International Organisation
European Foundation for the Care of Newborn Infants	Patients
European Society of Human Reproduction and Embryology (ESHRE)	BE/TE
European Sperm Bank	BE/TE
Federal Ministry of Health (MoH)	Public Administration
Federal Office for Safety in Health Care (BASG) / Austrian Agency for Health and Food Safety (AGES)	Public Administration
Fertility Europe	Patients
French Ministry of Health	Public Administration
Health Products Regulatory Authority	Public Administration
Health Products Regulatory Authority (HPRA)	Public Administration
Italian National Transplant Centre	Public Administration
Ministry of Health, Croatia	Public Administration

Organisation name	Type of stakeholder
Ministry of Health, Welfare and Sport	Public Administration
National Board of Health and Welfare	Public Administration
National Council for Assisted Reproduction (CNPMA)	Public Administration
State Agency of Medicines	Public Administration
Unaffiliated Individual [Name Redacted]	Public Administration
Vigilance Expert Subgroup	Standards Setting

Table 18 – Strengthening Oversight (Inspection, Authorisation, and Vigilance) – Authorities (25 May 2021)

Organisation name	Type of stakeholder
Agence de la biomedecine	Public Administration
Agence nationale de sécurité du médicament et des produits de santé (ANSM)	Public Administration
Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP)	Public Administration
Bulgarian Drug Agency	Public Administration
Commission Expert Sub-group on inspections in the Blood and Tissues and Cells Sectors	Public Administration
Croatian Ministry of Health.	Public Administration
Danish Patient Safety Authority	Public Administration
Directorate-General of Health	Public Administration
Embryo Protection Authority	Public Administration
European Commission	Commission/ EU Bodies
European Commission - DG SANTE	Commission/ EU Bodies
European Directorate for the Quality of Medicines (EDQM)	International Organisation
European Medicines Agency	Commission/ EU Bodies
Federal Ministry of Health	Public Administration
Federal Office for Safety in Health Care (BASG) / Austrian Agency for Health and Food Safety (AGES)	Public Administration
Finnish Medicines Agency (FIMEA)	Public Administration
Health and Youth Care Inspectorate	Public Administration
Health Products Regulatory Authority (HPRA)	Public Administration
Italian National Blood Centre	Public Administration
Italian National Transplant Centre	Public Administration
Krajowe Centrum Bankowania Tkanek i Komórek (National Centre for Tissue and Cell Banking)	Public Administration
MInisterio de Sanidad	Public Administration
Ministry of Health	Public Administration
Ministry of Health of the Republic of Croatia	Public Administration
National Transplant Organisation	Public Administration
Organizacion Nacional de Trasplantes	Public Administration
Paul-Ehrlich-Institut	Public Administration
Portuguese Blood and Transplantation Institute	Public Administration

Organisation name	Type of stakeholder
Portuguese Competent Authority in MAR (CNPMA)	Public Administration
State Agency of Medicines	Public Administration
State Institute for Drug Control	Public Administration
State Institute for Drug Control (SUKL)	Public Administration
Swedish Medical Products Agency	Public Administration

Table 19 – Strengthening Oversight (Inspection, Authorisation, and Vigilance) – Operators (26 May 2021)

Organisation name	Type of stakeholder
BIOBANK	BE/TE
Bone Marrow Donors Worldwide	Donors
Collectors and Fractionators of Plasma to PDMPs	Manufacturers
Committee for the Management of EuroGTP II project's Outcomes	Standards Setting
Cord Blood Association (CBA)	BE/TE
CoreSoHO	BE/TE
European Association of Tissue and Cell Banks	BE/TE
European Blood Alliance	BE/TE
European Commission	Commission / EU Bodies
European Commission - DG SANTE	Commission / EU Bodies
European Eye Bank Association	BE/TE
European Plasma Alliance	BE/TE
European Society for Blood and Marrow Transplantation (EBMT)	BE/TE
European Society of Human Reproduction and Embryology (ESHRE)	BE/TE
Fertility Europe	Patients
International Council for Commonality in Blood Banking Automation (ICCBBA)	Standards Setting
International Plasma Fractionation Association (IPFA)	Manufacturers
MedTech Europe	Manufacturers
NHS Blood and Transplant	BE/TE
Plasma Protein Therapeutics Association	Manufacturers
Vigilance Expert Subgroup	Standards Setting

Table 20 – Key Definitions - Improvements and Additions (1 June 2021)

Organisation name	Type of stakeholder
Agence nationale de sécurité du médicament et des produits de santé (ANSM)	Public Administration
Bone Marrow Donors Worldwide	Donors
Catalan Transplant Organisation (OCATT)	Public Administration
Centro nazionale Trapianti	Public Administration
Cord Blood Association (CBA)	BE/TE
Cryos International	BE/TE
Danish Patient Safety Authority	Public Administration
Directorate-General of Health	Public Administration

Organisation name	Type of stakeholder
Embryo Protection Authority	Public Administration
EU Commission - DG SANTE	Commission / EU Bodies
European Association of Tissue Banks	BE/TE
European Centre for Disease Prevention and Control	Commission / EU Bodies
European Directorate for the Quality of Medicines (EDQM)	International Organisation
European Eye Bank Association	BE/TE
European Foundation for the Care of Newborn Infants	Patients
European Network of TEs (eNOTE)	BE/TE
European Plasma Alliance (EPA)	BE/TE
European Society of Human Reproduction (ESHRE)	BE/TE
European Sperm Bank	BE/TE
Federal Office for Safety in Health Care (BASG) / Austrian Agency for Health and Food Safety (AGES)	Public Administration
Fertility Europe	Patients
General-Directorate of Health	Public Administration
German Ministry of Health	Public Administration
Health Products Regulatory Authority (HPRA)	Public Administration
Human Milk Foundation	Healthcare Provision
International Plasma Fractionation Association (IPFA)	Manufacturers
Italian National Transplant Centre	Public Administration
JMB Consultancy BV	Manufacturers
Krajowe Centrum Bankowania Tkanek i Komórek (National Centre for Tissue and Cell Banking)	Public Administration
Leitat Technological Center	BE/TE
Medical Products Agency (MPA) Sweden – Uppsala	Public Administration
MedTech Europe	Manufacturers
Ministry of /health	Public Administration
National Blood Center	Public Administration
National Transplant Agency	Public Administration
Organización Nacional de Trasplantes (ONT)	Public Administration
Plasma Protein Therapeutics Association (PPTA)	Manufacturers
Portuguese Competent Authority on MAR (CNPMA)	Public Administration
Prolacta BioScience	Healthcare Provision
Sanquin	BE/TE
State Agency of Medicines	Public Administration
Stichting Sanquin Bloedvoorziening - Bloedbank	BE/TE
Takeda	BE/TE
Vigilance Expert Subgroup	Standards Setting

Table 21 – Refining the Scope of the BTC Legislation (2 June 2021)

Organisation name	Type of stakeholder
Agence de la biomedecine	Public Administration
Bone Marrow Donors Worldwide	Donors
Catalan Transplant Organisation (OCATT)	Public Administration
Centrul Regional de Transfuzii Sanguine	BE/TE
Competent Authority for Blood and Transplantation Portgual	Public Administration
CoreSoHO	BE/TE
Danish Patient Safety Authority	Public Administration
Directorate of Health Norway (Competent Authority)	Public Administration
Directorate-General of Health	Public Administration
Embryo Protection Authority	Public Administration
eNOTE	BE/TE
European Association of Tissue Banks	BE/TE
European Commission	Commission / EU Bodies
European Commission - DG SANTE	Commission / EU Bodies
European Directorate for the Quality of Medicines (EDQM)	International Organisations
European Foundation for the Care of Newborn Infants	Patients
European Helicobacter and Microbiota Study Group	Healthcare Provision
European Medicines Agency (EMA)	Commission / EU Bodies
European Plasma Alliance (EPA)	BE/TE
European Society for Blood and Marrow Transplantation (EBMT)	BE/TE
European Society of Human Reproduction (ESHRE)	BE/TE
Federal Office for Safety in Health Care (BASG) / Austrian Agency for Health and Food Safety (AGES)	Public Administration
French Ministry of Health - Directorate-General for Health	Public Administration
German Ministry of Health	Public Administration
Goethe University Frankfurt	Academia
GRIFOLS	Manufacturers
Health Products Regulatory Authority (HPRA)	Public Administration
Human Milk Foundation	Healthcare Provision
International Plasma Fractionation Association (IPFA)	Manufacturers
Italian National Institute of Health	Public Administration
Italian National Transplant Centre	Public Administration
JMB Consultancy BV	Manufacturers
Krajowe Centrum Bankowania Tkanek i Komórek (National Centre for Tissue and Cell Banking)	Public Administration
Medical Product Agency	Public Administration
MInisterio de Sanidad	Public Administration
Ministry of Health, Croatia	Public Administration
Ministry of Health, Wellbeing and Sports	Public Administration
National Blood Center	Public Administration
National Board of Health and Welfare	Public Administration

Organisation name	Type of stakeholder
National Transplant Agency	Public Administration
Norwegian Directorate of Health	Public Administration
Parlemento, Portugal	Public Administration
Paul-Ehrlich-Institute	Public Administration
Pharmabiotic Research Institute	Manufacturers
Plasma Protein Therapeutics Association	Manufacturers
Prolacta BioScience	Healthcare Provision
Ravimiamet, Estonia	Public Administration
Regional Competent Authority - Castilla y León	Public Administration
State Agency of Medicines	Public Administration
Terumo	Manufacturers
UEG Stool Bank Working Group	Healthcare Provision

Table 22 – Ethical Principles (Voluntary Unpaid Donation, Prohibition of Profit from the Human Body and BTC Allocation) (8 June 2021)

Organisation name	Type of stakeholder
Agence de la biomedecine	Public Administration
Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP)	Public Administration
Bone Marrow Donors Worldwide	Donors
Centrul Regional de Transfuzii Sanguine	BE/TE
Committee on Bioethics (DH-BIO)	Ethics
CORESoHO	BE/TE
Council of Europe	Ethics
Cryos International	BE/TE
Danish Patient Safety Authority	Public Administration
Embryo Protection Authority	Public Administration
Estonian State Agency of Medicines	Public Administration
Ethics Committee of the State of Berlin	Ethics
EU Commission - DG JUST	Commission / EU Bodies
EU Commission - DG SANTE	Commission / EU Bodies
European Association of Tissue Banks	BE/TE
European Blood Alliance	BE/TE
European Directorate for the Quality of Medicines (EDQM)	International Organisations
European Eye Bank Association	BE/TE
European Foundation for the Care of Newborn Infants	Patients
European Group on Ethics in Science and New Technologies (EGE)	Commission / EU Bodies
European Haematology Association (EHA)	Patients
European Haemophilia Consortium (EHC)	Patients
European Patient Organisation for Dysimmune and Inflammatory Neuropathies (EPODIN)	Patients
European Plasma Alliance	BE/TE

Organisation name	Type of stakeholder
European Society for Blood and Marrow Transplantation (EBMT)	BE/TE
European Society of Human Reproduction and Embryology (ESHRE)	BE/TE
European Sperm Bank	BE/TE
Federal Ministry of Health	Public Administration
Fertility Europe	Patients
French Ministry of Health	Public Administration
General-Directorate of Health	Public Administration
German Ministry of Health	Public Administration
Health Products Regulatory Authority (HPRA)	Public Administration
Human Milk Foundation	Healthcare Provision
Instituto Português do Sangue e da Transplantação – IPST	Public Administration
International Federation of Blood Donor Organizations (IFBDO/FIODS)	Donors
International Lesbian, Gay, Bisexual, Trans and Intersex Association (ILGA-Europe)	Donors
International Patient Organisation for Primary Immunodeficiencies (IPOPI)	Patients
International Plasma Fractionation Association (IPFA)	Manufacturers
Italian National Institute of Health	Public Administration
Italian National Transplant Center	Public Administration
JMB Consultancy BV	Manufacturers
Krajowe Centrum Bankowania Tkanek i Komórek (National Centre for Tissue and Cell Banking)	Public Administration
Libera Università Maria Ss. Assunta	Ethics
Ministerio de Sanidad	Public Administration
Ministry of Health	Public Administration
Ministry of Health of Portugal - Instituto Português do Sangue e da Transplantação, IP	Public Administration
Ministry of Health of the Republic of Croatia	Public Administration
Ministry of Health, Welfare and Sports	Public Administration
National Board of Health and Welfare	Public Administration
National Transplant Agency	Public Administration
NHS Blood and Transfusion Service	BE/TE
Norwegian Directorate of Health,	Public Administration
Paul-Ehrlich-Institut	Public Administration
Plasma Protein Therapeutics Association (PPTA)	Manufacturers
Plasma Users Coalition (PLUS)	Patients
Portuguese Competent Authority on MAR (CNPMA)	Public Administration
Prolacta BioScience	Healthcare Provision
Queen Astrid Military Hospital/Belgian Defense	BE/TE
Regional Competent Authority of Castilla y León	BE/TE
State Agency of Medicines - Estonia	Public Administration
Thalassaemia International Federation	Patients
The European Sperm Bank	BE/TE

Organisation name	Type of stakeholder
The Human Milk Foundation and Imperial College London	Healthcare Provision
United European Gastroenterology (UEG)	Healthcare Provision
World Marrow Donor Association	Donors

Table 23 – Borderlines with Other Regulated Frameworks: Classification Advice and Interplay (9 June 2021)

Organisation name	Type of stakeholder
Agence de la Biomedicine	Public Administration
Agence nationale de sécurité du médicament et des produits de santé (ANSM)	Public Administration
Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP)	Public Administration
Catalan Transplant Organisation (OCATT)	Public Administration
Centrul Regional de Transfuzii Sanguine	BE/TE
Committee for Advanced Therapies (the CAT)	Commission / EU Bodies
CORESoHO	BE/TE
Danish Medicines Agency	Public Administration
Danish Patient Safety Authority	Public Administration
Embryo Protection Authority	Public Administration
EU Commission - DG SANTE	Commission / EU Bodies
European Association of Hospital Pharmacists (EAHP)	International Organisation
European Association of Tissue Banks	BE/TE
European Commission	Commission / EU Bodies
European Commission - DG SANTE	Commission / EU Bodies
European Directorate for the Quality of Medicines (EDQM)	International Organisation
European Federation of Pharmaceutical Industries and Associations (EFPIA)	Manufacurers
European Hematology Association (EHA)	Patents
European Hospital and Healthcare Federation (HOPE)	Healthcare Provision
European Medicines Agency (EMA)	Commission / EU Bodies
European Network of TEs (eNOTE)	BE/TE
European Society for Blood & Marrow Transplantation (EBMT)	BE/TE
Federal Office for Safety in Health Care (BASG) / Austrian Agency for Health and Food Safety (AGES)	Public Administration
Federal Office of Consumer Protection and Food Safety	Public Administration
Finnish Medicines Agency (FIMEA)	Public Administration
General-Directorate of Health	Public Administration
Health Products Regulatory Authority (HPRA)	Public Administration
Instituto Português do Sangue e da Transplantação – IPST	Public Administration
International Society for Cell & Gene Therapy (ISCT)	Manufacurers
Italian National Blood Centre	Public Administration
JMB Consultancy BV	Manufacurers
Krajowe Centrum Bankowania Tkanek i Komórek (National Centre for Tissue and Cell Banking)	Public Administration

Organisation name	Type of stakeholder
Medical Products Agency (MPA) Sweden	Public Administration
MedTech Europe	Manufacurers
Ministry of Health	Public Administration
Ministry of Health Germany	Public Administration
Ministry of Health of Portugal - Instituto Português do Sangue e da Transplantação, IP	Public Administration
Ministry of Health of the Republic of Croatia	Public Administration
Ministry of Health, Italy	Public Administration
Ministry of Health, Welfare and Sports	Public Administration
Minsiterio de Sanidad (Ministry of Health of Spain)	Public Administration
National Blood Center	Public Administration
National Board of Health and Welfare	Public Administration
National Transplant Agency	Public Administration
NHS Blood and Transplant	BE/TE
Norwegian Directorate of Health	Public Administration
Paul-Ehrlich-Institut	Public Administration
Pharmabiotic Research Institute	Manufacurers
Prolacta BioScience	Healthcare Provision
Regional Competent Authority of Castilla y León	BE/TE
State Agency of Medicines of Estonia	Public Administration
State Institute for Drug Control, CZ	Public Administration
UEG Stool Bank Working Group	Healthcare Provision
University Hospital Frankfurt	Academia

Annex 7: Stakeholder consultation outputs

This annex provides

- selected charts from the stakeholder surveys
- commentary on wider stakeholder consultation processes relevant to the objectives.

A7.1 Increase patient protection from all avoidable risks

This annex provides charts showing results generated by the establishment survey and NCA survey.

NCAs expressing an opinion were most confident in the potential for Option 2 to deliver consistent safety and quality rules, and least confident in Option 1.

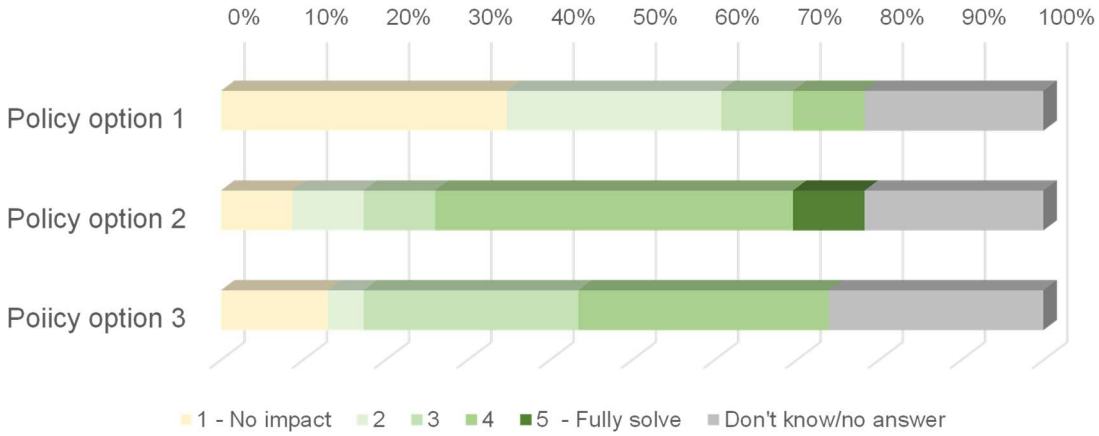


Figure 1. To what extent will each policy option solve the problem that consistent safety and quality rules are not applied within and across Member States? (n=23).

Source: Survey of NCAs

Respondents to the establishment survey that expressed an opinion were also most confident in Option 2, and least confident in Option 1. Stakeholders responding to the surveys were also most supportive of the potential of Option 2 to solve the problem of unequal protection of patients, with Option 3 next and Option 1 the least popular.

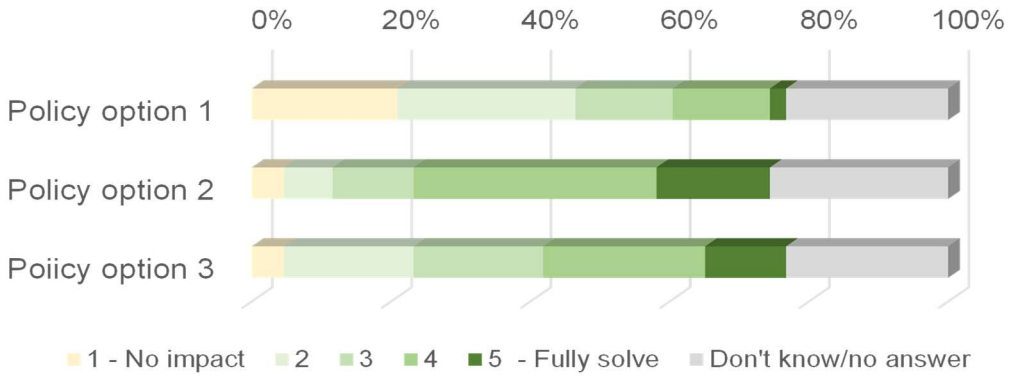


Figure 2. To what extent will each policy option solve the problem that consistent safety and quality rules are not applied within and across Member States? (n=43).

Source: Survey of establishments

NCAs that responded to questions about measures proposed under Objective 1 indicated that Option 2 and 3 would be more likely to solve the baseline problem of unequal protection of patients than Option 1.

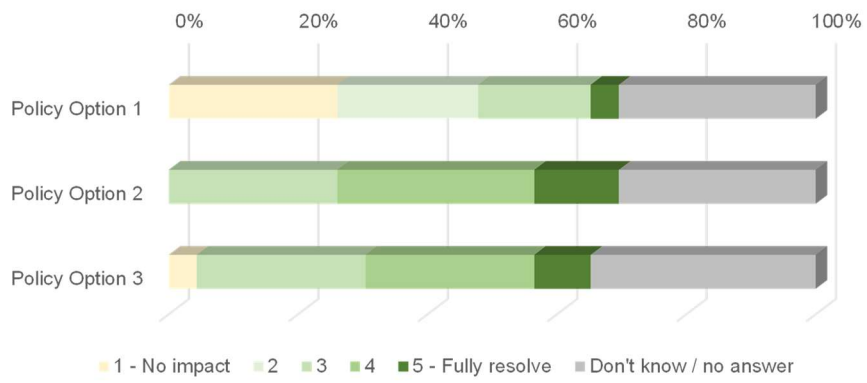


Figure 3. To what extent do the options address the problem of unequal protection of patients, within and across Member States? (n=23).

Source: Survey of NCAs . Question referenced measures proposed under objective 1.

Respondents to the establishment survey questions about measures proposed specifically to strengthen safety and quality had most confidence in Option 2 as a solution to unequal protection of patients

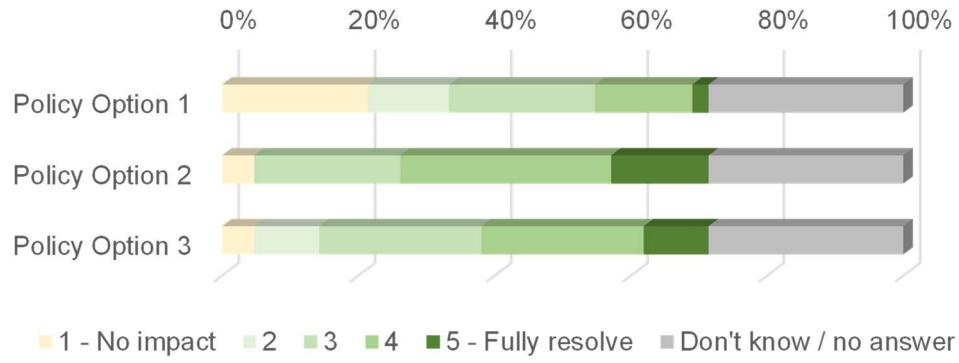


Figure 4. To what extent do the options address the problem of unequal protection of patients, within and across Member States? (n = 43)

Source: Survey of establishments

Impact on the agility of regulatory system: the ability of options to provide a dynamic regulatory system for BTC in which quality & safety requirements reflect current scientific and technical knowledge

Respondents to the NCAs survey were also more confident in Option 2

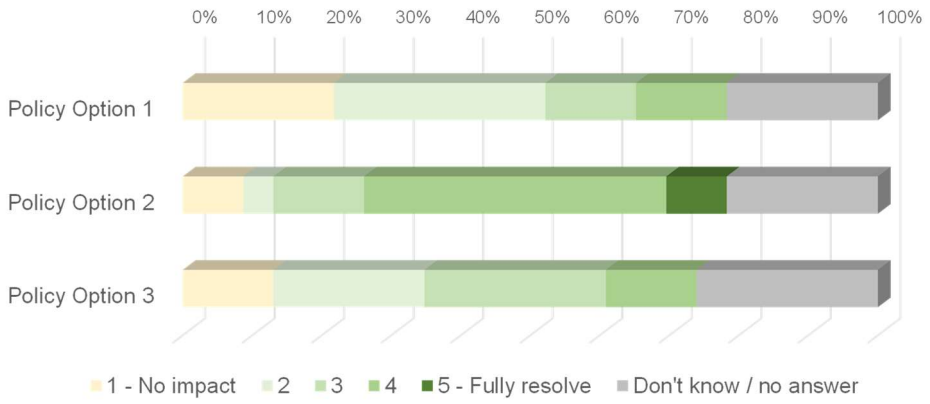


Figure 5. To what extent will each policy option solve the problem that safety and quality rules applied by BEs/TEs do not reflect the best scientific and technical knowledge in the BTC sectors?; (n = 23).

Source: Survey of NCAs

Respondents to the establishment survey had more confidence in the use of EU expert bodies (Option 2) as an approach to ensuring requirements are up to date than they had in either Option 1 or Option 3

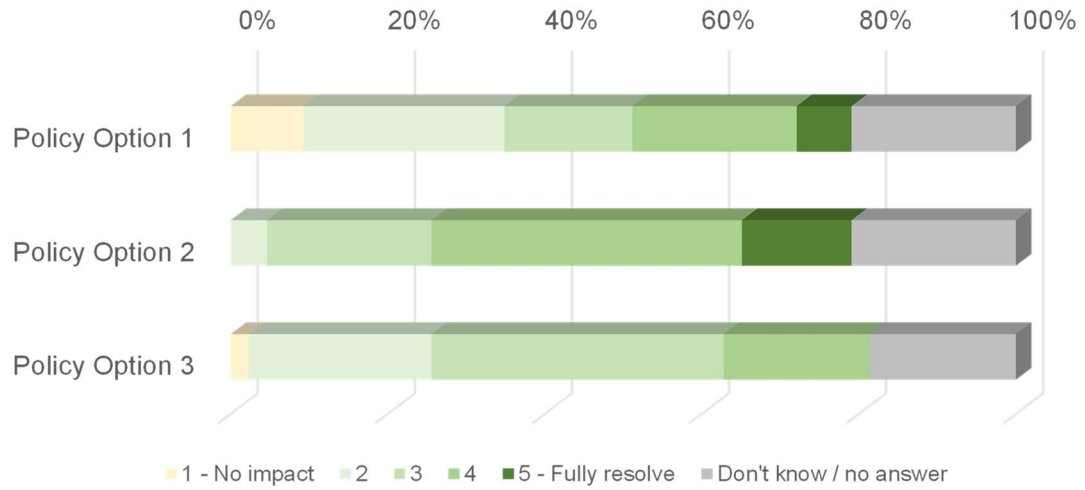


Figure 6. To what extent will each policy option solve the problem that safety and quality rules applied by BEs/TEs do not reflect the best scientific and technical knowledge in the BTC sectors? (n = 43).

Source: Survey of establishments

Workshop participants saw Option 3 providing the least agile mechanism for updating a quality or safety requirement

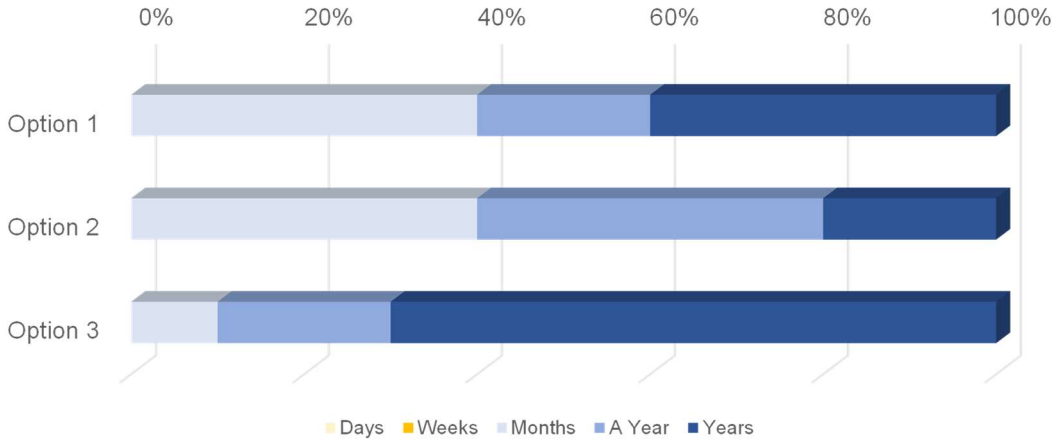


Figure 7. What is your best estimate of the time it would take to move from initiation of a review of a quality/safety requirement to an approval, issue and implementation of a new quality safety requirement under Policy Option [x]. (n = 10)

Source: Poll taken at Workshop 3, plasma group

Increase protection of BTC donors, and children born from donated sperm, eggs or embryos, from specific risks

Workshop participants indicated that Policy Option 2 offers the most appropriate approach to ensure comprehensive, prompt reporting of SAREs involving donors.

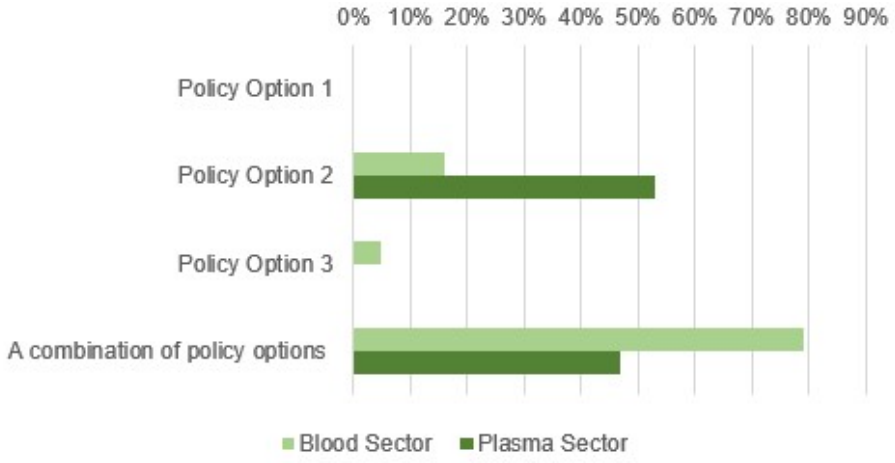


Figure 8. Which Policy Option would ensure comprehensive, prompt reporting of SAREs involving Donors?

Source: Participatory workshop: Strengthening Blood and Plasma Donor Protection) (n blood =19, n plasma = 15)

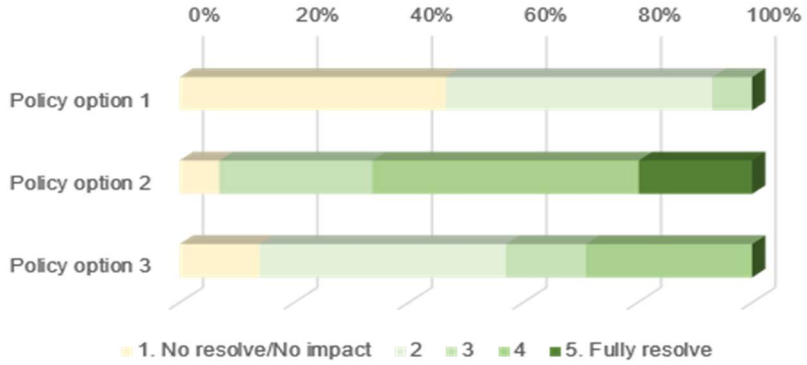


Figure 9. Compared to a scenario in which the EU's BTC legislation is not reformed, and looking out over the next ten years, to what extent will Policy Option [x] resolve the problem of comprehensive and prompt reporting of SAREs involving MAR Donors?

Source: Participatory workshop: Better Protection of MAR Donors and Children Born from MAR. Compared to a scenario in which the EU's BTC legislation is not reformed, and looking out over the next ten years, to what extent will Policy Option [x] resolve the problem of comprehensive and prompt reporting of SAREs involving MAR Donors? n=15

Workshop participants saw Policy Option 2 as being the option most likely to ensure that requirements for donor care are implemented and kept up to date in an efficient manner

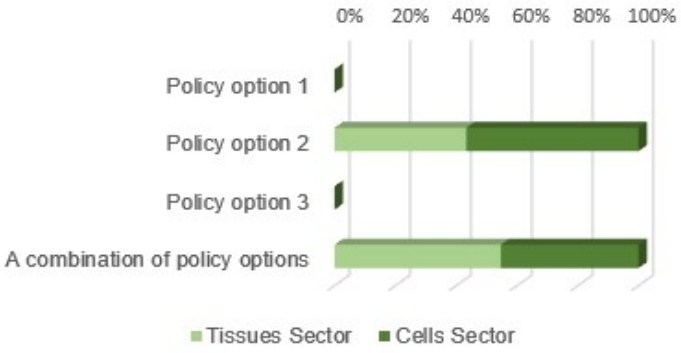


Figure 10. In your opinion, which policy option is best suited to ensuring that requirements for donor care are implemented and kept up to date in an efficient manner?

Participatory workshop: Better Protection of Donors for Non-Reproductive Tissues and Cells. Tissues sector=14, n Cells sector=19

The workshop on protection of MAR donors showed the strongest support for Option 2 as a means to reduce avoidable risks to MAR donors.

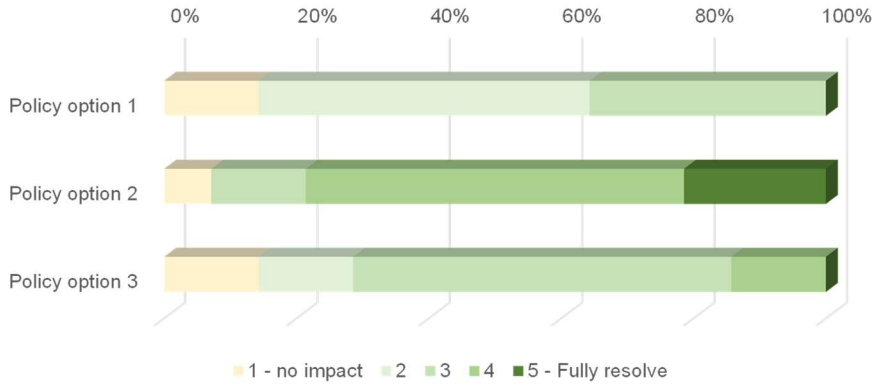


Figure 11. Compared to a scenario in which the EU's BTC legislation is not reformed, to what extent will Policy Option [x] resolve the problem of donors/offspring not being fully protected from avoidable risks? N= 14

Source: Workshop on better protection of MAR donors and children born from MAR. Participant poll.

The NCA survey suggests greater confidence in Option 2 as a mechanism for resolving the problem that donors are not currently fully protected from avoidable risks

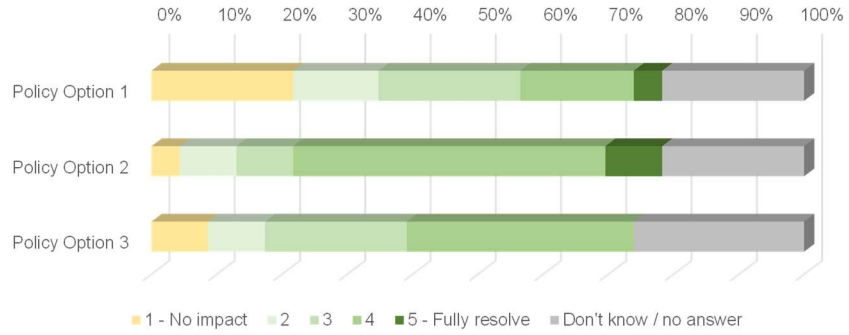


Figure 12: To what extent will each policy option solve the problem that donors are not fully protected from avoidable risks? n = 23

Source: NCA survey.

Respondents to the NCA survey had more confidence in Option 2 and 3 than Option 1 as a mechanism for protecting children born from MAR from avoidable risks

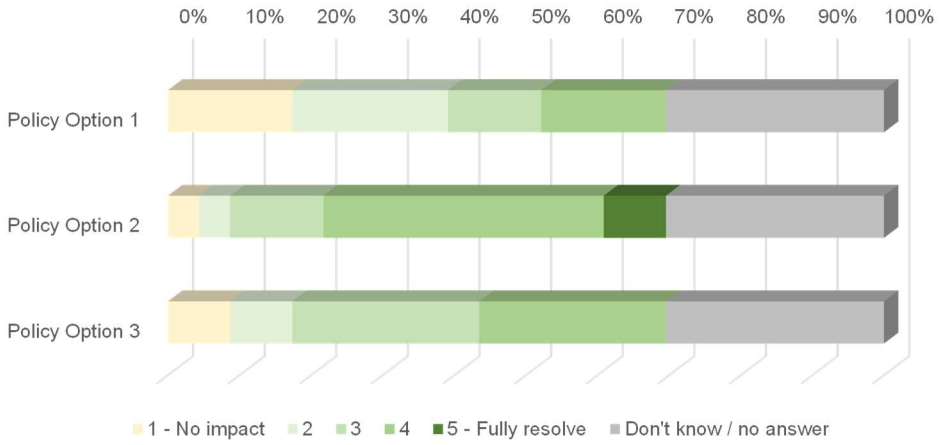


Figure 13. To what extent will each option solve the problem that children born as a result of MAR (MAR) are not fully protected from avoidable risks? n = 23

Source: NCA survey

A7.2 Avoid shortages of critical BTC therapies

Impact on the problem of decision-makers needing information with which to identify and manage risks to supply for critical BTC applications

NCAs see the proposed measures making a positive difference to the problem that decision-makers lack the information needed to identify and manage supply risks for critical BTC applications

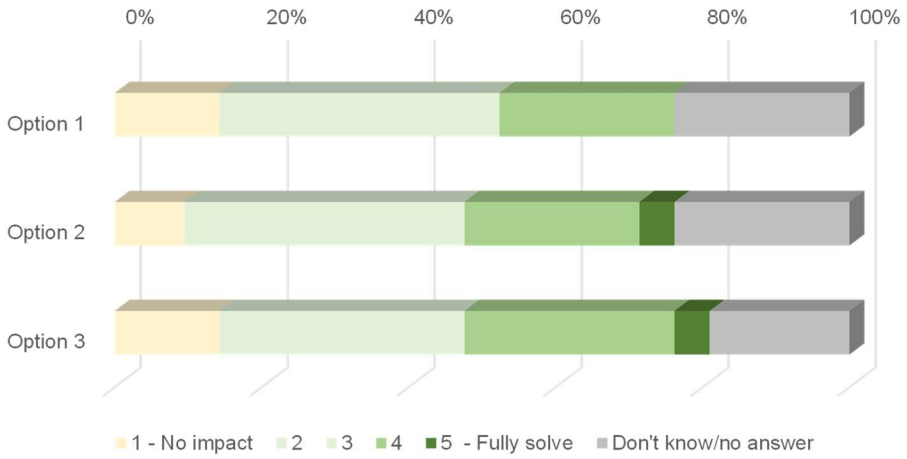


Figure 14: To what extent will each policy option solve the problem of decision-makers needing information with which to identify and manage risks to supply for critical BTC applications?

Source: NCA survey

Respondents to the establishment survey felt less able to judge the impacts of the measures for decision-makers but still foresee a positive impact

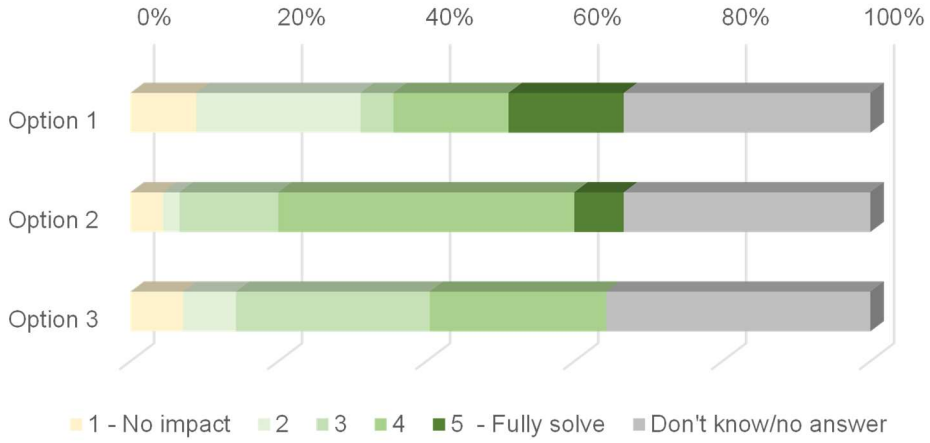


Figure 15. To what extent will each policy option solve the problem of decision-makers needing information with which to identify and manage risks to supply for critical BTC applications?

Source: Establishments survey.

Impact on collection of critical BTC in the EU

The NCA responses suggest caution about the impact of the proposed measures on collection of critical BTC

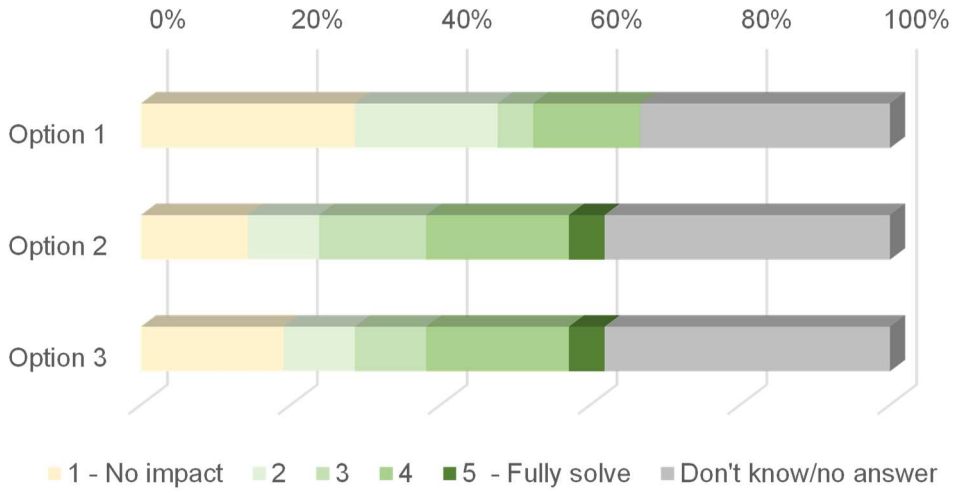


Figure 16. To what extent will the options increase the collection of critical BTC in the EU? n =23

Source: NCA survey.

Many of the respondents to the establishment survey were unable to give a view on whether measures would affect collection of critical BTC

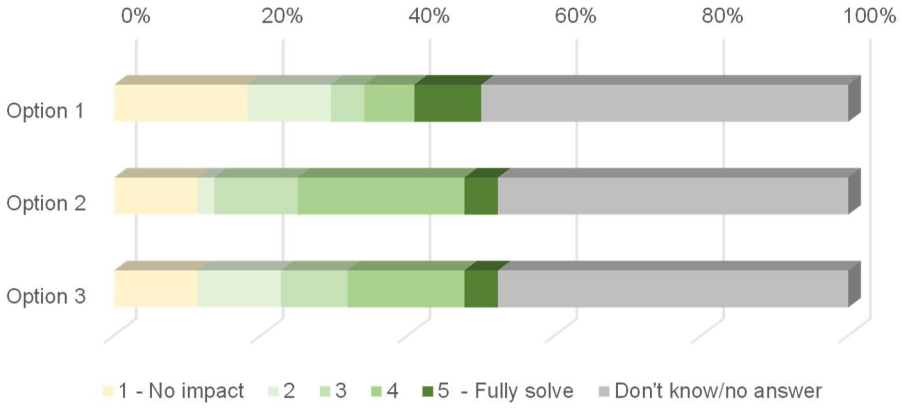


Figure 17. To what extent will the options increase the collection of critical BTC in the EU? n =44

Source: Establishment survey

Stakeholders are uncertain or doubtful of the measures' impact on risk of interruptions of supply and shortages relating to vis-à-vis third countries, and the EU's dependency on plasma imported from the US.

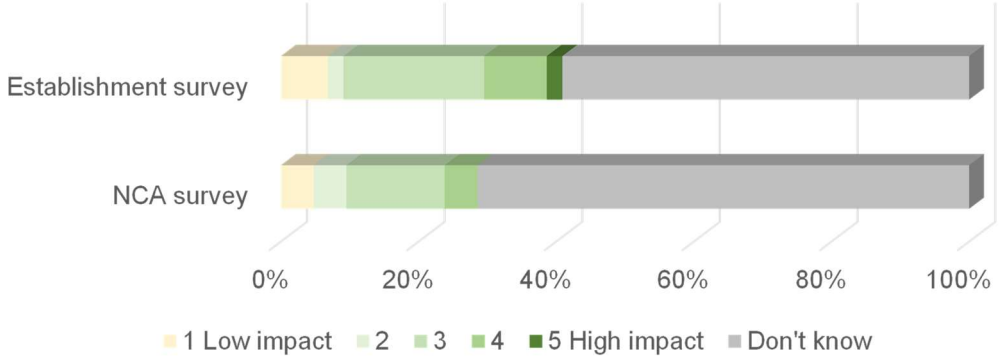


Figure 18. Question: What impact will the proposed options have on the risk of interruptions of supply and shortages relating to vis-à-vis third countries, and the EU's dependency on plasma imported from the US?

Source: Establishments survey and NCA survey.

Stakeholders have some confidence that the proposed measures will reduce the risk of critical shortages.

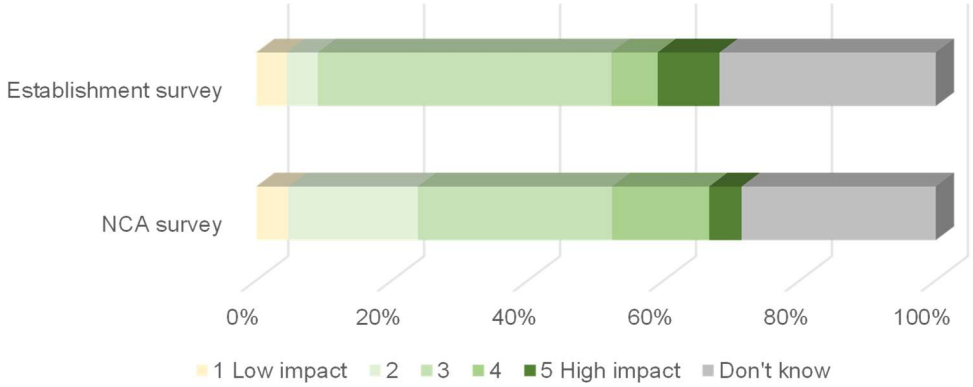


Figure 19. Survey responses. To what extent would the foreseen measures to monitor supply (including donations, exchanges between EU Member States, imports and exports, shortages) reduce the risk of critical shortages and help build strategic independence? NCAs n= 23, Others n = 43.

There is confidence that proposed measures will deliver comparable supply data.

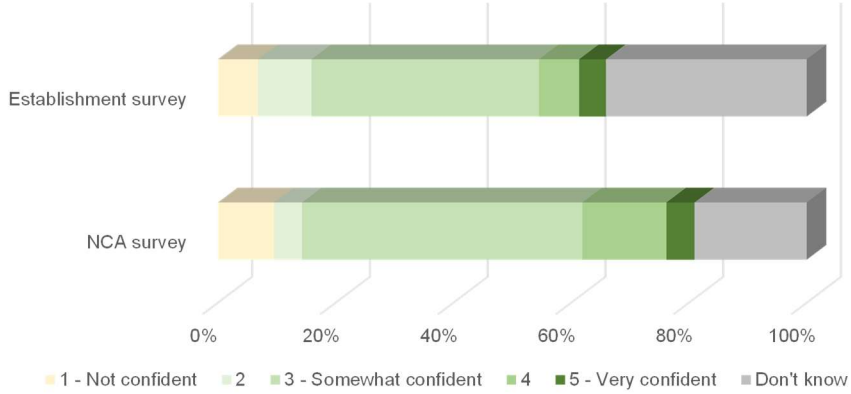


Figure 20. How confident are you that this option will provide sufficiency data that are comparable across the EU?

Source: Survey responses. NCAs n= 23, Others n = 43.

Impact on the EU's preparedness for future crises and public health emergencies

NCAs survey respondents' perspectives on the impact of options on the EU's preparedness for future crises and public health emergencies

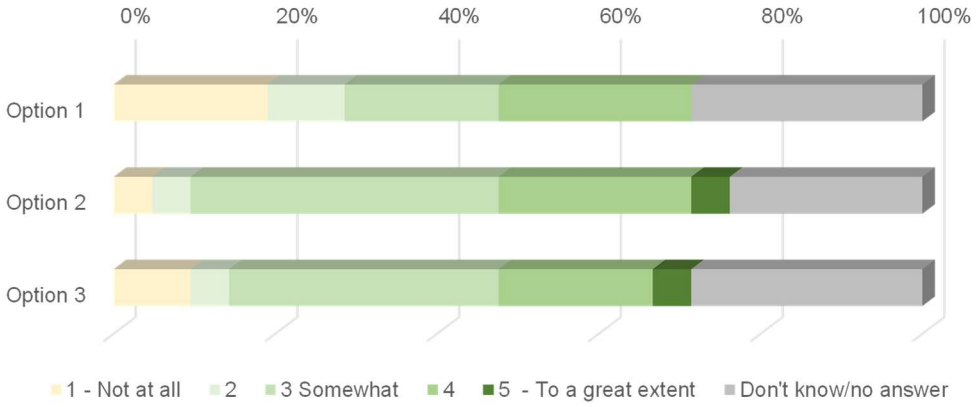


Figure 21. To what extent will each option improve the EU's preparedness for future crises and public health emergencies? n = 23

Source: NCA survey.

Establishment survey respondents' perspectives on the impact of options on the EU's preparedness for future crises and public health emergencies

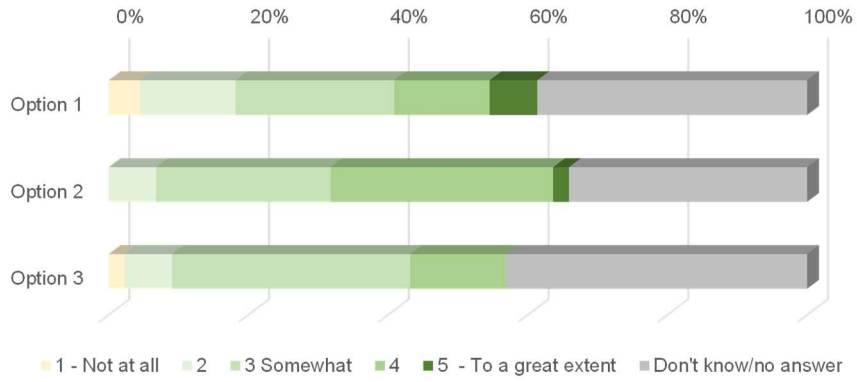


Figure 22. To what extent will each option improve the EU's preparedness for future crises and public health emergencies? n = 23

Source: Establishment survey.

A7.2 Innovation and research (Objective 4)

Though 40% provided 'don't know/no answer' responses, the remainder of respondents were on balance more favourably disposed to Option 2 than the alternatives as a mechanism to improve patient access to novel therapies

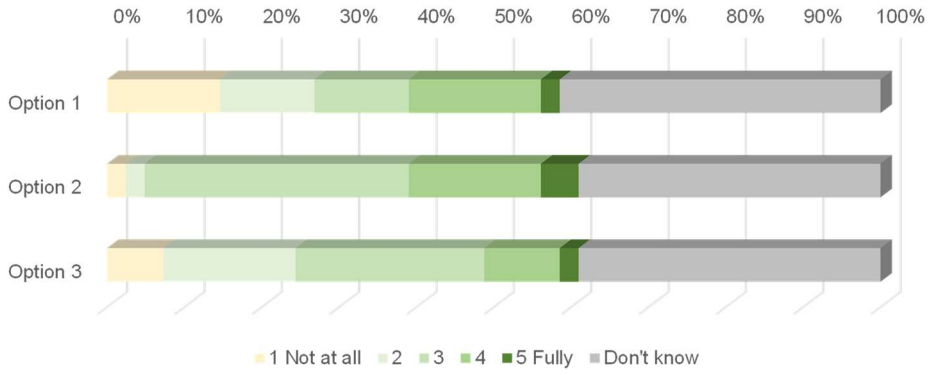


Figure 23. To what extent will each option improve patients' access to novel therapies? n = 41.

Source: Establishment survey.

Those NCAs responding were more confident in Option 2 than the alternatives

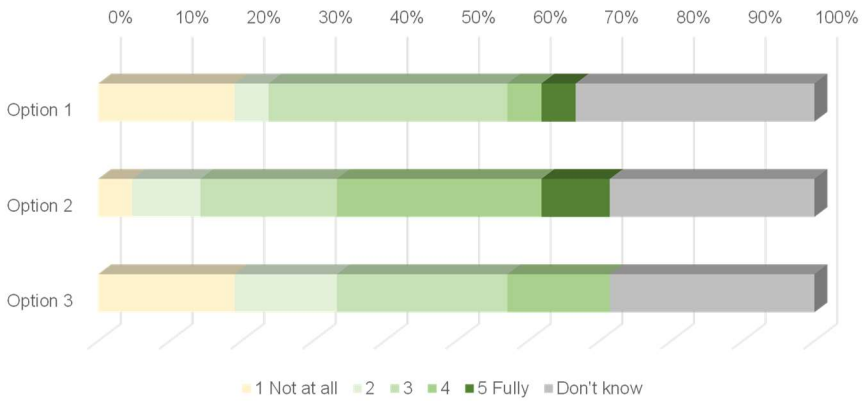


Figure 24. To what extent will each option improve patients' access to novel therapies? n = 21.

Source: NCA survey.

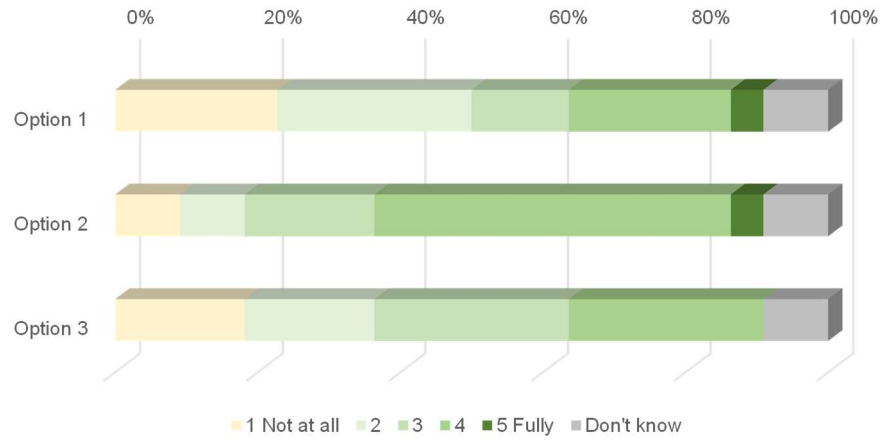


Figure 25. To what extent will each option provide a strengthened preparation process authorisation system that is outcome based? (n = 23)

Source: NCA survey.

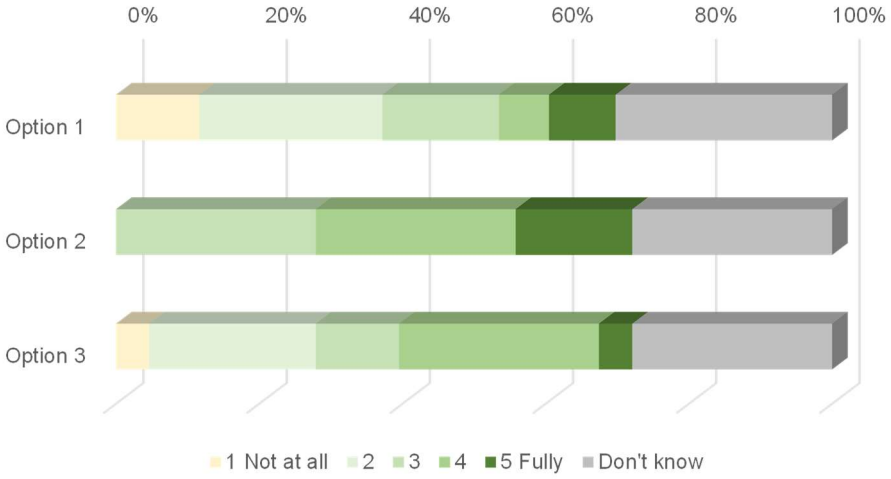


Figure 26. To what extent will each option provide a strengthened preparation process authorisation system that is outcome based? (n = 43)

Source: Establishment survey.

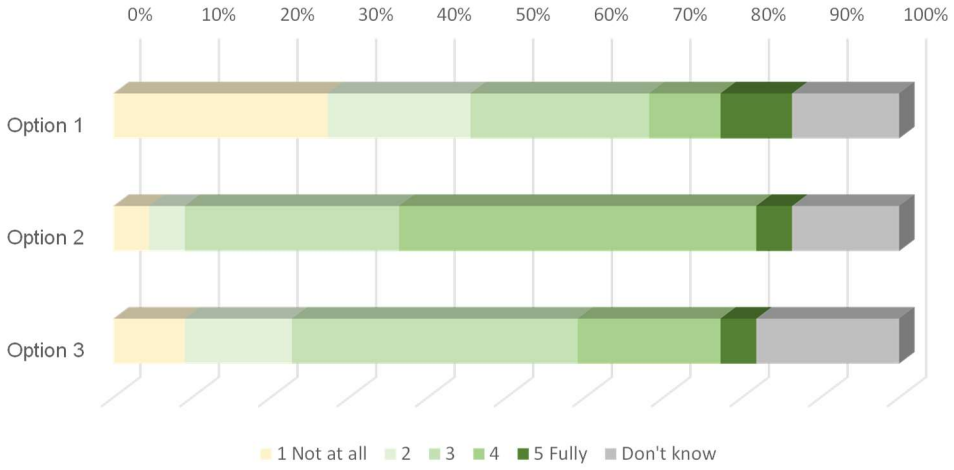


Figure 27. Impact on the problem that preparation process authorisation procedures for novel BTC applications are not fully harmonised across the EU? (n = 23)

Source: NCAs survey.

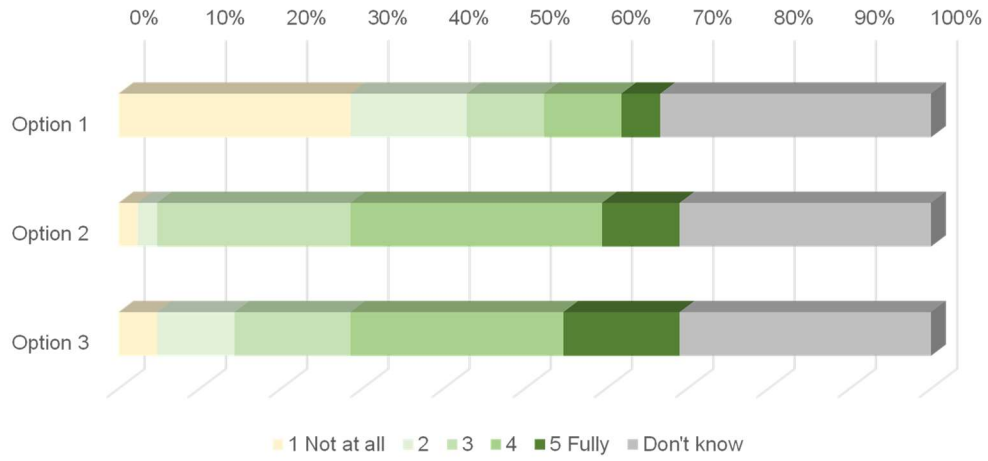


Figure 28. Impact on the problem that preparation process authorisation procedures for novel BTC applications are not fully harmonised across the EU? (n = 43)

Source: Establishment survey.

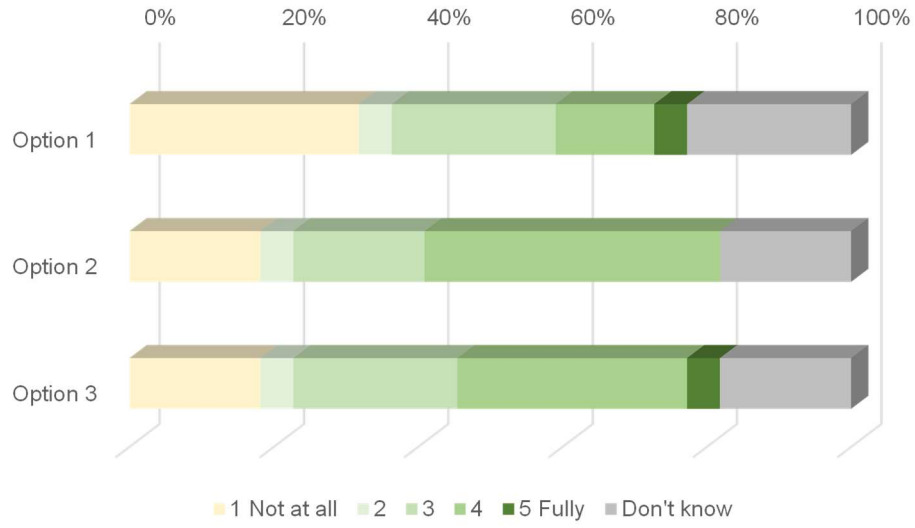


Figure 29. To what extent will the BTC classification/ clarification mechanism solve the problem of legal uncertainty for borderline BTC applications? (n = 23)

Source: NCA Survey

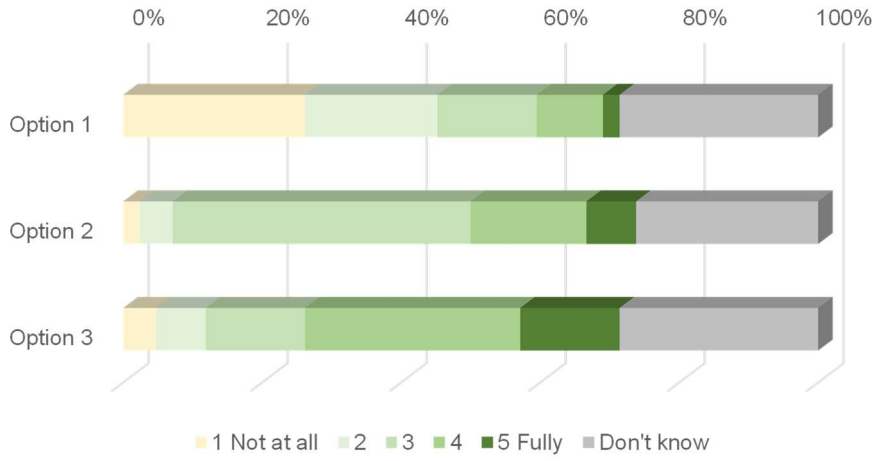


Figure 30. To what extent will the BTC classification/ clarification mechanism solve the problem of legal uncertainty for borderline BTC applications? (n =43)

Source: Establishment survey.

Responses at a workshop on border issues with other regulated frameworks expressed a clear support for increased interaction between the regulatory authorities.

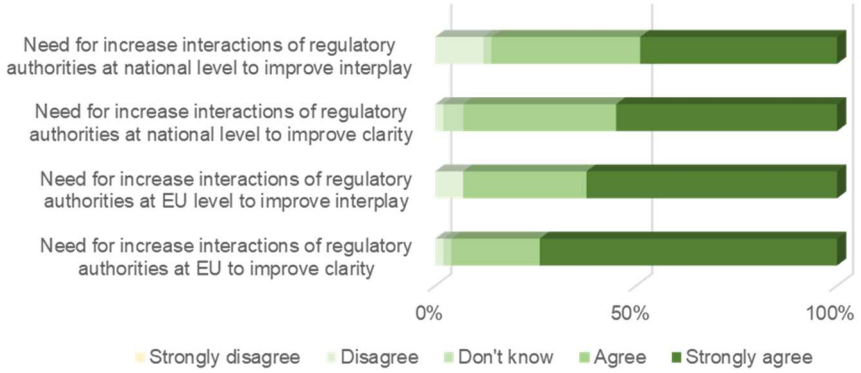


Figure 31. Do you agree that there needs to be increased interaction between the regulatory authorities at the EU level to improve clarity and interplay in relation to the provision of advice on the applicable regulatory framework for novel therapies? (N=105)

Source: Participatory workshop: Borderlines with Other Regulated Frameworks: Classification Advice and Interplay

Quality of governance: strengthening and harmonisation of oversight among Member States

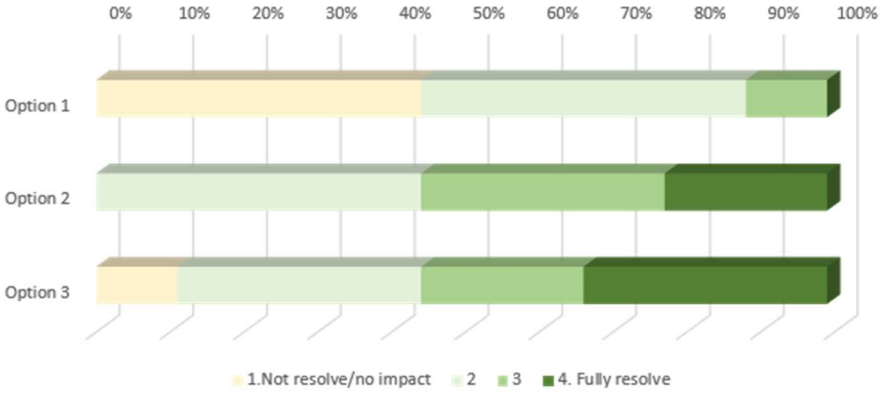


Figure 32. Options impact on resolving the problem of inspections conducted by national regulators not being performed objectively and competently – establishment perspective. Tissues and cells group n =11

Source: Participatory workshop: strengthening oversight – Establishments. Compared to a scenario in which the EU's BTC legislation is not reformed, and looking out over the next ten years to what extent will Policy Option [x] resolve the problem of inspections conducted by national regulators not being performed objectively and competently.

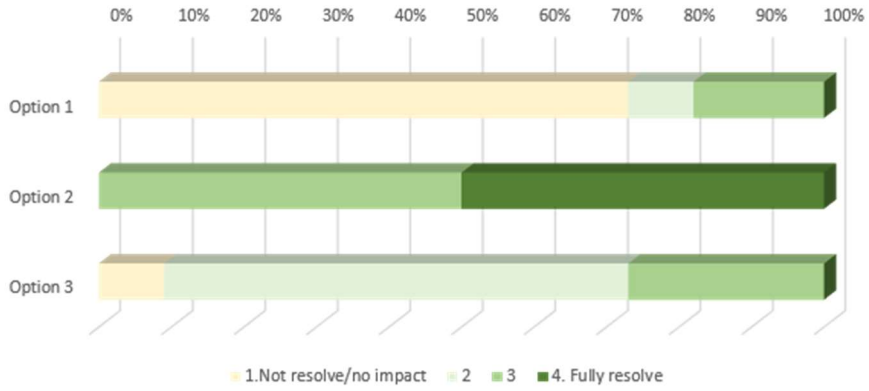


Figure 33. Options impact on resolving the problem of inspections conducted by national regulators not being performed objectively and competently – establishment perspective. Blood group=9

Source: Participatory workshop: strengthening oversight – Establishments. Compared to a scenario in which the EU's BTC legislation is not reformed, and looking out over the next ten years to what extent will Policy Option [x] resolve the problem of inspections conducted by national regulators not being performed objectively and competently.

There were differences between blood and tissue/cell groups in the oversight workshop for authorities in views on the options' impacts on inspections being performed objectively and competently - authority perspective

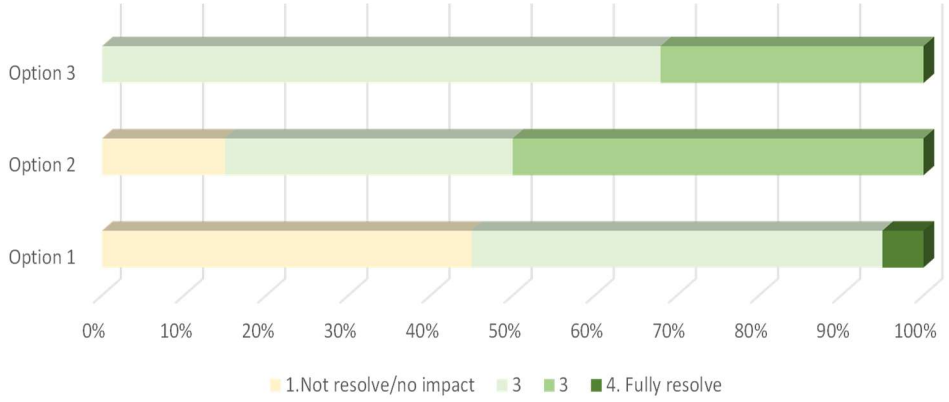


Figure 34. Compared to a scenario in which the EU's BTC legislation is not reformed, and looking out over the next ten years to what extent will Policy Option [x] resolve the problem of inspections conducted by national regulators not being performed objectively and competently.

Tissues and cells group n =17

Source: Participatory workshop: strengthening oversight – Authorities (blood and tissue sub-groups).

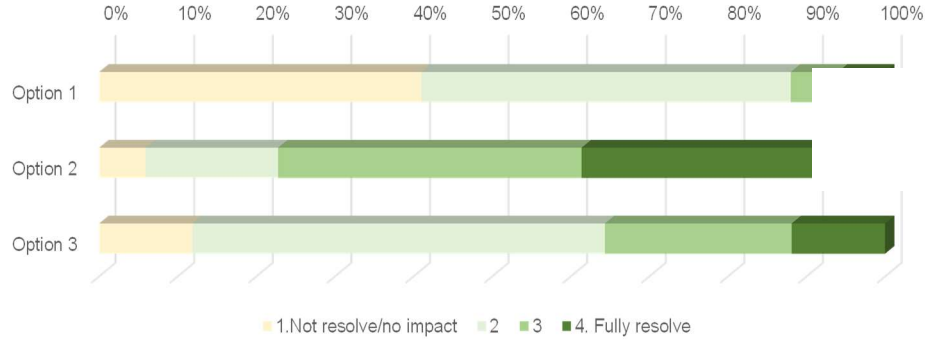


Figure 35. Compared to a scenario in which the EU's BTC legislation is not reformed, and looking out over the next ten years to what extent will Policy Option [x] resolve the problem of inspections conducted by national regulators not being performed objectively and competently. Blood group = 20

Source: Participatory workshop: strengthening oversight – Authorities (blood and tissue sub-groups).

Overall, respondents to the establishment survey were more confident that inspections will be performed objectively and competently if the measures proposed to strengthen oversight are adopted

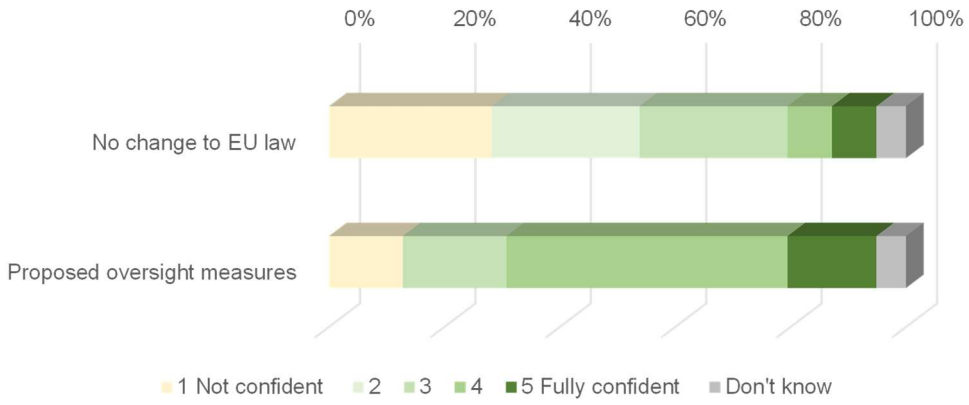


Figure 36. "How confident are you that competent authority inspections will be performed objectively and competently (i) if there is no change to EU law and (ii) if Option 2-1 is adopted?"; n = 39.

Source: Establishment survey

NCAs views on the objectivity and competence of inspections in the baseline and with the proposed oversight measures

Figure 37. "How confident are you that competent authority inspections will be performed objectively and competently (i) if there is no change to EU law and (ii) if Option 2-1 is adopted?"; n =23.

Source= NCA survey

Respondents to the NCA survey were, overall, positive that the measures would help to address inspectors' skills gaps

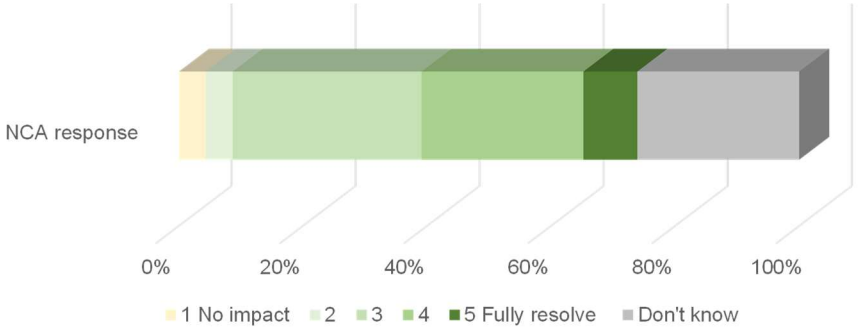


Figure 38. To what extent will the option solve the problem that skills gaps among inspectors can prevent inspections being completed to the expected standard? (NCAs only). n=23

Source: NCA survey.

Survey respondents expect the proposed measures to build trust among Member States, though not fully resolve current issues

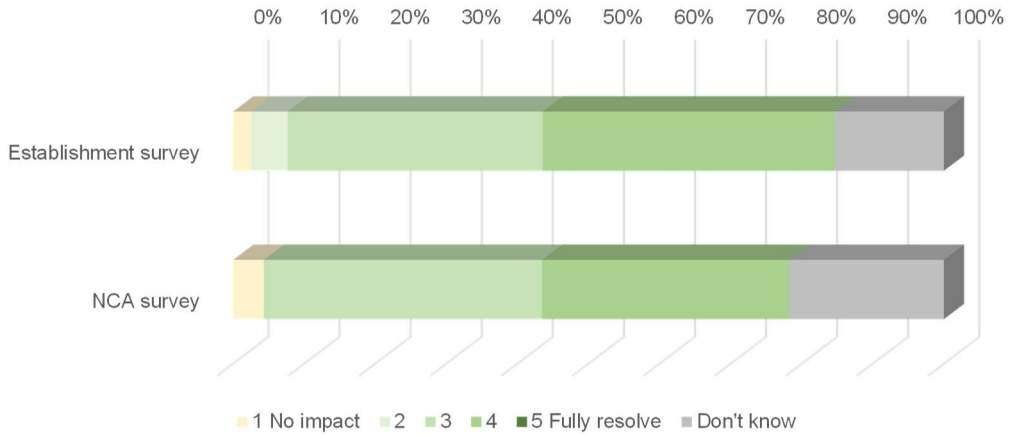


Figure 39. To what extent will the measures solve the problem of lack of trust/confidence among EU Member States? Est. survey, n=43; NCAs n = 23

Source: Establishment and NCA surveys.

Participants in the operators' workshop on oversight saw Option 2 as the option most likely to facilitate the mutual exchange of BTC across borders by building trust, confidence and harmonisation among Member States

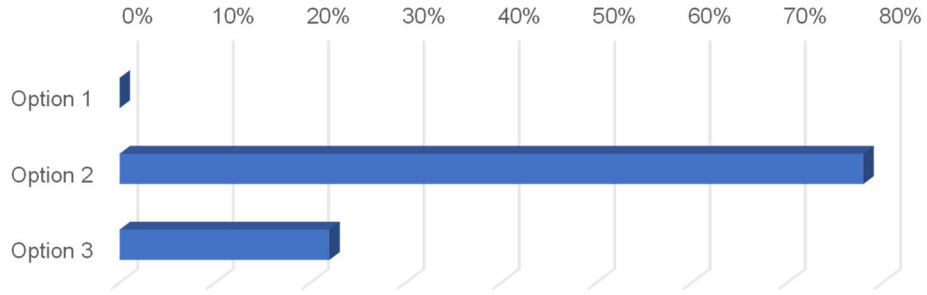


Figure 40. Which Policy option is best suited to strengthening harmonisation, confidence and trust among Member States and thus facilitate the mutual exchange of BTC across borders. Tissue group = 11 .

Source: Participatory Workshops on oversight.

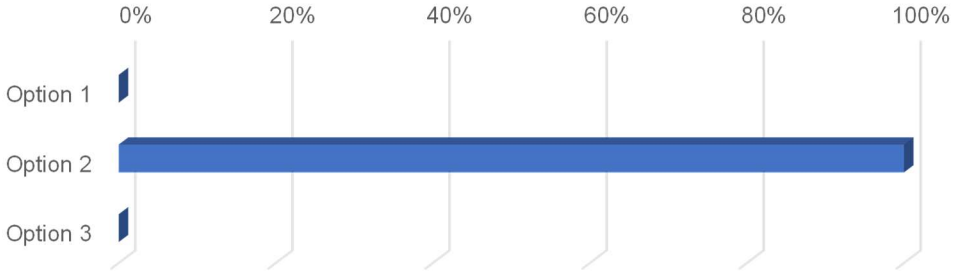


Figure 41. Which Policy option is best suited to strengthening harmonisation, confidence and trust among Member States and thus facilitate the mutual exchange of BTC across borders. Blood group=9 .

Source: Participatory Workshops on oversight.

A7.3 Stakeholder views on policy options

This section presents evidence on stakeholder perspectives on the impacts (as compared to the baseline scenario) of the policy options are presented in the following order.

A7.3.1 Health outcomes

Increase patient protection from all avoidable risks

Quality of technical guidance -mobilising relevant scientific and technical knowledge in the BTC sectors

Analysis of the Commission's Public and Targeted Consultations showed that, among respondents, professionals were seen as the most appropriate group for setting of technical rules in BTC allocation and distribution channels, while expert bodies were preferred by a majority of respondents for rules on air quality requirements, deferral/exclusion criteria and communicable disease testing, donor age limits, donor medical/behavioural history screening, follow-up of patients or offspring, genetic testing of gamete donors, quality controls, quality management, risk assessment for novel procedures, and storage conditions. Respondents tended to favour rules set in EU law for issues regarding contingency/emergency planning, consent, donor protection, donor reimbursement/

compensation, reporting (activity data reporting to the NCAs, SARE reporting to BE/TE and onwards) and traceability systems[154].

A poll at a workshop convened by the European Commission to discuss how technical rules for BTC can be kept up to date at EU level indicated that a majority of participants agreed or partially agreed that updates, scope, and specifics should be developed through technical rules developed by expert bodies, while a significant group also flagged a need for more information/discussion. When asked which rules should be defined in EU legislation, the most selected topics were donor protection rules, vigilance rules, traceability rules and requirements for activity data reporting to NCAs. A slightly smaller majority expressed support for quality management principles and contingency planning requirements to be defined in EU legislation, and slightly less than half of all participants also supported the inclusion of rules for risk assessment for innovation[155].

Increase protection of BTC donors, and children born from donated sperm, eggs or embryos, from specific risks

Increasing protection of donors

At a workshop convened for this study to discuss the better protection of MAR donors and children born as a result of MAR, 12 of 15 respondents to a poll agreed that there is a need to address inadequacies identified in relation to the limited protection afforded to MAR donors (particularly oocyte donors).

Stakeholder engagement suggests support for the proposed measures to protect donors based on expectations of positive impacts on health outcomes for donors.

A workshop on protection of blood and plasma donors convened for this study saw overall agreement that measures to strengthen blood and plasma donor protection were needed, and that any of the policy options would be an improvement on the *status quo*.

There was support for mandatory monitoring and reporting of donor reactions, irrespective of the impact of the reaction on the quality of the donated substance[156]. Option 2 was considered the most appropriate approach to ensuring comprehensive, up-to-date provisions for donor care, while it was felt that high level principles needed to be defined in the legislation (i.e. a combination of Policy Options 2 and 3).

There was also a strong support for adoption of internationally harmonised definitions for donation eligibility and reactions. Participants considered that donor eligibility criteria should be evidence-based and should be defined to optimise donor care. Harmonisation of donor eligibility ability criteria is especially desirable for plasma (which crosses EU borders at high frequency), although it was highlighted that local epidemiological differences should be taken into account. Participants felt there should be some form of long-term follow-up undertaken for donors, and that follow-up measures should be evidence based, while respecting the principle of proportionality.

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[154] Reported in Minutes of the Workshop with Stakeholders and Blood, Tissue and Cell Competent Authorities Substances of Human Origin Expert Group (CASoHO E01718) of 6 May 2021, DG SANTE.

[155] [155] Minutes of the Workshop with Stakeholders and Blood, Tissue and Cell Competent Authorities Substances of Human Origin Expert Group (CASoHO E01718) of 6 May 2021, DG SANTE

[156] In a poll in group focused on blood, 80% of the respondents answered 'yes' to the question "*Should the reporting of donor reactions become compulsory and include all donor (including autologous) reactions not those simply related to quality and safety*?" (with 20% answering 'don't know). In a parallel poll in a group focused on plasma, 86% replied 'Yes' to the question "*Should the reporting of donor reactions become compulsory and include all donor (including autologous) reactions not those simply related to quality and safety*?", 7% replied no and 7% 'don't know'.

A workshop on protection of donors for non-reproductive tissues and cells[157] explored the measures that could be introduced to better protect donors of bone marrow, peripheral blood stem cells, cord blood and any relevant replacement tissues donated during life. There was overall agreement among participants that measures that can help strengthen donor protection should be included in revised EU legislation.

Participants agreed that it would be more practical to have the high-level donor protection principles in the legislation (Option 3). However, Option 2 was seen as the preferable approach to setting donor care technical standards, allowing for agility and responsiveness and for inclusion of the professional bodies in setting standards.

Another workshop[158], attended by various representative groups and other organisations from the MAR sector, explored possible measures to improve MAR donor protection, especially for oocyte donors. These measures related to rules on eligibility for donation, donor health monitoring and long term follow up, particularly for oocyte donors. There was strong support for measures that would improve the protection afforded to oocyte donors.

The establishment survey attracted responses from two donor representatives which[159] favoured Options 2 and 3 over Option 1. The wider responses to that survey from other respondents showed a less clear pattern and featured a substantial number of 'don't knows'. The NCA survey showed higher confidence in Option 2.

Increasing protection of children born from MAR

There are recognised weaknesses in the protection provided by current BTC legislation to children born from MAR. The Commission's evaluation[160] of the current legislation concluded that the provisions for reporting transmissions of genetic conditions in offspring via vigilance programmes are unclear. The definition of 'serious adverse reaction' refers to outcomes in 'recipients', not clearly taking into account the offspring resulting from MAR using donated sperm or eggs. The main professional association for the MAR sector considers that the absence of mandatory requirements for monitoring the health of children born through MAR is an important gap in the legislation.

Avoid shortages of critical BTC therapies

NCAs see the proposed measures making a positive difference to the problem that decision-makers lack the information needed to identify and manage supply risks for critical BTC applications

40% of NCA respondents and more than 50% of respondents to the establishment surveys felt unable to comment on whether the measures would affect collection of critical BTC in the EU. Of those who did respond, 20%-30% thought the measures would have no impact. Many of the respondents to the establishment survey were unable to give a view on whether measures would affect collection of critical BTC.

[157] The event was attended by 60 representatives from invited organisations including representatives from national competent authorities for tissues and cells, professional societies representing TEs and clinical users, donor associations, EDQM (Council of Europe) and DG SANTE

[159] In response to the question: *"To what extent will each policy option solve the problem that donors are not fully protected from avoidable risks?"*

[160] Commission Staff Working Document. Evaluation of the Union legislation on blood, tissues and cells. {SWD(2019) 376 final}.

The proposed measures address preparedness and market transparency rather than providing direct interventions or plans to strengthen EU domestic supply. As such there is not a clear mechanism by which they would reduce risk of interruptions of supply and shortages relating to vis-à-vis third countries, and the EU's dependency on plasma imported from the US. This analysis is supported by feedback received via the surveys (Annex 7[161]) and accompanying remarks.

Greater knowledge about stocks and better coordination within Europe could help in tackling the problem over time. Nonetheless, a response based on monitoring and regulatory measures, while helpful, would not be sufficient and stronger supply-side measures would be needed if import dependency is to be reduced. There could be a concerted plan, supported by appropriate funding, for boosting plasma production from voluntary non-remunerated donors within the EU and diversification of supply. These conclusions are supported by views of the stakeholders consulted in the present study.

The 'transparency' measures will increase visibility of supply conditions and alert competent authorities to shortages. This measure may help reduce risks of shortages, however there are details yet to be defined that are relevant to how supply risk monitoring would work in practice, for example the definition of the definition of 'shortage' conditions that would trigger the notification to competent authorities by establishments. The stakeholders in the present research provided views supporting these points (Annex 7[162]).

There are details yet to be defined that are relevant to how supply risk monitoring would work in practice. Examples are the definition of the definition of 'shortage' conditions that would trigger the notification to competent authorities by establishments. The stakeholders in the present research provided views supporting these points (Annex 7[163]).

The specifics of the data that will be required and the associated sufficiency criteria are not yet defined, however it can be assumed that the proposed arrangements will deliver comparable data (Annex 7[164]). Stakeholder responses show confidence that proposed measures will deliver comparable supply data

Looking across all the measures proposed to tackle supply shortages, the main difference between options is the approach proposed to specification of the rules to be followed by establishments in developing contingency plans – the proposed supply data arrangements and facilities for regulators' support measures do not vary. There is comparatively little difference in the likely impact of options on overall preparedness and the EU's ability to manage future public health emergencies. However, the Option 2 solution of having rules set by EU expert bodies remains the preferred option. This conclusion is supported by feedback from the NCAs and respondents to the establishment survey (Annex 7[165]).

[161] Survey question: What impact will the proposed options have on the risk of interruptions of supply and shortages relating to vis-à-vis third countries, and the EU's dependency on plasma imported from the USA?

[162] Survey question: To what extent would the foreseen measures to monitor supply (including donations, exchanges between EU Member States, imports and exports, shortages) reduce the risk of critical shortages and help build strategic independence?

[163] Survey question: To what extent would the foreseen measures to monitor supply (including donations, exchanges between EU Member States, imports and exports, shortages) reduce the risk of critical shortages and help build strategic independence?

[164] Survey question: How confident are you that this option will provide sufficiency data that are comparable across the EU?

[165] Survey question: To what extent will each option improve the EU's preparedness for future crises and public health emergencies?

A7.3.2 Innovation and research

This section provides further evidence on how innovation, research and development may be impacted by the proposed package of measures being considered as part of the revision to the BTC legislation.

Regulatory coherence: the extent to which there is clarity as to which regulatory framework the substance or product belongs

A participatory workshop focused on borderline issues *(Borderlines with Other Regulated Frameworks: Classification Advice and Interplay)* was attended by a diverse range of 105 stakeholders[166]*.* The majority of stakeholders either agreed or strongly agreed that there needs to be increased interaction between the regulatory authorities at the EU and national level to (a) improve clarity in relation to decisions on the applicable regulatory framework for novel therapies and (b) to improve interplay for products that fall under more than one regulatory framework.

Most stakeholders engaged throughout the impact assessment process expressed support specifically for classification/clarification measures (M4.2-M4.4) to resolve the borderline issues. Over three-quarters of respondents to the Commission's Public Consultation (77%, 164 respondents) felt that an EU level structure/committee should co-ordinate decisions with equivalent committees in the medicinal products and medical device frameworks.

A clear preference for policy option was not identified in the NCA or establishment survey. The variation in responses per option in the surveys' questions on this issue may reflect some failure to pick up difficulties understanding the structure of the measures or options. In contrast, participants who took part in workshops (Workshop 11 in particular) and stakeholders engaged as part of research for the borderline case studies generally expressed support for Option 2.There were strong views expressed in the aforementioned workshop on borderline issues (Workshop 11) that under Option 2, it was more likely to have a classification mechanism which meets the need to be 'lean, quick and easy' and address all of the possible frameworks that might be relevant (medicinal products, devices, food, cosmetics, etc.).

Specifically in regard to M4.2, a key message emerging from Workshop 11 on borderlines was that establishing a BTC advisory mechanism will promote a common approach between BTC authorities. Clear definitions and good collaboration across regulatory frameworks will be the most effective measures to improve classification mechanisms, particularly given that the number of novel therapies at the borderlines are likely to increase.

To enhance the impact of M4.2, one NCA representative suggested decisions should be binding rather than advisory. This was also considered during the workshop on borderlines (Workshop 11) where participants in a breakout group discussed potential difficulties of resolving issues whilst legally binding decisions can still only be made by NCAs. Several stakeholders in the PRP and autologous adipocyte cells case studies also suggested that a mechanism which could provide a binding decision (as is the case with medical devices) would be preferable.

There was general agreement that if this was not possible, at the very least the committee should be made up of experts (including both professionals and clinicians), and follow a rigorous scientific methodology and decision-making process to ensure Member States trust and follow the advice. In response to the survey of establishments, one organisation representing manufacturers reflected that the most important thing was rather the agility

[166] The event was attended by 105 representatives from: EU institutions, organisations in charge of standards setting, pharmaceutical industry, advanced therapy medicinal products and medical devices organisations, national competent authorities (NCAs), BTC establishments representatives (banking and collection of SoHO), patient/donor organisations, with a predominance of stakeholders and authorities from the pharmaceutical sector.

and proportionality of the application procedure, so developers receive timely answers to their questions.

Respondents to the Public Consultation also noted considerations to take into account for a BTC classification advisory mechanism/committee, including that it requires integration with bodies in (AT)MP and MD, or at least good coordination, to avoid duplication. Hence, M4.2 should be implemented alongside M4.3 and M4.4 to be effective. A stakeholder interviewed for the PRP case study suggested that an overarching committee could be useful, subject to equal inputs from the relevant disciplines and avoiding pharmaceutical interests dominating. One stakeholder in the isolated hepatocyte case study stressed the importance of patient representation to ensure the perspective of the patient is considered.

An NCA recommended that the three areas (SoHO / Pharma / MD) had to be better coordinated. An expert interviewed for the SED case study, felt a 'one-stop-shop' model with a mechanism to address interplay issues (M4.3) would be particularly beneficial to also resolve issues where medical devices are used. A representative organisation representing manufacturers reflected that this mechanism would only work if SoHO / Pharma / Medical Devices have a veto or final vote as these sectors have relevant expertise. Another representative organisation representing manufacturers reflected that prior authorisation needs to be based on a common set of criteria across all Member States to avoid fragmentation and inconsistencies in decision making; 'major change' needs to be defined.

It was generally agreed that a benefit of a centralised advisory mechanism (M4.4) will be that at present, the same regulatory issues are faced repeatedly across Member States, therefore a mechanism will introduce efficiency for Member States and certainty for stakeholders as once a recommendation/advice had been provided via the mechanism the query would not need to be submitted again (reported by stakeholders in the FMT case study presented in Annex 9). The EMA and the CAT felt that a multidisciplinary EU centralised classification body, with experts from different sectors, should only exist for 'real' borderline issues: it should not prevent or delay the development of products for where the regulatory situation is reasonably clear. In this case, this body should not be the primary 'entry door' for classification, but instead act on referred borderline cases only based on precise criteria to be developed.

Much of the support for M4.4 was based on the assumption that this would also not compete with existing mechanisms (e.g. The CAT ATMP classification processes) as this would create further complexity, particularly if there were diverging opinions. There was general agreement that an overarching structure which clarifies respective mandates, or a single committee of experts with diverse backgrounds that could cover all the topics in the area, would prevent disruption or additional regulatory confusion. The EMA noted that this may, in turn, promote more innovation, since developers would have more certainty about the legal/regulatory regime and requirements that would apply to their products. It would also mean that products do not fall 'between the cracks' between different legislative frameworks, thereby ensuring there are adequate requirements for testing, authorisation and efficacy and safety monitoring for these products.

As with M4.2, there was a discussion in Workshop 11 focused on the committee described under M4.4 having powers to make legally binding decisions. In the absence of this, it was suggested that some sort of monitoring or follow-up process, as well as clearer communication/exchange of information between the different authorities, would significantly enhance this measure.

Regulatory coherence: the extent to which there is consistent/comparable regulatory requirements for BTC, including coherence across legal frameworks

A key message from the workshop on borderline issues (Workshop 11) was that when substances move between regulatory frameworks (e.g. when BTC are the starting material for the manufacture of a medicine or a medical device), effective communication on donor requirements for starting materials, traceability, vigilance, etc. between the relevant authorities is essential. In one breakout group, it was emphasised that good collaboration

at the EU level in this context would help to solve issues faced during inspections and authorisation at the national level.

Likewise, a regional tissue bank representative interviewed for a case study on decellularised heart valves suggested a coordination mechanism (M4.4) would be useful for improving oversight: *"We need to accept that during the process from obtaining material for, to the use of a product, there can be changing regulatory frameworks… and we need to coordinate this between the different expert bodies and competent authorities to ensure appropriate vigilance and pharmacovigilance. There is [currently] no connection and no coordination and communication between these aspects or the communication of adverse reactions".*

Respondents to both the establishment and NCA surveys generally demonstrated more support for Option 2 to tackle the problem that preparation process authorisation procedures for novel BTC applications are not fully harmonised across the EU. Across surveys, survey results on this indicator featured a high number of "don't knows", however, this might be explained by the lack of definition on what measures might currently look like in practice, particularly under M4.2-M4.4.

A stakeholder consulted as part of a case study on demineralised bone matrix (Annex 9) from a national blood and transplant service reported that a standardised risk assessment process (under Option 2 or 3) would be beneficial. The stakeholder suggested the example of the Good Practices for demonstrating safety and quality through recipient follow-up (EURO GTP II) project (which aims to set up the good practices applied to tissues and cells preparation processes and patient follow-up procedures) as an example of a useful tool for assessing novel products, as well as checking the risk of existing products.

Looking across Europe, participants in Workshop 1 mentioned mostly positive impacts of strengthened process authorisation procedures for novel BTC (4.5-4.7) including harmonisation, mutual recognition, reinforcement of trust, increased availability for patients to novel products and increased innovation. A stakeholder consulted for the pancreatic islets case study said that increased oversight of new/novel preparation processes will help to address the issue of some Member States not having similar standards or the infrastructure to ensure cell expansion or isolation processes are safe, efficacious and of good quality. Harmonisation measures, such as strengthened preparation processes, will also provide more opportunities for the cross-border supply of pancreatic islets. A stakeholder interviewed for a case study on cultured limbal cells reflected that strengthened preparation process authorisation will be beneficial as it would introduce a minimum standard of quality and safety at the EU level.

The main concerns from stakeholders revolved around the level of expertise needed in both establishments and authorities for a revised risk assessment process, and the length of time this would take – given there is often a need to be iterative (particularly at the early stage of innovating therapies) which may create significant time/resource pressures. However, one stakeholder engaged as part of the isolated hepatocytes case study (Annex 9) suggested that some costs would be offset by more coordinated regulation between sectors/countries (including sharing information/data on authorisation (M4.8)). A statement from the European Eye Bank Association also highlighted that measures, including sharing of preparation process authorisation information and related clinical data across the EU, will facilitate collaboration at EU level to clarify the regulatory status of limbal stem cell treatments[167]

There were also some comments from participants in Workshop 1 that some Member States already have considerably stringent systems and processes for authorising BTC which needs to be addressed under Option 2 or 3.

[167] European Eye Bank Association (2018). EEBA Statement on Stem Cell Applications in the Treatment of Ocular Disorders. Venice, 22 October 2018. (Accessed 24 June 2021]

Impact on innovation: the extent to which measures facilitates R&D

In general, respondents to the establishment and NCA survey expected all options to have a positive impact on innovation in the BTC sector.

Measures to resolve borderlines more efficiently (M4.2-M4.4) could allow more actors in the adjacent fields working together to provide those treatments at scale. Stakeholders interviewed for case studies on decellularised dermis and decellularised heart valves were in general agreement that having a BTC advisory committee (M4.2) could provide early clarity on the regulatory pathway to support R&D and ensure that developers had an upfront understanding of the different stages and costs involved in product development.

Sokal (2013) explains that being allowed to treat a few patients with ATMPs under the "hospital exemption" rule is important to preserve, as it allows researchers and physicians to explore new targets for cell therapies. A number of stakeholders suggested an overarching coordination mechanism (M4.4) could improve the use of, and trust in, the hospital exemptions pathway where the preparation is considered to be an ATMP.

More standardisation created by strengthened preparation processes (M4.5-M4.7) could also improve cross-border research activity. Additionally, these measures may provide further confidence and trust in the BTC sector as there is increased personalisation of medicine. An expert interviewed for the cultured limbal cells case study argued the whole field of regenerative medicine (particularly related to the eye repair treatments) are still pioneering therapies for single patient-use and measures to strengthen preparation processes and authorisations (M4.5-M4.6) will 'promote this new era of medicine'.

In response to the roadmap consultation, stakeholders from Aarhus University Hospital working on FMT therapies[168] reported that "*innovation is supported in transparent and versatile environments such as academic settings where investigator-initiated clinical trials may be performed with appropriate regulatory oversight. Recent initiatives within the EU support the continued consolidation of such trials, and this could be further supported through the present legislation".* Interviewed stakeholders, though generally in favour of the principle to generate more robust clinical evaluation data for high-risk, novel therapies (M4.7), cited concerns around costs/time required to do this and how this may stifle R&D. One stakeholder interviewed for the autologous adipocyte cells case study felt it was not reasonable to expect a "regular hospital to be able to conduct a clinical trial". A stakeholder interviewed for the chondrocytes case study felt that a 'one-size-fits-all' approach would hinder R&D if there was a requirement for collection of clinical data when even when there was a small patient population.

SMEs and large pharmaceutical companies developing BTC-derived products and treatments will be impacted by any changes to procurement and processing stages, as well as measures which define the pathway for bringing products to the market. Current data on commercial developers primarily exists on those manufacturing ATMPs, but this provides an indication of the size of the sector. As part of a survey conducted by Ten Ham *et al* (2018) into the challenges of ATMP development[169], established there were around 271 commercial developers active in ATMP development in 2017 in the EU (then the EU28)[170].

When regulatory pathways and frameworks are not clear, investors can become sceptical about investing, and a clearly defined pathway is a key factor in making investment

[168] Hvas, C.L. (2020). Blood, tissues and cells for medical treatments & therapies – revised EU rules: Feedback from: Aarhus University Hospital. (Accessed 26 July 2021). Available from: https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12734-Blood-tissues-and-cells-for-medical-treatments-&-therapies-revised-EU-rules/F1307554_en

[169] Ten Ham, R., Hoekman, J., Hövels, A. M., Broekmans, A. W., Leufkens, H., & Klungel, O. H. (2018). Challenges in Advanced Therapy Medicinal Product Development: A Survey among Companies in Europe. Molecular therapy. Methods & clinical development, 11, 121–130. https://doi.org/10.1016/j.omtm.2018.10.003

[170] This list includes active commercial developers involved in ATMP (GTMP, CTMP, Tissue engineered product, or combined ATMP) development for human use, established in or developing for at least 1 of the 28 EU member states.

decisions. In this case, there was general agreement across several case studies that M4.2-M4.4 could provide early clarity on the regulatory pathway to ensure developers were clear on different stages/costs involved in product development. Additionally, incorporating 'unregulated' therapies (such as FMT, DHBM and SED) into the scope of the BTC legislation (M1.2) could indicate its value and thereby enhance innovation and increased investment in these field. However, the cost of regulatory requirements needs to be justified by the benefits; regulatory measures need to be chosen carefully to not overburden actors and it is important to recycle/build on what guidance and best practice already exists.

As a stakeholder interviewed for the chondrocytes case study suggested that onerous clinical evaluation requirements (M4.7) could result in less private sector innovation, particularly where there are few participants to recruit and therefore trials need to run for longer (with accompanying costs). The stakeholder explained there is a *"very fine line between controlling the sector and ensuring robust evidence, and that can stifle investment and innovation".*

Impact on innovation: public sector innovation

Among respondents to the establishment survey, the high share of 'don't knows' indicates uncertainty but there was a slight preference for Option 2 as a mechanism to address challenges faced by public sector innovators. NCAs also viewed Option 2 as more favourable for public sector entities wanting to innovate. In any case, a recurrent finding from interviews with public sector stakeholders as part of the borderline case studies was that a heavy regulatory burden created by new measures (e.g., M4.5-M4.7) could also decrease the will and possibility of innovation in the public sector.

Stakeholders interviewed for the aforementioned case studies on cultured keratinocytes, cultured limbal cells and isolated hepatocytes felt the measures M4.2-M4.4 would strengthen coordination and communication between sectors and therefore enhance confidence and trust in public sector organisations. These measures could also and support more coordination/clarification around the hospital exemptions process, to allow for continued R&D in the public sector and level the playing field.

More consistent and better improved national process authorisations

The need for a strengthened preparation process authorisation system is already well-established. 155 respondents (72%) to the Commission's Public Consultation felt legal requirements should be introduced in the EU legislation for demonstrating safety, quality and efficacy when blood, tissues or cells are prepared or used in new ways. The funding of the GAPP Joint Action (an EU-funded action with the full title: *Facilitating the Authorisation of the Preparation Process for Blood, Tissues and Cells*) between May 2018 and 2021 demonstrated a commitment to support NCAs in improving the assessment and authorisation of novel BTC preparation processes.

Stakeholders consulted throughout the study have generally been positive about introducing an outcome-based measure to strengthen the preparation process authorisation system. Respondents to surveys for both establishments and NCAs generally felt positive that a strengthened preparation process was possible under all options. Most participants (81%) attending a dedicated workshop on authorising novel BTC[171] expressed support for M4.5 and M4.6. (first introduced during a presentation at the same workshop by the GAPP Joint Action Outcome consortium).

[171] Workshop 1: The event was attended by 80 participants from invited organisations, including national competent authorities (CAs), professional societies representing BTC establishments and clinical users, patient representative organisations and representatives from EU institutions (DG SANTE, HaDEA, EDQM)

Participants in the workshop generally preferred rules for conducting risk assessments and designing clinical studies be provided by EDQM under Option 2, and foresaw the value of using EDQM monographs to improve the standardisation of preparation processes. During their presentation in the workshop, the GAPP consortium also emphasised that a dynamic adaptation of the BTC Directives to rapid technological innovation should be granted through the use of continuously updated Technical Guides such as the EDQM Guide for the quality and safety of blood and tissues and cells. Representatives from the UK delivering serum eye drop treatments agreed that a joint regulation model for implementing these rules (which was dynamic and informed by experts) would be the best option *"as long as it is in one guide with some monographs, so then we know that it is an accepted BTC product and… so it has input from experts and competent authorities, and it will be clear what it is regulated under".*

Number of Member States sharing data on national authorisations

A stakeholder interviewed as part of the PRP case study felt that the IT platform (M4.8) proposed to share information across Member States on preparation process authorisations, as well as other data and/or experiences between establishments, could lead to greater transparency, especially if it mandatory and available publicly (with appropriate data protection management). Improved circulation of data and research results may lead to greater R&D in the sector (e.g. Through the promotion and development of certain techniques or processes) with downstream benefits to patient access (e.g. as a result of more products being developed and approved for use).

A statement from the European Eye Bank Association highlighted that measures, including sharing of preparation process authorisation information and related clinical data across the EU, will facilitate collaboration at EU level to clarify the regulatory status of limbal stem cell treatments[172].

PRP case study consultees reflected that measures to strengthen preparation processes would increase costs as each establishment will have to evaluate products in their setting, and not all EU countries have a centralised blood establishment organisation, therefore each fragmented establishment would have to create their own sets of validation data. As such the sharing of preparation process authorisations between Member States was strongly supported.

One stakeholder interviewed for the isolated hepatocytes case study also suggested increased oversight of preparation processes, including the need for clinical evaluation of novel processes, might increase costs. However, the stakeholder also agreed that some costs would be offset by more coordinated regulation between sectors/countries (including sharing information/data on authorisation (M4.8)).

A7.3.4 Good governance and administration

Impact on quality of inspections

Participants in two separate workshops on oversight convened for this study for representatives of (i) establishments and (ii) authorities were asked in polls to indicate their confidence in the proposed measures' likelihood of improving the quality of inspections.

There were some differences between blood and tissue/cell groups at the operators oversight workshop in participants views of the options' likelihood of delivering high quality

[172] European Eye Bank Association (2018). EEBA Statement on Stem Cell Applications in the Treatment of Ocular Disorders. Venice, 22 October 2018. (Accessed 24 June 2021]

inspections. There were also differences between blood and tissue/cell groups in the oversight workshop for authorities.

The proposed oversight measures will likely ensure that competent authority inspections will be performed objectively and competently. This point was reflected by the stakeholders consulted in the present research (Annex 7[173]).

The same issue was put to survey respondents. The results suggest that those replying to the establishment survey were, overall, more confident about the impacts of the proposed reforms on inspections than were NCAs.

Overall, respondents to the establishment survey were more confident that inspections will be performed objectively and competently if the measures proposed to strengthen oversight are adopted.

Survey responses suggest that NCAs are divided on the proposed reforms – a few appear to lack confidence that the proposals will mean inspections are performed objectively and competently, but more see the potential for them to deliver better outcomes

Impact on the skills of inspectors

The measures include provision of inspection guidance, issued by the Commission. The possibility (outside the legislative framework) of the EU organising training for inspectors has also been discussed.

The proposed measures are expected to have a positive impact on the problem of inspectors not having the skills required to conduct inspections to the expected standard. This conclusion is supported by the views of stakeholders consulted in the present study; see Annex 7[174] for further information.

NCAs participating in a workshop on oversight organised for this study were asked about the impact of the oversight measures on the problem of inspectors not having the skills required to conduct inspections to the expected standard. The results indicate that the proposed measures are expected to have a positive impact.

Participants in the NCA workshop on oversight saw the measures having a positive impact on the 'inspector skills gap', especially when packaged in Option 2.

In the NCA survey, participants that provided a response were mostly positive about the impact of the oversight measures on tackling the skills gap.

Respondents to the NCA survey were, overall, positive that the measures would help to address inspectors' skills gaps

Impact on trust/confidence among EU Member States

A recognised issue with the status quo, which is projected to continue in the baseline scenario, is Member State authorities lacking confidence in decisions made by counterparts in other countries. This can lead to duplication of authorisation processes, barriers to transfer of BTC between Member States, etc. The proposed measures under will resolve

[173] Survey question: "How confident are you that competent authority inspections will be performed objectively and competently (i) if there is no change to EU law and (ii) if Option 2-1 is adopted?"

[174] Workshop question: Compared to a scenario in which the EU's BTC legislation is not reformed, and looking out over the next ten years to what extent will Policy Option [x] resolve the problem of inspectors not having the skills required to conduct inspections to the expected standard?

Survey question: To what extent will the option solve the problem that skills gaps among inspectors can prevent inspections being completed to the expected standard?

this problem of a lack of trust and confidence among EU Member States, and this conclusion is supported by stakeholders consulted in the present study[175]. The survey responses suggest respondents are fairly confident that the measures will resolve this problem (in both cases almost all rated their confidence level at 3 or 4 out of 5, none answered '5').

Survey respondents expect the proposed measures to build trust among Member States, though not fully resolve current issues. In the workshop on oversight held with operators there was a strong message from participants that Option 2 would best achieve the goal of improving cross-border exchange of BTC. Participants felt that the measures in this policy option would help to improve harmonisation and trust between Member States.

[175] Survey question: To what extent will the measures solve the problem of lack of trust/confidence among EU Member States?

Annex 8: Stakeholder perspectives on the feasibility of specific measures

This annex provides information on points relating to the implementation of specific measures proposed in the legislative reforms. It is organised by reference to the five strategic objectives.

A8.1 Objective 1: Measures intended to increase patient protection from all avoidable risks

M1.2 – EU law is changed so that all SoHO/BTC for which the EU has legal competence are covered by EU safety and quality rules (bringing breast milk, faecal microbial transplants, etc. under EU law)

The proposals for legislative reform include a measure, incorporated into all options, that would extend the scope of the EU's BTC legislation to cover all SoHO/BTC for which the EU has legal competence (M1.2). This would apply a harmonised EU regulatory regime to activities and is expected to increase patient protection.

In an expert workshop[176] conducted for this impact assessment support study there was strong support for expanding the scope of the legislation to include new substances and therapies. Workshop participants supported including of FMT, DHBM, and SEDs. Several other substances, such as PRP were identified as potential candidates for inclusion. 40 of 43 (93%) expert respondents to a poll held during the workshop agreed that broadening the scope of the legislation on tissues and cells to include substances and treatments such as breast milk and FMT would increase safe and qualitative access to them for patients. There was also strong support for the scope of blood legislation to be extended to cover other blood products and treatments (such as fibrin glue and extracorporeal photopheresis) (14 of 18 expert respondents agreed). Participants considered that the biggest challenge to be addressed when extending the scope of the legislation would be achieving harmonisation – a consistent approach across the EU. This issue is tackled by other measures in the reform package.

The same concern about harmonisation may explain the variation between options in the responses to the establishment and NCA survey question on whether the policy options will solve the problem that some BTC applications fall outside the scope of the EU's safety and quality rules. The options are identical in scope (including the extension of the legislation to cover new areas) but the results show less confidence in Option 1 than in Option 2 or 3[177].

While the workshop saw strong support for expanding the legislation's scope, several participants raised concerns about ensuring that any legislation was proportional. For example, it was felt that the scope should cover substances for human use only, but that the scope should not extend as far as SoHO used for research.

Respondents to the establishment survey commented on the feasibility of implementing this measure. One manufacturer from the pharmaceutical industry recommended that requirements for competencies and education of qualified persons should be updated to reflect the newly introduced products (they require more microbial competencies than a traditional medical doctor background). A representative organisation for manufacturers suggested that the Commission would have to work in close partnership with expert bodies and all relevant stakeholders, including industry, to define the principles in a way that sets

[176] The 86 participants in the workshop included regulators, BTC banking/collection stakeholders, manufacturers of pharmaceuticals and medical devices, and patient or donor representatives.

[177] Results may also reflect a general preference for the Option 2 solution, irrespective of the specific issue.

a stable framework for dynamic adaptation of technical rules to new technologies and risks. A further stakeholder categorised as being part of an "other sector relevant to this consultation" suggested that the principles should be applicable to such substances, and include all bodily fluids.

Respondents to the NCA survey reported that there is a need for more capacity or resources for NCAs if this measure were implemented. As shown in Figure 1 and 2 below, survey respondents were more confident that the problem of BTC applications falling outside the scope of EU rules would be resolved under Option 2 than with the alternatives.

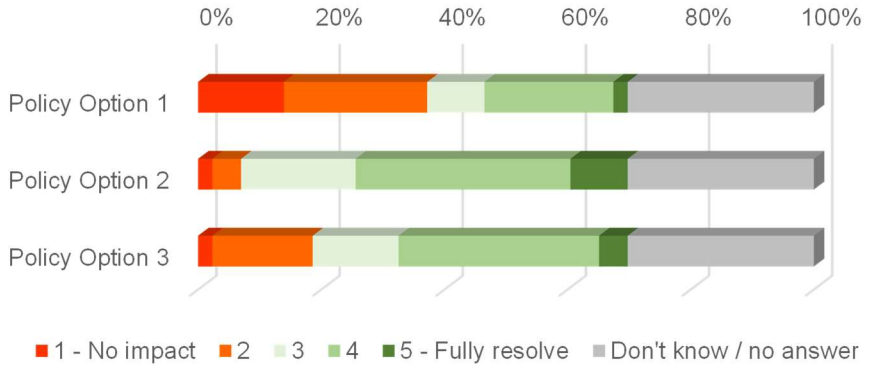

Figure 1. To what extent will each policy option solve the problem that some BTC applications fall outside the scope of the EU's safety and quality rules?

Source: Survey of establishments (n = 43)

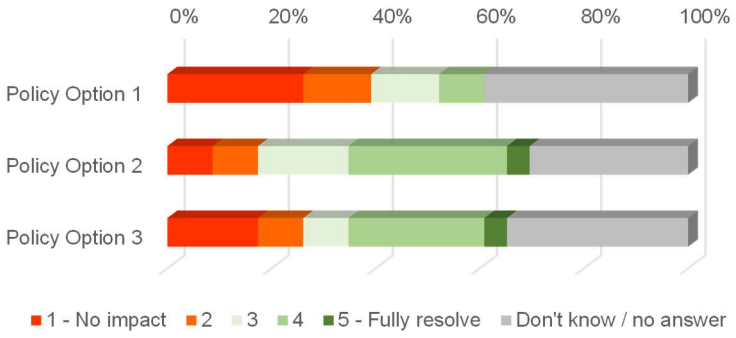

Figure 2. To what extent will each policy option solve the problem that some BTC applications fall outside the scope of the EU's safety and quality rules?

Source: Survey of NCAs (n = 23)

Some stakeholders consulted for the borderline case studies discussed access concerns for DHBM and FMT if the scope of the BTC regulations were expanded to include these products. The European Foundation for the Care of Newborn Infants requested that the Tissues and Cells Directive ensures equitable access to safe DHBM for preterm, sick, and low birthweight infants as a key theme of the legislation and accounts for the practical specifics of human milk donation[178]. The Oxford-PATH Human Milk Working Group[179] similarly recommended that "ethical principles of equity and fairness, reduction of

[178] European Foundation for the Care of Newborn Infants: Working Group on Human Milk Regulation. (2020). Making Human Milk Matter - The need for regulation in the European Union. Policy Recommendations. (Accessed 21 July 2021). Available from: https://www.efcni.org/wp-content/uploads/2021/01/2021_01_21_EFCNI_MakingHumanMilkMatter_PolicyRecommendations_final-small.pdf

[179] Israel-Ballard, K., Cohen, J., Mansen, K., et al. (2019). Call to action for equitable access to human milk for vulnerable infants. *The Lancet Global Health*. 7(11). DOI:https://doi.org/10.1016/S2214-109X(19)30402-4

vulnerability, and respect for autonomy and human rights" should shape the development of DHBM global, regional, and national guidelines and legislation.

A response to the roadmap consultation from the German Human Milk Bank Initiative[180] stated its support for regulating the use of DHBM but cautioned that regulations should not reduce DHBM availability. A stakeholder in the breast milk case study prepared under this current contract (Annex 9) acknowledged that EU regulation would increase harmonisation, but noted it will be important to ensure that regulation is sufficiently flexible to take into account how milk is used differently in different parts of the EU, and regulators should not implement constraints (though it is noted that BTC regulations do not directly regulate the use of products).

Another stakeholder consulted in the borderline case study stated that there also needs to be more investment in technologies and equipment used for milk banking. The stakeholder stated that incorporating DHBM into EU law would indicate that it is a valuable resource and would encourage Member States to increase investment. In response to the survey, a healthcare provider of transfusion of blood and blood components cited difficulties with DHBM being exchanged via the internet without appropriate tests from milk banks. The stakeholder recommended that breast milk be treated as human tissue and biological liquid as it is dangerous for the infant's health to consume breast milk from a donor without the appropriate microbiological tests being conducted.

A stakeholder consulted for the FMT study also discussed other (related) innovative microbiota products and treatments, including drugs made from microbiota in breast milk, as well as vaginal, oral, and skin microbiota, all of which could be affected by changes to legal frameworks. Aarhus University Hospital's response to the roadmap consultation[181] recommended that other human-derived microbiota communities be covered by BTC regulations. However, an interviewed stakeholder suggested that the regulations should not just include faeces and human breast milk but instead all microbiome samples should be considered.

The Netherlands Donor Faeces Bank's roadmap response[182] stated that proper legislation on faeces donation is needed to guarantee wide availability of stool preparations for FMT. Another stakeholder consulted for the FMT case study thought that including FMT in BTC legislation would increase accessibility and reduce problems of access. In a published journal article[183], Hvas *et al* suggest that regulating FMT as a tissue would allow for both hospital-based and commercial production, ensuring broad access.

A stakeholder consulted for the autologous adipocyte cells case study suggested that cosmetic procedures should be treated the same as other procedures. In the PRP case study a stakeholder recommended that, as the EU Medical Device Regulation 2017/745 regulates both contact lenses for vision and contact lenses for cosmetic purposes (coloured contacts), the BTC legislation should similarly include cosmetic indications to ensure the safety and control of cosmetic and aesthetic uses of BTC products such as PRP[184]. Other

[180] Sunder-Plassmann, A. (2020). Blood, tissues and cells for medical treatments & therapies – revised EU rules: Feedback from: Frauenmilchbank-Initiative (Human Milk Bank Initiative). (Accessed 27 July 2021). Available from: https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12734-Blood-tissues-and-cells-for-medical-treatments-&-therapies-revised-EU-rules/F1307808_en

[181] Hvas, C.L. (2020). Blood, tissues and cells for medical treatments & therapies – revised EU rules: Feedback from: Aarhus University Hospital. (Accessed 26 July 2021). Available from: https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12734-Blood-tissues-and-cells-for-medical-treatments-&-therapies-revised-EU-rules/F1307554_en

[182] Keller, J. (2020). Blood, tissues and cells for medical treatments & therapies – revised EU rules: Feedback from: Netherlands Donor Feces Bank. (Accessed 26 July 2021). Available from: https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12734-Blood-tissues-and-cells-for-medical-treatments-&-therapies-revised-EU-rules/F1307528_en

[183] Hvas, C.L., Baunwall, S.M.D., & Erikstrup, C. (2020). Faecal microbiota transplantation: A life-saving therapy challenged by commercial claims for exclusivity. *EClinicalMedicine*. 24. DOI:https://doi.org/10.1016/j.eclinm.2020.100436.(Accessed 06 July 2021). Available from: https://www.thelancet.com/action/showPdf?pii=S2589-5370%2820%2930180-2

[184] ICF/DG SANTE Participatory Workshop: Regulating Point-of-Care BTC Processing (bed-side and same surgical procedure) [12/05/2021]: Presentation by Nigel Tallboys "Regulating point-of-care BTC processing."

stakeholders reflected that it could be difficult to apply control measures or in cosmetic settings.

EU law amended to require Member States to publish more stringent rules in an accessible format (M1.3)

The measure rated as least feasible in implementation by both respondents to both the establishment and NCA surveys was the requirement for Member States to publish more stringent BTC national rules in an accessible format (M1.3).

Member States retain the legal competence to regulate and apply requirements that go beyond EU rules. Placing an obligation on NCAs to publish details of more stringent BTC rules (M1.3) is intended to increase transparency, help inform discussions about alignment of regulatory regimes and thus make a contribution towards harmonisation within the EU.

As noted above, NCA and establishment survey respondents were more sceptical about the implementation of this measures than most others. A representative organisation representing manufacturers recommended that “accessible format” be defined clearly, else differences in Member States’ interpretation would make practice highly divergent, putting burden on all stakeholders. Some respondents to the establishment survey and NCAs reported this measure could be labour-intensive or difficult to implement in practice.

Among the potential challenges to this model are:

- the reliability of ‘self-policing’ of this requirement by NCAs who will be need to decide whether their own rules are subject to the publication obligation. If rules seen by establishments as ‘more stringent’ are regarded by NCAs as simply complementary to EU requirements, then publication may not occur.
- whether channels for dialogue and potential challenge are available and clearly signposted if the publication does prompt other Member States or other actors to consider a response.

Potential risk mitigation measures addressing these issues include:

- a definition of ‘more stringent’ that is broad and clear enough to drive publication of rules that threaten harmonisation of the BTC regulatory environment experienced by blood and tissues establishments;
- a requirement for the publication of the new rule to be accompanied by details of contact points for engagement at the authority;
- a forum that supports dialogue within the EU among regulators and between regulators and establishments on regulatory barriers to exchange of BTC within the EU.

EU legislation is amended to require competent authority inspectors to evaluate the BTC establishments' risk assessments to ensure that they have been conducted effectively and that the rules set adequately manage the identified risks (M1.5)

Consultations suggest that NCAs see the application of this measure to Option 1 as difficult to implement. If establishments are legitimately able to make recourse to any international and national guidance or standards from other bodies in setting their rules (rather than being required to follow a single Member State or EU guidance) then additional complexity would be added to the NCA’s oversight task. There would be implications for time required, training, and overall cost.

The feasibility of such a measure was discussed in responses to the NCA survey. The main concern was that this would be very demanding and costly, and could lead to large demand on capacity. Another NCA reported that the heterogeneity of the different organisation could lead to difficulties for inspector assessments and harmonisation of the rules.

EU legislation is amended to require BTC establishments to assess risks associated with their donor selection, testing, collection, storage, processing and supply procedures and to set technical rules for safety and quality compliant with the "high level principles" in EU legislation (M1.6)

This Option 1 model for rule-setting is regarded as more problematic by some stakeholders and is less likely to deliver assured protection to donors. It devolves the choice of guidance to be used in rule-setting to individual establishments. Unless 'over-written' by Member State legislation, it could potentially lead to greater diversity of practice than is present now, if (for instance) a current requirement to follow national guidance is replaced by the option to use any national or international source.

Some respondents to the establishment survey reported that this measure would create significant implementation problems. Establishments (a blood/tissue establishment and a representative organisation representing manufacturers) and NCAs both expressed concern in the survey about varied approaches which still may be taken if this measure were implemented, either at the BE/TE level (particularly for smaller establishments) or the Member State level. A few respondents to the establishment survey (a standards setting body and a blood or tissue establishment) suggested clear instructions, mandatory testing, or joint inspections would help to facilitate enforcement.

EU legislation is amended to require establishments to 'take into account' ECDC/EDQM rules on quality & safety requirements; Member State expert group participates in the EDQM drafting and review process (M1.7)

In the stakeholder surveys, some establishments (including a representative organisation representing manufacturers and a stakeholder from "Other sector relevant to this consultation") and an NCA noted that frequent updates could have negative impacts on establishments (in a context where each change to the rules creates additional costs).

Some respondents to the establishment survey (including a standards setting body and a representative organisation representing manufacturers) cited the need for good representation of professionals and expertise in EDQM committees, including regular stakeholder consultations including industry (where much of the specialised knowledge resides). An NCA reported that there could be problems with implementation in national law requirements for "taking into account" because it lacks legal certainty.

A few NCAs reported that there could be language barriers; in some Member States, all requirements applied to establishments must be available be in national language (implying a need for the guidance produced by the EU expert bodies to be translated by EU institutions). A manufacturer from the pharmaceutical industry reported that the validation of certain clinical methods according to EDQM standards can be difficult or impossible. A few NCAs noted that national requirements are already aligned with existing guidance in this way.

EU legislation is amended to incorporate quality & safety requirements directly. It contains a mechanism for regular updates to respond to changing risks and technologies under Comitology rules (M1.8)

A common point of concern expressed by respondents to both surveys was the (slow) speed of the mechanism provided by this measure. An establishment reported it seems difficult to believe that it is possible to create a mechanism which will be able to update legislation as fast as technology changes in the area of MAR. An NCA noted that changing laws is a slow and very complicated process.

Some NCAs reported that stringent quality and safety technical requirements including regular updates are already implemented in their Member States.

A8.2 Measures to strengthen and harmonise oversight among Member States (Objective 2)

EU legislation is amended to incorporate oversight principles for the organisation and for staff in legislation (M2.1)

The list of principles established by the Commission which would be applied to NCAs and their staff will vary in the scale of change that they will demand of institutions and their officers. For some NCAs there will be no impact because they already conform.

In a participants' poll held during a workshop on Strengthening Oversight (Inspection, Authorisation, and Vigilance), which was attended by BTC competent authorities[185], most respondents indicated that oversight principles should be included in the revised BTC legislation and would contribute to the aim of strengthening oversight (although a significant number were not sure if this measure would be effective) (Figure 3).

Operators were much less confident in the impact of the principles. 100% of respondents in the blood break-out group indicated that they were 'not sure' that the principles proposed in the Options will ensure that oversight of the BTC legislation is independent and free from conflicts of interest. 64% of the respondents in the tissue/cell break-out group answered in the same way (Figure 4).

The most important concern expressed by the participants was that resources might not be made available to allow them to effectively implement the strengthened oversight provisions likely to be included in revised legislation.

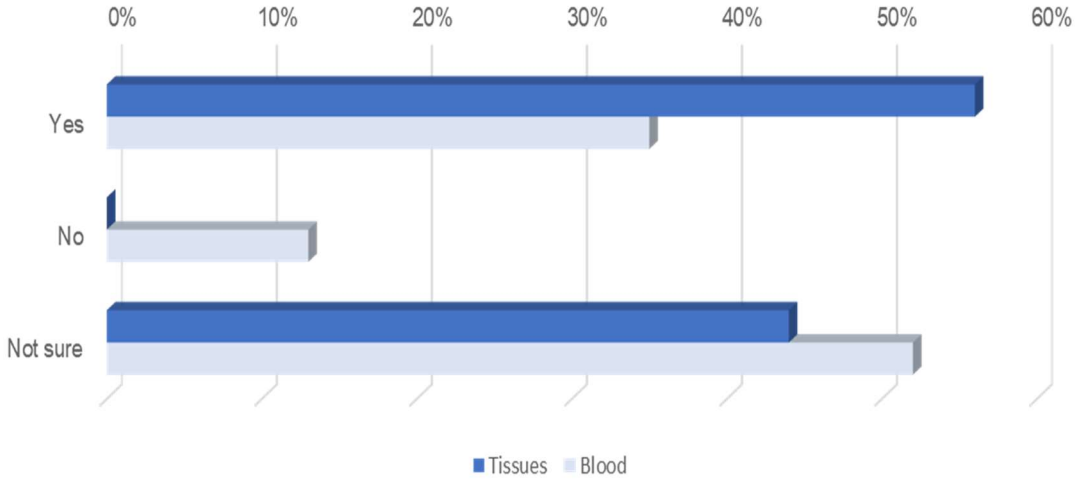

Figure 3. A significant number of authorities that attended the workshop were not sure that the principles proposed in the policy options will ensure that oversight of the BTC legislation is independent and free from conflicts of interest

Source: Participatory workshop: Strengthening Oversight (Inspection, Authorisation, and Vigilance) – Authorities. In comparison to the base line (the current situation), will the principles proposed in the Policy Options ensure that oversight of the BTC legislation is independent and free from conflicts of interest? Tissues/ Cells group n= 18, Blood group n= 23

[185] The event was attended by 58 representatives from BTC competent authorities and representatives from EU institutions

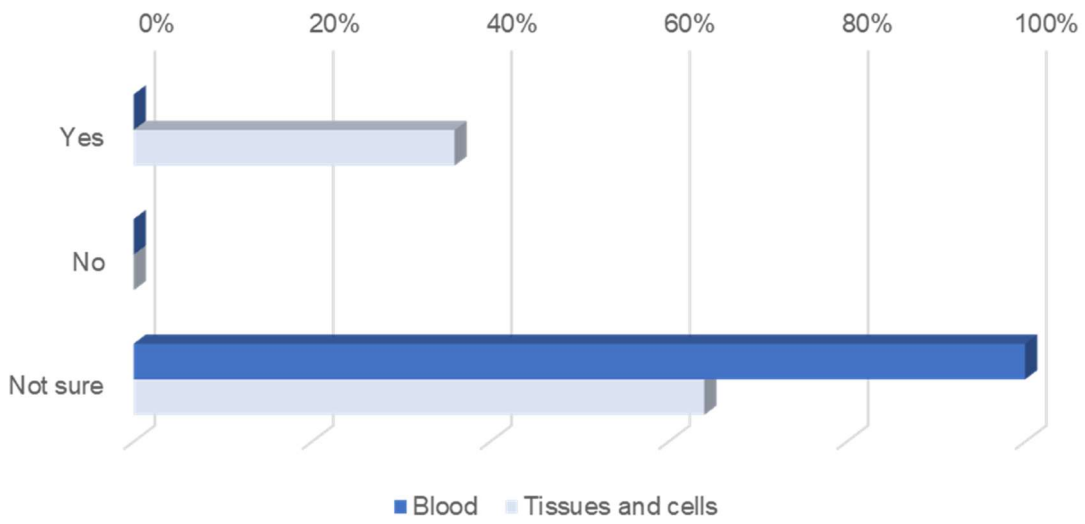

Figure 4. All operators present at the workshops were not sure that the policy options will ensure that oversight of the BTC legislation is independent and free from conflicts of interest.

Source: Participatory workshop: Strengthening Oversight (Inspection, Authorisation, and Vigilance) – Operators. In comparison to the base line (the current situation), will the principles proposed in the Policy Options ensure that oversight of the BTC legislation is independent and free from conflicts of interest? Tissues/ Cells group n = 11, Blood group n = 9

EU law is amended to obligate NCAs to base their inspection regimes on a risk-based approach (M2.2)

The data provided by the NCA consultation show that many countries have already applied some form of risk-based approach to inspection in their blood and/or tissue oversight regime. The flexibility available to the authorities in adjusting the frequency of inspections is constrained by the EU legislative requirement for establishments to be inspected at least once every two years.

Consultations with NCAs indicate strong interest in whether the two year requirement will be modified by the reforms (the measures as provided are silent on this issue). Lengthening the minimum period would provide more flexibility to regulators in deciding how to allocate resources (such as inspecting low risk establishments less frequently).

This study has not considered what the optimal maximum period would be for establishments of different risk profiles, taking into account issues such as risk management and costs to authorities and establishments.

The Commission will develop and maintain common guidance on oversight (M2.3)

Participants at the authorities' oversight workshop expressed strong support for inclusion of Commission guidance for the conduct of oversight activities in the revised legislation. There was strong suggest for compliance with the guidance being mandatory (of the tissues and cells breakout group, 78% were in favour; and of the blood breakout group, 73% were in favour).

There was majority support for The Commission Expert Sub-group on Inspections in the BTC sector and Vigilance Expert Subgroup being involved in developing the guidance (albeit with a difference between breakout groups – 86% in the blood group but only 56% in the tissue/cell group).

The European Commission conducts audits of national control systems (inspection, authorisation, vigilance), issuing recommendations and action plans for improvement when necessary (M2.4) & EU law is amended to implement a legal framework for Joint Member State inspections of BEs/TEs (M2.5)

The oversight workshop for authorities saw widespread support for joint inspections by Member States (90% in favour in blood break-out group; 71% in favour in tissue/cell breakout group) and for a system of EU audits of national oversight systems (86% support in blood break outgroup; 71% in favour in tissue/cell breakout group) (Figure 5). Similar support was expressed in the oversight workshop for operators. The group widely supported joint inspections as well as EU audits of national control systems (Figure 6).

Authorities raised concerns about how inspectors from different Member States might expect to see the more stringent requirements applied in their Member State, when inspecting in another Member State. Operators, on the other hand, expressed that if standards are different across different Member States, inspectors may disagree on the standard when conducting an inspection. The group highlighted the importance for operators to know exactly what requirements and standards they are being inspected against.

There was generally little support for publishing inspection reports from EU audits of national control systems or joint compliance inspections among authorities. The latter could be misinterpreted by the public; however, there was some support for publishing aggregated inspection data.

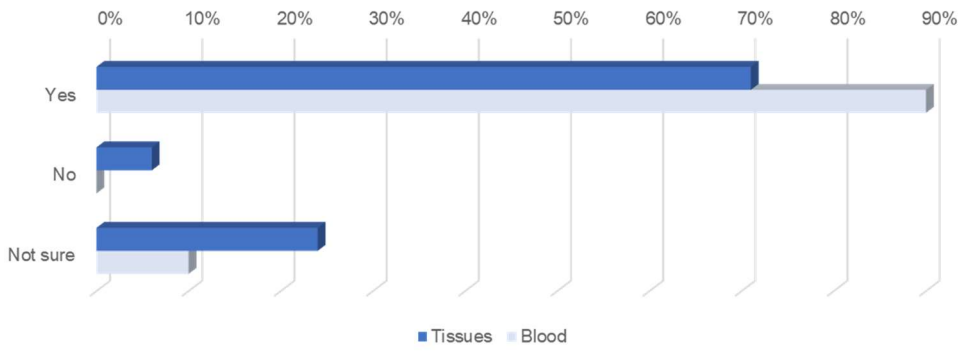

Figure 5. The oversight workshop for authorities saw widespread support for joint inspections by Member States (in both blood breakout room and tissues and cells breakout room)

Source: Participatory workshop: Strengthening Oversight (Inspection, Authorisation, and Vigilance) – Authorities. Do you support the proposal for a framework for joint compliance inspections (policy options 2&3) conducted by two or more Member States? Tissues/ Cells group n = 17, Blood group n= 21

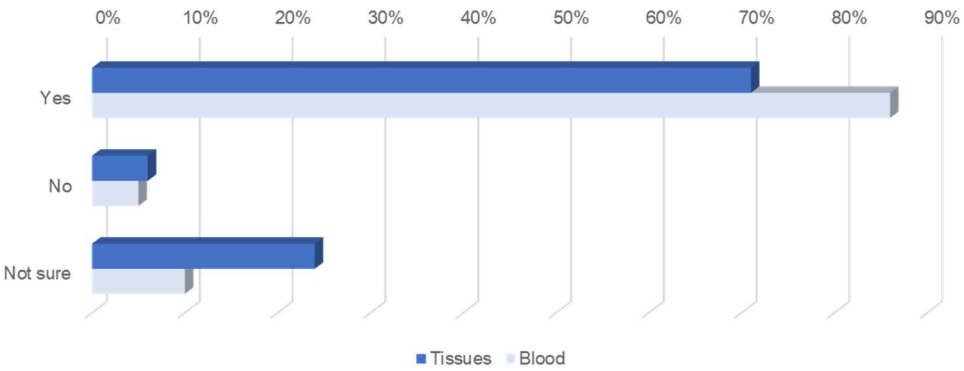

Figure 6. The majority of respondents also supported a system of EU audits of national oversight systems

Source; Participatory workshop: Strengthening Oversight (Inspection, Authorisation, and Vigilance) – Authorities. Do you support the proposal for the EU to conduct audits (policy options 1&2)of National control systems? Tissues / Cells group n= 17, Blood group n= 21

Finally, in reference to linked measure M2.6 (development of an IT platform for oversight), a European regulator noted the advantages of the IT platform for oversight to be able to communicate with existing IT systems of the EMA, especially in case BTC-based products are used in or become ATMPs.

Measures to increase protection of BTC donors, and children born from donated sperm, eggs or embryos, from specific risks

Responses to the NCA and establishment surveys (Figures 7 and 8) did not raise any 'red flags' about feasibility of the measures proposed, but as requirements are currently defined in general terms, some stakeholders had difficulty responding in detail in some contexts.

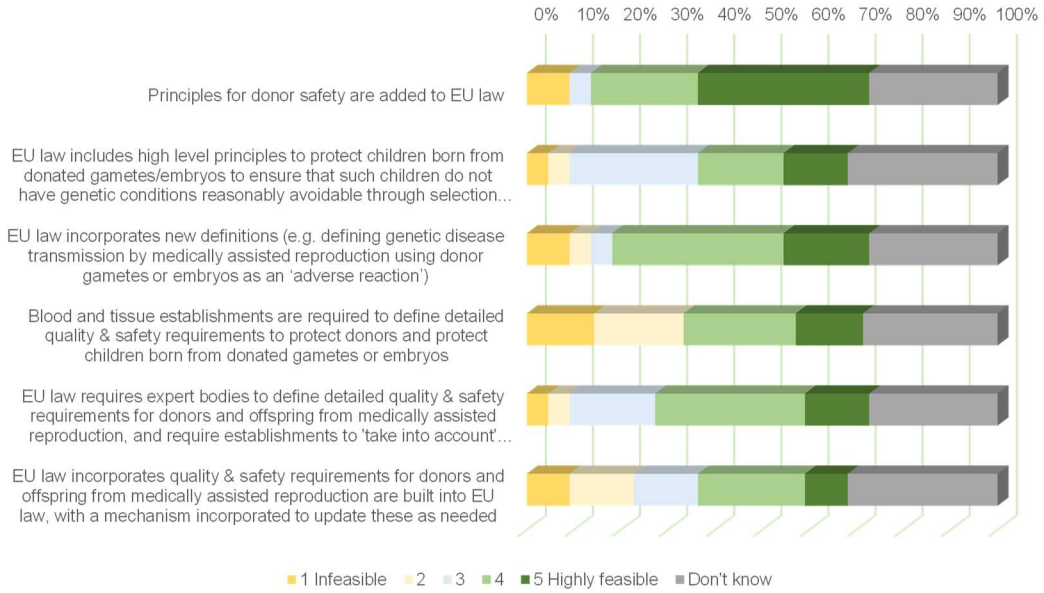

Figure 7. NCA responses on indicate some concerns with the feasibility of implementing the Option 1 model for setting rules intended to protect donors and children born from MAR

Source: NCA survey. Question: How feasible is implementation of each of the proposed measures and what do you see as the main issues to be addressed when implementing them? (n = 23)

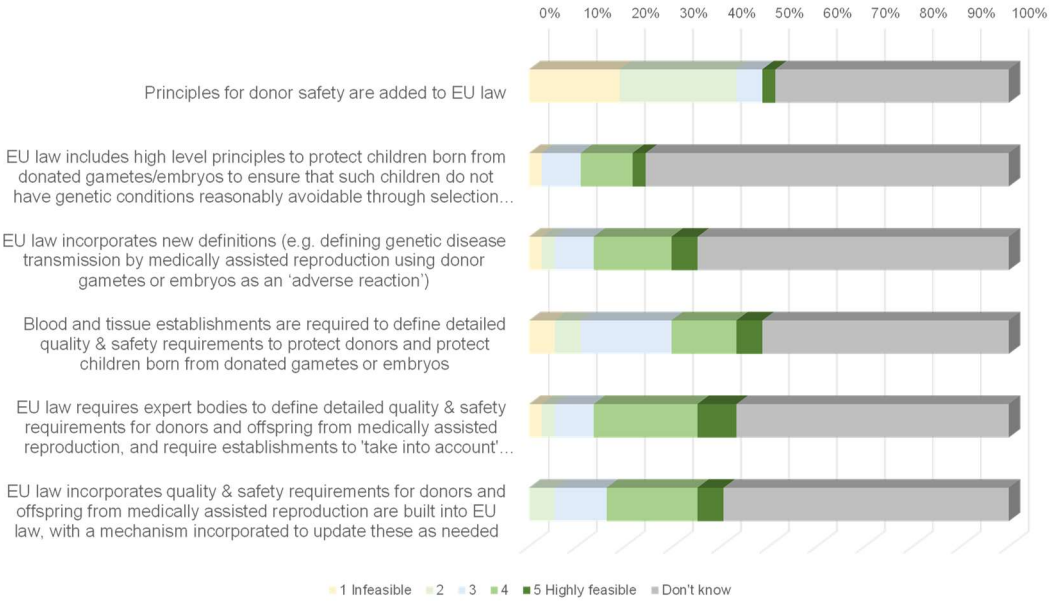

Figure 8. Many of the respondents to the establishment surveys were unable to make a judgement about the feasibility of measures but those who were did not raise major issues

Source: Establishment survey. How feasible is implementation of each of the proposed measures and what do you see as the main issues to be addressed when implementing them? n = 37

The responses to the establishment survey feature very high levels of 'don't know' to feasibility questions, which is likely to reflect the fact that many of the respondents are not directly involved in the MAR sector and so felt less able to comment on proposals specific to MAR activities.

Stakeholders provided recommendations on measures proposed to address Objective 3 in publicly available position papers supplied as part of the stakeholder engagement:

- The EBA suggested that Member States must ensure that all establishments authorised to collect BTC within their territory have access to the donation history of every donor regardless of where their previous donations were performed.
- According to the Committee of Ministers to Member States on establishing harmonised measures for the protection of haematopoietic progenitor cell donors, before providing consent, donors (related and unrelated) should receive appropriate information on the type(s) of tissues or cells to be donated, the collection procedures, the consequences and possible side effects of donation and the purpose or final use of the donated cells. This will help to ensure a free and informed decision, including the right to withdraw consent at any time.

High level principles to protect donors and offspring, and new definitions (M3.1, M3.2, M3.3)

At the 'MAR workshop' it was noted that high quality genetic testing of donors is the measure that gives the most effective protection to children born from donated gametes or embryos. There was support for defining a minimum list of genetic tests for donor screening at EU level, although ethical concerns regarding donors' right not to know were also raised. The group offered a range of suggestions to ensure genetic screening did not reduce the donor pool more than necessary, such as testing for conditions based on a threshold of prevalence in a given population and using genetic matching to allow donors with recessive conditions to remain eligible.

Measure M3.2 requires SARE monitoring for donors. This form of reporting is supported on a voluntary basis by a number of Member States already. In 2017, 710 cases of SAR in donors were reported by 21 countries. Of those, 34 were related to non-reproductive and 676 to reproductive tissues and cells[186].

When asked about the feasibility of M3.2, one establishment reflected that principles set in EU law are not enough to protect children. An NCA reported that the right of the donor "not to know" needs to be protected concerning any underlying genetic diseases that might be identified due to the genetic tests. Related to the feasibility of M3.3, an NCA noted that it is not an easy task to prove genetic conditions as transmitted from a donor (in cases such as different forms of autism).

The European Commission will develop the relevant component of an IT platform for quality & safety requirements (M3.4)

The multi-functional IT platform that the Commission has proposed would be used to disseminate details of EU rules and guidance. Under an Option 1 scenario the added-value of the IT platform to the Objective 3 agenda is less clear.

[186] European Commission, 2020. Summary Of The 2018 Annual Reporting Of Serious Adverse Reactions And Events For Tissues And Cells. (Data collected from 01/01/2017 to 31/12/2017 and submitted to the European Commission in 2018). Ref. Ares(2020)147169 - 10/01/2020. Online at https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/2018_sare_tc_summary_en.pdf . Accessed 11 August 2021.

EU law is amended to require BE/TEs to define detailed quality & safety requirements to a) protect donors (age and medical history eligibility rules, donation frequency rules, donation health monitoring rules, adverse reaction reporting rules etc.) and b) protect children born from donated gametes or embryos (donor genetic testing rules, new-born health monitoring rules, adverse outcome reporting rules etc.) (M3.5)

In the survey, a stakeholder from "Other sector relevant to this consultation" (responding to the establishment survey) and an NCA (responding to the NCA survey) reflected that this measure will require expertise and setting up these requirements could demand (scientific) expertise which is not feasible to require from every establishment.

EU law is amended to require expert bodies to define detailed quality & safety requirements (as above) for donors and children born from donated gametes or embryos and to require BE/TE to 'take into account' the rules issued by the expert bodies (M3.6)

In the NCA survey, an NCA suggested that there may be challenges in aligning national expert bodies and EU expert bodies. This would be more feasible if good communication is foreseen.

EU law is amended to incorporate detailed quality & safety requirements (as above) for donors and children born from donated gametes or embryos; and a mechanism incorporated to update these as needed (M3.7)

A number of respondents to the stakeholder surveys reflected that it could be difficult to keep pace with new insights that require adaptations in requirements. A standards setting body stressed the need to accommodate the global picture.

Other issues

Participants in a workshop held with various representative groups and other organisations from the MAR sector highlighted the need for improved traceability of donations to allow monitoring the number and frequency of donations. A proposal for an EU-level gamete donor registry was supported as a measure to improve protection of both donors and of children born from donated gametes and embryos. There was less support for a registry of children born from donated gametes and embryos, with concerns raised regarding whether this would provide benefits for individual children and might drive misleading associations between children born from MAR and certain conditions. There was a preference for integrating information on the health of these children into broader paediatric registries as an alternative.

The legislative proposals are currently silent on the issue of MAR donor registries and separate registries of children born as a result of MAR. There is an ambition for longer tracking of such children and, in the event of problems potentially attributable to a donor, for the relevant donor and associated gametes to be traced. Without registries it will be much more difficult, if not impossible, for this ambition to be realised. Various organisations and countries maintain registries of varying scope but there is not currently a consistent approach.

Many countries already have some kind of MAR registry but arrangements and status vary[187]. In a position paper, the EBMT cautioned against setting very rigid rules, as donors are considered on a risk-benefit basis so should be left to clinicians' judgement based on

[187] See for instance EDQM for European Commission. Comparative analysis of MAR in the EU: regulation and technologies. SANCO/2008/C6/051. Final Report. 2009

professional guidelines. Further, HSC treatment is affected by disruption to travel and transport including pandemics and other unpredictable events (e.g. natural disasters). The EBMT welcomed legislative measures to improve donor follow-up, particularly for related donors, and support for donor registries, noting their role and contribution to research, enhancing services and extending the range of cell products provided.

A8.4 Measures to facilitate innovation of safe BTC therapies (Objective 4)

NCAs responding to the NCA survey did not report prominent feasibility issues across any measures. Respondents to the establishments survey were somewhat more concerned about the measure related to evidence required for authorisation of novel applications of BTC (M4.6).

A position paper from ESHRE noted the importance of finding a balance between stimulating innovation and ensuring that new technologies are safe. If innovative technologies/therapies cannot be validated by the end users, data will not be available for assessment by the competent authorities or European expert bodies.

The EMA also noted that common international standards should be applied as much as possible and effort should also be made not to diverge from major third country jurisdictions (e.g. US) where possible.

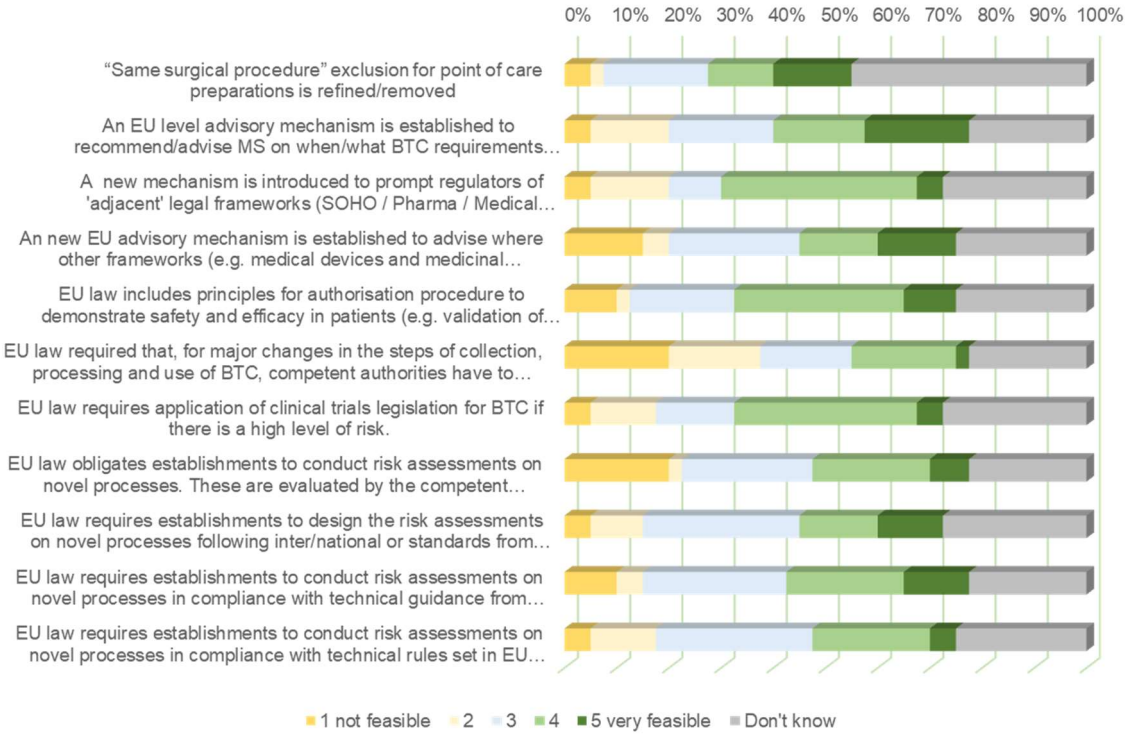

Figure 9. Many of the respondents to the establishment surveys were unable to make a judgement about the feasibility of measures but those who were did not raise major issues

Source: Establishment survey. How feasible is implementation of each of the proposed measures and what do you see as the main issues to be addressed when implementing them? N = 40.

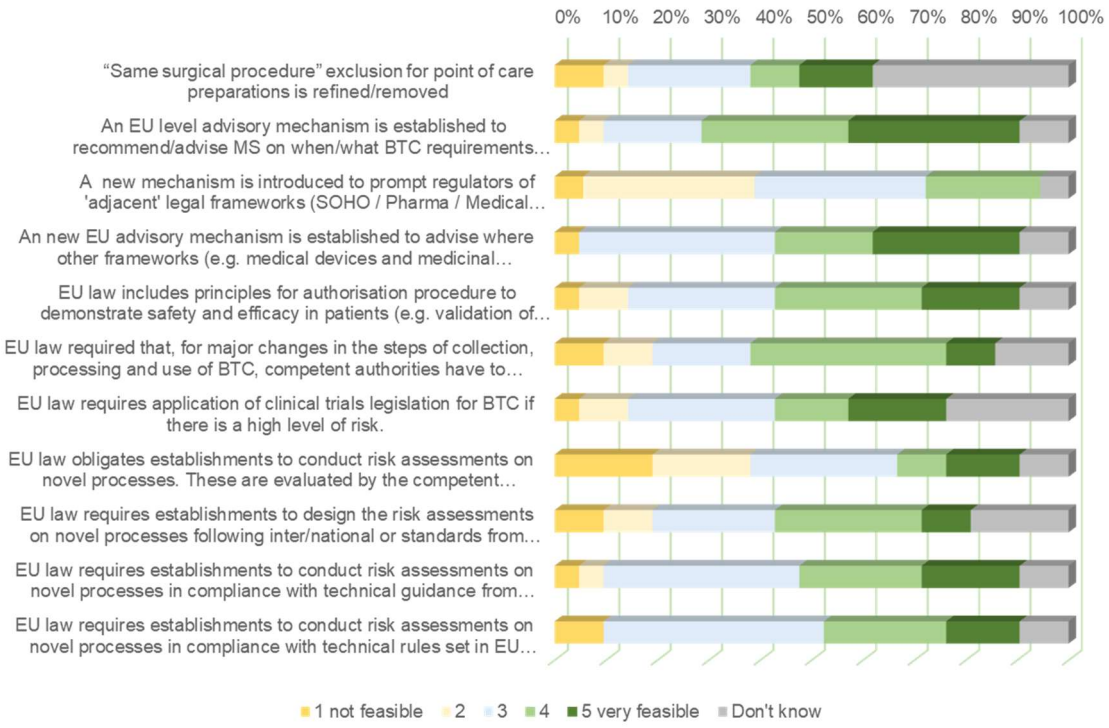

Figure 10. The NCA respondents largely found the measures feasible

Source: NCA survey. How feasible is implementation of each of the proposed measures and what do you see as the main issues to be addressed when implementing them? N = 21.

Point of care preparations: The "same surgical procedure" exclusion currently provided in the tissue and cell Directive for point of care preparations is refined / removed. (M4.1)

The proposals for legislative reform include a measure (M4.1), common to all options, to remove this exemption. A workshop was convened to discuss this issue under this impact assessment support study and attended by 58 representatives of NCAs, professional associations, the medical devices industry, hospitals and patient organisations, the Commission and EDQM. It also considered the potential impact of inclusion in the legislation of autologous blood components collected and administered at the 'point of care'.

There was a strong consensus among participants that BTC used in surgery, or next to the patient, should be regulated by the BTC legislation for both therapeutic and non-therapeutic preparations, if the BTC are processed in any way. The provisions should not, however, be equivalent to full blood or tissue establishment authorisation requirements but, rather, be limited to an authorisation of the preparation process, with a focus on efficacy. The authorisation requirements should be proportionate to the risks associated with therapy, in line with the proposals of the GAPP Joint Action, although the action had not specifically considered point of care BTC.

A suggestion of introducing mandatory registration of such point of care processes was also discussed. It might include activity data and vigilance reporting obligations, along with desk-based preparation process authorisation. It was noted that some of these processes also move the BTC under the ATMP legislation and that close regulatory collaboration would be important.

At a workshop held to discuss the scope of the legislation, participants were asked whether the same surgical procedure exclusion should not apply to a set of named tissue/cell

treatments. Half of respondents had no opinion; of those who did far more agreed that the exclusion should not apply than disagreed[188].

A number of respondents to the two stakeholder surveys reflected that this measure could be difficult to implement successfully as thousands of these kind of procedures are conducted in Europe each year. The feasibility will depend on many other factors including the processing method and the need for short term storage of preparation. A few NCAs reflected there could be a need for additional resources or capacity to carry this out.

Other stakeholders reflected that "same surgical procedure" should be clearly defined jointly with all relevant stakeholders to facilitate implementation, and that this should be subject to a convention with the tissue bank for the validation of controls. Some respondents to the establishment survey (a representative organisation representing manufacturers and "Other sector relevant to this consultation") suggested that provision should be made for emergency or urgent care situations.

A key issue emerging from the research completed for the PRP and autologous adipocyte case studies (Annex 9) is that revision of the legislation must consider rules for point-of-care preparations being used for cosmetic purposes to ensure these are used in a safe and controlled manner. This was echoed in a presentation provided by a stakeholder for Workshop 2 on point-of-care preparations (Annex 11), during which it was also emphasised that there needs to be further standardisation of the national authorisation processes for the use of autologous processes and point-of-care technology in the BTC sector to prevent barriers in the exchange of BTC between Member States.

Establishment of new EU level advisory mechanisms relating to: classification advice on internal BTC (M4.2), Interplay SoHO / pharma / MD (M4.3), and classification advice related to other legal frameworks (M4.4)

M4.2: Respondents to the establishment survey (a representative organisation representing manufacturers and "other sector relevant to this consultation") reflected that at present, some EU processes can be very time consuming and costly which can limit innovation. The mechanism needs to be agile and not procedurally burdensome so developers receive timely answers to such questions, according to a representative organisation representing manufacturers. An NCA respondent reflected that this should be a decision at the EU level, rather than merely advice.

M4.3: An NCA recommended that the three areas (SoHO / Pharma / MD) should be coordinated. A representative organisation representing manufacturers reflected that this mechanism would only work if SoHO / Pharma / Medical Devices have a veto or final vote as these sectors have relevant expertise. Another representative organisation representing manufacturers suggested that prior authorisation needs to be based on a common set of criteria across all Member States to avoid fragmentation and inconsistencies in decision making.

M4.4: Some respondents to the establishment survey commented that for ATMPs there is already a mechanism in place and the guidance is clear. A representative organisation representing manufacturers suggested that this measure could lead to further complexity in borderline issues if committees have divergent views, so there is a need to clearly delineate and respect scope and remit of authorities to advise on when the relevant framework applies.

Responses to the Public Consultation carried out by the Commission highlighted some potential negative aspects to a BTC classification advisory mechanism / committee, including that it would be advisory only (with decisions to be national), and that ATMPs are globally aligned which is important for exchange. Respondents to the Public Consultation

[188] Workshop on 'Refining the scope of the BTC legislation', 2 June 2021.. Tissues / Cells sub-group.

noted issues to consider in establishing a BTC classification advisory mechanism/ committee, including that it requires integration with bodies in (AT)MP and MD, or at least good coordination, to avoid duplication. Similarly, respondents indicated that such a committee requires equal representation across all sectors and needs to provide a voice for all actors (including professionals and clinicians).

A stakeholder interviewed for the FMT case study (Annex 9) commented that an advisory mechanism and harmonised, consistent advice would improve patient access and would potentially facilitate innovation and investment. Stakeholders engaged for the isolated hepatocyte case study reported that a new advisory mechanism to aid in the classification of their treatment would help to resolve borderlines more efficiently – and therefore allow treatments to be further developed and made available for patients – was generally welcomed by stakeholders interviewed for the autologous adipocyte cells case study (Annex 9).

Stakeholder made some recommendations on how to ensure effective implementation and ensure feasibility of the proposed advisory mechanisms. Key considerations are outlined below.

- **Input from experts**: Stakeholders from an organisation consulted for the FMT case study asked that an advisory body should not provide advice without having adequate engagement and advice from Member States experts. They cited an example from the US, suggesting that the classification 'without adequate expert input' of FMT as a drug led to some stool banks being shut down due to the increased costs associated with compliance with the drug legislation. Another stakeholder in the PRP case study thought it important to involve experts and stakeholders in this advisory task to bring the expertise and the competency required for specific cases - reportedly a strength of the Medical Device Coordination Group and the working groups for the MDR and medical devices. Another PRP case study stakeholder suggested that an overarching committee could be useful, subject to equal inputs from the relevant disciplines and avoiding pharmaceutical interests dominating. One stakeholder in the isolated hepatocyte case study stressed the importance of patient representation to ensure the perspective of the patient is considered.
- **Quick and easy procedures**: A FMT case study consultee recommended that classification advice be given quickly before Member States each develop their own rules and laws. An existing European regulator recommended a lean and simple procedure with clearly defined timelines for a centralised classification committee (M4.4). Additionally, it was suggested that the consultation should be initiated by any stakeholder (from the European Commission, NCAs, applicants or expert bodies) if pre-defined criteria are fulfilled. Alongside this, there could be a more regular exchange of information between the relevant bodies to foster mutual learning for regulators in different sectors, as the CAT interpretation of substantial manipulation / non homologous use.
- **Clarity and lack of competition**: A stakeholder in the autologous adipocyte cells case study stressed that any new classification measures should not compete with existing mechanisms; it is essential to know what regulatory pathways there are and to have predictability to understand how a product will be authorised. Any system which competes with the CAT classifications will be disruptive and could create more confusion. Similar concerns were reported in research for the PRP case study: stakeholders noted that multiple committees across the pharmaceutical and BTC fields would create a need for an overarching structure which clarifies their respective mandates, or a single committee of experts with diverse backgrounds that could cover all the topics in the area.

- **Binding decisions**: Several stakeholders in the PRP case study suggested that a mechanism which could provide a binding decision as is the case with medical devices rather than solely advice would be preferable. Stakeholders consulted about autologous adipocyte cells reported that even if a new advisory mechanism is not legally binding, it is important for it to have some weight behind it, for example Member States can trust that a decision was reached based on scientific methodology and rigorous decision-making.

A stakeholder from the CAT reported that in practice, the majority of products will not be borderlines, but there needs to be an alignment on principles, which implies that there have to be discussions of new developments. The CAT is dependent on the information it receives within product applications, which includes the intended use/mechanism of action of a product. If a product's intended use changes, approvals are invalidated; this should be taken into account in the proposed advisory mechanisms. In an interview with representatives from the CAT it was emphasised that there had to be an alignment in processes to reduce the risk of contradictory messages to applicants. As the CAT's remit is limited to differentiation of ATMPs from non-ATMPs there may value in the BTC advisory mechanisms being authorised to "pick up" issues which the CAT cannot.

Stakeholders consulted in the FMT and serum eye drops case studies suggested that an advisory mechanism could facilitate innovation and investment. According to an interviewee, in the case of serum eye drop treatments, this 'one-stop-shop' model (whereby a developer could put a question on regulation to one body and all the relevant advisory bodies could comment and agree on the outcome) would be particularly beneficial as serum eye drop treatments become combined with medical devices. A consultee for the pancreatic islet cells case study reported that having a cross-sector mechanism or committee which brings together various experts from the substances of human origin, medicinal product and medical devices committee will help to increase confidence, with implications for further research and development (e.g. more joint working between stakeholders).

The EU legislation will set principles for authorisation procedure to demonstrate safety and efficacy in patients (M4.5), and there is a Strengthened Preparation Process Authorisation (M4.6)

For M4.5, a few respondents to the establishment survey suggested this measure should involve other bodies, including other bodies for testing, and existing infrastructure and procedures (in adjacent frameworks). A representative organisation representing manufacturers suggested that the feasibility of this measure will depend on how Member States define risk and the validation procedures. A few survey respondents suggested that implementation of a new authorisation process under M4.6 could be demanding on time, staff, and finances of smaller inspectorates.

Some stakeholders (including a healthcare provider and a representative organisation for manufacturers) recommended increased coordination, for example structures for communication with healthcare professionals and other experts for the continuous updating of the steps proposed, or increased coordination between regulators in different legal frameworks. A representative organisation for manufacturers suggested that the measure should respect the scope of each authority in the context of the final product; a product should not be regulated under more than one legal framework but transition points and scope of authority should be clearly outline to avoid any overlaps that further complicate the system.

A hepatocyte case study consultee suggested increased oversight of preparation processes, including the need for clinical evaluation of novel processes, might increase costs and therefore needs to be proportionate to the number of patients that data can be collected from (e.g. small numbers in the case of hepatocytes). PRP case study consultees reflected that measures to strengthen preparation processes would increase costs as each establishment will have to evaluate products in their setting, and not all EU countries have

a centralised blood establishment organisation, therefore each fragmented establishment would have to create their own sets of validation data. As such the sharing of preparation process authorisations between Member States was strongly supported.

The EU legislation will set rules for implementing a clinical trial for BTC (if high level of risks) (M4.7)

Overall, there was support among all stakeholders about the need for proportionality in clinical investigations. A participant at the authorisation of novel BTC workshop (Workshop 1) suggested that a roadmap is needed to look at exactly what the clinical data evaluation plan would look like for novel products. Some participants noted that the BTC sector is primarily not-for-profit and felt that the costs and requirements needed to implement a clinical investigation were excessive. Participants also supported the suggestion that a clinical study is not required if an establishment starts to prepare BTC that are described in an EDQM monograph.

There were mixed views on whether the Clinical Trial Framework (2001/83/EC) should or could be considered for very novel and very high risk BTC. There was some discussion about including a principle / reference / requirement for clinical data feedback to be provided when BTC and novel BTC are utilised.

There was a lot of support among participants for clinical outcome registries to play a role in the collection of clinical data. It was noted that registries currently focus on collecting patient data, but that it would also be useful to collect quality attributes of the products. This was echoed elsewhere, for example, in the FMT case study it was mentioned that a European Consensus Conference of 28 experts from 10 countries[189] made a series of recommendations for FMT, including that "Appropriate FMT registries should be implemented, in order to collect data concerning indications, procedure, effectiveness and safety profiles". The creation of registries could help with data collection and help to address safety issues which may arise for FMT e.g. Through the collection of follow-up data. Participants noted that such registries can, however, be costly.

There was support for (anonymised) sharing of clinical data between Member States and between competent authorities to support increased innovation (through knowledge exchange) and increase access for patients (through increased availability of treatments resulting from an enhanced mutual recognition of authorisations).

An interviewee in the SED case study noted the potential to stifle innovation by increasing barriers to entry (e.g. with a requirement for clinical evaluation and risk assessments) and that such measures had to be proportionate. There were also additional costs and funding needs to consider, for example, costs of setting up clinical trials and registries. A consultee for the autologous adipocyte cells case study suggested that in the currently existing system it is unreasonable to expect a regular hospital to be able to conduct a clinical trial. A FMT case study consultee stated that introducing requirements for clinical trials should be considered carefully, as it could complicate processes and compliance be costly.

PRP case study consultees advised caution in introducing a requirement for clinical data as strict requirements for measuring efficacy could impact on patients' access to product such as PRP. They were cautious about the ability of smaller paediatric cases of PRP being used to adhere to clinical trial guidelines, and noted that terms such as "novel", "innovative", and "major changes in existing processes" (used to define when a clinical data requirement

[189] Cammarota, G., Ianiro, G., Tilg, H., et al. (2017). European consensus conference on faecal microbiota transplantation in clinical practice. *Gut*. 66. http://dx.doi.org/10.1136/gutjnl-2016-313017

should be applied) needed to be well-defined to ensure a standardised approach to clinical evaluations.

A statement from the EEBA suggested that measures including requirements for clinical data of high-risk novel preparations will facilitate collaboration at EU level to clarify the regulatory status of limbal stem cell treatments[190], and therefore demonstrate safety and quality of the limbal cells provided under the BTC framework while maintaining access and affordability for hospitals.

Stakeholders consulted for the EVs case study reported problems when conducting clinical trials across two countries due to differing national regulation, risk assessments and quality profiles. More coordination among regulation bodies at the EU level and standardising risk assessment models at the national level would make it easier for these cross-country trials to take place; this is especially important for early stage development (as in the EV sector).

A representative organisation representing manufacturers and a stakeholder from "Other sector relevant to this consultation" reported that the measure will ensure high level of patient protection but that care is needed not to create a parallel pathway for products that should be regulated under another framework where requirements already exist as this would only increase uncertainties for developers.

A respondent to each survey noted that clinical trials can be demanding, and this measure will take some time to implement. An NCA suggested the measure could be feasible if the risks are not assessed by the establishments themselves.

EU will develop an exchange (IT) platform for NCAs to exchange info regarding (novel) process authorisations (M4.8)

The GAPP baselining survey found that most competent authorities lacked access to a database on authorisations. In a breakout group during the workshop on borderline issues (Workshop 11) there was overwhelming support for the idea of a central IT platform at European level listing novel BTC / BTC processes. Breast milk case study consultees considered that a tool for sharing and obtaining advice, such as the proposed IT platform, would allow establishments to grow and innovate and will also facilitate mutual recognition. A stakeholder consulted in the pancreatic islets case study explained that the measure relating to collecting information that comes from authorising novel process at an EU level will be helpful to promote and develop techniques, and create opportunities for meaningful multicentric clinical studies.

A PRP case study consultee felt that the IT platform proposed to share information across Member States on preparation process authorisations, as well as other data and/or experiences between BEs would be very beneficial and lead to greater transparency, especially if it were mandatory and could be publicly consulted. This in turn may lead to improvements in patient access as a result of more products being deemed safe for use and efficient based on the experiences of other Member States.

A FMT case study consultee recommended that the proposed centralised exchange IT platform (to share information on national authorisation decisions) should include more information, including the history of the donor, information on the samples and procedures and information on anu drugs the sample may have been used in. This recommendation also applies to other microbiota collected from, for instance, the skin, vagina, lung, nose and mouth.

A FMT case study stakeholder questioned whether the IT platform should be mandatory for Member States or optional. A cultured keratinocyte case study consultee suggested a cost-benefit exercise was needed to ensure it will have the desired impact if use is voluntary.

[190] European Eye Bank Association (2018). EEBA Statement on Stem Cell Applications in the Treatment of Ocular Disorders. Venice, 22 October 2018. (Accessed 24 June 2021]

The same stakeholder also questioned whether it can be cheaper/better value for money to achieve the same goal through the work of the previous measures/actions.

A pancreatic islet cells case study consultee remarked that collecting information at EU level on authorised novel processes is a good idea if data protection risks are well managed. Other stakeholders wondered how willing private companies would be to share otherwise-proprietary information.

EU law is modified to obligate BE/TEs to conduct risk assessments on novel processes (M4.9, M4.10, M4.11, & M4.12)

Workshop discussions (Workshop 1 on authorising novel BTC) indicated strong support for use of a risk assessment tool such as that developed by the EU-funded Euro-GTP II and GAPP projects (as per Option 2). Representatives of the EMA Taskforce interviewed for the project supported taking a risk-based approach provided there was a 'lean process' that reduced complexity for regulators.

Comments on feasibility of implementation and impacts provided in the establishment and NCA surveys are provided below. The main concern expressed is the potential skills gap both at NCA and establishment level to meet this measure.

- M4.9: A representative organisation representing manufacturers and a stakeholder from "Other sector relevant to this consultation" reported that this measure could lead to less harmonisation and more deregulation, as oversight at the single establishment or competent authority level will lead to a lot of interpretation and subjectivity. Fragmentation can still occur if common standards are not interpreted and implemented in the same way across competent authorities. Establishments and NCAs alike commented on the high workload, expertise, and training required to carry out this measure, as some establishments will lack the capacity needed to design and perform risk assessments, and NCAs will also need additional resources. An NCA reflected that the risk assessment on novel processes regrading efficacy and outcomes cannot be done by inspectors as such tasks require specific technical knowledge that inspectors might not always have.
- M4.10: A few respondents to the establishment survey (including a healthcare provider) urged harmonisation of the inter/national standards as Member States may opt for different standards, but other respondents advised that there is currently no such international standard. A representative organisation representing manufacturers suggested that this measure would place disproportionate burdens on establishments with less experience in risk assessment design and implementation, and would need a standard approach, such as the Alliance of Blood Operators Risk Based Decision Making tool.
- M4.11: A few respondents asked that any new committee is set up in a timely manner and guidance documents published promptly to facilitate assessment procedures. Some respondents to the establishment survey were concerned that the legislative process is often not nimble enough to adapt to advances in science and technology so could still become outdated quickly. A standards setting body recommended that participation of professionals (transplant physicians). A representative organisation for manufacturers was concerned that giving establishments autonomy to govern themselves leaves too much opportunity for abuse.
- M4.12: A few NCAs and establishments reported that this measure could create a high workload and could take some time to implement, and that it will require additional audits and alignment of concepts at different levels. Similarly to M4.11, a few responses to the establishment survey noted the scope for improper implementation.

A PRP case study consultee saw implementing risk assessments for novel processes having the potential to lead to positive impacts on quality and safety provided a proportionate approach was taken. A statement from the EEBA noted that measures including implementation of a risk assessment model will facilitate collaboration at EU level to clarify the regulatory status of limbal stem cell treatments[191].

A FMT case study consultee noted that risk analysis processes are different for microbiomes, as the biomes of the donor and the recipient affect safety much more than the process followed, and so it should not be thought that applying the same process will lead to the same results. The stakeholder reported that FMT is used to treat *C. difficile* as a last available option for this life-threatening condition but that when use of FMT is explored for diabetes, autism, depression, and other cases, it is not the same situation and therefore there should be a framework to establish a basic proof of concept for patients with no other options.

A consultee for the EVs case study observed that inspectors had to be well-trained (to equivalent standards across Europe) and suitably qualified on the emerging area of EVs and familiar with the innovation in this area to be effective and support continuous improvements. One stakeholder described how use of the Failure Mode and Effects Analysis strategy (a step-by-step approach for identifying all possible failures that accepts a certain amount of risk) had led to a very productive interaction with authorities and ensured that innovation was not stifled.

The same consultee noted the potential for cost to accumulate if assessments are required even for small changes in processes.

A8.5 Measures to avoid shortages of critical BTC therapies (Objective 5)

The surveys' questions on feasibility of the supply data and emergency planning measures did not consistently any major barriers to implementation (Figure 11, Figure 12).

NCAs, establishments and other stakeholders have, however, noted (as a general comment across the proposals) that certain measures are not yet defined in enough detail for comments on implementation to be possible.

In this security of supply area, as elsewhere, the current proposals define a strategic approach but it is the detailed specification and approach to implementation that will shape the 'user experience' and feasibility.

Examples are:

- Clarity and practicality of supply data reporting requirements (e.g. standardised units for specific tissues, cells);
- Clarity of thresholds for reporting supply [interruptions]; and
- User interface for supply data reporting to be used by establishments, scope for automation, fit to existing data systems.

Contingency planning processes are expected to pose fewer implementation risks. Establishment contingency plans are required by regulators in some Member States and are also maintained by many establishments to satisfy requirements of other organisations in the supply chain (e.g. customers) and as part of the organisation's risk/quality management framework.

[191] European Eye Bank Association (2018). EEBA Statement on Stem Cell Applications in the Treatment of Ocular Disorders. Venice, 22 October 2018. (Accessed 24 June 2021]

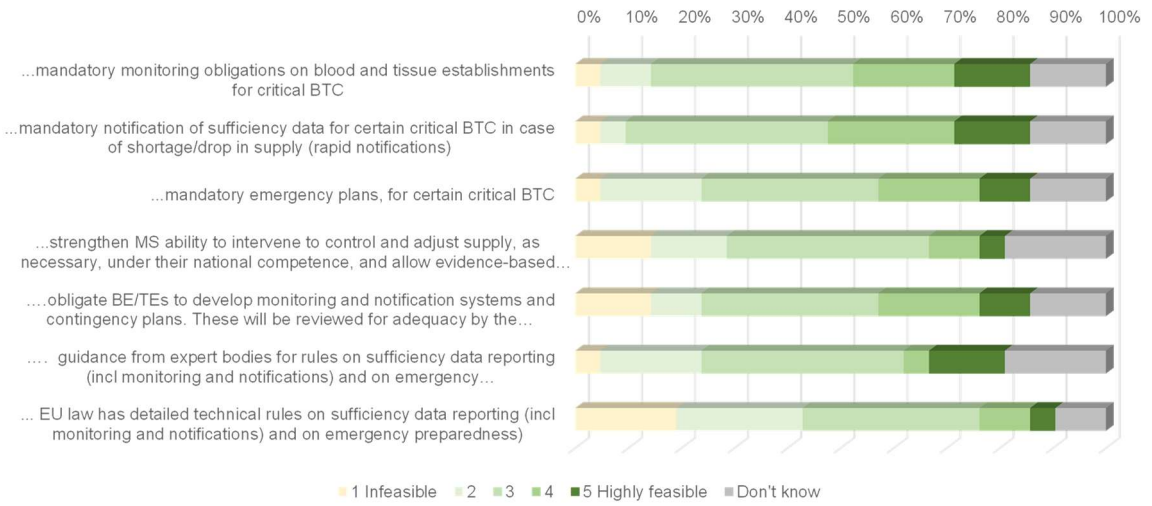

Figure 11. NCAs responses on feasibility of implementation of measures that are intended to improve security of supply

Source: Survey of NCAs (n=21). Question: How feasible is implementation of each of the proposed measures and what do you see as the main issues to be addressed when implementing them? N = 21.

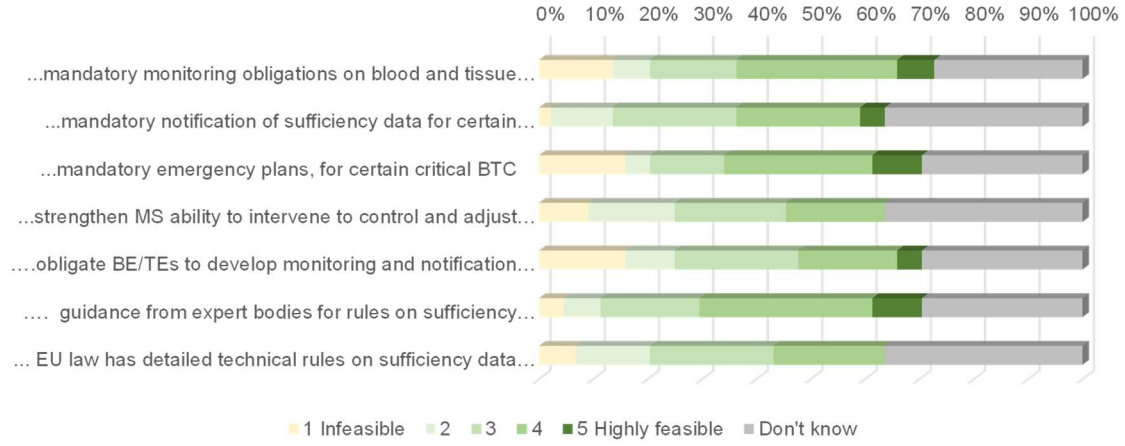

Figure 12. Responses to the establishment survey on feasibility of implementation of measures that are intended to improve security of supply

Source: Survey of establishments (n =44). Question: How feasible is implementation of each of the proposed measures and what do you see as the main issues to be addressed when implementing them?

EU law is amended to impose mandatory monitoring obligations on BEs/TEs (M5.1)

In the qualitative responses to the establishment survey, a representative organisation for patients noted that the monitoring obligations would need to be very clearly defined to avoid disparities in implementation. Others, including a representative organisation for manufacturers, suggested that ATMP manufacturers who hold tissue establishment licences should be exempt. A representative organisation representing manufacturers recommended making a distinction between TEs processing 'critical BTC' intended for therapeutic use and onward manufacture of ATMPs and medicinal products.

Some ATMP manufacturers are required to hold a tissue establishment license to import and store BTC materials solely intended for ATMP manufacture. Additional reporting requirements should not apply in this case as this has the potential to create additional unnecessary burden and duplicate reporting requirements already existing in pharmaceutical legislation for reporting of shortages.

EU law is amended to require mandatory reporting and notification of sufficiency data for certain critical BTC in case of shortage/drop in supply (rapid notifications) (M5.2)

A respondent to the NCA survey reported that this measure is expected to be easier to implement than continuous data reporting. A representative organisation for patients emphasised that the need for clear definitions (e.g. 'shortage' and 'drop in supply') to ensure that the reporting properly reflects the reality in each country / BE/TEs. Other respondents reported that for ATMP manufacturers who hold tissue establishment licenses this would be additional burden and duplicative to pharmaceutical requirements, and the primary challenge will be ensuring that all European BE/TEs will have the capacities, resources and expertise to fulfil these various obligations. A few establishments, including a representative organisation for manufacturers, questioned how this measure would work for autologous cell therapies, and indicated that for allogeneic treatments it will not have much impact as it does not address the actual issues of global harmonisation and export/import.

EU law is amended to require mandatory measures for emergency supply responses (M5.3)

A few respondents to the establishment survey suggested that cell therapies should be exempt from this measure and that harmonisation of import/export within EU and internationally should be the main solution for cell therapeutics. A representative organisation for patients asked for consideration to be given to these emergency plans in to ensure that they involve key stakeholders, such as patient organisations, as happens in some EU countries. An NCA suggested that the feasibility of setting up an emergency plan could be reduced if the supply of a critical BTC is scarce and vulnerable.

EU law is amended to strengthen Member States' ability to intervene to control and adjust supply, as necessary, under their national competence, and allow evidence-based support action at EU level. (M5.5)

Some respondents to the establishment survey stated that it is unclear how this measure would work - giving more autonomy to Member States generally does not facilitate innovation, it is better to resolve issues at EU level. A representative organisation for patients suggested that there would be significant disparities in the implementation of such measures, creating more divergence among countries such that patients relying on PDMPs would see greater inequalities of access.

EU law is amended to obligate BE/TEs to develop monitoring and notification systems and contingency plans. These will be reviewed for adequacy by the authority during inspection. (M5.6)

A respondent to the NCA survey was concerned about the time taken to establish these arrangements. A representative organisation for manufacturers was concerned about the burden placed on BE/TEs and the potential for suboptimal quality plans. A representative organisation for patients advised that the notification system and contingency plans should be very carefully developed to ensure a coherent implementation across BE/TEs. Other respondents to the establishments survey reported that this measure would not make sense for ATMP manufacturers that already have to address risk/drug shortage under medicinal product/ATMP guidance and looked for exclusion of ATMP manufacturers that currently hold a tissue establishment licence.

EU law is amended with references to guidance from expert bodies for rules on sufficiency data reporting (including monitoring and notifications) and on emergency preparedness/contingency. (M5.7)

A few responses to the establishments survey suggested that expert bodies should include or collaborate with patient organisations and professional societies. An NCA questioned whether commercial parties in this sector are willing to share relevant information. Another NCA noted that expert bodies do not always take into account the administrative burden associated with the collection of additional data that experts would like. A few respondents to the establishment survey reported that this measure is potentially a good solution, with caveats for ATMP manufacturers with tissue establishment licences that already fall under a different framework.

EU law is amended to include rules on sufficiency data reporting (including monitoring and notifications) and on emergency preparedness (M5.8)

Concerns outlined about implementation of this measure were similar to those described for M5.6 and M5.7. A representative organisation for patients noted the need for the rules to be reviewed on a constant basis and expressed doubt about whether the process for changing EU law would be swift enough to allow for this.

Annex 9: Borderline case studies

A9.1 – Summary

This annex begins with a summary of the key messages arising from the borderline case studies, and is followed by the individual borderline case studies.

Each case study follows the same structure:

- Part A describes the current preparation and use of therapy or product in question, followed by an overview of the regulatory issue.
- Part B provides an overview of judgements made my expert stakeholders consulted for each case study on how the proposed measures envisaged under the revised BTC framework would impact on the borderline/regulatory issue.

Potential effects of new measures on…	Description	Safety and quality	Costs and affordability	Patient access	Innovation and R&D	Conclusion
Currently unregulated substances Examples: Donated human breast milk (DHBM), Faecal microbiota transplants (FMT)	The current BTC legislation excludes certain substances of human origin from the scope of the legislation. A consequence of this has been that Member States have taken divergent approaches to the regulation of these substances and therapies derived from them.	M1.2 (extension of legal framework to currently unregulated SoHO) will introduce standardised safety and quality requirements (including any additional requirements introduced into the revised legislation e.g. for donor protection). Information exchange on national authorisation decisions (M.8) would be of benefit. Establishment of an advisory committee (M4.2) could facilitate harmonisation of standards. Related clarification measures (M4.3 and M4.4) facilitate manufacturing scale-up or further manipulation.	Costs can be expected for stakeholders following the implementation of standardised rules under M1.2 (extension of regulations to currently unregulated SoHO) and other measures to strengthen preparation process authorisations for novel products (M4.5-M4.8). Generally, stakeholders perceived costs to be justified by the benefits (e.g. enhanced safety and quality standards, regulation of the commercialisation DHBM and FMT). Regulatory costs must be justified by the benefits, and measures need to be chosen carefully to not overburden actors and it is important to build on what already exists.	Introduction of standardised rules under M1.2 (extension of legal framework to currently unregulated SoHO) could enhance harmonisation across the EU. This in turn would facilitate wider availability of therapies and more equitable access.	Incorporating unregulated therapies into EU law (M1.2) may encourage increased investment. An advisory mechanism (M4.2) would introduce efficiency and financial certainty for developers. Harmonising and standardising preparation processes would increase transparency, thus supporting innovation by making it clear when something becomes a starting material for a medicinal product.	Use of these substances is growing, and evidence indicates that in the future they may be further developed with more complex processing techniques to be used in a wider range of therapeutic applications. The development of these substances may in turn present borderline issues.
Therapies involving bedside processing Examples: Platelet rich plasma, Serum eye drops, Autologous adipocyte cells	There is a shift from products being produced and applied in traditional settings towards a 'bedside' process in which products are collected, processed and reapplied at once. This has created new challenges in terms of assuring appropriate quality, inspection and oversight.	Removing the same surgical procedure exemption and providing clarification regarding blood and blood components when not intended for transfusion could provide regulatory clarity and improve safety. Implementing risk assessments on novel processes (M4.5-M4.6) and requiring clinical evaluation of high-risk novel products (M4.7) may also positively impact on quality and safety. Measures supporting EU-level advice on 'adjacent' legal frameworks (M4.3 and M4.4) would be beneficial if therapies involving bedside processing use/combine with medical devices, if aligned with existing guidance.	Removal of the same surgical procedure exemption (M4.1) and providing clarification regarding the blood and blood components when not intended for transfusion may increase the portfolio of work for CAs with associated cost and resourcing implications. Measures to strengthen preparation processes (M4.5-M4.7) will increase costs as each establishment will have to evaluate products in their own setting (though sharing authorisation data between and within Member States (M4.8) would be beneficial to increase efficiencies). Costs were considered justified, but measures need to be chosen carefully to not overburden actors and build on what already exists.	Removal of the same surgical procedure exemption (M4.1) and providing clarification regarding blood and blood components when not intended for transfusion may help to ensure appropriate access. Measures to strengthen preparation process authorisations (M4.5-M4.8) could enhance transparency, helping to improve patient access as a result of more products being deemed safe for use and efficient.	Removal of the same surgical procedure exemption (M4.1) and providing clarification regarding blood and blood components when not intended for transfusion could support innovation and investment. Proposed measures would not discourage innovation if the burden of implementing them is managed. Expert consultation in the establishment of the advisory mechanisms (M4.2-M4.4) could also support greater innovation in bedside manufacturing processes by improving trust between sectors.	The interpretation of 'same surgical procedure' in the scope of the tissues and cells legislation varies across medical settings, creating diverging practices and standards. The interpretation of blood and blood components when used 'not for transfusion' in the scope of the blood legislation, varies throughout the Member States creating diverging practices and standards.
Products previously regulated under the BTC framework Examples: Cultured keratinocytes, chondrocytes, cultured limbal cells	The introduction of the ATMP legislation led to changes in the classification of products previously regulated under the BTC framework, and associated implications for how they can be produced.	Package of measures proposed under Objective 4 could help to bring products closer to the quality and safety standards of the ATMP Regulation, thereby increasing trust between adjacent sectors. Measures to collaborate at the EU level to clarify the regulatory status of treatments (M4.3 and M4.4) could enable classifications to be made earlier in development, therefore ensuring that all developers are working to the same standards.	Any measures which significantly increase resource and capacity requirements (e.g. M4.7) may disproportionally affect public sector hospitals, preventing them from working in these fields. Affordability could increase with a more streamlined regulatory framework, which prevents different rules in different markets.	Disproportionate impact on some public sector hospitals who cannot continue to produce these therapies due to high costs, impacting on access. Although the hospital exemption pathway (via the ATMP Directive) is a possible alternative route, implementation of this varies across Member States. Measures to strengthen preparation process authorisation (M4.5-M4.7) and more coordinated decisions on classifications (M4.3-M4.4) could support greater patient access even after products are commercialised.	Commercial interest is required to place products on the market. A clearly defined pathway is a key factor in making investment decisions (can be achieved through advisory mechanisms established under M4.2-M4.4). Mechanisms to coordinate with adjacent sectors (M4.3 and M4.4) might support improved public-private relationships, earlier in the development process. The new measures would not allow for reclassification back into the BTC framework.	The changes in classification of products under examination is often perceived to have limited patient access to previously widely available products. This reduction in availability is often linked to a lack of (affordable) commercial products as Member States often struggle to approve/obtain reimbursement for such products.

Potential effects of new measures on…	Description	Safety and quality	Costs and affordability	Patient access	Innovation and R&D	Conclusion
Interaction with the medical devices' legislation Examples: Demineralised bone matrix, decellularised heart valves, decellularised dermis	Some products do not fall under the current provisions of the BTC legislation, despite being SoHO. This has led to divergent regulation across Member States. Growth in use of these products may lead to opportunities for further manipulation creating future borderline issues.	The introduction of a proportionate and risk-based authorisation process (M4.5-M4.7) could encourage harmonisation of quality and safety standards. Proposed mechanisms for providing classification advice (M4.2) and improving coordination with adjacent sectors (M4.3-M4.4) could improve classification and oversight processes.	The addition of more measures could increase costs due to more requirements for data generation. This can impact on the capacity and resources of stakeholders in this field (and disproportionally the public sector). The magnitude of impact is dependent on what standards establishments are already working to.	Not perceived to significantly impact patient access – this is rather linked to factors such as the supply and availability of the relevant products; and the type of health and reimbursement system in place.	A perceived risk of overregulation in this area which may lead to developers stopping their activities due to higher costs and administrative burdens. A joint advisory committee (M4.4) may provide earlier clarity on the regulatory pathway to ensure an upfront understanding among developers of the different stages and costs involved in product development.	Use of these products is also growing, with potential for further manipulation which may lead to future borderline issues.
Coordination with the ATMP sector Examples: Pancreatic islets, isolated hepatocytes. Note: Five additional case studies were considered but information on these products was too limited to be able to draw general conclusions.	The classification of a product as an ATMP rests on scientifically complex distinctions, such as 'enzymatic digestion' and 'substantial manipulation'. This can create a lack of harmonisation in how products (even those which are similar to each other) are eventually regulated.	Greater coordination could reduce the variability of approaches taken across Member States, particularly for unproven therapies with multiple intended uses. It will also resolve the "black hole" when products fail to meet an ATMP classification. Some stakeholders felt the impact of a joint advisory committee (M4.4) would be greater if decisions were binding. Increased oversight of novel preparation processes (M4.5-M4.6) would help ensure adequate standards are in place for all starting materials regardless of how they are eventually used and regulated.	May be short-term (implementation) costs but the process of joint decision-making (M4.4) could ensure efficiencies in the longer-term. Smaller, less-resourced public sector organisations should have access to the same level of classification advice and expertise as commercial developers. Requirements to increase oversight of novel preparation processes (M4.6, M4.7) also need to be calibrated to the number of patients data can be collected from.	Measures to strengthen preparation process authorisations for novel products (M4.5-M4.8) encourage harmonisation, therefore improving access through cross-border exchange and acceleration in countries with limited treatments available. Patient representation in committees could support access.	Strengthening preparation process authorisations for novel products (M4.5-M4.8) and proposed clarification mechanisms (M4.2, M4.4) could help to increase confidence and trust between adjacent sectors. This in turn contributes to homogenous and agreed classifications and clarity on what regulatory pathway should be followed. But the revised BTC legislation must be agile to adapt to innovative therapies and fields.	The ATMP classification procedure has been used widely, and whilst the scientific recommendations are not legally binding, they are perceived to be routinely accepted by NCAs. Classifications are specific to the product and the indication. Changes to manufacturing process and or different indications can result in a different classification outcome. Extrapolation to 'similar' products or indications is therefore not straightforward.
Emerging fields with no clear regulatory pathway Example: Extracellular vesicles (EVs)	Discussions on how to classify novel products have increased in line with the growth in interest in this area. These discussions show a significant degree of uncertainty in how to regulate, which can lead to a high degree of variation as to what regulatory framework should be applied by different developers and NCAs.	Measures proposed to strengthen the preparation process authorisation for novel products (M4.5-M4.6, M4.7) were perceived to be appropriate for regulating very novel products. Greater standardisation of risk assessments across the EU (under Option 2 or 3) would ensure harmonisation of safety and quality standards across the EU (to promote cross-border exchange and mutual recognition). A risk assessment approach was considered a good first step in the regulatory process, regardless of how they are later regulated (and under which framework).	Cost and affordability of novel products is tied to the regulatory pathway. In an emerging field, where there is considerable innovation, higher regulatory costs may be inevitable to ensure high standards of quality and safety are maintained.	Implementation of a strengthened preparation process for novel products (M4.5-M4.6) as well as greater coordination between adjacent sectors (M4.4) was perceived to limit patient access to unregulated novel products still in the early phase of development.	Regulatory framework needs to be applied in a way to facilitate innovation – take a pragmatic and flexible approach to assessing risk. Having more coordination among regulatory bodies (M4.3-M4.4) and standardising risk assessment models at the national level (M4.6) may facilitate this. But other, wider aspects are also critical to supporting R&D (e.g., the expertise and training of inspectors).	A 'one size fits all' regulatory approach is not always suitable for novel products. Instead, a more agile approach to regulation is requested by stakeholders due to emerging (and quickly changing knowledge) about how and where material is obtained and the ways in which it can be used.

A9.2 – Autologous adipocyte cells

The stakeholders consulted for this case study were a group from an advocacy organisation for companies, academic research institutions, major medical centres and patient groups, as well as representatives from a national competent authority.

Part A: Definition of the borderline issue

Description of the borderline substance/product/application

Adipose tissue (fat) stores energy and cushions and insulates the body. Adipose tissue is found beneath the skin, as well as around internal organs. Autologous adipocyte cells can be used in a variety of anatomical locations and can be prepared in a spectrum of ways from minimal processing (pasteurisation) to complex processing (pooling to manufacture fortifiers for addition to human breast milk). There is a high level of interest in using autologous adipocyte cells from hospitals and industry.

Adipose-derived stem cells (ADSCs) are mesenchymal stem cells generally used in **regenerative medicine** due to their anti-inflammatory, anti-apoptotic, and immunomodulatory properties. The main mechanisms for cell repair and regeneration are ADSCs' low immunogenicity and their ability to self-renew, to differentiate into different tissue-specific progenitors, to migrate into damaged sites, and to act through autocrine and paracrine pathways[1]. ADSCs are similar to bone marrow mesenchymal stem cells, however they have an advantage as they can be easily and repeatably harvested using minimally invasive techniques with low morbidity[2]. The EMA considers that ADSCs should not be cultured and isolated mechanically and used only in the subcutaneous tissue[3].

Uses of autologous adipocyte cells

ADSCs can differentiate into various cell types of the tri-germ lineages, including osteocytes, adipocytes, neural cells, vascular endothelial cells, cardiomyocytes, pancreatic β-cells, and hepatocytes[4]. ADSCs have a wide range of potential uses, and one review describe their therapeutic potential as "enormous"[5]. ADSCs have a positive risk-benefit profiled in restoring **wound defects**[6], **bone regeneration**[7,8], and **autoimmune** and **neurodegenerative diseases**[9].

MSCs produce molecules with antimicrobial activity reducing pain and could potentially be beneficial countering **infections** and **cytokine storm**. MSC-derived exosomes are also potentially efficient and promising immunomodulators in treating ill **COVID-19** patients[10].

One editorial in Mayo Clinic Proceedings[11] described how in the US, there are widespread unproven "treatments" using autologous ADSCs, such as **facelifts**, **breast augmentation**, and therapies for **amyotrophic lateral sclerosis**, **spinal cord injuries**, **Parkinson disease**, **multiple sclerosis**, **Alzheimer disease**, **muscular dystrophy**, and other diseases and injuries.

A presentation at a EMA ATMP Workshop in 2014[12] stated that a non-homologous use procedure for adipose cells was Gram's Stain (a laboratory procedure used to detect the presence of bacteria and sometimes fungi in a sample) where adipose cells are used to patch a **stomach ulcer** or to patch or seal an **intestinal re-anastomosis**.

Details of the 42 indications for autologous adipocyte cells for which the Committee for Advanced Therapies (the CAT) has made a recommendation can be found in the table at the end of this case study (A9.2.1).

Current regulatory status of autologous adipocyte cells

When autologous adipocyte cells are procured, processed and re-transplanted in the same surgical procedure, they currently fall outside the EU regulatory framework. However, if they are procured, processed and stored they fall within the framework.

the CAT has made **42 recommendations** about classification for autologous adipocyte cells: in 37 cases it recommended classifying products or procedures as ATMPs, in four cases[i] it recommended classification as non-ATMP, and in one case it could not conclude[ii] (Viable autologous adipose-derived regenerative cells for autologous dermal filling). A breakdown of the types of ATMP classification recommendations made by the CAT is presented in Figure 1; the most common classification recommendation was Tissue-Engineered Product (Tissue engineered product), followed by a non-specific ATMP classification. Of the 37 cases, 24 were for treatments using ADSCs, and 13 were for non-stem cell adipose cells. During an interview with representatives from the CAT, it was agreed that it has been difficult to make recommendations about autologous adipocyte cells. In particular, it can be challenging to determine if a mechanism of action for an intended indication is the same as the normal action of adipose cells.

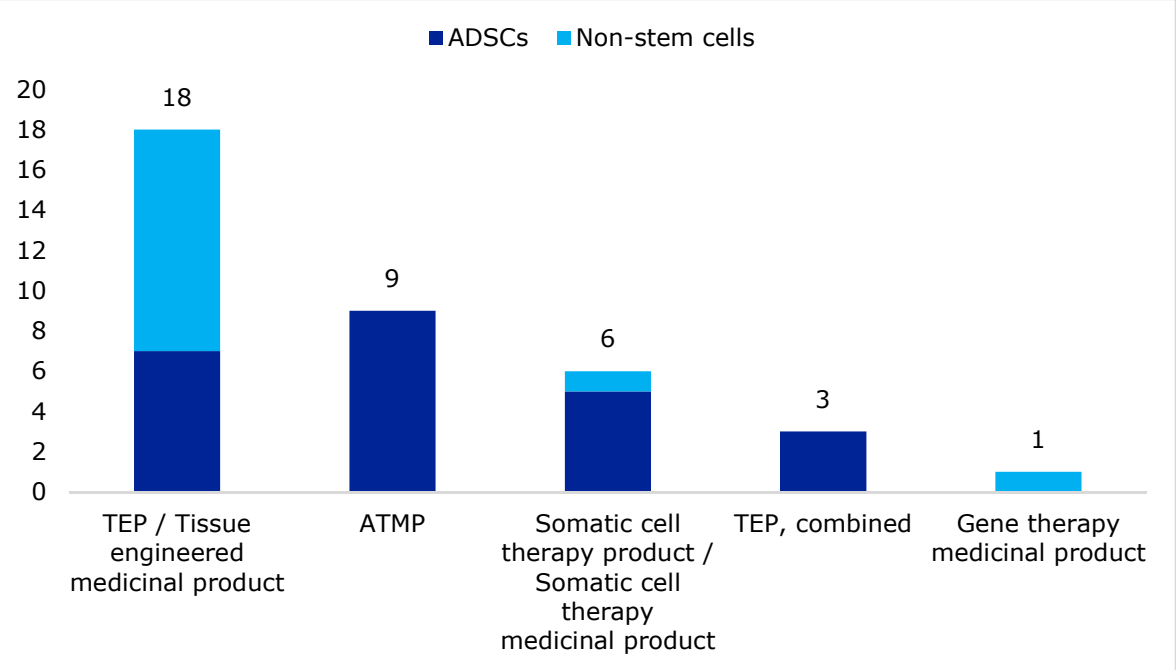

Figure 1. ATMP recommendations on autologous adipocyte cells made by the CAT[iii]

[i] The four cases were: (1) Autologous cells of stromal vascular fraction (SVF) of adipose tissue for cosmetic lipofilling in combination with fresh lipoaspirate; (2) Autologous collagen (AC) derived from human adipose tissue for cosmetic dermal filling; (3) Autologous, non-manipulated lipoaspirate containing adipocytes and stromal vascular fraction for autologous lipofiller; and (4) Autologous viable adipose-derived regenerative cells extracted from human subcutaneous fat from liposuction aspirates intended for the treatment of progressive hemifacial atrophy (Parry-Romberg syndrome).

[ii] Note that according to the CAT Rules of Procedure, in the event of no absolute majority position in favour of the concerned draft opinion, scientific recommendation/advice, the CATs draft opinion, scientific recommendation/advice is deemed to be negative.

[iii] A generic 'ATMP' classification is provided where the CAT has been unable to consider if the product meets the definition of somatic cell therapy or tissue engineering product due to the shortcomings in the information provided by the developer (e.g. regarding the claimed mode of action).

Source: European Medicines Agency. (2021) Scientific recommendations on classification of advanced therapy medicinal products[13]

Another expert consulted for this case study from a NCA stated that, as the CAT classifications are recommendations and therefore not legally binding, there is still significant variation across Member States in terms of enforcement. At a 2019[14] meeting of the Competent Authorities on Tissues and Cells, it was noted that Member States apply divergent regulatory frameworks, or no regulation, for certain therapies including autologous adipose tissue prepared in the hospital.

An expert from an NCA considered that including tissues and cells (as well as products such as adipose cells) in drug law, as is done in Germany[iv], is beneficial as it allows authorities to supervise if they wish, however there are limitations in terms of manpower to visit numerous hospital sites. The stakeholder, a representative of the German CA, reported that Germany is wary of losing its high standards, and in any changes to EU provisions they would like to see the possibility to keep the high national provision. The Treaty of the European Union does allow Member States to have more stringent standards than mandated by EU legislation.

Overview of the regulatory issue

Under current tissues and cells regulations, adipocyte cells are regulated if they are procured, processed (in another facility) and returned to the same patient, or procured, processed and stored.

However, the cells are not regulated if they are procured, processed and re-transplanted into the same patient in the same surgical procedure. This exclusion has had a wide impact, leaving a number of processes now carried out in hospitals and clinics unregulated at EU level, including procedures involving autologous adipocyte cells. A presentation at a EMA ATMP Workshop in 2014[15] outlined that procedures which are autologous and part of the same surgical procedure are excluded from the regulatory frameworks. Additionally, in a meeting of the Competent Authorities on Tissues and Cells in 2011[16], the CAs concluded that procurement of stem cells from autologous adipose tissue by Celution® and re-implantation within the same surgery process to the same patient was exempt from the Cell & Tissue Directive[v]. Due to this exemption, some treatments, such as use of adipose tissue as a reconstructive filler or for cosmetic indications, are administered to patients without any regulatory oversight of the safety, quality or efficacy of the product[17].

At a meeting of the Competent Authorities on Tissues and Cells in 2017[18], stakeholders suggested that the application of the “same surgical procedure” exclusion to these procedures is no longer appropriate as the use of these processing technologies is becoming increasingly widespread and are being used for procuring and processing ADSCs for a variety of indications often without any corresponding validation of quality or efficacy therefore they should be subject to some level of regulatory oversight not just a CE-marking of the device in which the substance is processed. There were also issues related to claims that adipose cells could help different conditions such as chronic cystitis, asthma, and stroke, which were made without adequate evidence of efficacy. CAs suggested that bedside technologies should be in the scope of the legal framework, but subject to specific/minimal conditions which only refer to the preparation process authorisation and include the demonstration of safety, quality and efficacy.

An expert from an NCA consulted in the present study stated that the borderline related to autologous adipocyte cells centres around two qualifiers for classifying an ATMP:

[iv] The German Tissue Act defines all tissues and cell preparations as pharmaceutical drugs governed by the German Drug Act

[v] This process was at the time used for reconstructive surgery, for example breast reconstruction.

substantial manipulation and non-homologous use. In 2015, the CAT produced a reflection paper to resolve issues around interpretation of these terms; this clarifies that if no substantial manipulation of the adipose cells/tissues takes place, the classification recommendation is based on the essential function and therefore not considered ATMPs. However, other clinical uses of non-substantially manipulated cells – such as adipose cells transplanted to other than fat tissue – would be considered to be ATMPs, unless the same essential function(s) and the characteristics of the administration site are considered to be the same. Nevertheless, one expert consulted for this case study suggested that there continues to be inconsistency in the interpretation of these terms across Member States, and in particular the application of the term 'non-homologous' use. The consequence of this is that similar products might fall into different regulatory frameworks across Member States.

Therefore, the perception of a borderline issue with autologous adipocyte cells may be caused by

- The same surgical procedure exemption;
- Use of autologous adipocyte cells without proven benefit;
- A lack of linkage or interaction between the BTC and medical devices frameworks;
- Difficulties interpreting when indications represent homologous use;
- Difficulties interpreting processing as substantial manipulation or not; and/or
- Varied and non-homologous national classifications.

Most of the methods used to isolate ADSC contain a collagenase digestion step and so the perceived borderline may also be caused by a lack of understanding or awareness of the CAT position on enzymatic digestion. For example, some enzymatic digestion processes will result in recommended ATMP classification whilst others do not[vi], according to the CAT Reflection paper on classification of advanced therapy medicinal products[19].

There are some similar interpretation issues vis a vis the interpretation of substantial manipulation in the US as in the EU. A presentation at a EMA ATMP Workshop in 2014[20] stated that the US FDA exempts autologous same surgical procedure cells and tissues in 21 CFR 1271.15(b). A 2015 editorial in Mayo Clinic Proceedings[21] outlines insights from three FDA Draft Guidance Documents including that the FDA "considers the same surgical procedure exception to be a narrow exception to regulation under Part 1271." A paper by Mazini and colleagues[22] notes that even when ADSC is collected, separation is still a source of debate, as the FDA guidance for human cell tissue products considers separation of non-adipocyte cell components from fat as more than "minimal manipulation." However, exception could be made if only rinsing, cleansing, and sizing processing were considered, suggesting a regulatory contradiction.

A key issue perceived by many stakeholders in the sector is that patients have far too easy access to unsafe/unproven therapies using adipocytes. In an interview with the CAT, a stakeholder explained there is 'a low threshold of accessibility' to extract adipose tissue as there is no specialised equipment required. This means there have been many therapies (often with unproven claims) made available to patients by physicians, which circumvent safety and efficacy requirements. Conversely, a written response to the Online Public Consultation on the Revision of the EU's BTC legislation by a representative of a public authority in an EU Member State suggested there may be potential impacts on patient

[vi] "Enzymatic digestion of a tissue to release cells is also considered to be substantial manipulation, when the aim is to dissociate cell-cell contacts and the released cells are administered into patients with or without subsequent manipulation. An example would be keratinocytes from skin, for which enzymatic digestion would destroy the tissue architecture and functional interactions of the cells, which cannot be regained in the cell suspension: this would be considered as substantial manipulation. If the enzymatic digestion leads to isolation of functionally intact tissue units (e.g. pancreatic islets) or there is scientific evidence that the original structural and functional characteristics are maintained, the procedure is not considered substantial manipulation."

access resulting from the borderline between BTC and ATMP frameworks. The stakeholder referenced the example of adipose-tissue derived mesenchymal cells (derived from belly fat) which are transplanted to the knee of the same individual to support regeneration of cartilage, and suggested that time taken to clarifying the borderline issue potentially impacts on the treatment being performed, at least in the short term.

Relatedly, issues with easy access to unsafe procedures have negatively impacted the safety and quality of autologous adipocyte cells. The editorial in Mayo Clinic Proceedings[23] which described various unproven and noncompliant treatments being offered in the US notes that this practice "prompts concerns about patient safety, direct-to-consumer marketing of unproven interventions, and the extent to which patients undergoing procedures at these businesses are being given all the information required to make informed choices." The use of autologous adipocyte cells as a "miracle drug" for ailments without evidence of actual benefit is a source of concern to a consulted expert from an advocacy organisation. An expert from the same organisation interviewed for this case study reported that businesses on the market are providing what they call "advanced therapies" while circumventing regulatory authorities. Another expert from this organisation reported that whenever it is unclear which regulations apply (as in the case of autologous adipocyte cells), loopholes will put patients at risk of harm as opportunists can exploit the system to create unsafe or non-efficacious products. Further, serious side effects have been seen due to ADSC therapies, including blindness in SVF-treated patients presenting macular degeneration[24], other injuries, and death[25]. Unsafe procedures have led to patients losing their eyesight and quality of life according to a consulted expert from the advocacy organisation.

Part B: Potential impact of measures proposed to resolve regulatory issues

The following sections discuss the impacts of the proposed measures being considered as part of the revision to the BTC legislation on different issues relating to autologous adipocyte cell treatments. Specifically, this section primarily considers measures under Objective 4 (M4.1 concerning the "same surgical procedure" exclusion, M4.2-M4.4 concerning strengthened clarification processes, M4.5-M4.6 concerning strengthened authorisation processes and M4.7 for requiring clinical evidence for innovations/new claims).

An expert from an NCA stated that while the Commission's overall goal is clearly to improve the BTC legislation, in the short term the goals should be better defined. Another overall consideration raised by consulted experts is that it is important to ensure sharp and clear use of terminology as is done in the pharmaceutical field. Particularly for products which start with donation under BTC and then then "cross" the regulatory borderline into pharmaceuticals, it is important to ensure consistent terminology – something that can be supported by a committee that can provide legal clarity and interact with adjacent regulatory frameworks (M4.2-M4.4).

Safety and quality

An expert from an advocacy organisation stated that it is important to ensure patient safety, citing scandals and safety concerns in the past and present. The expert felt that a source of difficulty with autologous adipocyte cells is that the cells are used for very diverse indications, and some use them in the context of ATMPs, while other uses should be considered ATMPs but skirt regulation. During the interviews, stakeholders proposed changes (in addition to measures already being considered as part of the revision to the BTC legislation) which would facilitate resolution of the borderline issues around adipocyte cells and improve quality and safety standards:

- An expert from an advocacy organisation reported that so-called cosmetic procedures should be treated in the same way as other procedures, as there should not be opportunities for stakeholders to avoid rules by claiming their procedure is

cosmetic. Another expert similarly stated that there is always a risk of contamination when cells are removed from the body, and this risk cannot be avoided by claiming a procedure is cosmetic.

- An expert from an NCA stated that quality control is difficult to do for autologous adipocyte cells, and there needs to be more process validation to ensure the process is working well in all clinics which are undertaking it. The expert called for more pressure on medical device providers selling single-use products to clinicians to have validation data ready on the device performance as well as on the product the device produces. Another expert from the NCA urged there should be a leading document for good practice for clinicians and good manufacturing practice.

Costs and affordability

An expert from an advocacy organisation stated that cost is a major concern for developers. The main thing which will increase affordability will be a clear regulatory framework which does not lead to a risk of having different rules in different markets. The more streamlined the process, the cheaper. The stakeholder also noted that this is a very new industry, and costs will go down as the volume of autologous adipocyte cell treatment increases.

Another expert from an NCA was in favour of clinical trial measures (M4.7), while noting that they are expensive and time-consuming and that in the existing system it is not reasonable to expect a regular hospital to be able to conduct a clinical trial.

An expert from an NCA stated that, whichever measure is adopted, it should be clear about what it means in practical terms of implementation in different countries. From a regulatory perspective it can be difficult to assess requirements, and time and resources will need to be invested to introduce new considerations to systems. However, other experts noted that affordability and cost is important but should not be criteria when selecting a measure as patient safety and quality should be the main consideration.

Patient access

A mechanism to resolve borderlines more efficiently – and therefore allow treatments to be further developed and made available for patients – was generally welcomed by stakeholders interviewed for this case study. However, an expert from an advocacy organisation reported that it is important that any new classification measures (M4.2-M4.4) do not compete with existing mechanisms; it is essential to know what regulatory pathways there are and to have predictability in terms of how a product will be authorised. Any system which competes with recommendations made by the CAT is going to be disruptive and could create more confusion. Even if a new advisory mechanism is not legally binding, it is important for it to have some weight behind it, for example Member States can trust that a decision was reached based on scientific methodology and rigorous decision-making.

Innovation, research and development

An expert from an advocacy organisation reported that when regulatory pathways and frameworks are not clear, investors can become sceptical about investing, and a clearly defined pathway is a key factor in making investment decisions.

One expert felt that the CAT is very clear on when the substantial manipulation and non-homologous use requirements apply, and as these terms are harmonised on a global scale the global convergence is in the interest of public health and supports the sector's global development capability and interest to invest in the sector.

Conclusions

According to Directive 2004/23/EC and 1394/2007, autologous adipocyte cells applied in a same surgical procedure (without being subject to any banking process) fall outside the scope of the BTC legislation and are also not considered an ATMP. However, if the adipocyte cells are procured as a starting material, substantially manipulated and/or used for non-homologous purposes, then all aspects (from collection to authorisation) are covered under the existing BTC and ATMP frameworks. Despite this separation, many classification questions on the appropriate regulation for adipocytes continue to arise. One expert suggested a clearer "handover" between regulatory frameworks, rather than an "interplay" would help, as would EMA guide on how this handover occurs as EU regulations are very complicated to decipher.

Appendix: the CAT recommendations on autologous adipocyte cells

Public description of active substance or product description	Indication (public) or therapeutic area	Outcome of classification	Date of the CAT recommendation
Autologous cells of stromal vascular fraction (SVF) of adipose tissue	Not medical or therapeutic claims pursued. Cosmetic lipofilling in combination with fresh lipoaspirate	Not an advanced therapy medicinal product	31/05/2012
Autologous collagen (AC) derived from human adipose tissue	No medical or therapeutic claims pursued. Cosmetic dermal filling	Not an advanced therapy medicinal product	31/05/2012
Autologous, non-manipulated lipoaspirate containing adipocytes and stromal vascular fraction	No medical or therapeutic claims pursued. Autologous lipofiller	Not an advanced therapy medicinal product	31/05/2012
Tissue like combination of osteogenic cells and demineralised bone matrix (Three-dimensional structure of demineralised bone matrix and autologous adipose-derived and differentiated osteogenic cells)	Intended for treatment of bone defects	Tissue engineered medicinal product	18/12/2012
Viable autologous adipose tissue-derived mesenchymal stem cells	Intended for the treatment of degenerative arthritis, osteoarthritis (OA), articular cartilage defects in the knee, ankle or hip joints	Tissue engineered product	14/05/2014
Autologous differentiated adipocytes derived from the subcutaneous adipose tissue	Intended for the treatment of primary perianal fistula	Tissue-engineered product	24/11/2014
Autologous adipose tissue derived mesenchymal stem cells	Intended for the treatment of amyotrophic lateral sclerosis	Somatic cell therapy product	27/10/2015
Autologous cells of stromal vascular fraction of adipose tissue	Intended for the treatment of pain associated with joint osteoarthritis	Somatic cell therapy medicinal product	25/11/2015
	Intended for the treatment of non-healing wounds and scarred tissue	Tissue-engineered product	25/11/2015
Human autologous stromal vascular fraction (SVF) cells and human autologous adipose-derived mesenchymal stem cells (ADSC) cells	Intended for the treatment of keloid scars	Tissue-engineered product	23/03/2016
Viable autologous adipose-derived regenerative cells	Autologous dermal filling	the CAT cannot conclude on the classification of this product	04/04/2016
Autologous cultured adipose derived mesenchymal stem cells	Intended for the treatment of non-healing wounds, specifically in tissues derived from mesenchyme e.g. fistula-in-ano, bone and cartilage defects, burns, trophic ulcers	Tissue engineered product	20/05/2016

Public description of active substance or product description	Indication (public) or therapeutic area	Outcome of classification	Date of the CAT recommendation
Human autologous stromal vascular fraction cells and human autologous adipose-derived mesenchymal stem cells	Intended for treatment of cutis laxa senilis	Tissue engineered product	16/09/2016
Autologous human adipose mesenchymal stromal cells, expanded in culture	Intended for cardiac repair	Tissue engineered product	13/10/2016
Autologous adipose derived mesenchymal stem cells, freshly isolated	Intended for the treatment of autoimmune drug resistant epilepsy	Somatic cell therapy medicinal product	06/06/2017
Cultured autologous adipose derived regenerative mesenchymal stem cells	Intended for the treatment of autoimmune drug resistant epilepsy	Somatic cell therapy medicinal product	06/06/2017
Autologous human adipose perivascular stromal cells genetically modified to secrete soluble TRAIL ligand	Intended for the treatment of TRAIL-sensitive cancers such as Ewing sarcoma and pancreatic ductal adenocarcinoma	Gene therapy medicinal product	06/06/2017
Cultured autologous adipose derived mesenchymal stem cells	Intended for the treatment of autoimmune drug resistant epilepsy	Somatic cell therapy medicinal product	06/06/2017
Human autologous adipose-derived stromal/stem cells (ADSCs)	Intended for the treatment of articular cartilage and bone defects	Tissue engineered medicinal product	16/06/2017
Autologous adipose tissue-derived mesenchymal stem cells	Intended for chronic wounds healing (venous leg ulcers, post-traumatic wounds)	Somatic cell therapy medicinal product	19/07/2017
Autologous adipose-derived stem cells seeded on a collagen matrix scaffold	Intended for the treatment of cancer-related lymphedema in breast cancer patients	Tissue engineered product (combined)	20/12/2017
Autologous adipose cells	Intended for the treatment of anal fistula	Tissue engineered product	26/04/2018
Autologous viable adipose-derived regenerative cells extracted from human subcutaneous fat from liposuction aspirates	Intended for the treatment of burn scars	Tissue engineered product	06/02/2019
	Intended for the treatment of progressive hemifacial atrophy (Parry-Romberg syndrome)	Not an advanced therapy medicinal product	06/02/2019
Cultured autologous adipose-derived stem cells on a scaffold	Intended for urinary diversion in patients requiring radical cystectomy for the treatment of bladder cancer	Tissue engineered product (combined)	06/02/2019
Autologous viable adipose-derived regenerative cells extracted from human subcutaneous fat from liposuction aspirates obtained by enzymatic isolation	Intended for the treatment of burn scars	Tissue engineered product	22/02/2019
	Intended for the treatment of progressive hemifacial atrophy (Parry-Romberg syndrome)	Tissue engineered product	22/02/2019
Autologous viable adipose-derived regenerative cells extracted from human subcutaneous fat from liposuction aspirates obtained by enzymatic isolation (using a proprietary system from manufacturer 2)	Intended for the treatment of progressive hemifacial atrophy (Parry-Romberg syndrome)	Tissue engineered product	22/02/2019
	Intended for the treatment of burn scars	Tissue engineered product	22/02/2019
Adipose tissue particles in a fibrin glue	Treatment of scar revision, burn wound, diabetic ulcer, and pressure ulcer	Not ATMP	26/04/2019
Adipose tissue derived mesenchymal stem cells	Amyotropic lateral sclerosis	ATMP	05/03/2020

Public description of active substance or product description	Indication (public) or therapeutic area	Outcome of classification	Date of the CAT recommendation
Autologous human mesenchymal stem cells derived from adipose tissue	Alopecia	ATMP	05/03/2020
	Hypertrophic scars	ATMP	05/03/2020
Autologous adipose tissue derived mesenchymal stem cells	Osteoarthritis	ATMP	22/04/2020
Autologous human mesenchymal stem cells derived from adipose tissue	Repair of cartilage lesions	ATMP	30/06/2020
	Diabetic foot syndrome	ATMP	09/10/2020
Adipose tissue derived stem cells or induced pluripotent stem cells transformed into insulin and glucagon releasing cells, cultured endothelial cells and fibroblasts/fibrocytes	Brittle diabetes mellitus type I	Tissue engineered product, combined	06/11/2020
Autologous viable adipose tissue derived mesenchymal stem cells	Muscle and tendon disease	ATMP	19/02/2021
	Perianal fistula	ATMP	19/02/2021
	Androgenic alopecia	ATMP	19/02/2021
Adipose derived vascular stromal cells	Wound healing in PRS as additional therapy to fistula surgery in patients with complex and therapy refractory perianal fistula	Tissue engineered product	25/09/019
Adipose-derived ex-vivo expanded mesenchymal stem cells	Treatment of diabetic foot ulcers	Tissue engineered product	25/09/019
Human autologous adipose tissue - derived mesenchymal stem/stromal cells	Bone and cartilage defects including osteoarthritis	Tissue engineered product	25/09/019

Source: European Medicines Agency. (2021) Scientific recommendations on classification of advanced therapy medicinal products.

[1] Mazini, L., Ezzoubi, M., & Malka, G. (2021). Overview of current adipose-derived stem cell (ADSCs) processing involved in

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[13] European Medicines Agency. (2021). Scientific recommendations on classification of advanced therapy medicinal products. [Accessed 14 July 2021]. Available from: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/advanced-therapies/advanced-therapy-classification/scientific-recommendations-classification-advanced-therapy-medicinal-products

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A9.3 – Chondrocytes

The stakeholders consulted for this case study were two clinicians highly experienced in performing chondrocyte procedures, working in Spain and the UK respectively.

Part A: Definition of the borderline issue

Description of the borderline substance/product/application

Chondrocytes are the resident cells of cartilage. In embryos, they are prominent tissues which act as a template for the development of skeletal elements but in adults the distribution of permanent cartilage is much more restricted and is necessary for mechanical support, growth and movement[1]. Chondrocytes are isolated within a voluminous extracellular matrix (ECM) that is neither vascularised nor innervated and therefore can exist in a low oxygen tension environment[2].

Uses of chondrocytes

The main clinical use of chondrocytes is for treating articular cartilage defects of the knee through autologous chondrocyte implantation (ACI) treatments. A biopsy is taken arthroscopically to remove normal cartilage from a patient and chondrocytes are extracted and expanded *in vitro* to increase the number of cells. A few weeks later, the chondrocytes are re-implanted into the damaged joint(s), with the intention of restoring normal function. The procedure is used primarily for knee joints at present, but has been tried in other joints[3]. The short-term benefits of ACI include pain relief in the affected joint while the long-term benefits include the prevention of osteoarthritis which might subsequently lead to the requirement for a knee replacement[4].

In the UK, in 2017, NICE (The National Institute for Health and Care Excellence) recommended that ACI should only be used under certain conditions, e.g. if the person has not had previous surgery to repair articular cartilage defects, if the defect is over 2 cm^2, and if the procedure is done at a tertiary referral centre[5]. One of the experts interviewed for this study suggested similar conditions/restrictions were in place in other countries using chondrocytes. Although the cost of ACI for treating symptomatic articular cartilage defects of the knee varies across different settings due to confidential manufacturer discounts, NICE recommended that the cost of cells should not exceed a maximum of GBP 16,000 (close to EUR 19,000)[6].

The increasing prevalence of osteoarthritis and musculoskeletal system disorders is expected to contribute to the increase in value of the ACI market. One of the experts interviewed for this study suggested the main future developments in the use of chondrocytes was the move towards allogenic use, for which there are a number of clinical trials currently taking place[i]. An article in Bloomberg in 2020, outlined, (according to Coherent Market Insights), that the Europe allogeneic human chondrocyte market is expected to be valued at USD 3,440.5 million in 2027 and is expected to exhibit a compound annual growth rate (CAGR) of 10.2 % during the forecast period (2020-2027)[7].

Current regulatory status of chondrocytes

Three indications of autologous chondrocytes have been recently classified by the CAT as ATMPs specifically tissue engineered products (TEPs)[8]:

[i] For example, according to an expert interviewed for this case study, the UK is planning a clinical trial (within in the next two years) to manufacture a new allogenic therapy using chondrocytes from recently deceased donors. In another trial in the Netherlands, allogenic stem cells from bone marrow were combined with patients own chondrocytes (not expanded) and the trial is now looking to be repeated in the US.

- **Autologous expanded viable chondrocytes** for the repair of symptomatic, localised, full-thickness cartilage defects of the knee joint in patients with closed epiphyseal growth plates (January 2021)
- **Autologous knee-derived chondrocytes** for the treatment of knee joint cartilage lesions (December 2019)
- **Autologous knee-derived chondrocytes** with autologous fibrinogen/ Autologous knee-derived chondrocytes with allogenic fibrinogen/ Autologous knee-derived chondrocytes with fibrin glue for the treatment of knee joint cartilage lesions (December 2019)

These classifications were made on the basis that the active substance contains autologous expanded viable chondrocytes; the manufacturing process involves substantial manipulation (or the product contains /consists of engineered cells which have been subject to substantial manipulation); the product would be indicated for regeneration of damaged cartilage; and the claimed primary mechanism of action of the product is the regeneration, repair, and replacement action[9]. The above products have not yet proceeded to Marketing Authorisation Application (MAA) stage.

Since implementation of the ATMP Regulation in 2007, a number of ATMPs designed for cartilage repair have been approved for use in the European Union (EU):

1. **A. MACI (matrix-applied characterised autologous cultured chondrocytes)**

MACI is a commercial product consisting of autologous chondrocytes seeded on a collagen membrane of porcine origin[10]. MACI is used for the repair of symptomatic, full-thickness cartilage defects of the knee[11]. Several studies have demonstrated the value of using MACI rather than the surgical procedure microfracture to treat symptomatic knee cartilage lesions and defects. The SUMMIT (Demonstrate the Superiority of MACI implant to Microfracture Treatment) trial of patients with one or more symptomatic focal cartilage defect of the femoral condyles or trochlea and a baseline Knee Injury found that the treatment of symptomatic cartilage knee defects ≥3 cm(2) in size using MACI was clinically and statistically significantly better than with microfracture treatment, with similar structural repair tissue and safety[12]. This was confirmed at the 5 year follow-up point[13]. MACI had a European marketing authorisation for the repair of symptomatic, full-thickness cartilage defects of the knee between 3 cm^2 and 20 cm^2, however as of 2017 the marketing authorisation was suspended citing commercial reasons. This was driven by the closure of the European manufacturing site in 2014 due to a lack of sales and insufficient reimbursement by countries. Consequently, MACI was no longer available to the public.

B. ChondroCelect®

ChondroCelect was the first ATMP approved in the EU[14] in 2009. ChondroCelect® was approved for use in the treatment of cartilage defects (including of the femoral condyle)[15,16]. An article from the venture capital firm Ysios Capital[17] stated that for ChondroCelect, cells were taken from the patient's own knee, multiplied to reach a large quantity, and then re-implanted at the site of the defect. ChondroCelect can be delivered nine weeks from the day of biopsy[18]. The Active Substance in ChondroCelect was a centrifuged pellet of 4 to 12 million cells that are expanded ex vivo, harvested and washed. The expansion process was designed to preserve the integrity and function of the cells and particularly to maintain the cells' ability to produce hyaline cartilage[19]. A study in Belgium found ChondroCelect® increased quality-adjusted life year (QALYs)[ii] gained and reduced osteoarthritis-related

[ii] One QALY is equal to one year of life in perfect health, and is calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). More information can be Source: NICE website. Accessed 29 September 2021. https://www.nice.org.uk/glossary?letter=q#:~:text=One%20quality%2Dadjusted%20life%20year,a%200%20to%201%20scale).

costs when compared to microfracture[20]. The superiority of ChondroCelect over microfracture treatment in terms of primary clinical endpoint of enhanced efficacy formed the basis of the EMA approval of ChondroCelect[21].

ChondroCelect was also the first ATMP to be granted national reimbursement[22]. However, this was only achieved in three countries: Spain, Belgium, and the Netherlands[23]. The MA for Chondroselect was subsequently withdrawn from the EU at the request of the marketing authorisation (MA) holder. A timeline of ChondroCelect's approval and withdrawal is presented below, based on an article from the venture capital firm Ysios Capital[24]. The EMA's public statement regarding ChondroCelect's Marketing Authorisation withdrawal[25] was as follows:

ChondroCelect was withdrawn from use in the EU in 2016, as the marketing authorisation holder (TiGenix NV) notified the European Commission of its decision to permanently discontinue the marketing of the product for commercial reasons[26] including *"the regulatory environment around autologous chondrocyte-based cell therapy products in Europe leading to a difficult competitive landscape for ChondroCelect, together with the lack of reimbursement in key European countries"*[27].

C. Spherox (chondrosphere®16)

Spherox (received Marketing Authorisation in the EU in 2017) consists of small spheroids of neocartilage composed of expanded autologous chondrocytes and their associated matrix. It is used to treat articular cartilage defects of the femoral condyle and knee patella[28]. Spherox is available as a suspension for implantation into the knee joint in adults and adolescents (whose bones in the joints have finished growing) where the affected area is no larger than 10 cm². During reimplantation, the chondrocyte spheroids attach to the cartilage within 20 minutes[29]. In the first study involving 100 adults, Spherox was compared with microfracture (a type of surgery used to treat defects in cartilage) and was shown to be just as effective[30]. One of the stakeholders interviewed for this case study estimated the cost of Spherox varied considerably, based on the market borders and volumes of use e.g. it was £10,000 in the UK[31], cheaper in Germany as it is domestically-manufactured (6,000 EUR) and higher still in the US ($50,000).

Overview of the regulatory issue

According to one expert, the ATMP classification provided to ACI treatments is 'appropriate' in the legal sense as cells are expanded but, in the expert's opinion, this classification has led to their over-regulation as they are a relatively safe cell therapy compared to others involving different cell types (e.g. stem cells, embryonic cells) which are inherently riskier to use. The expert stated that the current regulation of chondrocytes is not proportional to the level of risk, as this has been an established therapy for many years prior to ATMP classification. This leads to significant barriers in the use of chondrocytes.

National authorisation procedures have also impacted on the use of chondrocyte treatments. In the UK, for example, chondrocytes had been previously used (prior to ATMP regulation) for around 20 years until a review process was instigated by the National Institute for Health and Care Excellence (NICE) in 2012. According to an expert interviewed for this case study, the reason for the review was a perceived lack of sufficient evidence to demonstrate cost-effectiveness in the use of ACI over other available treatments. During the five year review process, the use of ACI stopped, other than in one hospital (with GMP-compliant laboratories) that was able to offer ACI as part of clinical trials in in the UK.

According to the expert, despite the authorisation for use of ACI in the UK (with specific conditions) in 2017, the lengthy review process meant that hospitals lost their license to manufacture chondrocytes. Now, even though ACI has continued, it is often limited to a few hospitals and many patients do not want to travel when other (albeit potentially inferior) treatments are available. Although ACI has been approved for use 3-4 years, it is only being

performed in four hospitals in the UK. Two of these hospitals have only performed one operation each (as they had been set up but then temporarily shut down due to Brexit and the need for an export license). This has had major consequences for patient access: whilst NICE had estimated that 500 patients would be able to receive this therapy every year, in reality only a tenth of this (50 per year) are receiving it which means there is 'massive unmet need'.

Another expert, who works in a public hospital in Spain, explained that they had been heavily involved in the development of chondrocyte culture in the BTC setting until the implementation of the ATMP regulation led to a change in classification. At this point, BTC establishments across the EU had to stop treating their existing patients and instead had to use a product developed by a private pharmaceutical company. The main impact of the change in regulation was the increased cost of the commercial product, which the stakeholder stated was far more expensive than the treatment they had been providing before in the public hospital. Across the EU, the expert estimated that the price increased by approximately five to six times from 7000 EUR to 35,000-45,000 EUR for one knee. According to the same stakeholder, a key factor in driving up the cost was the need to obtain authorisation from EMA. The same stakeholder explained that the costs posed a significant barrier to patient access as most countries could not afford to reimburse the cost of this treatment. In some countries, such as Spain, this has led to the treatment no longer being offered to patients - public hospitals cannot afford the commercial product or to set up the GMP-approved facility to manufacture their own chondrocytes.

In Belgium, a convention agreement for the reimbursement of ChondroCelect stated that the reimbursement price (EUR 19,837 for one application, excluding surgical and hospital costs) of ChondroCelect was almost ten times higher than the Belgian price of conventional autologous chondrocyte cultures (which were not ATMPs and not approved by EMA)[32]. Therefore, in Belgium reimbursement of the procedure was limited to patients under 50 years of age. The authors of a paper outlining the Magistral Preparation of ATMPs[33] argued that with such conditional reimbursement, not all Belgian patients in need can benefit, which contradicts with the fundamental principle of equal access to healthcare. The authors conclude that the increase in pharmaceutical production costs and marketing authorisation requirements reduces patient access to advanced therapies. The authors of the VALUE report[34] reported that ChondroCelect® has raised questions of cost effectiveness which relate both to its price and to its efficacy relative to current best standard care.

Another impact of overregulation is on innovation. According to an expert interviewed for this case study, although there is a strong history of chondrocyte use in Belgium, Spain, Germany and in several Scandinavian countries (Norway, Sweden), growth of chondrocyte treatments in Europe has been stifled by the variation and changes in regulatory classifications over the years. Another expert agreed that Europe had driven progress in chondrocyte treatments over the last two decades, but the restrictions posed by the ATMP classification and the subsequent cessation of treatment in several countries means that the EU will fall behind with R&D in this area. The experts agreed that in most countries, the limitations posed by the regulation mean that clinicians are now focused on looking for different treatments (e.g. in Austria they are exploring the use of a cartilage fresh graft).

Part B: Potential impact of measures proposed to resolve regulatory issues

The following sections discuss how the range of measures proposed to revise the BTC legislation may impact on the regulation of chondrocytes. Specifically, this study refers to several measures under Objective 4 (M4.2-M4.4 concerning strengthened clarification processes and the establishment of a BTC advisory mechanism, M4.5-M4.6 concerning strengthened authorisation processes and M4.7 concerning the collection of clinical data).

Safety and quality

One expert felt that the proposed package of measures under Objective 4 (specifically M4.5-M4.7) would not significantly change anything for the use of chondrocytes as it is already a low-risk therapy but one which is now classified as an ATMP under that Regulation. However, the expert felt that where there will be implications for products out there which are 'getting under the radar' (e.g. bone marrow concentrate, PRP) or 'falling into a regulatory gap'. This would help to bring these products closer to the requirements of the ATMP regulation,

An expert hoped that strengthening the preparation processes (M4.5.M4.6) would increase trust between regulatory sectors, further confirming that the BTC sector is prioritising quality and safety and this, alongside enhanced collaboration, could help more fluid decision-making on products such as chondrocytes (as a current issue is that once a classification recommendation is made for an ATMP, this often is not challenged).

Costs and affordability

According to one expert, cartilage is a good example of a low-risk cell therapy, but this is sometimes difficult to explain to authorising bodies who often want to see the same level of evidence for this product as other riskier cell therapies. The implementation of M4.5-M4.7 in the BTC sector should address this and ensure proportionality. For example, generating clinical evidence from patients eligible for ACI is very difficult as the actual number of patents which are suitable to go into a trial are different to the overall (potential) patient population – patients have to be excluded from the trial if they have associated problems (e.g. with their ligaments) to reduce compounding factors. The expert estimated that only 5-7% of patients are suitable for a trial and as consequence they take a long time and lots of money to undertake. The expert concluded that things should be easier, quicker and cheaper than they are for cartilage therapies currently.

Patient access

According to one expert, measures M4.2-M4.4 would facilitate a more rounded discussion of whether cell therapies, with the same risk level as chondrocytes, could instead be regulated under a strengthened tissue framework (with stronger preparation authorisation systems in place through the implementation of M4.5-M4.6), instead of the ATMP framework given the significant implications on patient access.

Innovation, research and development

Both experts interviewed for this case study agreed that the next steps to consider in the regulation of chondrocytes related to allogenic uses (which is easier and cheaper to manufacture and inhibits the need for a second operation). One expert stated that that although the routine clinical use of allogenic treatments will take a number of years (in part due to the low number of eligible study participants), the hope is that this route would not require the same level of regulation. For example, in the UK, the hope is that it could be regulated in a similar way to bone and tendons and so hospitals would not need to obtain a Human Tissue Association (HTA) license (they could instead set up a service level agreement with HTA-approved cartilage centres) which would remove a *"chunk of the regulatory pathway".* However, it is unclear how the risk status of allogenic chondrocyte therapies may differ from autologous chondrocyte therapies.

Conclusions

In regard to autologous chondrocytes, as this product 'fits' the current definitions of an ATMP provided by the CAT (agreed by the experts interviewed for this case study) then, irrespective of the level of risk, any decision to regulate it under a different framework would

be open to legal challenge, e.g. by developers who have already invested in placing their product on the market.

The current regulation of many chondrocyte therapies as ATMP has clearly had an impact on innovation and access. While some companies have ceased to offer these therapies as ATMP for commercial reasons, the BTC establishments, who developed and offered therapies prior to the classification as ATMP, have been restricted in their possibility to offer this therapy with implications for patient access.

The arguments put forward by both clinicians interviewed for this case study indicate that there may be a possibility for a more rounded discussion of whether cell therapies, with the same risk level as chondrocytes, could instead be regulated under a strengthened tissue framework (with stronger preparation authorisation systems in place through the implementation of M4.5-M4.6) and enhanced collaboration and co-operation with the CAT and EMA, instead of singularly applying the ATMP framework given the significant implications on patient access highlighted here.

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A9.4 – Consolidated case study examining the ATMP classification process

This case study examines recommendations made by the CAT on five novel products/therapies to understand the ATMP classification process.

Product	Use / indication
Autologous bone marrow cell aspirate, concentrated	Treatment of bone defects including fractures, bone cysts and necrosis
Banked leukocytes with cancer killing activity	Treatment of metastatic pancreatic ductal adenocarcinoma
Human allogeneic amniotic membrane, sterile, cryomilled and lyophilised	Treatment of Symptoms of Osteoarthritis
Minimally manipulated-Autologous Omental Film	Treatment of Renal traumatic/disease condition
Modulated immune cells	Prophylactic use in solid organ transplantation and therapeutic use in autoimmune disease

An interview was held with representatives from the CAT to better understand the ATMP classification process. During this interview, none of the five cases were specifically discussed – though there was a short discussion on access to bone marrow (which links to Case 1). The main view articulated by the representatives was that they did not perceive the five cases to be representative of the CAT classification procedure.

The findings presented under each case are limited by a lack of information on the product/substances. This is because, following the existing ATMP regulation, the EMA has the obligation to protect commercial and confidential information submitted by applicants until a product is approved. Additionally, due to the product's innovative and propriety status, there is very little other publicly available information (e.g. academic papers) available at this stage.

Statements on the regulatory status of each of the five products/substances are based on the limited information available via published ATMP classification decision papers. Although the decisions specify why a decision was made to classify a product as an ATMP or not, it does not (a) provide an overview of the evidence or claims made by the developer in support of their application or (b) follow up on products which are not classified as ATMPs (which means it is not possible to know what they are/should be classified as).

Part A: Definition of the borderline issue

Autologous bone marrow cell aspirate, concentrated

Human bone marrow represents a source of mesenchymal stem cells (MSCs) as well as growth factors and cytokines, which gives it anti-inflammatory and regenerative properties for various tissues, including cartilage and bone[1]. MSCs represent only 0.001% of nucleated cells, bone marrow aspirate concentrate (BMAC) has been used for its potential benefits including disease modifying and regenerative capacity for cartilage pathologies, such as cartilage degeneration, defect, and osteoarthritis[2].

In an interview with the CAT, one representative explained *"pretty much any physician can extract bone marrow, so there is lower threshold for accessibility… depending on when you change the indication, how much change there is in the intended use or indication, determines whether this is a… cell-based product".* This means the CAT receives many classification requests from applicants for products across a whole range of intended clinical uses, and the CAT has to assess each case on where or not this intended use should be considered as homologous use or not.

Autologous bone marrow cell aspirate (concentrated) is used for bone repair in a variety of bony defects such as fractures, arthroplasty, bone cysts, osteonecrosis, or avascular necrosis[3]. A clinic in the UK[4] reported that it uses bone marrow cell aspirate to treat a wide range of conditions and injuries: knee pain (including Knee Osteoarthritis), hip pain (including Sacroiliac Joint Pain), ankle & foot pain (including Plantar Fasciitis), shoulder pain (including Rotator Cuff Tears), elbow pain (including tennis elbow), wrist/hand pain, and jaw TMJ. A recent study[5] noted that injecting bone marrow cell aspirate is often marketed as "stem cell therapy", however caution should be exercised as bone marrow cell aspirate represents a "heterogenous agglomeration of numerous cell types, most of which are in the hematopoietic lineage and not the mesenchymal cell lineage".

In 2021, the CAT classified autologous bone marrow cell aspirate (concentrated) as a tissue-engineered product, on the basis that it consists of cells or tissues that are not intended to be used for the same essential functions in the recipient and the donor, and is presented as having properties for being administered to human beings with a view to regenerating, repairing a human tissue[6].

Banked leukocytes with cancer killing activity

Banked allogenic leukocytes (stimulated granulocytes isolated from selected donors with high cancer killing activity) are used for treatment of metastatic Pancreatic Ductal Adeno Carcinoma[7].

According to a monthly report produced in January 2017, the CAT recommended that banked leukocytes with cancer killing activity, intended for the treatment of metastatic Pancreatic Ductal Adeno Carcinoma, should not be classified as an ATMP[8]. It was explained by the CAT that this initial classification of January 2017 was revisited by the CAT in April 2017 based on additional information provided by the applicant on the manufacturing process involved.

In April 2017, the CAT provided the recommendation that banked allogenic leukocytes (intended for the treatment of metastatic Pancreatic Ductal Adeno Carcinoma) should be classified as a somatic cell therapy medicinal product on the basis that the product contains cells that have been subject to substantial manipulation and the proposed mode of action is immunological mode of action[9]. A representative from the CAT explained the decision to classify this product as a somatic cell therapy rests on the 'banking' process which involves cell expansion (considered substantial manipulation).

More information on the process of classification was not available as the CAT is unable to publish commercial or propriety information.

Human allogeneic amniotic membrane

The amniotic membrane is the innermost foetal membrane, usually discarded following birth. The membrane (and stem cells isolated from it) have bacteriostatic and anti-angiogenic properties which make them potentially useful in regenerative medicine[10]. Amniotic membrane has been shown to reduce pain, regulate the inflammatory process, improve wound healing and epithelialisation, and act as a physical barrier for exposed wounds. It has been investigated for potential use in the treatment of skin burns, as a

scaffold biomaterial in the reconstruction of the ocular surface, in head and neck surgery, and to prevent tissue adhesion in abdominal, head and pelvic surgery[11].

According to one source (Leal-Martin et al., 2021), more than 10,000 human amniotic membranes (from 330,128 non-reproductive tissues) were distributed in 2017 among 4500 recipients in 25 countries of the EU, with 172 institutions (between biobanks and private institutions) processing, preserving, storing or distributing human amniotic membranes[12]. As noted in the BTC evaluation study[13], the Eurocet database recorded 432 intra-EU imports, 110 extra-EU imports, 1,333 intra-EU exports, and 845 extra-EU exports of amniotic membrane in 2016. Leal-Martin et al. note amniotic membrane is used both commercially and by tissue banks (including the Barcelona Tissue Bank and the German Institute for cell and tissue replacement and the German Society for Tissue Transplantation). Keera SRL (Italy) currently produces a freeze-dried extract of fresh human amniotic membrane for ophthalmic applications as a commercial product[14].

A 2019 study suggested the intra-articular injection of human AM delays histological changes of cartilage in osteoarthritis[15]. A 2020 review[16] stated that orthobiologics, including amniotic products, have been gaining interest for the treatment of various orthopaedic conditions including osteoarthritis. The review concluded that while amniotic products seem effective in animal studies, human clinical trials are lacking, and further investigation is needed to determine whether amniotic products have a role in the treatment of osteoarthritis and other orthopaedic pathologies.

In 2021, the CAT recommended that human allogeneic amniotic membrane (sterile, cryomilled[i] and lyophilised (freeze-drying)) for treating the symptoms of osteoarthritis should not be classified as an ATMP[17] on the basis that:

- It does not contain or consists of cells or tissues; and
- It does not contain an active substance which contains or consists of a recombinant nucleic acid administered to human beings with a view to regulating, repairing, adding or deleting a genetic sequence.

The CAT do not perceive there to be any borderline or regulatory issues with this particular classification. It is of note, however, that NCAs have previously raised the issue of how to classify amniotic membrane at two meetings. During one meeting in May 2008, it was suggested that amniotic membrane for use on the corneal surface should be regulated under Directive 2004/23/EC given the homologous use (i.e. it performs the same essential function in the eye as in the placenta). This coincides with the position taken by the Food and Drug Administration (FDA)[18]. A few years later, during a meeting of authorities in December 2011, it was agreed (following a request for confirmation by the Belgian Competent Authority) that amniotic membrane used as a wound dressing and/or barrier for treatment and management of burn wounds is covered by the Directive 2004/23/EC[19].

Minimally manipulated-Autologous Omental Film (MA-Omental Film)

MA-Omental film is used for the treatment of renal traumatic/disease condition[20]. The omentum is a large flat adipose tissue layer on intraperitoneal organs (e.g. The stomach) which has key biological functions in immune-regulation and tissue regeneration[21].

In 2021, the CAT recommended that MA-Omental film for treating renal traumatic/disease condition should not be classified as an ATMP[22] on the basis that it:

[i] The act of cooling or chilling a material and then reducing it into a small particle size.

- Does not contain an active substance which consists of a recombinant nucleic acid administered to human beings with a view to regulating, repairing, adding, deleting a genetic sequence; and
- Does not contain cells that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered nor does it contain engineered cells or tissues.

Thus, according to the CAT, MA-Omental film does not fulfil any of the three definitions of an ATMP (GTMP, Tissue engineered product, sCTMP). If the developer was deemed to have submitted sufficient data in support of their application, then this classification is conclusive; if not, the classification might change when more data become available. This information is not available to the public.

Modulated immune cells

Modulated[ii] immune cells (MICs) of the peripheral blood can be used to prevent diseases from occurring during solid organ transplantation (e.g. kidney transplantation), and for therapeutic use in autoimmune disease (e.g. multiple sclerosis)[23].

Modulated immune cells intended for prophylactic use in solid organ transplantation and therapeutic use in autoimmune disease was classified by the CAT in 2019[24] as not ATMP, on the basis that it does not consist of cells that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered and does consist of cells that are intended to be used for the same essential function(s) in the recipient and the donor.

As part of the ATMP classification process, the CAT explains that they will look at substantial manipulation and non-homologous use. If not substantially manipulated (e.g. simple cell selection, no culturing or extensive enzymatic digestion), products will be classified as not-ATMP as long as the mechanism of action of these cells is considered homologous. As explained by representatives from the CAT, the main classification challenges relate to distinguishing between homologous and non-homologous use. The CAT relies on data provided by the applicant and information on intended use, as well as clinical and quality-based expertise, to make recommendations on a classification.

Overview of the regulatory issue

Representatives from the CAT stated that ATMP classification procedure has been used widely, with over 500 classifications issued to date. The applicants include pharmaceutical companies, but also SMEs, academic developers and hospitals. The procedure is fast (60 days) and is free of charge. The scientific recommendations from the CAT are not legally binding, but nevertheless perceived to be accepted by the NCAs[iii].

In case of cell-based therapies, the CAT will base its classification on two aspects: substantial manipulation and essential function. These two criteria as defined in the ATMP Regulation, and further clarifications can be found in the CAT reflection paper on the classification of ATMPs (EMA/the CAT/600280/2010 rev.1). The same criteria are used in many parts of the world (e.g. US, Canada, Japan) to determine the cell-based products that need a pre-authorisation approval (ATMPs).

[ii] Immune system modulation (or immunomodulation) involves the use of therapy to modify the immune response, often to prevent tissue damage resulting from an excessive response.

[iii] The CAT do not systematically track outcomes resulting from the classification, but in more than 500 classifications the CAT is not aware of any classification that has been contradicted by a Member State.

the CAT draws on a breadth of expertise from across the Member States which also means they have a system for *"bringing the classification experience back to [national] agencies… which leads to a broad acceptance of decisions in Member States".* Further, the publication of the CAT's reflection paper – where they have provided further clarification of the definitions for substantial manipulation, non-homologous use – has helped to clarify the regulatory pathway for the applicants and ensures the consistency of the classification conclusion of individual cases.

However, representatives from the CAT interviewed as part of this process reported that a difficulty faced is that their scope is limited in that they can only classify a product as an ATMP or not an ATMP, and they cannot go a further step to advise if a product should be developed as a medicinal product or a tissue/cell. The stakeholder described this as a "black hole" as if a product is classified by the CAT as not an ATMP, developers struggle with fragmented advice or knowing where to go.

Additionally, the CAT do not systematically follow-up on products once their classification recommendations have been made, though there are other less formal ways of tracing what follows from the classification (e.g. They have records of ATMPs that make it to clinical trial stage, and records of meetings with national component authority inspectors).

Part B: Potential impact of measures proposed to resolve regulatory issues

Due to the aforementioned limitations in data collection, it has not been possible to examine if the introduction of new measures under the revised BTC legislation could improve the regulatory situation of the five cases.

Conclusions

The ATMP classification procedure has been used widely, and whilst the scientific recommendations are not legally binding, they are perceived to be routinely accepted by NCAs. Classifications are **specific to the product and the indication**. Changes to manufacturing process and or different indications can result in a different classification outcome. Extrapolation to 'similar' products or indications is therefore not straightforward.

The five case studies presented above lack sufficient information to explain any regulatory issues in depth. This is a result of limited information on the evidence informing recommendations due to the CAT being unable to publish commercial or propriety information, and limited information on the current regulatory status of products that are not classified as an ATMP by the CAT due to a lack of a systematic follow-up process.

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A9.5 – Cultured keratinocytes

Two experts on this subject were interviewed for this study, both clinicians who have experience with delivered the treatment as well as the regulation in their respective countries (Sweden and Belgium).

Part A: Definition of the borderline issue

Description of the borderline substance/product/application

Cultures of human epithelial cells (keratinocytes) are used to form coherent epithelial tissue sheets to accelerate the healing of burn wounds, to initiate the healing of chronic skin ulcers and to stimulate the healing of autologous skin donor sites[1].

Use of cultured keratinocytes

Autologous skin grafting is a standard treatment for skin loss, in the absence of developments of synthetic or semisynthetic skin substitutes with biological properties similar to fresh viable human skin[2]. However, skin autografting is often impossible in burn patients, due to a lack of healthy skin donor sites and to the general condition of these patients[3], and does not often lead to acceptable functional and cosmetic outcomes (e.g. scar tissue and skin contractions)[4].

By growing autologous skin cells (keratinocytes) in vitro, to be applied with a meshed split skin graft, the burn will heal faster with less scarring. An autologous skin biopsy is taken and cells are cultured during some weeks to form skin sheets. Keratinocytes are delivered to the wound bed in the form of sheets or sprays[5] and often grafted together with allogeneic skin on burn wounds and chronic wounds. These stimulate the wound bed to heal faster and achieve definitive coverage of the wound[6].

As both stakeholders contributing to this case study explained, the patient population requiring cultured keratinocyte treatment is very small each year comprises mainly severely burned patients. Demand is unpredictable and spasmodic. A single incident might result in the need for many grafts for the same or a number of patients over a period of weeks or months. This might be followed by a long period without any demand for grafts.

Keratinocyte graft production was regulated exclusively by national regulations until 2004, when it became regulated by the Member State's transposition of Directive 2004/23/EC. Following the publication of Regulation No. 1394/2007 on ATMPs, the Committee for Advanced Therapies (CAT) recommended that cultured keratinocytes be reclassified as ATMP in 2010.

Overview of the regulatory issues

Cultured keratinocytes have gone from unregulated and prepared in research/hospital settings, to being regulated under the tissues and cells legislation, to the current situation where the product is regulated as an ATMP. This decision rests on the consideration that cell culture is a substantial manipulation. The CAT also suggest that the mode of action relevant to the intended indication has to be considered (e.g. whether the keratinocytes have a pharmacological, immunological or metabolic action).

Separately, but of relevance to this case study, according to the CAT the use of enzymatic digestion of a tissue to release cells such as keratinocytes should be considered substantial manipulation, even if subsequent culturing does not take place, as the aim is to dissociate cell-cell contacts which would destroy the tissue architecture and functional interactions of the cells, which cannot be regained in the cell suspension[7]. However, this too has been regulated differently across Member States: nine EU Member States regulate keratinocytes

separated from skin by enzymatic digestion, without culture, as tissue and cell; seven regulate it as an ATMP, two decide on a case-by-cases basis, and three do not regulate[8].

One stakeholder felt that there are still some challenges regarding interpretation, despite clarification attempts by the CAT. The same stakeholder explains that in regard to autologous cultured keratinocytes, the issue of substantial manipulation is questionable and challenging since the in-vitro situation tries to mimic the in-vivo situation in every aspect. The purpose of the keratinocytes in-vivo is to proliferate – a situation that is kept during the culturing situation.

National experience of the classification of cultured keratinocytes as an ATMP[9,10,11]

The Queen Astrid Military Hospital (QAMH) in Brussels established a human keratinocyte production unit in the late 1980s with the aim of producing autologous keratinocyte sheets for immediate use on critically burnt patients. Alongside culturing autologous cells, donor keratinocytes for allogeneic use were also grown by the hospital. These could be cryopreserved for later use. The first patients were grafted in 1987 using the 'Rheinwald and Green' technique (which has since been optimised). Since then, the QAMH used keratinocytes as auto-and allografts in more than 1,000 patients, primarily to accelerate the healing of severe burns. The use of keratinocytes for treating burn wounds or chronic skin wounds was reimbursed by the Belgian social security system[i].

The hospital worked in compliance with the European Tissues and Cells Directive 2004/23/EC and remained compliant with specific Belgian regulation and guidelines as defined by the Belgian Health Authorities and advised by the Belgian Superior Health Council. The hospital's keratinocyte bank was licensed by the Belgian Federal Public Service for Health, Food Chain Safety and Environment. The keratinocyte bank was initially inspected (in view of the prolongation of the licenses) by the Belgian hospital inspection authorities, and later by Belgian Federal Agency for Medicinal and Health Products (FAMHP).

Following the reclassification of cultured keratinocytes (on which the QAMH was not consulted), they could only be produced and placed on the market as human medicinal products, in compliance with the ATMP regulation. The Belgian "ATMP Hospital Exemption" framework was considered not applicable, because these cultured cells are produced and used routinely. For a few years, the hospital operated in a 'legal grey zone' as the it did not have a medicinal product manufacturing licence, a pharmaceutical production environment nor a pharmaceutical marketing authorisation licence for keratinocytes produced on its premises. Following this, the Belgian Ministry of Defence had no other choice but to invest €5.3 million in a cleanroom facility for GMP (keratinocyte) production.

In April 2019, the Belgium Competent Authority organised a "GMP for ATMP" inspection during which it was concluded that the facility does not remain compliant with the GMP for ATMP guidelines because the products are manufactured without "approved dossier", despite numerous inspections by the competent authorities in the past 25 years which had never revealed any safety or quality concerns. According to one stakeholder interviewed for this study, to meet the ATMP requirement would necessitate an increase in production costs for the hospital, impacting the end-user. For example, one article suggests compared to the actual (2020) hospital-based cost for culturing and delivering keratinocyte cultures to the patient (fully reimbursed by the Belgian social security system, but not fully compliant to the ATMP regulatory framework) – which is 6.74 EUR/cm^2 with full grafts ranging from 24,000 EUR (20% total body surface area burned) to 110,000 EUR (90% burned) – implementing ATMP legislation would increase the production-costs at least ten-fold[12].

[i] After having documented the efficacy at a not-for-profit production cost.

Higher costs would lead to higher prices to be charged for the same product, without any additional benefit for the patients.

This was illustrated by Tigenix, a Belgian company that was the only one that produced a cultured keratinocyte treatment that reached the market. It withdrew the product because the reimbursement system could not pay for it and the business was therefore not viable. One stakeholder states that when universities were making that 'same product' it was reimbursed at €2000 for treatment, but this jumped to €20,000 per application when it became commercialised as an ATMP.

Ultimately, the QAMH had no option but to halt production and cease all keratinocyte-based treatments. No equivalent commercial keratinocyte product is currently available across the EU. Additionally, QAMH faced issues when collaborating with private companies who were pushing for cultured keratinocytes to be used for cosmetic, for-profit ventures (e.g. putting keratinocytes with fluorescent hydrogels to sell for sunburn) instead of their previous clinical use (for severely burnt patients).

Another regulatory issue concerns the hospital exemptions pathway. Under Regulation No 1394/2007 of the European Parliament and of the Council on Advanced Therapy Medicinal Products, EU Member States have the freedom to authorise the production and use of custom-made ATMPs in hospital settings at the national level as an exemption to the general obligation to follow a centralised ATMP marketing authorisation procedure[13]. The exemption can only be granted for products or therapies prepared on a non-routine basis, prescribed for individual/single groups of patients, applied in the hospital setting and on patients treated under a medical practitioner. Under this hospital exemption, national requirements on quality, traceability and pharmacovigilance apply which are intended to be equivalent to those required for centrally authorised products[14]. The HE pathway is valuable as it allows the use of specially adapted ATMPs for a single patient/patient group where other treatment options are scarce.

However, there are several differences in how HEs are applied across the EU[15], with interpretation varying on aspects e.g. The number of patients which can be treated under the exemption, the definition of 'non-routine', as well as the definition of a hospital[16]. This can amplify the lack of harmonisation across the EU.

Both stakeholders who contributed to this study argued that, although the preparation of cultured keratinocytes was a well-established process in many TEs, the classification as an ATMP came with significant cost implications associated with achieving marketing authorisation or even a hospital exemption, and that these posed a threat to the availability of therapy to the hospitals[17]. According to Pirnay (2012), this put the preparation of these tissue and cell products outside the capability of many TEs, due to the higher costs of having to comply with the medicinal products legislation, which potentially restricted access to novel tissue and cell therapies that were not of significant commercial interest[18].

Additionally, patient access can be hampered by this lack of commercial interest. Even before the introduction of the ATMP legislation, Belgian Defence had previously signed (in 2003) a four-year contract (2003-2006) with a Belgian biotech company, to commercialise keratinocyte productions of the QAMH. However, only a year into their contract, the biotech company started phasing out keratinocyte production due to poor sales compared to the business plan, meaning QAMH resumed production of keratinocyte sheets and sprays again in 2005[19]. This relates to a wider point regarding the types of treatment for which HEs are sought. As one stakeholder explained, the products are often autologous and can contribute to saving lives but importantly, often lack commercial value, resulting in a lack of interest from the pharmaceutical industry, and incentives in development and placement of those products on the market.

Cultured keratinocyte products have evolved in the academic sector, often in collaboration with the public healthcare sector. Although the HE pathway currently provides a treatment

for a patient (group) where the treatment alternatives are scarce, this impacts on the innovation process since the interest in innovating further reduces if there is no interest from developers and the public/academic sector is not authorised to provide the service.

The impact of the existing regulation of cultured keratinocytes is demonstrated in Sweden where there is only one product has been granted a marketing authorisation from the Swedish competent authority within the hospital exemption, which is effective until 2022[ii]. One stakeholder working for a tissue establishment in Sweden explains they have been contacted by other Member States (Finland (Helsinki) and Norway (Bergen)) when they had patients with very severe loss of skin, and culture of autologous skin has been the last option. Although in both of these cases this treatment was not needed (due to mortal injuries) the stakeholder explains that it revealed a serious limitation with their authorisation only having a national remit.

Part B: Potential impact of measures proposed to resolve regulatory issues

The following sections discuss how the range of measures proposed to revise the BTC legislation may impact on the regulation of cultured keratinocytes. This case study focuses on several measures under Objective 4 (M4.1 concerning the same surgical exclusion, M4.2-M4.4 concerning strengthened clarification processes, M4.5-M4.6 concerning strengthened authorisation processes and M4.7 concerning clinical data).

Safety and quality

One stakeholder working for a hospital suggested that the measures proposed under Objective 4 (to facilitate innovation of safe BTC therapies) would be adequate and appropriate to increase and assure high quality and safety – particularly implementing a strengthened risk assessment process (M4.5-M4.6). Other benefits would be increased transparency for products like cultured keratinocytes, which in turn would lead to greater confidence in the safety and quality of other Member State processes (and thereby increase cross-border trade).

The same stakeholder explained that, in regard to the 'same surgical procedure' (M4.1), although it is relevant to refine or remove the criteria for autologous keratinocyte treatments, it is crucial that the legislation do not interfere in detail as this is best evaluated by the profession itself. The interpretation of 'same surgical procedure' differs in different medical settings, and a less stringent definition enables an extension of the first operation to the second – if something needs to be performed in between. Likewise, with strengthening the preparation processes, it is important that the 'details' are left to the experts: *"the inspectors/authorising committees seldom have such detailed knowledge in each product as the professionals. There must be a healthy balance so that rules and regulations contribute and assures high quality and safety and not makes the development and usage of new products unfavourable".*

Costs and affordability

One stakeholder explained that cultured keratinocytes is already a high-cost cell therapy since it is very laborious (in regard to the manpower and levels of expertise/experience needed) and therefore it is important that new demands (specifically under M4.5-M4.7) do not radically increase the cost making the product unaffordable. When asked to estimate the size of cost increase, they suggested an increased administrative cost of 20% for those involved in developing and delivering the treatment, and an additional increase in

[ii] This authorisation was preceded by a close dialogue with the Swedish Medicinal Product Authority, concluding that the HE was the only regulatory path available, since the use of autologous keratinocytes was a clinically established cell therapy (regulated as a tissue preparation) since the 1980s.

compliance and regulatory costs (which would vary depending on the Member State practices that currently exist). This could all lead to higher costs for the end-users if passed downstream.

Patient access

According to one stakeholder the proposed reforms to the BTC legislation, particularly those relating to Objective 4 (M4.1-M4.12) will not increase the patient access to cultured keratinocyte treatments, but, on the contrary, there is a potential risk for decreasing the access to the treatment for the patients. For example, there is a substantial risk for too many detailed demands from the competent authority increasing the administrative and regulative burden, which in turn closes down establishments/bodies (e.g. Those still processing cultured keratinocytes under the tissue and cell legislation) banks previously delivering this treatment.

On the other hand, another stakeholder suggests that the harmonisation of interpretations could also strengthen the possibility to deliver the product to the patients across the EU, thereby increasing access to safe and effective treatment in countries which previously did not regulate or use cultured keratinocytes.

Innovation, research and development

There are already emerging borderline products on the market (globally) according to one stakeholder, mainly focusing on dissolving epidermis into a single cell suspension that is applied (sprayed) on to the wound – the whole procedure is prepared at the operating theatre and enzymatic digestion is used to release the cells. As stated above, this process is regulated differently across Member States. Another stakeholder also described an Australian company that is marketing kits where the surgeon can just isolate the keratinocytes, put them into a device and spray them onto the patient in a one-step surgical procedure which means it is not clear what legislation applies (as autologous treatments like this are not regulated under the tissue and cells directive currently). This implies that the revision to the BTC legislation would help to resolve future regulatory concerns arising from innovation in the field.

One stakeholder explained that a heavy regulatory burden created by new measures (e.g. clinical trials or evaluations for high risk BTC treatments or products) (M4.5-M4.7) may decrease the will and possibility of innovation: "*there is a risk that an increased demand on regulatory work for a potential product may discourage further work and development".* However, an advisory mechanism for classification was seen as a possible way towards harmonisation in the EU, thus solving some of the issues highlighted previously in this case study. The same stakeholder noted that in particular, an interplay mechanism for adjacent frameworks would be an appealing model that will contribute to the same interpretation and implementation for keratinocyte-derived products.

Conclusions

This case study on cultured keratinocytes illustrates many of the implications of borderline cases including different interpretation of the laws by different competent authorities, the lack of harmonisation between Member States and the variation in use between countries of the ATMP hospital exemption provision. In the case of cultured keratinocytes, it also appears the regulatory burden of changing classification from BTC to ATMP has also considered disproportionate and stopped its use in most countries, due to high costs, limiting access of the product to patients. To provide access to these therapies by commercial actors, there needs to be a commercial interest to develop products and bring/keep them on the market. If commercial products are withdrawn, eventually there will be no access through the pharmaceutical pathway either.

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A9.6 – Cultured limbal cells

The main stakeholder interviewed for this case study was a representative from a regional eye bank in Italy. Some feedback was also provided by stakeholders for a national healthy authority.

Part A: Definition of the borderline issue

Description of the borderline substance/product/application

The surface of the cornea is composed of an epithelium which is renewed by limbal (stem) cells. These cells can be cultured and transplanted back into the damaged limbal region of an eye. There are a few surgical options in terms of where the limbal cells come from and how they are transferred. For example, stem cells can be taken from the uninjured limbal tissue in a patient's healthy eye (patient autograft) or, alternatively, taken from a living, related donor or dead donor and transplanted into the diseased eye of the recipient (allograft). An extension of this is a keratolimbal allograft, where the entire limbus is taken from a dead donor to deliver a large number of stem cells to the recipient[1].

Uses of cultured limbal cells[i]

Cultured limbal cells are mainly used to treat chemical and physical ocular burn injuries which have created Limbal Stem Cell Deficiency (LSCD) as conventional corneal transplant is ineffective in these cases.

Burns to the eye can destroy the corneal limbus (the border between the cornea and the sclera as shown in the diagram below), causing a deficiency of limbal cells. If left untreated, LSCD results in chronic pain, burning, photophobia, inflammation, new blood vessels growing across the front of the eye, stromal scarring and the reduction or complete loss of vision[2]. Thus, the aim of culturing limbal cells is to restore the surface of the eye, achieve corneal clarity and improve vision.

Cultured limbal cells have been used worldwide since 1997 to treat LSCD[3]. This is a rare disease in the EU, with a reported frequency of 1-9/100.000[4]. Another source confirms that 3 in 100,000 people in the EU are affected by LSCD due to ocular burns, which is equivalent to about 15,000 people[5].

Before the introduction of Regulation No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation No 726/2004, limbal stem cells were regulated under Directive 2004/23/EC setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. Following the introduction of the ATMP Regulation which defined the concept of a 'tissue engineered product'[ii], limbal stem cells were classified by the CAT as a somatic stem cell therapy as the cell culturing process meets the definition of 'substantial manipulation'. Under this regulation, ATMPs require following a centralised procedure to obtain a marketing authorisation and fulfil the same regulatory standards as other pharmaceuticals. To allow for the use of cultured limbal stem cells without a central marketing authorisation, the ATMP Regulation permits nationally authorised hospital exemptions for use with custom-made ATMPs used in a hospital setting for a specific patient (ATMP Regulation, Article 28)[6].

In 2014, the Committee for Advanced Therapies (the CAT) recommended that a marketing authorisation should be granted to Holoclar®, a cultured limbal stem cell product, for the

[i] An illustrative diagram of the eye can be found on Mednotes (http://mednotes.co.uk/clinical-anatomy/head-musculoskeletal/anatomy-of-the-eye/)

[ii] A medicine containing engineered cells or tissues, which is intended to regenerate, repair or replace a human tissue. For more information, see advanced therapies (EMA Glossary).

treatment of moderate and severe LSCD[7]. At the time of application for marketing authorisation of Holoclar, 219 patients in 21 centres had already been treated using this therapy (the same treatment in form of transplantation of autologous cultured limbal stem cells) between 1998 and 2007[8]. The authorisation was granted on the basis of these clinical data generated during the previous hospital use, under the BTC framework; the sponsor identified that in 135 of the 219 patients (61.6%) information was available for the efficacy and safety analyses[iii] that could support the marketing authorisation application[9,10]. Adverse events related to the use of Holoclar (or associated procedures) were reported in 17% (19/113) of treatments in one clinical study, with most of these eye-related. Based on the risk-benefit profile, the EMA concluded this safety profile was acceptable but recommended a continued follow-up study[11].

Because the number of patients with limbal stem cell deficiency due to burns to the eyes is low, Holoclar was designated as an 'orphan medicine' in November 2008. This meant that the developers benefited from ten years of market exclusivity once the product was approved for marketing[12]. During this time no other treatment for the same condition will be allowed onto the market, if it is considered similar, to allow companies to recover their investment before competition emerges from other developers.

What is Holoclar? How does it work?

Holoclar is a tissue engineered product which takes a specific number of stem cells from the patient's healthy limbus during a biopsy.

The cells obtained during the biopsy are transported to the manufacturing facility at Holostem Terapie Avanzate in Italy (a spin-off company of the University of Modena), where they are prepared and grown in a unique culture to create a new layer of healthy tissue. After a minimum of 50 days, the healthy tissue layer is sent back to the hospital to be implanted into the patient's damaged eye. In this case, each Holoclar product is unique to the patient and intended as a single treatment (which can be repeated if required)[13].

Clinical studies have found that in more than 70% of treated patients, a stable and transparent surface of the cornea was restored as a result of the use of Holoclar, and these results were maintained long-term[14].

In February 2015, Chiesi and Holostem Terapie Avanzate (joint developers) received conditional approval from the European Medicines Agency (EMA) for the use of Holoclar in the EU. This approval was made following an 'adaptive pathway' approach[iv], used by the EMA to authorise treatments and facilitate timely patient access to new medicines through iterative development[15]. Given that it is difficult to collect data on limbal transplants due to low patient numbers, this approach enabled the developers of Holoclar to gather evidence through real-life use in addition to clinical evaluation data. Chiesi received marketing authorisation in Europe in 2016; this was the first stem-cell-based product to be approved as an ATMP in Europe. The sponsorship was transferred to Holostem in June 2020[16]. According to press release by Chiesi, *"as a result of this agreement, Holostem will be able to optimise the application of Holoclar and facilitate patient access to the drug by interacting*

[iii] Study HLSTM01 (Retrospective evaluation of the efficacy and safety of autologous cultivated limbal stem cells transplantation for restoration of corneal epithelium in patients with limbal stem cell deficiency due to ocular burns) was performed based on data from two Italian centres in Milan and Rome (as these two centres treated the majority of all patients that received Holoclar from 1998 to 2007). This first study involving 106 patients aimed to evaluate efficacy and safety of Holoclar treatment. Supportive study HLSTM02, which evaluated the safety of the product, with supporting evidence for efficacy, included 29 LSCD patients from 7 Italian centres with 29 transplantation events (EMA, 2014). Since then, the data has been confirmed with Study HLSTM04 which was a follow-up study

[iv] Adaptive pathways is a scientific concept for medicine development and data generation which allows for early and progressive patient access to a medicine. The approach makes use of the existing European Union (EU) regulatory framework for medicines. More information can be found here: https://www.ema.europa.eu/en/human-regulatory/research-development/adaptive-pathways

with the network of European clinics, which will be in direct contact with the production and control of the product"[17].

Overview of the regulatory issue

Cultured limbal cells provide an example of a therapy that was developed by TEs under the tissue and cells legislation, but is now considered (under the recommendation of the CAT) an ATMP. This section provides an overview of the impacts resulting from this regulatory classification.

Impact on patient access: Although there is no publicly available data on the number of patients that have been treated with Holoclar in the EU, one interviewee pointed to an overall reduction in the number of patients receiving treatments due to the high cost of the commercial product, with the eye bank representative describing the possibility of delivering the same treatment (with similar safety and effectiveness levels) at a more affordable cost.

The criteria laid down in Article 28 of EU Regulation 1394/2007 (which amends Article 3 of Directive 2001/83/EC) permits Member Stats to authorise the use of custom-made ATMPs prepared on non-routine basis in the absence of a marketing authorisation under the Hospital Exemptions (HEs) provision. Member States generally do not grant HEs in situations where a fully validated, centrally approved ATMP is available for the same indication in the same patient population. One interviewee described challenges in obtaining hospital exemptions for LSCD therapies; their eye bank has applied for hospital exemption nine times, and eight of these applications have been denied by the component authority and one was left unanswered. According to a representative from a leading eye bank in Italy interviewed for this case study, this meant that when Holoclar received marketing authorisation, university hospitals and research centres had to stop treating their patients with limbal stem cells cultured in their own hospitals/research. These were the same hospitals that developed therapy and demonstrated its efficacy prior to the ATMP authorisation.

Views on whether HEs should be permitted for treating LSCD are mixed. During a meeting with DG SANTE in 2018, the European Eye Bank Association (EEBA) agreed that HEs should be permitted for LSCD to improve patient access, particularly as many organisations wanting to provide limbal stem cell grafts are from academia or are non-profit institutions[18]. Conversely, as one article sets out, a current (general) issue with HEs is the risk that this process can lead to 'class B' products and conflicts with the ATMP industry for which non-profit and academic institutions do not have legal resources[19].

Impact on costs: An expert at the university hospital where therapy was developed explained that Holoclar is considered an expensive treatment (estimated at EUR 100,000 per eye). This has created knock-on costs for operators and national health systems, as most public hospitals or research centres do not have the budget/insurance to pay for the product. This leads to a situation where fewer patients are being treated than before. For example, one interviewed expert explained that his university hospital went from being certified to produce the same therapy for a total of EUR 12,000 and treating over 200 patients until 2014 (roughly 10-15 patients per year), to not being able to afford Holoclar and therefore not being able to treat anyone since 2015.

Additionally, according to a paper by authors affiliated to Holostem (Magrelli, Merra and Pellegrini, 2020) although the cost of each traditional therapy could appear lower[v] than the

[v] Data on LSCD costs up to surgery provided by Magrelli et al. based on information collated by NICE (2017). This provides the following estimates: limbal conjunctival autograft (€21,893), conjunctival limbal allograft tissue from living relatives (€65,479), keratolimbal allograft (€77,393), simple limbal epithelial transplantation (€21,000), best supportive care (€88,377) and Holoclar (€93,907).

cost of an advanced therapy, there is some evidence which suggests that ATMPs can lead to cost-savings in other ways (e.g. reduced hospital stays and nursing costs)[20]. The paper estimates that based on the percentage of failure of the treatment, under Holoclar, there would be a total potential cost of €206,802 in failures in ten years (follow-up) compared to €220,943–€618,639 for simple limbal epithelial transplantations. Additionally, the total potential partial cost including surgery was estimated at €300,709 for Holoclar by the authors compared to €241,943–€ 639,639 for simple limbal epithelial transplantations.

Impact on innovation: One consulted expert explained that for 'pioneering' therapies like LSCD treatments, there is still room for development and innovation, but one of the knock-on consequences of there being only one product on the market is that they are unable to collect more clinical data on the safety/efficacy of other LSCD treatments. This further stifles research and development in this area.

Another point of contention in regard to cultured limbal cells is that Holoclar was approved entirely on the basis of retrospective data which had been collected by not-for-profit and public institutions. An interviewee explained that the current regulation permits companies to 'take advantage' of data produced in public environments, as well as their own financial resources, to obtain marketing authorisation. In contrast, the interviewee cites the difficulties they have in obtaining authorisation as a not-for-profit organisation or research centre. For example, there are high costs to meet the standard required for regulatory approval, including funding for recruiting/training specialist staff and premises for culturing cells that need to be kept regulatory compliant year on year.

Impact on quality and safety: According to a paper by authors affiliated to Holostem (Magrelli, Merra and Pellegrini, 2020) using an ATMP like Holoclar has several advantages, including the use of a smaller amount (1–2 mm^2) of limbal tissue required (as this smaller amount can be cultured into higher amounts)[21]. As one interviewee explained, a small biopsy is advantageous because it makes the procedure less invasive, compared to the traditional technique of using conjunctival limbal autografts[vi] (Kenyon's technique). However, it is only possible to take a small biopsy if there is a GMP-certified facility. Other advantages of Holoclar described by Magrelli et al. include standardisation of the preparation process, and the ability to repeat the treatment in both eyes[22].

An additional, linked issue described by the EEBA to DG SANTE during a 2018 meeting[23] is that although in some Member States, the central authorisation of Holoclar has stopped the provision of limbal stem cell grafts by tissue banks, in others the supply continues under the ATMP HEs framework.

Impact on fundamental rights of a patient: According to the individual views of one interviewed expert, with regards to autologous donations, if a patient consents to use their cells to prepare a therapy that is applied to themselves, they should then have the right to choose the surgeon and facility to prepare this. However, this is not possible if only a commercial route can be followed.

Part B: Potential impact of measures proposed to resolve regulatory issues

The following sections discuss how the range of measures proposed to revise the BTC legislation may impact on the regulation of cultural limbal cells and other similar products. Specifically, this study refers to several measures under Objective 4 (M4.2-M4.4 concerning

[vi] One article suggests that a conjunctival limbal autograft (where stem cells are taken from the patient's healthy eye) requires a large amount of donor tissue from the healthy eye (equivalent to around 40% of the available donor cornea), which increases the risk of damage to the donor's healthy eye and the treatment cannot be repeated in case of failure (Magrelli et al., 2020).

strengthened clarification processes, M4.5-M4.6 concerning strengthened authorisation processes).

Safety and quality

The development of Holoclar required demonstration of an adequate level of quality manufacturing and Good Manufacturing Practice (GMP) compliance. However, the demonstration of safety and efficacy of LSCD therapies outside Holoclar indication remain rather challenging, according to a statement made by the EEBA because:

- Centres use different techniques and materials, such as the type of culture (from isolated cells or explant) and scaffold (e.g. amniotic membrane or fibrin glue).
- Centres have different quality control checks on the final product.
- Each centre treats patients with different degrees/diagnoses of LSCD.
- Source of the donor tissue (autologous or allogenic) can also differ.

This is therefore assumed that there is a need to generate preparation and authorisation of a range of different grafts and therapies based on limbal stem cells. The EEBA statement concludes that efforts should be made in order to collaborate at EU level to clarify the regulatory status of such treatments, and whether preparations that have not been authorised as ATMPs can be authorised under the BTC legislation[24]. It might therefore be assumed that the measures proposed under Objective 4 (including M4.2-M4.4) could facilitate this collaboration, and therefore demonstrate safety and quality of the limbal cells provided under the BTC framework while maintaining access and affordability for hospitals.

The main expert interviewed for this case study agreed there is still a long way to go with harmonisation across the EU and explains the need to *"find a way to regulate, to set up a European standard, that would allow not-for-profit institutions which are not industrialising their processes, but preparing processes for single patients… to work to a minimum [standard] of quality and safety… acceptable at the European level".* Thus, the expert was generally in favour of measures to strengthen the preparation process authorisation (M4.5-M4.6), within the BTC framework.

In both interviews, stakeholders supported the idea of an advisory committee for substances of human origin (SoHO) to help support classification of future LSCD therapies. Likewise, stakeholders were also supportive of a mechanism to increase coordination with the CAT (M4.2), with one interviewee citing this would help to facilitate discussions about what approach is best for different treatments taking into account aspects like safety, access and affordability.

Costs and affordability

Holoclar is the only licensed product available in EU for LSCD and therefore has a 'monopoly' in the market. As already presented in this case study, the introduction of this product has been perceived to reduce affordability, with interviewees suggesting this has had knock-on consequences on patient access. Discussion on the measures did not suggest there was a clear route to improving affordability under the BTC legislation, as long as the ATMP classification remains.

However, as one interviewee stated, there is a risk that the implementation of additional measures to improve quality and safety can create additional cost pressures for institutions (e.g. Those who are trialling new approaches to treating LSCD with different indications to that treated by Holoclar).

Patient access

As outlined previously, experts interviewed for this present case study felt patient access could be restricted because in some countries, operators would not be able to afford Holoclar, particularly where reimbursement systems are not in place.

None of the measures being considered under the revision of the BTC legislation were discussed in relation to improving patient access, though it was pointed out that more coordination may help to understand these issues better at the EU level. According to one interviewee, the measures might facilitate preparation of safer therapies for different indications than that treated by Holoclar, thereby increasing patient access. Another option might also be better regulation for obtaining cadaveric allogeneic limbal stem cells, thereby avoiding the key issues raised with obtaining these cells from living donors, whilst ensure safety and quality requirements remain in place.

Innovation, research and development

Currently, although many products reach early clinical studies, few of them obtain marketing authorisation due to limited resources and a high workload[25], and there are many challenges for public developers to accept the standards and requirements for ATMPs (e.g. high costs required with maintaining Good Manufacturing Practice (GMP) facilities such as cleanrooms). Additionally, as one article sets out, with cultured limbal cells, the small batch size makes obtaining funding for clinical trials difficult in the first place.[26] However, according to one source, the increasing use of limbal cells for regeneration might drive further eye bank activities, e.g. as supplier of starting materials and/or as processing entity[27]. This suggests a need to support tissue banks with innovation.

The main expert interviewed for this case study reinforced this message, arguing that apart from a few therapies, the whole field of regenerative medicine and in particular, those therapies relating to eye treatments, are still in the 'pioneering' era of personalisation, where therapies are being tailored for single patients. As such, the measures to enhance safety and quality principles (i.e. Those relating to the strengthened preparation process authorisation) are needed to 'promote this new era of medicine'. The same interviewee also suggested that the process for hospital exemptions had to be improved to allow for continued research and development in the public sector, where the preparation is considered to be an ATMP.

Additional measures may also be considered to facilitate innovation, research and development in this area. For example, the EEBA have previously stated that a European registry of university and research hospitals across Europe working on treatment of LSCD outside Holoclar label indication would be useful to increase harmonisation of protocols, standardise data collection on follow-up outcomes and timelines, evaluation clinical efficacy and safety[28]. According to feedback from a representative of a regional eye bank provided as part of the BTC evaluation roadmap feedback[29], this would also be valuable if products like Holoclar were dropped (e.g. in the case of not seeing expected returns) as this would make these diseases/pathologies orphan again, with a knock-on effect on patients.

Conclusions

This case study outlines the possible impacts resulting from the re-classification of an existing and well-established BTC therapy as an ATMP. In particular, since the authorisation of this Holoclar, there have been reported issues with supplying this treatment to patients in eye banks in Italy (where the treatment was first established) as well as in other countries where reimbursement systems are not in place. Therapies for LSCD continue evolving to include alternative cell types and clinical approaches, suggesting similar decisions on classifications will need to be made in the future. In this respect, experts interviewed for this

study suggested that new measures to provide greater clarity and strengthen coordination with the CAT will help to ensure there is a clear regulatory pathway for developers.

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A9.7 – Decellularised dermis

The stakeholders consulted for this case study were two experts working in a tissue bank and an expert working in a public hospital.

Part A: Definition of the borderline issue

Description of the borderline substance/product/application

In cases of significant tissue injury or disease, tissue autografts are often considered the gold standard. Decellularised tissues such as dermis (skin) have been readily available as an allograft[i] since 1995 and several tissue banks now offer decellularised dermis to surgeons for routine clinical use[1].

What is decellularisation? Ilustrative explanation is provided by ACS Biomater (2016)[2]

Decellularisation is the process by which cells are removed from tissues, but particular properties are retained in a three-dimensional structure of the tissue and its extracellular matrix (ECM)[ii] components[3]. A major advantage of using an ECM scaffold is that over time the allograft tissue becomes part of the host and is recellularised in vivo, reducing the need for anti-inflammatory/anti-rejection drugs as well as the need for further operations[4]. Recent advances in regenerative medicine have also involved adding recipient cells to a decellularised tissue, either in advance in the laboratory or at the point of transplant, making the procedure 'personalised'[5]. This latter approach is not the subject of this case study. Methods of decellularisation include using ionic and non-ionic detergents, enzymatic or biologic agents, and physical forces[6].

Decellularised dermis (otherwise known as acellular dermal matrix (ADM)) is one of the most common types of decellularised tissue products[7]. In a five-year forward looking assessment of skin grafts, the Rathenau Institut concluded that they will remain the first choice for patients with burn wounds and other dermatological diseases which require skin grafting, and there will be a further increase in its application to facilitate the enhanced return of the recipient's epidermis at the wound site[8]. The process of decellularising skin usually takes more than one treatment and is much longer compared to protocols for decellularising other organs due to the high collagen density in skin tissue[9].

Uses of decellularised dermis

Decellularised dermis is used for a range of **skin replacement treatments**, including burns and wounds. Burn injuries are a significant clinical burden in the EU, with 0.2 to 2.9/10,000 inhabitants severely burnt on an annual basis[10]. Although many more synthetic and semisynthetic dermal matrices and skin equivalents are available today for wound treatment, allogeneic human skin allografts remain a major therapeutic choice for extensive deep/hard-to-heal burns and wounds[11]. Decellularised skin grafts have significantly improved clinical outcomes by promoting wound healing, shortening hospitalisation time, controlling pain and protecting dermal and subcutaneous structures (e.g. cartilage, tendons, nerves and bones)[12].

Decellularised dermis is also used for **reconstructive surgery** (e.g. hernia repairs, periodontal tissue reconstruction, rotator cuff tendon repair, breast reconstruction, abdominal wall repair etc)[13]. The use of decellularised dermis for use in breast surgery was first described in 2001 and have become a common component of implant-based

[i] The transplant of an organ or tissue from one individual to another unrelated individual of the same species.

[ii] Part of the dermis composed of collagens, elastin, and glycosaminoglycans (GAGs) with embedded fibroblasts, the major cellular constituents. The ECM scaffold supports tissue regeneration by providing support, tensile strength, and attachment sites for cell surface receptors; and through facilitating wound healing.

breast procedures (both aesthetic and reconstructive)[14]. Although the ECM structures of the dermis are different based on where tissues are obtained, each of them can be reconstructed using the decellularised dermis – in this way, they are not closely dependent on their original functions[15].

Finally, decellularised dermis is increasingly being used for **cosmetic/aesthetic surgeries**. In a paper for the WHO Bulletin, Pirnay et al. (2010) noted that plastic surgeons have found 'off-label' uses for human donor skin, such as for penis widening and lip enhancement. The authors also note that dermal matrix derived from donor skin has an economic value that is four times more when used for cosmetic or reconstructive procedures than when used in burn wound surgery[16].

Globally, there are many commercially available biological scaffolds which have been used to treat partial thickness burns, skin wounds and diabetic ulcers[17]. These often are manufactured in the US, and commonly from human cadaver and porcine/bovine sources. In the case of human donors, the tissue is screened for infectious agents (e.g. HIV, hepatitis, and syphilis).

The market for both commercial allografts and xenografts (in particular bovine-derived xenografts) in the EU has been less successful than the US. According to one commentator, this is because there is a general aversion toward the implantation of grafts sourced from deceased human donors due to ethical concerns as well as additional regulatory hurdles on human tissue banks throughout Europe[18]. The same commentator noted that "*the level of regulatory intensity varies between European nations, with some being more accepting of allografts provided the tissue was donated domestically [in the US]"*[19]. While some products, like AlloDerm©, have been sold in Europe in the past, over time, stringent regulations surrounding the sale of human tissue have meant it is less readily available in Europe. According to European tissue and cell legislation (Directive 2004/23/EC), companies producing human-derived ADMs outside the EU are not allowed to commercialise them in Europe, as they are regulated as a tissue and cell product and not a medical device. This means human-derived ADMs manufactured and regulated as a medical device in the US, for example, cannot receive a CE mark which ensures conformity of a medical device with all relevant requirements in the EU[iii], making import of this product challenging[20].

To date, only one human-derived ADM manufactured in Europe has undergone prospective assessment under licence: MODA[21] (described in further detail in the box below). Accordingly, synthetic mesh remains dominant throughout Europe, which can be used for aspects such as hernia repair, stress urinary incontinence, and pelvic floor reconstruction[22].

Matrice Omologa Dermica Acellulata (MODA)[23]

In 2006, the Skin Bank of the Burns Unit of the Bufalini Hospital (Cesena, Italy) and the Rizzoli Orthopaedic Institute (Bologna, Italy) co-developed a dermal decellularisation technique. Then, in 2009, the Skin Bank obtained national approval from the Italian National Transplant Centre and National Health Institute to produce and the first human cadaver donor–derived ADM: MODA. Since 2009, MODA has been successfully used for several clinical indications, including: orthopaedic, burns, for complex abdominal wall repairs, and in breast reconstruction.

Overview of the regulatory issue

Decellularised dermis is seen to be regulated in divergent ways across the Member States[24], with most regulating as a tissue. A Commission survey of EU tissue and cell

[iii] CE Mark certification verifies (self-certification using a Notified Body) that the device meets all regulatory requirements of the Medical Devices Directive

competent authorities indicates 13 regulate under the tissues and cells legislation, while seven have no current regulation or do not have therapy[25].

As set out in the study to support the evaluation of the blood and tissues and cells legislation, the introduction of new legislation on medical devices in 2017 (Regulation (EU) 2017/745) led to further questions about the scope of Directive 2004/23/EC[26]. For example, there had been discussion at the Medical Device Coordination Group's subgroup on Borderline and Classification as to whether tissues from which cells have been removed (or rendered nonviable) should be considered as 'derivatives' and under the scope of the new Medical Device Legislation[27]. During two national competent authority meetings held in February and November 2017 respectively, the Commission confirmed the revised medical devices legislation would cover devices manufactured utilising derivatives of tissues or cells of human origin which are non-viable or are rendered non-viable. Derivatives are defined in the new Regulation as being substances extracted from tissue. However, it was clarified that non-viable tissues and cells themselves would not fall within its scope. This means, that whilst certain products (e.g. collagen fillers) are covered by the medical device regulation – provided they fit its definition of device and derivative – other decellularised matrixes like human skin remain regulated under the tissue and cells legislation. Despite those clarifications at the time, discussions on this interpretation continue.

The combination of cultured cells (out of the scope of this study) adds an additional element of complexity and its classification will then depend on what is considered to be the mode of action (modification to the physiological or metabolic action of the dermis).

Part B: Potential impact of measures proposed to resolve regulatory issues

The following sections discuss how the range of measures proposed to revise the BTC legislation may impact on the regulation of decellularised heart valves. This case study focuses on certain measures proposed under Objective 4 (M4.3 and M4.4 concerning strengthened clarification processes and the establishment of a coordination body across adjacent legal frameworks, M4.5-M4.6 concerning strengthened authorisation processes). As the same interviewees provided input to the decellularised dermis case study, this section is the same across both case studies.

Safety and quality

One tissue bank representative explained that, although the measures to strengthen authorisation and preparation processes (M4.5-M4.6) would enhance safety, they are already working to GMP or equivalent standards (adapted to tissue preparations). The representative further explained that *"during the last [few] years GMP has evolved a lot and … [is] responding perfectly to the requirements we need in the in the tissues field. And I think what we need now is to focus in applying the applicable requirements to tissues".*

In consideration of the proposed measure to implement risk assessments as part of applications for preparation process authorisations (M4.6), one stakeholder explained this was a good approach and should be applied instead of creating lists of included/excluded treatments/products which are defined by 'negative' criteria. The stakeholder further suggested it is important to define the scope of these processes e.g. does risk assessment just mean submitting a dossier to the competent authority where you assess the risk of the specific use of that tissue during the surgical act? In the stakeholder's opinion, the risk assessment needs to be proportionate and uncomplicated, essentially informing whether clinical application of a substance prepared in a certain way is a safe practice or not.

Finally, one representative from a tissue bank also reflects on a mechanism for coordination between regulatory frameworks (M4.4) being useful for improving oversight: *"We need to accept that during the process from obtaining material, to the use of a product, there can be changing regulatory frameworks… and we need to coordinate this between the different*

expert bodies and competent authorities to ensure appropriate vigilance and pharmacovigilance. There is no connection and no coordination and communication between these aspects including the communication of adverse reactions".

Costs and affordability

According to a representative from a tissue bank, many TEs have already supported the development of good practices (e.g. Through EU-funded joint actions) which have helped them to change their quality management systems, and this will mean it would be 'easy' to adapt to new requirements imposed by the package of measures considered under Objective 4. In a number of Member States, some of the measures would only replicate what is already happening so the costs are likely to be with Member States not already working to stricter requirements.

Patient access

In regard to patient access, two stakeholders felt the package of measures being considered under Objective 4 would not hugely change things in regard to treatments involving decellularised tissues (as long as they are considered a tissue preparation). Rather, much more depends on (a) the type of health system in place and (b) the type of reimbursement system in place.

Innovation, research and development

Continued improvements in the processes applied to heart valves for transplantation (, e.g. The application of growth factors facilitating re-cellularisation by recipient's own cells) will throw into question the regulatory status of different products/treatment. In this case, stakeholders interviewed for this present case study were in general agreement that having a body which could make joint decision at the EU level (M4.4) would provide early clarity on the regulatory pathway and ensure that developers had an upfront understanding of the different stages/costs invovled in product development. One stakeholder commented that the interplay mechanism (M4.3) should ensure there were experts in the tissue field who could contribute or comment on the recommendations regarding classifications, which would aid (re)development or handover processes.

Conclusions

The introduction of new legislation on medical devices in 2017 raised questions about whether tissues from which cells have been removed (or rendered nonviable) should be considered as 'derivatives' as medical device. At the time the new regulation was published, DG SANTE and DG GROW issued a joint memorandum to authorities to explain that tissue matrices were not considered 'extracted' from tissue (unlike substances such as collagen). This provides one example of how joint decision making on 'borderline' issues is required – and indeed, how measures such as those being considered under the revision of the BTC legislation (in particular M4.2-M4.4) would support this.

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A9.8 – Decellularised (human) heart valves

The stakeholders consulted for this case study were two experts working in a tissue bank and an expert working in a public hospital.

Part A: Definition of the borderline issue

This case study focuses on heart valves here that are decellularised but not repopulated with recipient cells (which would require tissue engineering).

Description of the borderline substance/product/application

The human heart has four valves: the aortic, mitral, tricuspid and pulmonary valves. Heart valves are responsible for blood flow from the atria to ventricles and from ventricles to arteries. They open to allow blood to be pumped forward, and they close to prevent blood from flowing backward.

Valvular heart disease (VHD) is an umbrella term for dysfunction with any of the heart's four valves. The function of the heart valve can be altered by pathologies such as rheumatic fever or infective endocarditis, as well as congenital heart defects. In aortic stenosis the aortic valve opening becomes narrow (stenotic), limiting the amount of blood pumped by the heart. In mitral regurgitation the mitral valve does not close completely, meaning that blood can flow backward, reducing the heart's ability to pump blood. This can lead to heart failure and arrhythmias. Valvular heart diseases are common in the general population; they affect >2% of the population and are associated with increased mortality[1].

Treating VHD requires either surgical repair or replacement. In 2003, the annual number of patients requiring heart valve surgery was estimated at 290,000 globally, and as the world population continues to grow and age, that number was expected to triple to more than 850,000 by 2050[2]. Currently, mechanical and bioprosthetic valves (often made of bovine pericardium[i]) are the most accessible form of heart valve replacements. However, both of these approaches have significant disadvantages. For example, mechanical valves require lifetime treatment to thin the patient's blood, and bioprosthetic heart valves degenerate within eight to ten years, meaning a reoperation is necessary (entailing a higher risk for the patient)[3].

Cryopreserved allograft valves can also be transplanted, and this procedure is performed regularly in Europe. Each year, approximately 2000 human heart valves (pulmonary, aortic and occasionally mitral), are transplanted in Europe and there are approximately 20 heart valve banks[4]. However, since cryopreserved allogeneic heart valves contain donor cells with associated antigens, they can initiate an adverse host response. Human donor cryopreserved allografts, like bioprosthetic valves, also fail to regenerate in vivo and cannot grow and develop in the recipient[5]. In contrast, more recently developed decellularised homografts appear to lead to improved outcomes such as a high resistance to infections and reduced reoperation rates[6,7]. As Jashari (2021) concludes in an article reflecting on the progress made in the transplantation of human heart valves by a tissue bank in Brussels, *"the implementation of new technologies, such as decellularisation, as a standard procedure for treatment with allograft valves might offer further improvements in allograft quality and [an] increase in durability"*[8].

[i] A fibrous sac that encloses the heart and great vessels.

Using decellularised heart valves to treat valvular heart disease

Given the shortage of heart valve donors and limits to existing treatments, researchers began exploring the use of tissue-engineering to develop viable and functional engineered constructs to treat VHD[9].

Decellularisation is essentially a 'washing' process which removes viable (living) cells from tissues, but retains particular properties in a three-dimensional collagen scaffold of the tissue and its extracellular matrix components[10]. Methods of decellularisation include using ionic and non-ionic detergents, enzymatic or biologic agents, and physical forces[11]. Complete removal or inactivation of resident cell antigens and nucleic acid remnants is required to avoid recipient rejection or vascular injury of the implanted tissue. Hence, this process helps improve graft compatibility and transplantation outcomes; the removal of donor cells is considered to accelerate the repopulation of the tissue with recipient cells after application[12]. Decellularisation can prevent immune reactions in the recipient, acting as a "scaffold", which can be combined with various other cells by the principles of tissue engineering[ii] (outside the scope of this study)[13].

Following the early work of the Hannover Medical School and approval of decellularised human heart valves for transplantation by the German Competent Authority, two EU-funded, multi-centric studies (ESPOIR[iii] and ARISE[iv]) were carried out on patients with pulmonary or aortic valve malformations. These studies focused on decellularisation and implantation (without seeding of recipient cells) which researchers found brought significant improvements with a much lighter regulatory burden that repopulating with cultured recipient cells (which would be considered an ATMP). ESPOIR included 200 patients and ARISE included 120 patients[14]. The human valves were decellularised by Corlife oHG (a part of the Hanover Medical School). Decellularised valves were implanted in Austria, Belgium, France, Germany, the Netherlands, Italy, Moldavia, Spain, Switzerland and United Kingdom[15].

The early results of these two trials showed superior results of decellularised heart valve allografts: ESPOIR showed lower re-operation rates was possible with such a treatment, compared to mechanical and bioprosthetic valve replacements[16].

Other researchers have also reported promising results during the last 5 years (e.g. Boethig et al. 2019[17]; Horke et al. 2020[18]). The two main reported advantages of decellularising heart valves include:

- A quick manufacturing process and short time from manufacture to deployment in a patient which means it is possible to avoid cryogenic preservation processes.
- A lack of vital donor cells after decellularisation which increases recipient tolerance of the graft and thereby increased preservation of good valve function. In paediatric patients, this means that potentially only one heart valve transplant may be required during their lifetime if the implanted valve will increase in size as part of the recipient's natural growth[19].

[ii] Once decellularised, matrices can be seeded with various cardiovascular cells, including endothelial, progenitor and myocardial cells, in order to generate functional tissues which can be transplanted into patients (these are ATMPs).

[iii] In January 2012, the European Union funded the European Clinical Study for the Application of Regenerative Heart Valves, coordinated by Hannover Medical School, Germany, with a grant of 5.2 million euros over a period of five years. The core aim of ESPOIR was the implementation of a clinical study in regenerative medicine which investigated the safety and efficacy of an innovative tissue-engineered human heart valve. Before the start of the ESPOIR project, only 45 children and young adults had been treated with donated human heart valves (homografts) which had undergone special decellularisation treatment by Corlife oHG, in Chişinau (Moldova) and Hannover (Germany).

[iv] Between 2015 and 2017, another multi-centric trial was carried out using cell-free aortic valves for the replacement of diseased aortic valves in children and young patients (ARISE Trial 2015).

Donor shortage, high costs, and lack of good quality heart valves have so far limited the broad clinical adoption of decellularised heart valves[20]. Only a few TEs currently decellularise heart valves in Europe.

Overview of the regulatory issue

In recent years, advances in knowledge in the field of cell biology and biotechnology has enabled the development of technologies such as decellularisation to support the development of tissue and cell preparation processes. In this particular case, classification decisions or arguments have been made for regulation as a tissue, as a medicinal product (non-ATMP) and as a medical device.

As set out in the underlying rationale of the ARISE trial, translating research in regenerative medicine *"from bench to bedside is frequently hampered by lengthy and complex regulatory procedures"*[21], particularly when regulatory paths at national level are unclear and products are intended to be available across Europe given the lack of harmonised procedures[22]. In this case, a Commission survey of EU tissue and cell authorities indicates the following current situation: 15 regulate decellularised heart valves under the tissue and cell legislation but five do not regulate or not have therapy[23]. In Germany, where Corlife was based and the decellularisation was performed for the ESPOIR and ARISE trials, the tissue and cell legislation is transposed into the medicinal product framework and all tissue products are subject to marketing authorisation in the same way as medicines. Thus, decellularised valves were authorised there as medicinal products and distributed from there to many other countries as medicinal products.

A very different regulatory argument is put forward by Hoppe (2013)[24]. According to Hoppe, on the one hand, a decellularised heart valve is similar to a transplant in that the valve is simply improved before being implanted by the removal of immunogenic material. On the other hand, Hoppe argues that regulatory approach seems to neglect that decellularisation entails the removal of all vital donor cells from the collagen matrix (in order to promote cell repopulation of the valve once it is in place in the patient). Hoppe concludes that the tissue and cell legislation therefore should not apply and leads to overregulation and inflexibility in how decellularised heart valves can be used. It is notable, however, that many tissues regulated currently under the tissues and cells legislation do not, in fact, contain viable cells at the time of human application and containing viable cells is not included as a criterion in the scope of Directive 2004/23/EC. Representatives from one tissue bank interviewed for this study explained they have not perceived there to be an existing borderline issue with decellularised heart valves: "we obtain them, we process them, we distribute and can use them without issue under the tissues and cells legislation".

The ESPOIR consortium faced regulatory confusion at the time of applying for the approval of the decellularised pulmonary heart valve in 2012. One key issue was whether they should be regulated under the medicinal products or medical devices framework. The classification for medical devices is based on Regulation No. 2017/745/EU.. Under Article 1 of Regulation 2017/745, the medical devices legislation applies to devices manufactured utilising derivatives of tissues and cells which are non-viable or rendered non-viable; and a lack of pharmacological, immunological, or metabolic activity. Derivatives are defined as having been 'extracted' from human tissues[v]. At the time of the introduction of new legislation on medical devices in 2017, DG SANTE and DG GROW issued a joint memorandum to

[v] Article 2(17): 'derivative' means a 'non-cellular substance' extracted from human or animal tissue or cells through a manufacturing process. The final substance used for manufacturing of the device in this case does not contain any cells or tissues;

authorities to explain that tissue matrices were not considered 'extracted' from tissue (unlike substances such as collagen).

Despite the argument set out above (regarding the lack of viable donor cells following decellularisation), and there being only a mechanical function as a heart valve, the regulatory decision taken for ESPOIR was to treat the homografts as medicinal products or under the tissues and cells legislation in Germany[vi], the Netherlands, Belgium, U.K., Italy and Moldavia[25]. In contrast, however, the decision was taken in Switzerland that decellularised human heart valves should be considered as medical devices, highlighting differences in interpretation. Since the ESPOIR trial, there has been continued discussion – including at the time of drafting the new medical devices regulation – on whether tissues from which cells have been removed (or rendered nonviable) should be considered as 'derivatives', and so as being extracted from human tissue, and should therefore fall under the medical devices legislation.

A lack of harmonisation can impact clinical research and development and therefore patient access to novel therapies. For example, in order to implement a cross-border and multi-centre trial, the ESPOIR consortium[vii] spent almost three years obtaining approval for the decellularised heart valve and the setup of the study from the relevant regulatory authorities and European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. According to the project report summary: *"this was the first time that the authorities in all of the participating countries had been faced with the combination of regulatory approval for a decellularised human heart valve, cross-border movement of human tissue preparations, and the approval of a study testing such preparations"*[26]. It is acknowledged that this case was particularly complicated because of the specific German transposition of the tissue and cell legislation into the medicinal product framework.

Part B: Potential impact of measures proposed to resolve regulatory issues

The following sections discuss how the range of measures proposed to revise the BTC legislation may impact on the regulation of decellularised heart valves. Specifically, this study refers to several measures under Objective 4 (M4.3 and M4.4 concerning strengthened clarification processes and the establishment of a coordination body across adjacent legal frameworks, M4.5-M4.6 concerning strengthened authorisation processes). As the same interviewees provided input to the decellularised dermis case study, Part B is the same in both case studies.

Safety and quality

One tissue bank representative explained that, although the measures to strengthen authorisation and preparation processes (M4.5-M4.6) would enhance safety, they are already working to GMP or equivalent standards (adapted to tissue preparations). The representative further explained that *"during the last [few] years GMP has evolved a lot and … [is] responding perfectly to the requirements we need in the in the tissues field. And I think what we need now is to focus in applying the applicable requirements to tissues".*

In consideration of the proposed measure to implement risk assessments as part of applications for preparation process authorisations (M4.6), one stakeholder explained this was a good approach and should be applied instead of creating lists of included/excluded treatments/products which are defined by 'negative' criteria. The stakeholder further

[vi] More information can be found here: https://www.pei.de/EN/medicinal-products/tissue-preparations/heart-valves/heart-valves-node.html

[vii] The ESPOIR consortium brought together seven leading European clinics for paediatric cardiac surgery (London, Leiden, Padua, Zürich, Leuven, Chisinau and Hannover), four tissue banks (European Homograft Bank, Deutsche Gesellschaft für Gewebetransplantation, Fondazione Banca dei Tessuti di Treviso and Euro Heart Valve Bank), and an innovative bio-tech company, Corlife oHG.

suggested it is important to define the scope of these processes e.g. does risk assessment just mean submitting a dossier to the competent authority where you assess the risk of the specific use of that tissue during the surgical act? In the stakeholder's opinion, the risk assessment needs to be proportionate and uncomplicated, essentially informing whether clinical application of a substance prepared in a certain way is a safe practice or not.

Finally, one representative from a tissue bank also reflects on a mechanism for coordination between regulatory frameworks (M4.4) being useful for improving oversight: *"We need to accept that during the process from obtaining material, to the use of a product, there can be changing regulatory frameworks… and we need to coordinate this between the different expert bodies and competent authorities to ensure appropriate vigilance and pharmacovigilance. There is no connection and no coordination and communication between these aspects including the communication of adverse reactions".*

Costs and affordability

According to a representative from a tissue bank, many TEs have already supported the development of good practices (e.g. Through EU-funded joint actions) which have helped them to change their quality management systems, and this will mean it would be 'easy' to adapt to new requirements imposed by the package of measures considered under Objective 4. In a number of Member States, some of the measures would only replicate what is already happening so the costs are likely to be with Member States not already working to stricter requirements.

Patient access

In regard to patient access, two stakeholders felt the package of measures being considered under Objective 4 would not hugely change things in regard to treatments involving decellularised tissues (as long as they are considered a tissue preparation). Rather, much more depends on (a) the type of health system in place and (b) the type of reimbursement system in place.

Innovation, research and development

Continued improvements in the processes applied to heart valves for transplantation (e.g. The application of growth factors facilitating re-cellularisation by recipient's own cells) will throw into question the regulatory status of different products/treatment. In this case, stakeholders interviewed for this present case study were in general agreement that having a body which could make joint decision at the EU level (M4.4) would provide early clarity on the regulatory pathway and ensure that developers had an upfront understanding of the different stages/costs invovled in product development. One stakeholder commented that the interplay mechanism (M4.3) should ensure there were experts in the tissue field who could contribute or comment on the recommendations regarding classifications, which would aid (re)development or handover processes.

Conclusions

Decellularised heart valves are being regulated differently across Member States based on how regulators interpret the process of decellularisation or have transposed the tissue and cell legislation. The main issue to resolve is whether decellularised heart valves are regulated under the tissues and cells legislation or as a medicinal product, or if the removal of donor cells means they could also be considered under the medical device framework.

Decellularised heart valves represent a good example for an evolving tissue replacement solution which requires continual evaluation of quality, safety and efficacy. As described in a final summary of the ESPOIR project, as there is limited experience in these procedures

for new medical therapies or devices to date, it is important to provide clear authorisation models and regulatory pathways for this rapidly developing area of medicine[27].

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A9.9 – Demineralised bone

The stakeholders consulted for this case study were a representative from a national blood and transplant service, an academic from a university hospital which supplies DBM, and stakeholders from a non-profit tissues and cells institute, which supplies transplants from human cells and tissues (including DBM).

Part A: Definition of the borderline issue

Description of the borderline substance/product/application

Demineralised bone matrix (DBM) is a specialised allograft product produced by acid extraction of allograft. It is made from cortical bone[1] and contains type I collagen, non-collagenous proteins, and a variable number of matrix-associated bone morphogenetic proteins (BMPs) osteoinductive growth factors which are made available to the host environment through the demineralisation process[2].

Bone is demineralised through decalcification procedures, and DBM is used as a bone graft substitute to treat allogenic bone defects as it provides a degradable matrix and contains many osteogenic agents[3,4]. AN expert from a national blood and transplant service noted that DBM itself was developed in the 1960s, and the first patent was granted in the early 1990s, since when many companies have produced it either using glycerol or other agents. DBM comes in various formats: it is commercially sourced as putty, paste, sheets and flexible pieces[5]. TEs have developed DBM into other products such as bone-gel with glycerol or hyaluronic acid, also called hydrogel, bone-flex, or bone-putty[6]. DBM can also be combined with other substances evaluated in animals[7], or gelatin (to provide a scaffold) and an amino polysaccharide with attractive biological properties[8].

Uses of DBM

DBM is considered by trauma and orthopaedic surgeons as useful for a wide range of clinical indications in trauma and orthopaedic surgery[9]. DBM does not provide structural support but is instead surgically placed to **fill** bone defects and cavities[10].

A systematic review from 2017[11] concluded that DBM products have been most extensively investigated in spinal surgery, with limited evidence for its use as a bone graft extender in posterolateral lumbar fusion surgery. DBM products are not thoroughly investigated in trauma surgery, with weak evidence supporting its use as a bone graft extender.

A paper by Hinsenkamp & Collard[12] compared DBM to recombinant bone morphogenetic proteins (rhBMP), as an alternative for osteoinduction with a higher concentration of bone morphogenetic proteins. The paper concluded that considering osteoinductive properties, safety and availability, DBM seemed superior to rhBMP. An expert from a university hospital which supplies DBM reported that this is because DBM has a more “natural” and balanced profile of proteins.

The authors of one paper[13] reported that “some uncertainty exists clinically about the validity of various claims made by commercial vendors about DBM-containing products”.

An expert from a national blood and transplant service reported that DBM represents a multi-million-dollar industry, and it is mainly produced commercially by a number of companies. An article from 2006[14] estimated that more than 500,000 bone grafting procedures with DBM were performed annually in the US. A paper from 2012[15] reported that about a fifth of the $1 billion per year bone grafting market was focused on using DBM products in bone repair and regenerative strategies. Experts from a non-profit tissues and cells institute reported that within the last ten years more than 55,000 units have been distributed by them worldwide (note this was mainly in Germany and the EU). An expert

from a university hospital which supplies DBM reported that, in 2019, they provided around 1500 preparations of DBM, and in 2020 this number had shrunk to approximately 1000.

A report by the Rathenau Instituut[16] stated that just under 15,000 units of DBM were exported from the US to the EU in 2013. The report concluded that looking at this substantial import, it would be possible to conclude that there are general and specific shortages in the EU[17]. An expert from the UK reported that in the UK at least, if any establishment wishes to import human tissue they must have an authorisation from the Human Tissue Authority (HTA), and to the stakeholder's knowledge commercial companies in the UK do import and supply DBM, however they have the appropriate HTA import licenses.

Different methods and procedures seem to impact the efficacy of DBM. One academic article[18] stated that different DBM configurations may vary considerably in terms of their bone inductive activity due to biologic properties of the graft, the host environment, and the methods of allograft preparation. Varied efficacy could also be caused by differences in particle size and shape, donor selection criteria, protocols for collection and storage, and DBM carrier materials. Another article[19] also stated that variable clinical response is due partly to nonuniform processing methods among bone banks and commercial suppliers. A systematic review from 2017[20] concluded that the available evidence about the effectiveness of using DBM in trauma and orthopaedic surgery is of poor quality and mainly comes from retrospective case-series. The authors recommended that more prospective, randomised controlled trials are needed to understand the clinical effect and impact of DBM in trauma and orthopaedic surgery.

An academic article by van der Stok and colleagues[21] noted that the number of commercially available DBM products is constantly increasing, potentially due to regulation which allows new products to enter the market quickly (i.e. in the US, DBMs are not regulated under 510(k) regulation but are considered minimally manipulated tissue for transplantation).

The report by the Rathenau Instituut[22] noted that by distributing DBM, TEs generate additional income as they are reducing surplus cortical bone stock (by using surplus cortical bone) while addressing clinical needs. However, consulted stakeholders from a non-profit tissues and cells institute reported that DBM requires time consuming recovery from post-mortem donors or living donors. According to these stakeholders, DBM can only be obtained when donor identification, anamnestic and consent procedures and recovery procedures are properly integrated in the day-to-day work of hospitals, and hospitals can receive financial reward for their voluntary contribution. As hospitals are not presently obliged to collect DBM, increasing the burden and cost associated with DBM could reduce the number of hospitals which do collect DBM.

Overview of the regulatory issue

The source of regulatory confusion surrounding demineralised bone is the interplay with the medical device legislation: demineralised bone contains non-viable cells (therefore potentially "derivatives"), and the combination of demineralised bone with scaffolds adds an additional element as primary versus ancillary action determines classification in the medical devices legislation.

In a paper from 2010[23], Alison Wilson (of CellData Services) noted that products consisting exclusively of non-viable cells and tissues without primary immunological, metabolic, or pharmacological mode of action (including DBM) are excluded from the ATMP Regulation. The author noted that "until an alternative means of regulating these products, such as amendment of the Medical Device Directive, is introduced, they will remain subject to national rules or unregulated as is currently the case". MedTech Europe, a European trade association representing the medical technology industries, reflected that a clear definition in the scope of Directive 2004/23/EC is still missing, and indicated this may mean a continued lack of clarity on when and how to apply it, in turn causing issues when classifying a new product as a medical device (expressed in the previous evaluation study[24]). MedTech

Europe has stated in other forums[25] that the current legal framework is restrictive in terms of allowing for uptake of innovative technologies, and that full clinical trials are not always feasible nor necessary. They also described that a lack of full harmonisation of safety and quality requirements for blood, tissues and cells impacts on the medical technology industry. This may apply to innovation in DBM, for which the new Medical Devices legislation could have supported more innovation and/or ensure quality and safety for DBM. Overall, some stakeholders may feel that bringing the BTC legislation closer to the standards of the Medical Devices legislation could increase confidence, or could make it easier when BTC products are used as starting materials for medical devices.

Despite these views, the creation of the MDR did not in fact include such products. During the tissue and cells NCA meeting in February 2017[26] and in a subsequent meeting in November 2017[27], the Commission confirmed that the revised medical devices legislation would cover devices manufactured utilising derivatives of tissues or cells of human origin which are non-viable or are rendered non-viable – but that non-viable tissues and cells themselves would not fall within its scope. This means that demineralised bone or other decellularised matrixes like human skin would not fall under its scope and instead would remain regulated under the tissue and cells legislation. The Commission also produced a message to the NCAs for Tissues and Cells in which they specified "demineralised bone matrix (DBM), i.e. bone from which inorganic minerals are removed, or other non-viable or acellular human tissues or tissue matrices, will continue to be covered by Directive 2004/23/EC on tissues and cells"[28].

the CAT recommended classifying "Tissue like combination of osteogenic cells and demineralised bone matrix (Three-dimensional structure of demineralised bone matrix and autologous adipose-derived and differentiated osteogenic cells)", which is intended for bone defects, as a **tissue-engineered medicinal product** in 2013[29]. This decision was taken as the product consists of engineered cells, not because of the inclusion of DBM.

In a meeting of the NCAs in 2019[30], a survey indicated that Member States apply **divergent** regulatory frameworks (or no regulation at all) for therapies including demineralised bone combined with gel or putty. A Commission survey of EU tissue and cell authorities indicated that 11 Member States regulated demineralised bone combined with putty or gel under tissue and cell legislation, one regulated it as a medical device, one regulated it as a medicinal product (non-ATMP), and three did not have therapy[31]. An expert from a national blood and transplant service reported that to their knowledge, in many countries it is regulated as a tissue. In the UK, the HTA has clarified that "non-viable tissue and cell products such as demineralised bone matrix…will not be covered by the MDR. They will continue to fall under the EUTCD (Directive 2004/23/EC on tissues and cells) and be regulated by the HTA"[32]. In Germany, DBM is regulated as a **tissue preparation** under the German Medicinal Product Act §21 / §21a, which obligates the requester to provide data and risk analysis regarding the safety and efficacy of the tissue transplant[i].

In the US, the FDA has taken a slightly different approach: it determined that while DBM alone is regulated solely under section 361 of the Public Health Service Act[ii], when DBM is turned into a putty or paste through the addition of additives including sodium hyaluronate, glycerol, or calcium phosphate, it is regulated under the medical device provisions of the Federal Food, Drug, and Cosmetic Act. This decision was made because the components "are intended to affect the structure or function of the body by assisting in the filling of bone voids, and they do not achieve their primary intended purposes through chemical or metabolic action"[33].

[i] Reported by experts from a non-profit tissues and cells institute.

[ii] Regulation solely under section 361 requires establishments to adhere to regulations designed to prevent the transmission of communicable disease, but does not require premarket review or notification for such products.

Part B: Potential impact of measures proposed to resolve regulatory issues

The following sections discuss the impacts of the proposed measures being considered as part of the revision of the BTC legislation on DBM. This case study mostly refers to M4.5-M4.6 concerning strengthened authorisation processes. It also considers M1.2 under Objective 1 (change in scope of the tissues legislation).

Compared to the baseline, the consulted experts generally reflected that - as there are not pressing concerns related to DBM - the measures are unlikely to have much positive impact on DBM, and in fact, could even make the current regulatory situation more complex. More specifically, experts from a non-profit tissues and cells institute reported that while transparency in the system may improve, quality and safety would not change, and affordability, patient access, innovation, research, and development, and self-sufficiency and sustainability for DBM would worsen. The following sections discuss the impacts (or lack thereof) of the proposed measures being considered under the revision of the BTC legislation on different specific issues relating to the regulation of DBM.

Safety and quality

M1.2 under Objective 1 refers to a change in scope of the BTC legislation. Stakeholders have expressed their opinions on DBM classification and potential re-classification, discussed in the following paragraphs.

In response[34] to the public debate on the Revision of the European Legislation on Medical Devices, The European Association Medical devices - Notified Bodies (TEAM-NB) stated that the MDR should include products manufactured utilising non-viable human tissues or cells that are not substantially manipulated, such as human demineralised bone, dermis or heart valves, in order to ensure sufficient patient safety.

In contrast, all stakeholders consulted for the present case study reflected that DBM should be regulated as a tissue. Consulted experts from a non-profit tissues and cells institute reported that as long as the definition of “derivative” is not changed, DBM is clearly not and cannot be a medical device, as it is a tissue which has had minerals removed from it, and therefore remains a tissue. As a point of illustration, the experts stated that the minerals which are removed to make DBM could be considered derivatives, but the substance which remains is clearly not a derivative. An expert from a university hospital which supplies DBM reported that changing DBM’s classification to a medicinal product would “increase regulation without increasing quality”, and noted that if DBM were reclassified this would necessitate reclassifying many products including tendons.

Experts from a non-profit tissues and cells institute urged that it must be officially clarified that DBM cannot be a medical device, otherwise there is a risk that a CE mark could be granted to DBM due to a misunderstanding of the term “derivative”. The experts stated that suppliers from outside the EU may be motivated to pursue registering DBM as a medical device, as this allows a supplier to sell their product in all EU Member States, and this must be prevented as these suppliers are not necessarily complying with the EDQM guide for safety. This would also mean DBM would not be traceable through SEC codes which could impact safety. The stakeholders recommended that such clarification could be granted through classification advice (M4.2 or M4.3), if it provided a reliable mechanism or platform through which notified bodies and the regulatory bodies for tissue preparations could have a platform together, make a decision, and distribute that decision to all relevant parties. In contrast, an expert from a national blood and transplant service reported that the “handover” (demarcation) between BTC regulations and medical devices regulations is clear at present, and an advisory mechanism or committee (such as those proposed in M4.2-4.4) would not add value in the case of DBM. The expert reported that the proposed measures would be most suited to addressing more novel products and cases.

An expert from a national blood and transplant service, as well as an expert from a university hospital which supplies DBM, reported that DBM has been used for 30 years and is well-established and safe. DBM does not contain any DNA and is sterilised through gamma radiation, so it is very safe by the time it is being used by a surgeon. Indeed, there have reportedly not been any SAR or SAE reports on DBM. An academic paper from 2012[35] concerning musculoskeletal allografts (including DBM) concluded that "at present, these allografts provide orthopaedic surgeons with a useful and safe tool to repair bone defects…When all the quality and safety requirements are fulfilled, adverse events and reactions should be extremely rare". According to the experts, the proposed measures would therefore not improve the quality or safety of DBM for patients. Neither would they improve safety for donors, as the expert from a national blood and transplant service reported that when bone is collected it is not known how it will be used (it is not collected specifically for DBM). Similarly, an expert from a university hospital supplier of DBM reported that sometimes, private commercial banks have more money and can therefore provide high levels of safety, however for products such as DBM these safeguards are not necessary as the product is already safe and therefore the only impact of such increased safety measures is increased price.

Stakeholders provided a few other comments about the safety of DBM and related products:

- An expert from a national blood and transplant service reported that, in addition to DBM, they provide a range of products using bone granules. The expert reported that some surgeons use mineralised bone granules and mix them with substances such as blood and bone marrow and apply this to patients[iii], and in these cases the surgeons could be unhappy with the proposed removal of the "same surgical procedure" exemption (M4.1). Experts from a non-profit tissues and cells institute reported that, in response to M4.1, surgeons and physicians facing higher regulatory efforts could stop their activities. The experts also reported that M4.8 (IT platform) could place a higher burden on surgeons.
- Experts from a non-profit tissues and cells institute made an additional recommendation that NAT Testing, instead of antibody testing, should become an obligatory measure, especially as long as the use of validated inactivation methods for microorganisms and viruses is not standard in the EU. This would ensure processing methods address viruses as opposed to just using antibiotics.

Costs and affordability

An expert from a national blood and transplant service, as well as an expert from a university hospital which supplies DBM, expressed a desire for DBM remain regulated as a tissue, as regulating it as a medical device would greatly increase the price. One of the experts (from the UK) reported that if DBM became a medicinal product due to any of the proposed measures, this would necessitate DBM being licensed by the UK Medicines and Healthcare products Regulatory Agency (MHRA) which would require lengthy and costly clinical trials[iv]. Such trials would not enhance safety, because as discussed above, the stakeholder reported that DBM is already very safe and well-established, with very few adverse reactions. The stakeholder expressed support for DBM remaining as a tissue. Experts from a non-profit tissues and cells institute similarly expressed that as DBM is a "grandfather product" which has been on the market for many years, clinical investigations would be costly and unnecessary, as well as being difficult to do as there is not academic interest in investigating older products.

[iii] Note a consulted expert from a university hospital which supplies DBM reported that there are some cases of surgeons mixing DBM with autologous platelet-rich plasma (PRP) to make a sort of putty.

[iv] The expert did not provide an estimated cost figure, but noted that Phase 1-4 clinical trials can cost millions of pounds.

The expert from a national blood and transplant service reported that, at present, producers of DBM test a sample on a rodent, and producers subsequently state that it has been shown to stimulate bone growth on a rodent but it has not been tested on humans. This form of words is used because if claims were made guaranteeing stimulated bone growth in humans, this would likely require testing and proving this for every batch of DBM. If DBM became regulated as a medicine or medicinal product, tests on every batch could become necessary which would be costly to implement.

Expert stakeholders from a non-profit tissues and cells institute estimated that if the proposed measures were introduced, direct compliance costs would be 20% higher. The same experts reported that any additional obligation to the hospitals regarding documentation or collection and reporting of data to the competent authorities (M4.6-M4.8) will add burden to their volunteer contribution and will likely reduce the number of donations. The experts stressed that revisions to current BTC provisions should consider whether changes will "directly or indirectly put specific additional burden on the hospital staff that is involved in tissue donation…and how can a partnering tissue bank under the threat of further expanding rules for data protection, help such hospitals to fulfil additional expectations of the Competent Authorities".

Patient access

The American Association of Tissue Banks (AATB), in reply to the Public Consultation on the Regulation on ATMPs[36], made recommendations to ensure that authorities do not inadvertently adversely affect availability of human tissues currently covered by Directive 2004/23/EC of the European Parliament and Council. The AATB recommended that regulation on ATMPs should explicitly exclude DBM added to a carrier agent as an ATMP whereas now they are regarded as "tissue" under Directive 2004/23/EC and further assessed under national law by each Member State.

Innovation, research and development

An expert from a national blood and transplant service and an expert from a university hospital which supplies DBM described some trends in DBM research and innovation[v]. The experts reported these changes will not present confusion, uncertainty, or safety concerns which need to be resolved by the proposed measures.

Conclusions

The stakeholders consulted in the present case study did not report that there are pressing safety, cost, access, or innovation concerns or obstacles for DBM. DBM has been in use for many years, has a strong safety record and clinical indications and there appears to be no need to reclassify it from its current 'tissue status'. It seems that the proposed measures may be better suited for resolving issues with products which are more novel.

Tissues and cells legislation has fewer reporting requirements than medical devices legislation, however the addition of more measures to tissues and cells law could increase costs. These increased costs for DBM could mean that fewer banks (in the public sector) would be able to operate in Europe, as for example many cannot meet existing GMP requirements.

[v] For example, the use of a very thin slice or fibre of bone rather than a powder, which can be demineralised and wrapped around a site.

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A9.10 – Extracellular Vesicles

Two expert representatives from the International Society for Extracellular Vesicles were consulted for this case study.

Part A: Definition of the borderline issue

Description of the borderline substance/product/application

Extracellular vesicles (EVs) are small, nanometric membrane particles derived (secreted) from various cell types. All cell types can produce extracellular vesicles leading to considerable heterogeneity in form and structure. According to one article[1], EVs can broadly be classified according to their cellular origin into:

- Exosomes: Membrane-bound EVs released by immune cells which shuttle proteins and genetic information between both neighbouring and distant cells[2].
- Microvesicles (MVs): Small vesicles that originate from plasma membrane, regarded as mediators of stem cell function, enabling and guiding their regenerative effects[3].
- Apoptotic bodies: Small sealed sacs containing information and substances from dying cells[4].

As described during an interview for this case study, EVs intrinsic components are derived from the surrounding bodily fluids (including plasma). They are in constant dynamic equilibrium which means there can be millions in circulation even in the same bodily fluid. There are many different cell types, which can secrete many different types of EVs as a response to different stimuli. This is one of the key points of interest with EVs: the status of the cell is reflected in the EVs secreted.

Uses of extracellular vesicles

The use of EVs is limited and mostly experimental at present. Although there has been a significant increase in the number of scientific publications that describe the physiological and pathological functions of EVs, there are currently no approved EV products worldwide. More than 500 clinical trial studies have been initiated to assess therapeutic value of MSCs in various diseases according to the www.ClinicalTrials.gov database[5].

EVs are expected to offer opportunities for the development of a new class of therapeutics. For example, there are ongoing experiments with EVs from stromal cells (in the inner ear) to combat the side effect of cochlear implantations. As one interviewee described, researchers are looking at use of EVs to enrich mesenchymal stem cells (MSCs) in the bone marrow e.g. for solid tumour therapy. Because of their cell-to-cell communication, EVs can have a huge role in cancer treatment, influencing tumour progression, metastasis, and therapeutic efficacy[6]. Recently, some researchers have also been exploring the potential EVs from MSCs and possibly other cell sources as treatments for COVID-19[7].

According to the stakeholders interviewed for this case study, part of the complexity surrounding EVs is that it is very difficult to distinguish between compact particles, membrane and soluble factors. This means it is not possible to predict or identify therapeutic active substance or component from the other material around them (e.g. lipid composition, growth factor, cytokines, RNAs, etc.).

In regard to the preparation process, experts interviewed for this case study suggested the need for a large volume of liquid to isolate EVs as this requires undergoing a process of centrifugation and passing the liquid through nano-filters to identify the vesicles. In order to agree on the clinical indications of these different vesicles, the interviewees also suggested a need to establish a production process and production steps which are practical, scalable

and can produce reproduceable batches. Additionally, they suggested observing activity and researching the parent cells of these vesicles to assess whether a higher concentration of a specific component of these EVs (e.g. membrane compartment or some vesicle-bound molecules) can be better enriched. It is important to also undertake physical/chemical characterisation of these vesicles (e.g. molecular surface, particle count) to ensure that batch-to-batch variation is limited. This may help in producing future functional assays. The interviewees also discussed having a proof-of-concept in mice models; once these are achieved, there is a clearer production process to follow to support them to get into the clinical evaluation phase.

Overview of the regulatory issues

EVs are complex, novel products whose use as new therapeutic modalities are only now being explored. This means that there is no existing regulatory approach. It was generally agreed by consulted stakeholders that it is difficult to have a global statement/classification for these products as it is a developing field, and there needs to be sufficient information on intended use and context. The CAT interpretation is that if there is a therapeutic claim, they would be medicinal products. There have been cases of extra-cellular vessels from genetically modified cells, and this has been classified as gene therapy because they were considered the vehicle for the recombinant nucleic acid to the patient. Developers mainly use the principles of the ATMP legislation for these products as there is no other legislation. The CAT representatives also stated there are currently only a minor proportion of EVs are taken out/not cultured and therefore fall under the tissue and cells legislation, but grouping EVs as a whole is not suitable.

Over the last few years, discussions on how to classify EVs have increased in line with the growth in interest in this area. These discussions show a significant degree of uncertainty in how to regulate EVs. For example, in a document outlining comments received on 'Reflection Paper on classification of advanced therapy medicinal products'[8], the European Blood Alliance (EBA) outline that they believe that extracellular vesicles are an emerging field of new treatment modalities, which usually relies on cells as starting material, thus suggesting extracellular vesicles could be regulated as ATMPs. In response to this, the Committee for Advanced Therapies (the CAT) states: "*Regulation 1394/2007 defines that ATMPs must be composed of genes or cells. If this is not the case (e.g. for extracellular vesicles), such products cannot be classified as ATMPs. Further classification of such products is in the remit of NCAs".*

In April 2021, the 'Task Force on Regulatory Affairs and Clinical Use of EV-based Therapeutics' of the International Society for Extracellular Vesicles (ISEV[i]) produced a letter requesting to work with regulators to contribute their collective expertise to the development of applicable regulatory guidance for EVs. In the same letter, it is explained that *"existing and partly harmonised international regulations may require special interpretation if applied to EV-based products"* and that *"a 'one size fits all' regulatory approach is unlikely to be appropriate"*[9]*.* As described by stakeholders during an interview for this case study, this is particularly because, other animals, plants and even prokaryotes can produce EVs, suggesting a wider scope for EV-based therapeutics which go beyond human-derived materials.

[i] ISEV is a professional association founded in 2011 for basic researchers and clinical scientists involved in the investigation of EVs. There are currently more than 1500 members from academia, healthcare institutions, and industry. The Task Force is focusing on translating relevant regulatory guidance and their application to EVs as investigational new drugs (INDs) in clinical studies and to support safe and effective EV-based treatment concepts worldwide.

During the interview for this study, experts in the field of EVs and representing ISEV argued that they perceived these products to be a biological product, and therefore neither a cell nor an ATMP. According to Part I of Annex I of Directive 2001/83/EC, a biological medicinal product is a product that contains a biological substance, and is defined by reference to its method of manufacture. As such, the experts interviewed for the case study said they follow the regulation governing biologicals, arguing that it is not possible to circumvent safety pharmacology[ii]. At the same time, the experts explain they are 'very much oriented on ATMP regulation', as there may be instances where this needs to be applied (e.g. if there is a genetically modified cell which secretes an EV fraction, and which may contain a gene-therapeutic product). The experts also discussed the importance of manufacturing in licensed environments to avoid access to unlicensed, unproven therapies. This is already an issue, e.g. some clinics already marketing products of uncertain benefit (e.g. injecting exosomes).

The letter from ISEV concludes that a case by-case risk-based approach (such as that proposed by the GAPP consortium[iii]) depending on the EV source and manufacturing processes may be meaningful for developing EV-based products[10]. An example provided in the interview undertaken for this case study outlined how anti-cancer drugs, which are toxic for entire body, could be packaged and shuttled around in EVs, which could help to reduce dose about 100-fold, providing an opportunity to enrich target organs by using EVs as delivery vehicles. This is currently experimental (at the level of lab research) but might be a future therapeutic modality that gives rise to regulatory issues. In other words, you have a product which has to be regulated for chemical and biological properties which are currently not clearly defined. Examples like this suggest there are several future regulatory challenges to be overcome as a result of the complexity of EVs/EV preparations. The letter from ISEV suggests that safety standards for cell and tissue-based products may be of use as valuable roadmaps to guide regulation of EV therapeutics[11]. During the interviews, stakeholders agreed that a completely new tailored regulations for EVs was not needed, as the EV therapies themselves will be so heterogenous.

Part B: Potential impact of measures proposed to resolve regulatory issues

The following sections discuss the impacts of the proposed measures on different issues. Specifically, this study refers to Objective 1 (to expand the scope of the BTC legislation to cover all SoHO except organs and several measures under Objective 4 (M4.2-M4.4 concerning strengthened clarification processes, M4.5-M4.6 concerning strengthened authorisation processes, M4.7 for requiring clinical evidence for innovations/new claims).

Safety and quality

Generally, stakeholders interviewed for this case study felt that the measures proposed to strengthen the preparation process authorisation for novel products (M4.5-M4.6, M4.7) were appropriate for regulating EVs. One stakeholder noted that in her GMP-approved facility they already implement many of the current measures and those being suggested to improve safety and quality.

The experts interviewed for this case study further argued that secreted EVs not containing viable cells should have at least a lower risk compared to transplantation of living cells as they are simply enriching the medium of the cells. Hence a risk based approach (such as

[ii] This uses the basic principles of pharmacology in a regulatory-driven process to generate data to inform risk/benefit assessment on whether administering a product to human populations is likely to be unsafe.

[iii] The funding of the GAPP Joint Action (an EU-funded action with the full title: Facilitating the Authorisation of the Preparation Process for Blood, Tissues and Cells) between May 2018 and 2021 demonstrated a commitment to the assessment and authorisation of novel BTC preparation processes.

that proposed by GAPP and under consideration in M4.5-M4.6) will need to be completed, depending on the process methodology used, to derive EVs.

The experts agreed with the measure to implement risk assessments in every tissue and cell establishment – arguing they already do it on regular basis in the GMP environment. However, there needs to be standardisation of these risk assessments, as otherwise different risk assessments will lead to different answers and a lack of equivalency, preventing cross-border exchange.

Of the policy options discussed for implementing M4.5-M4.6, the stakeholders felt that Option 1 (decentralised model of regulation) was the most appropriate one for EVs at this point, since the products are still too novel for any other option to work effectively. One of the stakeholders added that if all EV producers implemented 'properly done' risk assessments, safety and quality would not be compromised.

Costs and affordability

It is too early for stakeholders to comment on how affordability of EVs might be impacted by the implementation of new measures governing such products.

In regard to costs, one stakeholder commented that the more risk assessments establishments have to do, the more costs there are and the more time it will take to do something. For complex processes, high costs, will be inevitable, especially if a new risk assessment is needed for even small changes in processes.

Patient access

It is too early in the development of EV-based therapeutics to consider how measures might affect patient access. One stakeholder described there being a long time span before patients will be able to access EVs treatments outside of a clinical trial setting, but there are no real alternatives to shorten this timespan, due to costs/resources and the need to fully understand (and collect robust evidence on) the science and ethics.

A key issue at the moment is reducing patient access to unregulated EV-based products since they are still in the early phase of development – as of June 2020, there were no approved extracellular vesicle or exosome-based therapies worldwide[12]. The ISEV Task Force has issued a publicly available patient information and safety notice with the view to draw the attention of consumers to potential safety issues with the use of unregulated EV-based therapeutics, which are already being promoted[13].

Innovation, research and development

EVs are innovative and complex, and there is a lot of learn, and therefore any regulatory framework needs to be flexible and facilitate this learning process. However, the interviewees agree that regulation has to be adhered to. One expert stated they have had a good experience so far with their national regulator who interacts with the CAT committee, and provides assistance on what reference/standard to follow without delaying activities. Issues are likely to arise if they are conducting clinical trials across two countries due to differing national regulation, risk assessments and quality profiles associated with different regulatory classifications. Interviewees agree that having more coordination among regulatory bodies at the EU level (M4.2-M4.4) and standardising risk assessment models at the national level (M4.6) would make it easier for these cross-country trials to take place. This is a very important point in delivering a way forward.

Generally, when considering Objective 4 measures as a package, stakeholders felt that Option 3 (a fully centralised regulatory model) would impede innovation, whilst Option 1 (a decentralised approach) would work if implemented alongside a better inspection regime.

Although Option 2 (a joint regulation model) would be preferable and hopefully having guidance from different expert bodies would allow for a more uniform/better approach across the EU, the experts explained this would still lag behind development and innovation.

As part of the wider discussion on measures, it was felt that inspectors had to be well-trained (to equivalent standards across Europe) and suitably qualified on the emerging area of EVs and familiar with the innovation in this area to be effective and support continuous improvements. Additionally, a pragmatic approach to assessing risk had to be implemented. For example, one stakeholder described implementing an Failure Mode and Effects Analysis approach which is a step-by-step approach for identifying all possible failures but accepts a certain amount of risk; this has led to a very productive interaction with the authorities and ensured that innovation has not been stifled.

Conclusions

Thus far EVs are unregulated and, due to the possibility to obtain EVs from several areas, there are many used/indications which suggests that a one size fits all regulatory approach will not work for this class of products. Indeed, EVs can be a therapy in itself, or used as a vector, or enhancer for therapies. In order to support innovation in this area, there was general agreement among stakeholders that a flexible regulatory approach was required to facilitate the learning and development process. Stakeholders felt that a case by-case risk-based approach (such as that proposed by the GAPP consortium) depending on the EV source and manufacturing processes may be meaningful for developing EV-based products. Risk assessments were considered a good first step in the regulatory process, regardless of how they are later regulated (and under which framework). It is nonetheless of great significance for the BTC sector to consider the future regulation of EVs, particularly as they are obtained from humans and there is a need to screen and select donors for SoHO.

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A9.11 – Faecal Microbiota Transplantation (FMT)

The stakeholders consulted for this case study were a representative from a non-profit organisation focusing on digestive health (the stakeholder also works at a faeces bank), a representative from a regulatory science expertise centre, and a general expert on FMT.

Part A: Definition of the borderline issue

Description of the borderline substance/product/application

Faecal Microbiota Transplantation (FMT) is a rapidly growing therapy that targets and modulates the human intestinal microbiota. The use of FMT is shown to be highly effective in patients with recurrent Clostridioides difficile (C. difficile) infection. An expert consulted for this case study noted that it has not been possible to mimic the composition of intestinal microbiota, therefore donor faeces remains an irreplaceable substance for use in the treatment of life-threatening diseases.

FMT can be autologous or allogenic and it can be prepared in a spectrum of ways from minimal processing through to complex processing (enrichment) to genetic manipulation, and can be administered through an enema or a tube through the nose[1]. In a response to the roadmap consultation, stakeholders from Aarhus University Hospital reported that the active substances in donor faeces are unknown, and may include intestinal bacteria, viruses, parasites, metabolites, human cells, and other substances excreted from the human intestine[2].

One expert interviewed for the study reflected that currently the intention is to distribute samples from few centres to multiple clinics within the Europe: 1874 procedures within 31 centres have been carried out in 2019 according to a very recent study by Baunwall and colleagues[3].

FMT has been used for decades and is widely used in Europe as a treatment for *C. difficile*, and is seen as superior to all other known treatments for *C. difficile*[4]. An observational study from 2019[5] conducted in a public Danish referral centre for gastroenterology estimated that the average cost of FMT for *C. difficile* was €3,095. Total hospital costs for treating patients with *C. difficile* dropped by 42% the first year after FMT's were introduced as the treatment of choice for *C. difficile*, largely due to reduced hospital admissions and length of stay.

Uses of FMT

Established indications for FMT include treating Recurrent C. difficile and Refractory or fulminant C. difficile[6]. An expert noted that clinical use of FMT has revolutionised the treatment potential in patients with recurrent, refractory, or fulminant *C. difficile* infection, and the treatment is now routine in most countries.

A 2019 randomised trial[7] compared FMT to the antibiotics fidaxomicin and vancomycin for treating recurrent *C. difficile* and found that a combination of FMT preceded by 4–10 days of vancomycin 125 mg 4 times daily was superior to just fidaxomicin or vancomycin. A 2020 systematic review and meta-analysis[8] concluded that FMT is effective for treating recurrent *C. difficile*, and the effect is strongest with repeat FMT or if FMT is delivered through lower gastrointestinal endoscopy.

Experimental indications include cases of Multidrug resistance[9], Irritable bowel syndrome[10,11], Ulcerative colitis[12,13], Decompensated liver cirrhosis[14], bone marrow transplant, and Crohn's disease[15]. There is a high level of interest in FMT from the industry and from academia, and there are thought to be over 100 ongoing clinical trials related to FMT[16].

Overview of the regulatory issue

The regulatory issue of FMT was initially raised by the Netherlands in a Meeting of the Competent Authorities on Tissues and Cells in 2012[17], and the competent authorities concluded that bacterial flora does not fall under the provisions of the Directive 2004/23/EC. Later, at a meeting in 2014[18], the regulatory status of FMT was discussed as the UK cited evidence of the growing use of FMT. In FMT the active agent is the gut flora and not the human cells, however cells are present in the transplant, therefore at this meeting the UK (and other Member States) requested clarification on an appropriate legal framework for faecal transplants. Dr Simon Goldenberg(a microbiologist and infection control doctor in the UK), confirmed that the active component in FMT is not the faeces itself, but rather the bacterial microorganisms (gut flora) in the faeces[19]. An expert consulted for this study stated that this is the main source of the regulatory issue, as the active part of FMT is not the human cells and this is why it has, to date, been excluded from the BTC regulations. Similarities were drawn between FMT and other SoHo products such as human breast milk.

At the following meeting in December 2014[20], the Commission concluded, after consulting with its legal services, that this type of substance did not fall within the scope of Directive 2004/23/EC (or any other relevant Union legislation) because the cells contained therein were not the active component of the treatment. However, it was also concluded that human breast milk and FMT are to be considered substances of human origin, and therefore fall under the scope of Article 168.4(a) of the Treaty on the Functioning of the European Union. As noted in the previous BTC evaluation study, this lays down a mandate for the adoption at EU level of measures setting high standards of quality and safety with respect to all substances of human origin. Currently, Member States are free to decide on the most suitable framework, either by creating a specific regulatory framework at national level or by applying one of the existing legislative frameworks. In a more recent meeting in 2019[21], it was reiterated that while FMT does not meet the definitions of 'tissues and cells' in Directive 2004/23/EC, they are considered substances of human origin and, therefore, competence is granted in the Treaty to regulate at EU level.

There are various potential points of regulation for FMT: donor-related (recruitment, screening), processing (preservation and modification e.g. additives, mixing and cultivation) and clinical application (administration and follow-up). Regulation varies for unprocessed donor faeces (tissue-like) and standardised advanced therapy medicinal products (drug-like)[22].

The lack of certainty about where FMT should be regulated has led to **significantly divergent approaches being taken** across Member States. At a meeting of the Competent Authorities on Tissues and Cells in 2019[23], a survey indicated that in two Member States FMT falls under Tissue and Cells safety and quality requirements, in four Member States under Medicinal product requirements (non-ATMP), and in two Member States other requirements. 13 Member States had no regulation covering FMT. For example, the *UK*, Germany, Ireland and France regulate it as a medicinal product, while Italy regulates as a human cell/tissue product.

It is arguable that FMT treatments are not 'borderline substances' *per se* – rather the current inconsistencies in how FMT is regulated may have negatively impacted on R&D into FMT and potentially resulted in restricting access to the treatment where overly stringent regulatory requirements have been put in place. An academic article from Merrick and colleagues[24] stated that "Regulation seeks to improve quality and safety, however, lack of standardisation creates confusion, and overly restrictive regulation may hamper widespread access and discourage research using FMT." An article in Medical Device Network[25] reported that inconsistent regulation and a lack of access to FMT has caused some patients to undergo dangerous at-home procedures using a family member's faeces and a blender to mimic FMT. This is dangerous as it does not involve screening donor faeces, and the colon or rectum can be damaged during self administration of an enema. A response to the

roadmap consultation from the Netherlands Donor Feces Bank[26] suggested that proper legislation on faeces donation is needed to ensure regulation by competent authorities as well as to provide/define the required framework for quality assurance, auditing and biovigilance. A consulted expert also reported that some companies store patients' own faeces for "future use" with the idea that if that patient needed FMT in the future their stool could be used (as is done with cord blood storage), however these claims may lack a scientific basis, and therefore it is important FMT is regulated adequately.

Patient access also seems to currently be sub-optimal for FMT. A paper by Verbeke and colleagues[27] reports that "safe and regulated access to faecal microbiota transplantation currently still largely depends on the country where the patients are living in". A consulted expert (who works at a stool bank) similarly described how a doctor in Germany was unable to access FMT treatment for a patient with graft-versus-host disease, as regulation of FMT as a medicine in Germany sets requirements on banks which they are not able to meet. The expert specified that if patient lived in the Netherlands, where FMT is regulated under tissues and cells, the treatment would have been accessible. This disappointing outcome demonstrates how un-harmonised regulation leads to issues with patient access. Further, as discussed above patients are "accessing" the procedure by doing it themselves at home in a dangerous way.

A consulted expert also reflected that applying the medicinal regulatory framework (as done in some Member States) is seen by some as being "stricter" or better, however this does not address perceived donor access issues to FMT treatment that may arise if the standards that are set are too onerous for hospitals to comply with and, that are not based on risk with regards to quality and safety. Non-anecdotal evidence that donor access has been restricted in this way was not found.

Part B: Potential impact of measures proposed to resolve regulatory issues

The following sections discuss the impacts of the proposed measures being considered as part of the revision of the BTC legislation on different issues relating to FMT treatments. Specifically, this study refers to: Measure 1.2 (to bring FMT under the competence of BTC legislation), Measure 3.7 (EU law incorporates quality and safety requirements for FMT donors), and several measures under Objective 4 (M4.2-M4.4 concerning strengthened clarification processes, M4.5-M4.6 concerning strengthened authorisation processes, M4.7 for requiring clinical evidence for innovations/new claims and M4.8 concerning sharing of data on authorisations between Member States).

One proposed measure for FMT is to bring the treatments into the scope of the BTC legislation (M1.2); see the box below for examples of stakeholders' views on this.

There have been repeated calls from stakeholders to include FMT in the BTC framework (M1.2)

Some stakeholders (the sector[28], Aarhus University Hospital[29]) would generally like to see FMT and intestinal microbiota incorporated into the revised BTC framework. In an article by Verbeke and colleagues[30] it is proposed that FMT should be brought into the existing medicinal products framework They argue that if it was regulated under the Medicine's framework the hospital exemption could be applied ensuring that patients continue to have access and that marketing authorisation of faecal microbiota for a given disease would immediately grant all citizens of the European Union access to the treatment, avoiding unnecessary replication of clinical trials due to different regulatory demands per country.

In a letter to the editor[31], Keller and colleagues strongly counter this position by stating that 'only in the case of modification to the donated faeces, other than those necessary for the conservation of the microbial community, does the product made of the donated faeces become comparable to a drug'. They therefore recommend that the Tissue and Cells Directive (2004/23/EC) is the most appropriate legal framework for FMT. Although they caveat this with the following observation, 'If eventually future research results in the replacement of FMT by standardised mixtures of bacteria (or another yet undiscovered stool extract that could theoretically underly the clinical effects of FMT), these should indeed be regulated as a drug or pharmaceutical product'.

Other stakeholder views on the appropriate regulatory framework for are as follows. The Intestinal Microbiome-based Medicines European Task Group (IMM-ETG) was of the view that intestinal microbiome whole ecosystem-derived products should be regulated as medicinal products under Directive 2001/83/EC, as long as they are 'intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process'. The task group further states that such products intended for use in a clinical trial should follow quality requirements for all medicinal products[32].

Responses to the roadmap consultation from the French Secrétariat général des Affaires européennes[33] and L'Agence nationale de sécurité du médicament et des produits de santé[34] stated that France supports the creation of EU legislation on faeces donation (including testing, eligibility of donors, and establishment authorisation).

An academic article which mapped some examples of different approaches to FMT regulation[35] indicated that the US, Canada, and Australia are investigating or undertaking a Biological agent classification for FMT, with stringent regulation and restricted use. In the US, the FDA treats faecal transplants as a biological drug and requires doctors to file an Investigational New Drug (IND) application to administer it, although this was waived for C. difficile[36,37].

If FMT were included in the scope of the revised BTC legislation (M1.2), there still remain questions about the level of oversight that should be applied to FMT and also questions around how the technical standards should be implemented.

For the policy options, an interviewee was in favour of Option 2 (the joint regulation model) using the EDQM as the expert body, as the EDQM is taken seriously by many experts and would easily allow for use of the EDQM's tissue guide alongside other international guidelines (although note that suggested guidelines were not described). Another expert did advise that there would need to be more microbiota expertise in the EDQM. Issues seen with Option 3 (the centralised regulation model) included that legally binding requirements could be very complicated and not flexible enough to respond to evolutions in the field. Option 1 (the decentralised regulation model) was seen as relying too heavily on knowledgeable stakeholders which may not be available in every Member State.

The sub-sections below describe the potential impacts of including FMT in the BTC legislation, and different measures which could be taken to enhance the quality, safety, costs, access, and innovation of FMT.

Safety and quality

Regulating FMT within the BTC framework laws (M1.2) is seen as a way of increasing the safety and quality of FMTs and potentially leading to increased standardisation of processes. If the scope of BTC legislation were clarified or expanded to include FMT, stakeholders have reflected on what considerations should be taken into account. In order to improve the quality and safety of FMT generally, stakeholders have recommended that regulators consider certain principles, outlined below:

- To ensure general quality and safety, regulators should ensure quality measures[38,39] (so that faeces that meets rigorous quality standards with minimal risk), efficacy[40] (monitored by an independent organisation to protect patients and ensure evidence-based medicine), donor screening and testing[41], and adequate storage, labelling, packaging, and distribution[42].
- Another common theme was that stakeholders recommended ensuring traceability[43,44], biovigilance[45], and pharmacovigilance[46] of FMT to detect adverse effects.
- To ensure the safety of donors, stakeholders emphasised the need for donors to have their rights protected, including being informed[47] (including on long-term risks and given to all stakeholders), and anonymous[48].

More specific measures and recommendations for the regulation of FMT are described below.

Several interviewed experts felt that the most useful measure to resolve issues with FMT would be the establishment of an EU level advisory mechanism (M4.2 and related measures M4.3 and M4.4) which could e.g. clarify whether FMT is a TC transplant or whether (due to manufacturing scale up or substantial manipulation) it's a starting material for a medicinal product. An expert reported that previously, it has been difficult to find advice, and health inspectorates, the EMA, and the Commission were unable to help in providing regulatory certainty about FMTs regulatory status. The same regulatory issues are faced repeatedly across Member States, so an advisory mechanism could help resolve this. Further, the stakeholders urged that an advisory body should not provide advice without having adequate engagement and advice from Member States experts: in the US the classification of FMT as a drug without adequate expert input led to some stool banks being shut down due to the increased costs associated with compliance with the drug legislation. One expert recommended that this classification advice must be given quickly (i.e. before Member States start making their own rules and laws, as this could lead to 27 different rules and which point advice from a central body would be pointless).

A European Consensus Conference of 28 experts from 10 countries[49] made a series of recommendations for FMT, including that "Appropriate FMT registries should be implemented, in order to collect data concerning indications, procedure, effectiveness and safety profiles". The creation of registries could help with data collection and help to address safety issues which may arise for FMT e.g. Through the collection of follow-up data. Similarly, a proposed exchange (IT) platform to share information on national authorisation decisions (M4.8) was seen as useful by a consulted expert, although they questioned if using such the IT platform should be mandatory for Member States rather than optional. Another expert interviewed for this case study from a regulatory science expertise centre reported that microbiota forms the raw materials of many drugs, and there is currently no harmonised framework to document the origin of bacterial strains and collect information on the donor and the faeces collected. In other words, the expert reported that the collection of faeces must be regulated independently of what the faeces will be used for subsequently,

so considering faeces only through the lens of FMT is a mistake as pharmacovigilance is key for all procedures in which faeces and its components are used. The stakeholder recommended that the proposed centralised exchange IT platform (M4.8; to share information on national authorisation decisions) should include more information, including the history of the donor, information on the samples and procedures and information on anu drugs the sample may have been used in. This recommendation also applies to other microbiota collected from complex ecosystems, such as the vagina, skin, lung, nose, and mouth. This expert proposed that that the substance, i.e. faeces, should be put into the scope of the BTC regulation for donor selection and testing, (and that this IT platform should be used), but then all the following steps should fall under medicines' framework.

This recommendation was made because for several reasons: microbiota transplantation may carry a high level of risk for recipients; safety is not only related to the absence of pathogenic and adventitious agents or diversity, but also to the composition and microbial functions of the donor as well as recipients' characteristics; and microbiota transplantation assessment should introduce considerations of Benefit/risk balance for non-life-threatening indications because long term consequences of microbiota transplantation are unknown. The expert specified that current practices in microbiota transplantation are no longer in line with the definition of "minimally manipulated", and capsules and freeze drying would not apply to the definition provided by an NIH-funded study by Hoffman and colleagues[50] as it affects differently varieties of species within a sample. Overall, due to these considerations, the expert proposed that microbiota products should be developed with a "quality by design mindset" and therefore the medicinal product framework provides the best insurance of appropriate quality, safety and efficacy assessment as well as long-term monitoring of safety and efficacy for the patients.

The representative from a regulatory science expertise centre reported that risk analysis processes are different for microbiomes, as the biomes of the donor and the recipient impact safety much more than the process followed, and it should not be thought that applying the same process will lead to the same results. The expert reported that FMT is used to treat C. difficile when it is the last possibility for this life-threatening condition. However, as FMT is explored for diabetes, autism, depression, and other cases, it is not the same situation and therefore there should be a framework to establish a basic proof of concept for patients with no other options. This links to measures under consideration for strengthening the preparation process under M4.5-M4.6.

Finally, a representative from a non-profit organisation focusing on digestive health reflected that FMT is not like a drug and should not be classified as such, as it is rather more like blood. FMT ends up as an unstandardised preparation due to the varying material received from a donor, whereas drugs are standardised (by definition). The Intestinal Microbiome-based Medicines European Task Group (IMM-ETG) similarly accepts limited quality control of the "final product against specific release criteria or analysis of the final composition for comparison with initial donor microbiota" for FMT, as it is different to industrial products which use a standardised process.[51] A response to the roadmap consultation from Aarhus University Hospital[52] argued that future legislation should not allow commercial exploitation of donors (linked to M3.7); an interviewed expert claimed that treating FMT similarly to other unstandardised procedures from donors would accomplish this.

Costs and affordability

According to an expert from a digestive health non-profit organisation, tissue banks calculate the price of FMT as less than EUR 2,000 for preparation, with a treatment cost close to EUR 3,000. However, if FMT were produced by commercial companies as a medicinal product they would not offer FMT for this price, and the stakeholder cited rumours the price could be closer to EUR 5,000-10,000, therefore keeping FMT as a non-commercialised product will keep the price down.

An interviewed FMT subject expert reported that an advisory mechanism (M4.2) would introduce efficiency and certainty for stakeholders as once a recommendation/advice had been provided via the mechanism the query would not need to be submitted again. Another consulted expert from a digestive health non-profit organisation stated that introducing requirements for clinical trials (M4.7) should be considered carefully, as they could complicate processes and be costly to conduct.

Patient access

The Netherlands Donor Feces Bank's roadmap response[53] stated that proper legislation of faeces donation is key to guarantee wide availability of stool preparations for FMT. A consulted expert digestive health non-profit organisation similarly felt that including FMT in BTC legislation (M1.2) would increase accessibility and reduce problems such as the previously described patient who could not access FMT in Germany. In an academic article[54], Hvas and colleagues also suggest that regulating FMT as a tissue would allow for both hospital-based and commercial production, which would ensure broad access. An expert reported that an advisory mechanism and harmonised, consistent advice (M4.2-M4.4) would improve patient access and would potentially facilitate innovation and investment.

Stool banks are a mechanism by which FMT could be delivered. The box below describes a stool bank model and its potential impacts.

Stool banks

An article from 2016 indicated that groups in Latin America, Asia, Germany, and elsewhere in Europe were interested in opening stool banks[55]. Most stool banks are non-profit institutions and follow a similar model to blood banks[56]. A response to the roadmap consultation from the Netherlands Donor Feces Bank stated that stool banks have been founded to facilitate safe and cost effective FMT, and to enable quality assurance[57]. In a letter to the editor[58], Keller and colleagues advocated for stool banks as they can reportedly produce ready-to-use donor faeces suspensions for treatment of patients, improve the quality and safety of FMT by centralisation and Standardisation, increase the cost effectiveness of FMT, and facilitate research. A journal article by Mikkelsen and colleagues[59] states that the framework of Directive 2001/83/EC10 already applies to any product derived from human stool and manufactured on a routine basis using an industrial process, and stool banks use systematic manufacture in a batch-wise process on a routine basis, and therefore "bears the hallmarks of an 'industrial process'". However, a journal article from 2016 noted that some companies were developing FMT products which could make stool banks unnecessary[60].

One stakeholder (who works at a stool bank) recommended that there should be a similar model to blood banks whereby the government must pay for and ensure accessibility of stool and stool banks. The stakeholder proposed that stool banking could even be done as part of blood banks, which is an approach taken in Denmark. An article by Jørgensen and colleagues[61] also notes that blood centres are large and pre-established, and blood and faeces share many of the same dependencies. Therefore, the paper recommends that FMT services could be established and embedded within the blood bank infrastructure, and blood donors could also potentially be used as faeces donors. However, note that this model would be problematic if FMT were regulated under the T& C legislation. Aarhus University Hospital's response to the roadmap consultation[62] also suggested that the blood bank model ensures a high volume of donors and donations, and for FMT, adequate access to donor material is key for citizens' access to treatment.

Innovation, research and development

In response to the roadmap consultation, stakeholders from Aarhus University Hospital[63] reported that "Innovation is supported in transparent and versatile environments such as academic settings where investigator-initiated clinical trials may be performed with appropriate regulatory oversight. Recent initiatives within the EU support the continued consolidation of such trials, and this could be further supported through the present legislation."

A group of companies called the ''Pharmabiotic Research Institute'' in Europe seeks to improve market access for microbiome therapeutic products; this group advocates for classifying FMT as a drug. The ''Microbiome Therapeutics Innovation Group (MTIG)'' in the US is a similar group with similar aims[64]. However, in a letter to the editor[65], Keller and colleagues argued that classifying FMT as a drug will cause a lengthy and costly registration processes, and will lead to a sharp rise in costs for FMT. Similarly, an article by Hvas and colleagues[66] argued that industry advocacy for regulating FMT as a drug could lead to a selective regulation which may impose serious and unjustified limitations on the research into and clinical use of FMT at cost to patients. An interviewed expert also advised against classification as a drug, as if companies package stool in a certain way and call it a drug, this could stall innovation. Rather, these companies should work towards a standardised bacterial product and then classify that as a drug which could replace FMT. However, this stakeholder was clear that if manufacturers enrich or remove strains, or change the microbiota, it is widely agreed that this should be considered a drug.

A FMT expert reflected that market access and market exclusivity have been key ambitions for industrial players. The potential for profit is very large, and investments are made accordingly, particularly in the US. The expert reflected that a focus on both industrial innovation and academic innovation should be encouraged.

An expert from a regulatory science expertise centre also discussed other (related) innovative microbiota products and treatments, including drugs made from microbiota in breast milk, as well as vaginal, oral, and skin microbiota, all of which could be affected by changes to legal frameworks. Aarhus University Hospital's response to the roadmap consultation[67] recommended that other human-derived microbiota communities could be included in changes to BTC regulations. However, the expert cautioned that if a decision is taken for FMT this does not necessarily mean it will relate to the other products. Faeces and maternal milk shouldn't solely be included in the regulations, but rather all microbiome samples should be considered.

Conclusions

Current inconsistencies in how FMT is regulated across Member States may have negatively impacted on research into FMT and potentially resulted in restricting access to the treatment where overly stringent regulatory requirements have been put in place. If the measures being considered as part of the revision of the BTC legislation were put in place, this could avoid/resolve some of the long-standing questions on FMT regulation that Member States have struggled with. In particular, the measures relating to the creation of advisory bodies and the introduction of an exchange (IT) platform could help to resolve the issues some Member States have faced. Regulating FMT within the BTC framework laws is seen as a way of increasing the safety and quality of FMTs and potentially leading to increased standardisation of processes. This is also linked to access, and standardising regulation could lead to more equitable access. Further, regulation and an accompanying advisory mechanism could increase financial efficiency and certainty for stakeholders. Finally, innovation and development related to FMT and other microbiota could be increased by the proposed measures. In conclusion, it is appropriate to say that overall there is support for including FMT in the scope of the future BTC legislation.

Appendix 1: Example FMT classifications by Member State

Member State	Classification
Netherlands **Italy**	Human cell/tissue product, whereby there is tiered regulation according to risk, and the low risk tier covers tissues and cells that are not 'substantially manipulated'[68].
Belgium	Human cell/tissue product, whereby there is tiered regulation according to risk, and the low risk tier covers tissues and cells that are not 'substantially manipulated'[69]. The Superior Health Council of **Belgium** acknowledged in 2015 that FMT could evolve towards the status of medicine when the product becomes a more specified product concerning the composition of the active substance(s) or the possibility of an industrial production process[70].
UK **Germany**	Non-biologic Medicinal product (a drug), with variable regulation according to jurisdiction[71,72]
Ireland	Non-biologic Medicinal product (a drug), with variable regulation according to jurisdiction[73]
France	Non-biologic Medicinal product (a drug), with variable regulation according to jurisdiction[74,75,76]
Denmark	When Denmark received an application for authorising a Tissue Establishment to provide FMT for treatment of recurrent C. difficile, the NCA recommended to the TE to follow the standards included in the EU tissue and cells regulatory framework and laid down in the Danish Tissue Act. The approach in Denmark (as of 2019) is that the tissue and cell framework is the appropriate one for hospitalised patients with Clostridioides difficile infection treated with FMT, applied in cryobags or in capsules, and receiving a transplant from one donor[77].
Austria	Considered a therapeutic intervention not defined as a drug or subject to the Medical Devices Act or to the Austrian Transplantation Act. AS of 2017, FMT faecal is available in Austria for patients suffering from C. difficile infection, and other indications can be treated under the settings of a clinical trial[78].

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A9.12 – Human breast milk

The expert stakeholders consulted for this case study were a consultant and expert in human milk banking and breastfeeding, and a group of experts from a National Competent Authority (NCA).

Part A: Definition of the borderline issue

Description of the borderline substance/product/application

Vulnerable infants, such as preterm neonates with low birthweight, are at greater risk of morbidity and mortality from severe digestive complications, infections, and delayed growth or development[1]. Donated human breast milk (DHBM) has nutritional properties and is also used to enhance immunity in preterm infants in cases where a mother cannot breastfeed at the time of the baby's birth. In a presentation at a recent workshop[2], an expert outlined that the main benefits of DHBM in preterm infants are decreased risk of necrotising enterocolitis, better food tolerance, shorter hospitalisation, and increased breastfeeding rate once the mother is able to breastfeed. Future potential indications and uses of stem cells derived from breast milk include tissue repair (anti-inflammatory; anti-apoptotic; anti-necrotic), regenerative medicine (stroke-associated pathologies; neurodegenerative diseases; diabetic-induced infertility; spinal cord injury; liver therapeutic application), and immunomodulation[3].

The WHO recommends that low birth weight infants "who cannot be fed mother's own milk should be fed donor human milk", a recommendation which is relevant for settings where safe and affordable milk-banking facilities are available or can be set up[4]. It has been estimated that over 800,000 infants worldwide receive DHBM yearly[5].

DHBM can be prepared in a spectrum of ways from minimal processing (pasteurisation) to complex processing (pooling to manufacture fortifiers for addition to human breast milk). According to an academic article[6], over 600 human milk banks have been established across more than 60 countries, with most in Europe, the US, Asia, and Brazil. A survey conducted in 2014 of 27 countries (mostly EU Member States) indicated that half of the countries had established breast milk banks and procurement centres, alongside standard operating procedures for the collection, storage, and use of DHBM. Expert stakeholders from an NCA reported that there are three main models for milk banks: hospital banks which are led by neonatal units, community banks led by blood banks, and a mixed model whereby donor selection is carried out in a neonatal unit and the subsequent processes undertaken within a milk bank. Another expert reported that some hospital-based milk banks, alongside supporting pre-term babies in the hospital environment, also support mothers and babies in the surrounding community in cases where a mother is not able to breastfeed.

Overview of the regulatory issue

The regulatory issue of interest here is whether the Tissues and Cells legislation is the appropriate regulatory framework for DHBM.

The increasing use of DHBM and the concomitant growth of milk banks across Member States in the EU have led to questions on the regulatory status of DHBM being raised at Tissues and Cells Competent Authorities (CA) meetings. At a CA meeting in 2013[7], a discussion on the subject indicated that most Member States regulated DHBM through food safety authorities. It was noted during the discussions that the donated milk was not only or always used solely as a source of nutrition but was also used for its therapeutic qualities and therefore close collaboration with food safety authorities was necessary. In 2014[8], DG SANTE advised that based on the definition of food as provided in the Regulation 178/2002 banked milk could in principle be covered by the EU food legislation, however this issue had not been brought to the attention of Directorate E (safety and food chain).

Representatives from four Member States (DE, LU, NL, SK) argued that it should be considered as food. However, a representative from CoE/EDQM stated that DHBM should not be covered exclusively by the food legislation due to e.g. The donor-related safety issues. The minutes of the meeting do not provide details on what the donor-related safety issues are, however, a subject expert consulted for the present study reported that risks to donors include: blocked ducts if they stop expressing/donating their milk in an uncontrolled way and, that donating large amounts of milk could impact the mother's nutritional status. Significantly, potential risks to infants fed with DHBM include exposure to infectious diseases or chemical contaminants if the donor is infected or using illegal or prescription drugs, and contamination of the milk if it is not processed and stored properly[9].

At the following meeting in December 2014[10], the Commission concluded, after consulting with its legal services, that this type of human derivative did not fall within the scope of Directive 2004/23/EC, or any other relevant Union legislation. However, DHBM is to be considered a substance of human origin (SoHO), and therefore falls under the scope of Article 168.4(a) of the Treaty on the Functioning of the European Union. As noted in the BTC evaluation study[11], the Treaty lays down a mandate for the adoption at EU level of measures setting high standards of quality and safety with respect to all substances of human origin. For SoHO that are currently within the mandate of the Treaty but not adopted into legislation Member States are free to decide on the most suitable framework, either by creating a specific regulatory framework at the national level or by applying one of the existing legislative frameworks.

Breast milk is included in the EDQM's Guide to the Quality and Safety of Tissues and Cells for Human Application[12]. However, the lack of certainty about where DHBM should be regulated has led to significantly divergent approaches being taken across Member States. At a Meeting of the Competent Authorities on Tissues and Cells in 2014[13], the results of a survey of the 27 Member States indicated that only a third had legislation that would cover the use of DHBM for allogeneic use, and in seven of these countries the Ministry of Health was responsible for these legal requirements[i]. In those Member States with regulation, seven regulated allogenic human milk as "other food" (an undefined concept) and seven regulated it as food. Consulted stakeholders from an NCA reported that aside from Member States taking different regulatory approaches to the regulation of DHBM there are other important (technical) differences being practised across Member States that may impact on the quality and safety of the milk, including whether a pre- and post-process microbiological culture is carried out, different methods for preserving milk after expression or donation (e.g. freezing), and methods for pasteurisation.

Expert stakeholders reported that inconsistent regulatory approaches and the lack of harmonisation has the potential to adversely impact the safety and quality of DHBM. At a meeting of the Competent Authorities on Tissues and Cells[14], it was reflected that the emergence of applications of breast milk for therapeutic purposes may require a reassessment of the existing regulatory approaches and closer cooperation between food safety CAs and tissue and cell CAs in order to ensure that disease transmission risks and ethical issues linked to donation are suitably dealt with. A journal editorial by Kent[15] noted that some banks are exploitative, unsanitary, or provide milk to people who use it for questionable purposes and therefore appropriate regulation of milk banking is necessary. Finally, a subject expert reflected that regulating DHBM as a food has negative ethical and safety implications, and further food regulation (in the UK at least) is fragmented across different agencies.

Further, a donor's baby, while neither a donor nor recipient, is a relevant stakeholder who could be impacted by their mother donating milk. A response to the roadmap consultation from an EU citizen[16], as well as an expert consulted for this case study, stated that there has been an increase in commercialised human milk, which could lead to potential

[i] Further information about the regulations and laws DHBM was regulated under was not available in the meeting minutes.

exploitation of mothers. Adequate consent procedures for donors are key, as it is important for a mother to understand that if she donates milk, her baby may need to be fed with formula which may be less beneficial than the mother's milk. Other stakeholders from an NCA reflected that there are websites in Spain and other countries where DHBM is marketed and sold and that currently these commercial entities and the services that they offer are not subject to adequate oversight to ensure the quality and safety of DHBM.

The use of DHBM is increasing, for example one academic article[17] stated that in Canada the use of pasteurised DHBM is "making a comeback" as a life-saving medicine for very low birthweight infants as it provides the best nutrition available for all infants in need of supplementation. However, there is still room for improvement in terms of access to DHBM: one recent study in Germany, Austria, and Switzerland[18] concluded that DHBM is underutilised in most neonatal units caring for premature babies, with the main barrier to use being a lack of access. It has been estimated that around 500,000 infants born prior to 32 weeks lack access to DHBM[19]. The COVID-19 pandemic has exacerbated access issues, due to difficulties with maintaining sufficient donors, transport logistics, safe handling, and contingency planning[20]. Expert stakeholders reported that as Member States have different quality and safety standards for DHBM this can also impact cross-border exchange of milk and therefore access, A "call to action" in the Lancet[21] stated that more human milk banks are needed, as they help ensure a reliable supply of milk, as well as a strong global breastfeeding culture to enable all vulnerable infants to have access to DHBM.

An expert reflected that there is great potential for DHBM to be used more widely than it currently is, which is not realised due to a lack of investment. The expert reported that research and development into the topic of breastmilk in general is somewhat stigmatised, partially because of fears of being seen as paternalistic or as to be telling parents how to feed their babies.

Part B: Potential impact of measures proposed to resolve regulatory issues

The following sections discuss the impacts of the proposed measures being considered under the revision of the BTC legislation on different issues relating to the regulation of DHBM. Specifically, this study refers to: Measure 1.2 (to bring DHBM under the competence of BTC legislation), Measure 3.1 (high level principles to protect BTC donors), Measure 3.7 (EU law incorporates quality and safety requirements for DHBM donors), and several measures under Objective 4 (primarily M4.2-M4.4 concerning strengthened clarification processes).

As noted in the BTC evaluation study[22], breast milk banks are proliferating across the EU, and whilst most Member States regulate this through food & safety authorities, the emergence of therapeutic applications (e.g. use of breast milk stem cells) means that this allocation may need to be reassessed. One proposed measure for regulating DHBM is to bring it **into the scope of the BTC legislation** (M1.2) which is a measure which seems to be highly supported by key stakeholders. For example:

- It was reported in a Meeting of the Competent Authorities[23], that the sector would generally like to see DHBM incorporated in **the revised BTC framework**. In a presentation at a recent workshop[24], it was argued that European regulation will improve the availability, quality, and safety of DHBM for preterm and sick infants. A response to the roadmap consultation from The Human Milk Foundation[25] stated that this NGO supports including DHBM in **new EU legislation** and urged that milk donors should have access to the best level of emotional support, particularly bereaved donors, which is likely best offered by the non-profit sector. The Oxford-PATH Human Milk Working Group (a working group of technical and policy experts in nutrition, human milk banking, human rights, bioethics, and maternal, new-born, and child health)[26] identified key actions which should be addressed, including prioritising DHBM guidance at regional and national levels through **regulation**.

- A policy recommendation from the European Foundation for the Care of Newborn Infants Working Group on Human Milk Regulation[27] made requests for including breastmilk in any revision of the **Tissues and Cells Directive**, including that it should recognise human milk as the best option for preterm, sick and low birthweight infants and that it should include a delegated act on DHBM to be developed in close cooperation with key stakeholders in infant care and human milk safety.
- Responses to the roadmap consultation from the French Secrétariat général des Affaires européennes[28] and L'Agence nationale de sécurité du médicament et des produits de santé[29] stated that France supports the creation of **EU legislation on breast milk** (including establishment authorisation, inspection, requirements on eligibility of donors, testing, quality and safety).

If DHBM was included in the scope of BTC legislation, there remain questions around what, for example, would be an appropriate level of oversight taking into account the risks associated with the DHBM. Overall, one expert stakeholder agreed that the proposed measures would represent an improvement over the current "baseline" situation.

For the policy options, an interviewee stated that if DHBM were brought within the scope of the tissues and cells legislation, the legislation should not go so far as to mandate how milk banks operate. Rather, guidance on operation of banks should be determined at the national level with guidance from a body such as the EDQM. This seems to align most with Option 2 (expert body guidance) rather than Option 1 (a decentralised regulatory model) and Option 3 (a centralised regulatory model).

The sub-sections below describe potential impacts of including DHBM in BTC legislation, and different measures which could be taken to enhance the quality, safety, costs, access, and innovation.

Safety and quality

Improving and standardising donor selection, testing, and storage is important to ensure the risk of disease and chemical contaminant transmission is reduced for babies receiving DHBM. A consulted subject expert reflected that the most pressing issue for quality and safety is that DHBM should be regulated in each country; this could be at the EU level but it is not necessary as long as regulation is ensured. Other consulted expert stakeholders reflected that establishment of a new EU level advisory mechanism (M4.2) to make recommendations to/advise Member States on when and what BTC requirements should be applied would resolve some of the issues described above, as it would facilitate harmonisation of standards ensuring that all EU citizens have access to the same level of Q&S

The European Foundation for the Care of Newborn Infants requested (i.a.) that the Tissues and Cells Directive endorses recognition, support, and regulation of human milk banks in Europe[30]. Specific recommendations for regulations on milk banking to protect donors and their babies were also given, for example a consulted expert reflected that due to the aforementioned exploitation of donors, as well as the variation between the ethical standards of Member States or even individual milk banks, it would be useful to have a regulatory framework which ensures a common ethical framework. The expert stated it would be difficult to achieve this without having some sort of regulation which brings DHBM in line with other substances of human origin. An ethical framework would help ensure that mothers who provide their milk are not exploited in any way and that donations are voluntary. It should also be ensured that donations are only made of surplus milk, and donors should have the opportunity to explore and understand if milk is truly surplus or if they may need it for their baby later. Donors can often be bereaved mothers of babies who have passed away, and emotional support should be provided in these cases. Finally, according to one consulted expert stakeholder, donors should be made aware of all risks, for example that if they stop donating milk abruptly this may result in blocked ducts which

may cause mastitis and that donating large amounts of milk could impact the mother's nutritional status.

Costs and affordability

A subject expert reflected that costs increased when blood banks became regulated, and similar increases should be expected for milk banks if regulated. However, costs borne by milk banks will help ensure quality and safety and are therefore worthwhile. Other expert stakeholders from an NCA reported that measures which support surveillance of DHBM would be welcomed, despite potential costs and administrative burdens for countries which do not currently have high standards.

A response to the roadmap consultation from The Human Milk Foundation[31] stated that stronger regulation is needed to ensure that the increasing commercialisation and commodification of DHBM does not impose undue pressure on non-commercial enterprises. The NGO noted that such legislation has the potential to introduce costs in the operation of human milk banks, and therefore reduce the number of operational milk banks in Europe. They therefore urged support for milk banks to become compliant with the regulations.

Patient access

The European Foundation for the Care of Newborn Infants requested (i.a.) that the Tissues and Cells Directive (M1.2) ensures equitable access to safe DHBM for preterm, sick, and low birthweight infants as a key theme of the legislation and accounts for the practical specifics of human milk donation[32]. The Oxford-PATH Human Milk Working Group[33] recommended that "ethical principles of equity and fairness, reduction of vulnerability, and respect for autonomy and human rights" should shape the development of DHBM global, regional, and national guidelines and legislation. A response to the roadmap consultation from an EU citizen[34] noted that DHBM is provided not only to infants born prematurely or of low birth weight, but also to a number of other infants who are in medical need of the unique health benefits afforded to those who receive a human milk-based diet. The citizen urged that all Europeans should have equity of access to the choice of the best evidenced options for feeding their infants.

A response to the roadmap consultation from the German Human Milk Bank Initiative[35] voiced support for regulating the use of DHBM but cautioned that regulations should not reduce the availability of DHBM. An expert also acknowledged that EU regulation would increase harmonisation, however it will be important to ensure that regulation is sufficiently flexible to take into account how milk is used differently in different parts of the EU, and regulators should not implement constraints which could mean some Member States are restricted. For example, some milk banks support families in a surrounding community by providing milk to non-hospitalised babies who nevertheless need DHBM, so regulation should not restrict DHBM to only be used for those in a hospital as this could reduce access. Note that BTC regulations do not regulate the use of products.

Mathilde Cohen of the University of Connecticut School of Law (US) recommended that the FDA regulate DHBM to protect consumers using unregulated peer-to-peer milk markets. Cohen recommended that milk from peer-to-peer milk markets should be regulated as food; milk from for-profit companies as a drug; and milk from non-profit milk banks as a human tissue. This would create "a balance between cost and safety", as those less able to comply with strict and costly requirements (peer-to-peer markets) would not have to, yet for-profit companies would still need to conduct clinical trials, applications for approval, and standardised production procedures[36]. In Europe, the Human Milk Foundation recommended that when milk is purchased from an individual (as in most for-profit milk companies), this should follow high regulatory standards, however peer-to-peer milk sharing that is based on altruism should not have to comply with milk bank regulations[37].

Innovation, research and development

An expert stated that DHBM should not regarded as a high-risk novel application, as sharing milk across families is an ancient human practice and milk donation is not an innovative practice.

However, there is currently not much investment or research into other novel uses of human breast milk. A subject expert stated that there needs to be more investment in technologies and equipment used for milk banking. The expert stated that incorporating DHBM into EU law (M1.2) would indicate that it is a valuable resource and would encourage Member States to increase investment.

Expert stakeholders reflected that a tool for sharing and obtaining advice, such as the proposed IT platform, would allow establishments to grow and innovate and will also facilitate mutual recognition.

The European Foundation for the Care of Newborn Infants requested (i.a.) that the Tissues and Cells Directive should include the need for EU-wide research and data collection of human milk donation and use[38]. Similarly, The Oxford-PATH Human Milk Working Group[39] recommended addressing biomedical and social science research gaps to inform global and national DHBM strategies. An expert reflected that there should be more investigation into how milk banks are organised at the national level, as more banks is not necessarily the best approach, and centralised or regional banks (as with blood banks) may be more appropriate. Research and investment of this type may also widen access to milk.

Conclusions

DHBM falls at the borderline of the food legislation and the tissues and cells legislation. Current inconsistencies in how DHBM is regulated across Member States may have negatively impacted on the safety and quality of the milk, the ethical treatment of donors and their babies, and access, innovation, and research related to DHBM. If the measures being considered as part of the revision of the BTC legislation were put in place, this could avoid or resolve some of the long-standing questions on DHBM regulation that Member States have struggled with. In particular, the measures relating to the creation of an advisory body and the introduction of an exchange (IT) platform could help to resolve the issues some Member States have faced. Regulating DHBM within the BTC framework laws and providing dedicated safety and quality rules or guidance, are seen as a way of increasing the safety and quality of DHBM through standardisation of processes relating to the DHBM. Standardisation of standards and the rules concerning voluntary donations could lead to more equitable access. Innovation and development related to DHBM (which has been lacking until the present) could be increased by the proposed measures.

In conclusion, it is appropriate to say that overall there is support for including DHBM in the scope of the future BTC legislation.

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A9.13 – Isolated hepatocytes (hepatocyte transplantations)

The stakeholders consulted for this case study were a representative from a regional transplant centre, a clinician from a university hospital working with isolated hepatocytes, and a legal adviser for a national health board.

Part A: Definition of the borderline issue

Description of the borderline substance/product/application

Advanced liver disease accounts for 3.5% of global mortality[1], and recent data shows that approximately 29 million people in the EU suffer from a chronic liver condition[2]. Liver disease presents a significant health and economic burden and currently Orthotopic liver transplantation (OLT) is the main treatment for liver disease. However, availability of suitable donor organs falls short of clinical demand. As reported in 2019 by EDQM, in the EU-28 there were only 7940 transplants in 2018 of which 2.8% were from living donors[3], and on average approximately 7,300 liver transplants are performed annually in Europe as a whole[4] (with a total of 119,803 between 1988 and 2015[5]). Additionally, for patients eligible for liver transplants, there are also long waiting times: according to data collected by the European Liver Transplant Registry (ELTR) almost half of patients in Europe had a waiting time of more than three months for a transplant due to a worldwide shortages in donor livers[6].

According to representatives from one organisation consulted for this case study, many of the disorders treated by liver transplantation are diseases caused by hepatocyte (liver cell) dysfunction. Hepatocytes isolated from human stem cell populations retain their liver-specific functions and so can help repair liver damage[7] resulting from acute liver failure, chronic liver diseases and several inherited metabolic disorders of the liver[8].

Uses of isolated hepatocytes

Hepatocyte transplantations (HTs) have been proposed as a promising treatment for advanced liver disease and metabolic diseases of the liver[9]. Preclinical and clinical data demonstrates that following transplantation, hepatocytes integrate into the liver architecture, grow and proliferate to repair the damaged liver or replace part of the liver, and provide long-term restoration of the defective biochemical function[10,11]. Isolated primary hepatocytes are widely used for pharmacological and clinical purposes:

1. Isolated mature hepatocytes can be used as a bridge to liver transplantation. Critically ill patients on the waiting list for liver transplantation can receive hepatocytes with the intention to prolong survival until a whole organ is available for liver transplantation. This group also includes very young children e.g. diagnosed with urea cycle disorders at birth in which acute liver transplantation is not feasible due to body size and logistics[12]. Common isolation methods include non-enzymatic cell isolation, in vitro liver enzymatic digestion, and in vivo liver perfusion. During isolation, precautions are taken to reduce cell damage and maintain cell viability and adherence. Hepatocytes are mainly infused through the hepatic portal vein (HPV)[i] or transplanted through the spleen and abdominal cavity. Both freshly isolated and cryopreserved hepatocytes can be used.

[i] HPV is a blood vessel that carries blood from the gastrointestinal tract, gallbladder, pancreas and spleen to the liver.

2. Hepatocytes can be expanded by culture prior to transplantation to act as a treatment for patients with congenital metabolic diseases of the liver (e.g. urea cycle defects, Crigler–Najjar syndrome, glycogen storage disease type I)[13] or for acute liver failure. Following isolation of the hepatocytes, cells can be cultured in vitro in order to achieve the quality attributes required for transplantation. At present, there are many in vitro hepatocyte culture techniques[ii] but techniques continue to be further developed and improved to overcome challenges such as loss of specific functions and apoptosis. After integration, donor cells can proliferate and repopulate the host liver driven by local growth factors and cytokines.

The number of cells needed to compensate for a single gene defect is lower than that for acute liver failure (for the latter, this is estimated to be ~10-15% of the liver cell mass, meaning multiple patients can be treated from one donor liver)[14].

3. Hepatocytes that are grown from stem cells (including cells with induced pluripotency) and may be subjected to genetic manipulation. To overcome the shortage of donor hepatocytes, many attempts have been made to generate functional hepatocytes from multiple types of cells (e.g. induced pluripotent stem cell (iPSC) lines). This advance in the field of regenerative medicine has demonstrated the ability to grow miniature organ-like tissues in the laboratory. For example, Takebe et al. (2013) grew liver buds (organoids) which could be transplanted in a drug-induced mouse liver failure model[15]. Currently, challenges still remain in translating these findings into the clinic.

The advantages of HT compared to OLT include:

- HT is a less invasive and complicated procedure with lower morbidity and mortality[16].
- Cells isolated from a single liver can be used for multiple recipients, and viable hepatocytes can be isolated from livers deemed unsuitable for OLT[17].
- Cells can be cryopreserved and stored until needed (including at short notice).
- Unlike OLTs, HTs are reversible procedures as patients keep their native liver (in the case of graft failure, the patient is returned to their pre-transplant state)[18] and there is the possibility of repeated transplants.
- The cost of hepatocyte transplantation is estimated to be one-tenth the cost of OLT[19], so multiple hepatocyte transplantations could be performed in the same patient in a cost-effective manner[20].

The first experimental attempt of hepatocyte transplantation was in 1976. More than 100 cases of human hepatocyte transplants had been performed globally as of 2015/16 (more recent data is not publicly available)[21]. Between May 2008 and 2016, one of Europe's dedicated HT centres – the Hepatic Cell Therapy Unit (HCTU) in La Fe Hospital in Valencia – had performed nine HTs (5 in adults and 4 in children)[22]. As of July 2013, 16 children had also been treated by HTs at King's College Hospital, with the main indication being children with urea cycle defects[23].

Autologous HTs were first performed in Japan in 10 patients suffering from acute exacerbation of chronic liver disease using autologous hepatocytes from partially resected liver but led to uncertain results[24]. Allogenic HTs are now used more routinely in clinical practice due to improved outcomes and other advantages over autologous HTs. Currently, human primary hepatocytes are mainly derived from the livers rejected for OLT, but the quality of these donor organs can be poor - affecting the yield, viability, and function of

[ii] Examples include cell block technique for cells cultured in adherence, hepatocyte, and non-parenchymal cell mixed culture method, single collagen gel layer culture method, double collagen gel layer (sandwich) culture method, microcarrier adhesion culture method, microcapsule culture method, spherical aggregate culture method, microfluidic channel culture method, and bioreactor culture system.

isolated hepatocytes. Thus, according to one paper by Zhou et al. (2020) alternative sources of liver cells are being actively sought[25].

Overview of the regulatory issues

As outlined above, isolated hepatocytes can be used in different ways. A key concern is therefore ensuring the correct regulatory framework applies when different protocols are being applied to the preparation of hepatocytes for treatment.

Human heterologous liver cells (for infusion) fulfilled the requirement of medicinal product and cell therapy medicinal product as stated by EMEA/412541/2005[26]. However, a Commission survey indicates the following current situation for cells separated from tissue by enzymatic digestion without expansion (including keratinocytes, hepatocytes etc.): nine Member States regulate as tissues and cells; seven regulate as an ATMP; two decide on a case-by-case basis depending on manipulation and use; and three do not have these therapies or do not regulate them[27].

One notable hepatocyte product that has been assessed by the Committee for Advanced Therapies (the CAT) for classification as an ATMP is Heparesc. The CAT classified Heparesc as a somatic cell therapy[iii] (ATMP) due to the culturing process whereby the enzymatic digestion results in single cell dispersion which is known to change the cells characteristics (e.g. surface markers, genome expression profile)[28].

Heparesc

Heparesc, intended for the treatment of urea cycle disorders in paediatric patients, was produced by two developers (Cytonet GmbH and Ci KG) and contained living cells from the liver of a healthy donor (but who's liver had been declared not suitable for OLT according to US national standards[29]). These cells were then manipulated and frozen for long-term storage. The medicine was to be given by slow injection through a tube inserted by a surgical procedure into the HPV.

The applicant submitted an application for Marketing Authorisation to the European Medicines Agency (EMA) for Heparesc on 5 December 2013, through the centralised procedure. In 2015, marketing authorisation was denied as although the clinical safety profile was acceptable, the clinical trial design[iv] and clinical efficacy were judged to be unsatisfactory[30]. This assessment was confirmed in October 2015 during a re-examination procedure[31] involving experts in the treatment of urea cycle disorders[32].

As noted in the CAT's Reflection paper[v] on classification of advanced therapy medicinal products, when the process of enzymatic digestion changes the cell characteristics then it is considered to be substantial manipulation. In an interview with the CAT for the present study, it was noted that the main driver for producing the reflection paper was to make it simpler for stakeholders to understand how classification recommendations are reached. Enzymatic digestion was an area of particular confusion prior to the paper's publication as the CAT were making recommendations which *prima facie* appeared contradictory - some

[iii] This refers to any biological medicinal products that has been subject to substantial manipulation so that their biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, and/or they contain tissues or cells that are not intended to be used for the same essential function(s) in the recipient and the donor.

[iv] During the evaluation procedure, EMA's Committee for Medicinal Products for Human Use had concerns about the design and conduct of the studies, which cast doubt on their results and whether these could have occurred by chance.

[v] [v] European Medicines Agency (2014). Reflection paper on classification of advanced therapy medicinal products. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-reflection-paper-classification-advanced-therapy-medicinal-products_en.pdf

products that were enzymatically digested were classified as non-ATMP, whereas other products were classified as ATMPs.

However, the CAT's classification of Heparesc is only provided as guidance and a different processing methodology may result in a different classification e.g. if the process of enzymatic digestion did not change the characteristics of the cells and they were used for the same essential function they may conclude that it is not an ATMP. The CAT's recommendation only applies to Heparesc (using mature isolated hepatocytes) and not all HT preparations, because different processes will/can result in different classifications.

One comment provided by a stakeholder in response to a reflection paper on the classification of ATMPs suggests some confusion with the classification of HTs as an ATMP: "*it is not completely clear… why cells collected by tissue dissociation e.g. with collagenase would be in some cases minimally manipulated (pancreatic islets) whereas in other cases more than minimally manipulated (e.g. hepatocytes)"*[33]. Therefore, despite the clarification provided in the CAT's reflection paper, there is still some confusion as to when enzymatic digestion constitutes substantial manipulation and when it does not.

Representatives from a Swedish university hospital consulted for this case study stated that previously other centres that had hepatocyte transplantation programmes using both fresh and cryopreserved cells as a transplantation procedure (e.g. King's College London, La Fe Hospital, Valencia and Cliniques Saint-Luc, Brussels) **did not** consider that the preparation of hepatocytes for transplantation met the definition of an ATMP. The representatives from the Swedish university hospital had initiated a research project themselves in 2010 to evaluate HTs as a complementary treatment for acute liver failure and metabolic liver disease. Following the acquisition of local ethics permits to treat patients, they established a 'near-GMP' isolation procedure that was inspected and authorised by the Swedish Health and Social Care Inspectorate (IVO). A few years later – and after two patients with metabolic liver disease had already been treated with HTs – the Swedish Medical Products Agency (MPA) suggested that cell transplants could be ATMP and thus products/procedures should always go through the Swedish MPA. This decision was made following media coverage of another cell transplant project in Sweden.

The university hospital contacted the MPA to enquire on the validity of the previous IVO authorisation, and why isolated hepatocytes were considered as an ATMP, and subsequently to apply for formal classification. The hospital representatives argue that, in the case of their research project, transplantation of isolated hepatocytes is not an ATMP because the hepatocytes are isolated from a donated organ or liver segment via enzymatic digestion, cleaned and transplanted into a specific patient within hours of the isolation. The cells are transplanted into the same site as they were taken from (the liver) and perform the same tasks as before. Importantly, they also argue that the enzymatic isolation of human hepatocytes preserves the original structural and functional characteristics of the hepatocytes (maintaining polarity and all metabolic functions)[34]. However, according to the consulted stakeholders, the Swedish MPA opined that the hospital's procedure was similar to Heparesc and asked the university hospital to send a request to the CAT instead. Representatives from the hospital have not yet submitted this request. Again, the issue appears to revolve around the process of enzymatic digestion and whether it changes the essential function or characteristics of the cells.

As already outlined, HTs are considered safer, less invasive, and more cost effective than transplanting a whole organ. However, confusion as to the appropriate regulatory pathway may be limiting their use as an alternative treatment for liver disease. Another stakeholder from Sweden agreed that the decision to treat HTs as an ATMP has had an impact on patient access. The main issue is that university hospitals use public funding and don't have the resources to meet the full requirements for ATMPs (e.g. funding for and patient recruitment to clinical studies) and this has led to a standstill of the HT programme. The

stakeholder also said: *"We have a transplantation process which has been carried out for many years, and is working… and patients are getting treatment… now if everyone was to consider it an ATMP, it will be many years before you get a product fully approved, which delays treatment".* In the meantime, the stakeholder stressed there have been no major safety or efficacy concerns reported for hospital-prepared HTs performed under the BTC framework. Linked to this, there may be additional issues around affordability if therapy is placed on the market as a commercial product[vi].

One stakeholder explained this also impacts on public sector innovation; there is no incentive to compete with companies who can produce commercial products, particularly given existing donor cell shortages.

Part B: Potential impact of measures proposed to resolve regulatory issues

The following sections discuss how the range of measures proposed to revise the BTC legislation may impact on the regulation of isolated hepatocytes. This case study refers to several measures under Objective 4 (M4.2-M4.4 concerning strengthened clarification processes, M4.5-M4.6 concerning strengthened authorisation processes and M4.7 concerning clinical data).

Safety and quality

Stakeholders were generally in agreement with the proposed measures to strengthen preparation processes in order improve safety and quality (M4.5-M4.6). Some countries already have stringent rules in place for novel cell therapies. For example, representatives from the Swedish university hospital stated that they were already meeting the standards expected under the ATMP regulation regarding the safety/quality of their systems, processes and facilities (described as near-GMP standard and approved by the IVO).

A stakeholder from Spain stated that within their own national legislation, they have a mechanism for the authorisation of investigational tissue and cell products which requires that the development of novel tissue and cell products must demonstrate quality, safety, efficacy with clinical data. The end product is assessed and authorised by the regional competent authority only if it receives a positive opinion from a national committee made up of experts in the field. In the case of hepatocytes, if a clinical team wanted to carry out clinical research for patients experiencing liver disease, they would first need to have the research approved by an ethics committee at the hospital and then seek the approval of a national committee of experts. If a positive opinion is given by the committee the proposal is submitted via a coordinated procedure to the national and regional component authorities (who meet at least 3-4 times a year). The research has to be approved by this coordinated body after which the regional transplant committee can authorise the research project.

Costs and affordability

One stakeholder suggested increased oversight of preparation processes, including the need for clinical evaluation of novel processes (M4.7), might increase costs and therefore needs to be proportionate to the number of patients that data can be collected from (e.g. limited numbers in the case of hepatocytes.

According to stakeholders engaged for this case studies, most centres in Europe perform HTs under the tissue and cell legislation, with cells transplanted immediately when they are ready (and the patient arrives to the hospital at the same time as the isolation starts leading

[vi] The rough cost for a single hepatocyte isolation in the public sector hospital in Sweden was roughly €1000 for materials, with an additional overhead cost (e.g. staff cost and rent). No information was obtainable for the cost of commercial products.

to efficiencies and a superior cell therapy). The same stakeholders added that classification as an ATMP would add tremendous additional need for training, administration, testing, time and cost. Regulation under ATMP legislation would most likely stop all current HTs in Europe and patients would lose this treatment opportunity. Further research and development in this area would be seriously hampered.

Patient access

There is a perception that patient access has been limited by the historic recommendation (from 2005, even before the ATMP regulation was bought in) that human heterologous liver cells for urea cycle disorders were a cell therapy medicinal product eligible for centralised approval (as per EMEA/412541/2005).

Whilst TEs and hospitals have had to or chose to stop preparing HT treatments, no alternative HT therapy has been offered under the ATMP framework. Representatives from the Swedish university hospital suggested the only way to restart their programme would be to continue to regulate it as before given they are working with limited public funding. They considered that a new advisory mechanism to aid in the classification of treatments be helpful. Other interviewees agreed that a mechanism would help to provide homogenous advice and provide a shared perspective from different areas (e.g. SoHO, medicinal products and medicinal devices) which would reduce regulatory confusion for establishments and competent authorities alike (M4.3-M4.4). One stakeholder emphasised the importance of patient representation and involvement in making recommendations about classifications to ensure that the perspective of the patient is considered given that they are the end-users.

Innovation, research and development

There has been a lack of commercial interest in HTs, with Cytonet stopping their activity due to the lack of a commercially viable product. As one stakeholder explained, it is difficult for companies to get organs for isolation of cells and the long-term efficacy of HTs is yet to be realised. The same stakeholder stressed that more clinical research is needed in public sector hospitals.

As this area of treatment evolves it is clear that, for innovators and researchers to be confident in taking their work forward, there needs to be a higher level of certainty as to which regulatory framework their treatment/product will be regulated under. As noted above, the current regulatory situation in Europe with regards to hepatocytes is one of uncertainty and inconsistency which may be hampering innovation and research in this field.

Conclusions

There is a high degree of variability in approaches taken across Member States to the regulation of hepatocytes, although it has not been possible to identify whether identical products are being classified differently or whether the different approaches (classification outcomes) simply reflect different preparation processes. Measures to strengthen coordination/communication between sectors and EU/national bodies (M4/2-M4.4) may possibly have the advantage of having this overview and be in a position to provide guidance on why some HTs are tissue and cell products and others are referred to the CAT.

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A9.14 – Pancreatic Islets

The stakeholders consulted for this case study were a representative from a national transplant organisation and a legal adviser for a national health board.

Part A: Definition of the borderline issue

Description of the borderline substance/product/application

Pancreatic islets (or the islets of Langerhans) are cells which can be prepared from donor pancreas. Pancreatic islets contain insulin-producing 'beta' cells which can be injected into the liver and used as an alternative to pancreas transplantation in patients with type 1 diabetes. Since the first report of islet transplant as a treatment for diabetes (using sheep pancreas fragments in 1894), significant progress has been achieved with the first successful series of islet allografts recorded in 19901.

Using pancreatic islets to restore glucose regulation in type 1 diabetes patients

Type 1 diabetes is an autoimmune disease which results in the permanent destruction of beta cells of the pancreatic islets. Roughly 15 per 100,000 people in Europe have Type 1 diabetes [2] with new cases rising by 3.4% per year across the region[3].

Type 1 diabetes causes reduced insulin which can lead to too much sugar in the blood. Insulin injections and the regular monitoring of blood glucose levels have remained the primary treatment for Type 1 diabetes, though chronic diabetic complications can still develop in a substantial proportion of subjects with diabetes and generally show a progressive worsening over time.

Transplantation of insulin-producing cells can be of assistance in restoring proper glucose regulation. Early attempts did not achieve long-term outcomes; 447 attempts to treat type 1 diabetes with islet transplantation were made between 1974 and 2000, but less than 10% of patients maintained insulin independence after one year[4]. This changed with the Edmonton Protocol, introduced in 2000, which suggested the use of sufficiently large islet transplant mass prepared from two or more donors. This has resulted in the progressive improvement of clinical results as seen in the Collaborative Islet Transplant Registry annual reports[5].

The preparation of pancreatic islets requires a good quality donated pancreas. After receipt of a pancreas in the tissue establishment, islet cell grafts are prepared and characterised[6].

Once isolated, the medical team can infuse the insulin-producing islets through a thin tube, placed in the main vein that transports blood from the intestines to the liver. Once infused, the islets are transported by the bloodstream into the liver, where they begin making the right amount of insulin to regulate the blood sugar.

Europe is considered to be the most active region in the field of pancreatic islet transplantation[7]. However, the application of pancreatic islets remains relatively limited compared to other regenerative tissues. It is suggested their use might increase significantly if research leads to further clinical progress[8,9] and access to donated pancreases of adequate quality can be improved Globally, as of 2012, 1,085 patients had undergone islet transplantation at 40 international sites since 2000 (752 allografts, 333 autografts)[10].

According to a study on the tissue and cells economic landscape, in 2012 there were eight authorised pancreatic islet TEs in the EU. Poland reported 13 donations and 10 transplantations of pancreatic islets cells in this same year[11]. The same study reported that about 35% of all TEs (181) are authorised to process replacement tissues, including pancreatic islets, but that the supply of islets is insufficient (as at least one good quality organ is required, and the availability of organs is limited)[12].

A more recent web-based questionnaire completed by 11 isolation facilities[i] participating at the Ninth International European Pancreas and Islet Transplant Association (EPITA) Workshop on Islet-Beta Cell Replacement in Milan in 2018, suggested there were 445 islet isolations per year over the last 3 years from deceased organ donors and 53 from patients, which resulted in 120 allograft and 40 autograft infusions per year in Europe[13]. The survey also found huge differences among facilities in the procurement and preparation of islets, with different thresholds for the acceptance among facilities[14].

Regarding the preparation of human pancreatic Langerhans' islets intended for use with the same essential function[ii] in recipients as in the donor, the Committee for Advanced Therapies (the CAT) recommended that they should not be classified as an ATMP as they are not substantially manipulated[15,16]. The possible classification of pancreatic islets as an ATMP was discussed by the CAT as part of a presentation on classifications for a workshop on borderline issues organised for the present impact assessment study. According to the CAT, if the pancreatic islets are subject to enzymatic digestion and isolated as functionally intact tissue units or there is scientific evidence that original structural/functional characteristics are maintained, this is not considered substantial manipulation, and therefore the final preparation would not be considered an ATMP.

This recommendation on classification is not directly applicable to other pancreatic beta cell products which may undergo more complex processing[17]. For example, in 2020, the CAT considered the classification of a treatment for type I diabetes mellitus based on insulin producing pancreatic islet cells derived from human embryonic stem cells. They classified this as a somatic cell therapy medicinal product on the basis that it consists of cells that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered; and the claimed mechanism of action is metabolic, based on secretion of insulin by the human embryonic stem cell derived pancreatic beta cells[18].

Overview of the regulatory issues

Products consisting of cells or tissues may be at the regulatory borderline between Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells and the ATMP regulatory framework (Regulation No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation No 726/200).

Member States have previously questioned whether pancreatic islets are covered by Directive 2004/23/EC[19]. For example, at the third meeting of the Competent Authorities on Tissues and Cells (May 2009), it was highlighted that the main 'borderline' issues relate to whether/how pancreatic islets are regulated by Directive 2004/23/EC[20]. In particular, questions were asked by Member States as to whether the organ legislation should apply given they are collected from organs previously intended for transplantation[21].

Regulatory classification of pancreatic islets depends on the manipulation and functional integrity of the islets (including encapsulation)[22]. Some authors have commentated that this criteria for classification can lead to ambiguity for developers using pancreatic islets. For example, Izeta et al. (2016) consider the application of the same essential function criterion as a contradiction because the CAT does not consider subcutaneous implantation of pancreatic islets to be an ATMP, despite the fact that subcutaneous location does not represent the same histological environment as the pancreas[23].

[i] Two from Italy and one each from Belgium, Czech Republic, France, Germany, Netherlands, Norway, Sweden, Switzerland, and United Kingdom.

[ii] Replacement of a tissue as its whole or functional unit of a tissue

Raposio and Ciliberti (2017) point to the confusion around the use of collagenase for enzymatic digestion, which is considered a minimal manipulation when used for pancreatic islets but suggested to be regulated as substantial manipulation for other cells, for example ASCs from adipose tissue[24]. The reasoning presented by the CAT is that enzymatic digestion of a tissue to release cells is considered substantial manipulation, but it is not substantial when the aim is the "isolation of functionally intact tissue units" (e.g., pancreas islets). However, Izeta et al. also highlight the enzymatic digestion of the pancreas to isolate pancreas islets does destroy the pancreas architecture, and that islet transplantation does not restore all the functional interactions that islets previously had in the pancreas tissue[25]. As one stakeholder interviewed for this study described, this could therefore be perceived as an 'artificial distinction'.

The classification of pancreatic islets is important given the various impacts this has on quality, safety, access and cost. It can be argued that the current framework allows for too much variability in terms of quality and safety. For example, one survey of isolation facilities in 2018 found that every islet isolation centre has its own procedures and processes within their centre's unique regulatory processes and procedures, donor organ availability and quality, local processing facility requirements, and financial considerations – with implications for the control of the source material, isolation process, quality of the islets obtained and ultimately the graft outcomes[26].

In contrast with the EU, in the US, allogenic pancreatic islets for transplantation are considered biological drugs by the Food and Drug Administration (FDA)[27]. This is based on the premise that biological characteristics of (allogenic) pancreatic islets may change during 72 hours of incubation in culture media[28]. This means that a biological license application (BLA) approval is required[iii] before transplantation. As outlined in the box below, a number of commentators have argued that this classification has had negative consequences on innovation and patient access. Other authors also note there would be a significant cost impact related to the classification of pancreatic islets as ATMP in Europe. In particular, there are implications of GMP regulations for islet production including costs associated with GMP certification, which can prevent the establishment of new islet transplant centres[29].

Arguments against regulating allogenic pancreatic islets as a biological drug in the Untied States

Witkowski et al. (2021) argues that islets are 'human micro-organs' and encompass the same characteristics as other organs for transplantation . Pancreatic islets remain intact during processing (pre-transplantation) and are not more than minimally manipulated. Post-transplantation, the islets form new vascular connections and integrate with the recipient's circulation. This means they are a form of cellular therapy and not a drug. Elsewhere, Dębska-Ślizień et al. (2019) also highlight that an Islets for US Collaborative[iv] trial found that biological properties and in vivo function of human islets are not significantly affected by the 72 hour incubation period and so there is no need to *"regulate allogeneic human islets as restrictively as a biological drug"*[30].

Witkowski et al. provide several other arguments against the regulation of pancreatic islets as biological drugs in the US[31], for example:

[iii] A BLA is required if islets are for allogenic use between unrelated people. Under Section 361 of the Public Health Service (PHS) Act, BLAs are not required for autologous transplant cases or if islets are for allogenic use in first- or second-degree relatives. However, if islets are used between unrelated people (allogeneic transplant), BLA and drug related regulations (Section 351, PHS Act) are required by the FDA.

[iv] The Islets for US Collaborative comprises more than 50 medical experts and leaders in the fields of transplantation and diabetes from leading US academic institutions who have longstanding concerns about the regulatory status of islet transplantation in the US (www.isletsforus.org).

- **Safety and quality:** Drug manufacturing regulations do not provide appropriate regulatory oversight of patient care and clinical outcomes.
- **Costs:** US academic transplant centres – which have successfully processed human islets for transplantation in clinical trials without a BLA – are not in a position to sponsor a BLA or meet financial and legal BLA demands.
- **Ethics:** It cannot be considered ethical to commercialise human islets for transplantation, especially when this is deemed unethical (and even unlawful) with other organ transplantation procedures (e.g. kidneys).

Dębska-Ślizień et al. argue that currently pancreatic islets cannot be offered as a standard of care to patients in need in the US[32]. Likewise, Witkowski et al. (2021) estimate the number of patients treated with islet transplantation dropped to only a few per year nationally (from 176 transplants between 1999 and 2005 and 123 between 2006 and 2010, to 84 between 2011 and 2015 and just 11 between 2016-2019)[33].

Furthermore, Dębska-Ślizień et al. draw comparisons between the 'over' regulation of islet transplantations in the US compared to regulation as a tissue for transplantation in Poland (under the authority of Poltransplant and the National Center of Tissue and Cell Banking[v]). According to the authors, this ruling *"enabled more rapid clinical development while maintaining the quality of the islet product and the efficacy of the procedure"*[34]. This is evidenced by the Polish Ministry of Health approving islet transplantation (both from allogenic and autologous sources) as an alternative to pancreas transplantation and as a standard-of-care procedure fully reimbursed by the Polish National Health Fund in 2011, as well as the opening of a second islet transplantation centre in Poland in 2018 (Medical University of Gdansk[vi])[35].

Part B: Potential impact of measures proposed to resolve regulatory issues

The following sections discuss how the series of measures proposed to revise the BTC legislation may impact on the regulation of pancreatic islets. This case study refers to several measures under Objective 4 (M4.2-M4.4 concerning strengthened clarification processes, M4.5-M4.6 concerning strengthened authorisation processes and M4.8 concerning sharing of data on authorisations between Member States).

Safety and quality

As already noted, isolation facilities follow a number of varying procedures and processes within different framework for quality management and demonstration of efficacy. To address this, one stakeholder commented that increased oversight of new/novel preparation processes (M4.5-M4.6) would help ensure that all centres have adequate standards in place, or the infrastructure needed, to ensure isolation processes are safe, efficacious and of good quality.

Despite the success of islet transplantation, as already noted widespread utilisation of the procedure remains hampered by the shortage of good quality donor pancreas.

Costs and affordability

One stakeholder considered that if there is only one body (e.g. The CAT) responsible for classifying products which fall at the borderline of various regulatory frameworks, there is a potential for bias (towards the medicinal products classification) which could ultimately affect the affordability of a product. This point was addressed by the CAT representatives

[v] Poland's first clinical islet allotransplantation took place in 2008

[vi] In its first year, the centre already performed five successful islet isolations and transplantations

interviewed, who stated they have very clear, objective and well-communicated basis for making decisions on borderline products. Nonetheless, having a coordination mechanism in place or the basis for more collaboration (M4.2-M4.4) would help to ensure the appropriate regulatory pathway is followed from the outset.

Patient access

One stakeholder considered that measures to strengthen the islet isolation process (M4.5-M4.6) would help to provide greater patient access to islet transplantation due to increased standardisation and harmonisation, permitting cross-border exchange and acceleration in countries where there is currently limited treatment of this kind available for people with type 1 diabetes.

Innovation, research and development

One stakeholder commented that there is a perceived lack of confidence from the medicinal products sector in TEs, despite the volume of pancreatic islet transplants they prepare and the associated low level of serious adverse reactions and events that result. Having a cross-sector mechanism or committee which brought together experts from across all the interconnecting areas of healthcare, science and regulation where substances of human origin are used (i.e. BTC transplants/transfusions , medicinal products and medical devices) (M4.2-M4.4) would help to increase confidence, with implications for further research and development (e.g. more joint working between stakeholders). Additionally, it would contribute to homogenous classifications and would make it clear what regulatory pathway should be followed.

One stakeholder explained that the measure relating to collecting information that comes from authorising novel process at an EU level would be a good idea, as long as data protection could be managed well (M4.8). This would be helpful to promote and develop techniques, and create opportunities for meaningful multicentre clinical studies.

Conclusions

Although there is now little regulatory uncertainty within the EU as to where islets fall in terms of regulation this case study highlights how fine the line can be between when a product is classified as an ATMP or as a BTC product, resting as it often does on disputed distinctions, such as the debate with regards to ‘enzymatic digestion’ and when it constitutes ‘substantial manipulation’. This debate continues despite the CAT’s reflection paper which aimed to clarify when certain processes (e.g. enzymatic digestion) either remained minimal manipulations or moved into substantial manipulations. So, whilst there may be regulatory certainty, the premise upon which the certainty rests are frequently contested both in relation to islets as well as other borderline products such as keratinocytes or hepatocytes. Similarly, the processes for isolating islets are ‘complex’ but not considered to be ‘substantial’ – clarifying the differences between novel, complex processes and processes that are substantial would perhaps increase understanding of how classifications are made.

Furthermore, the situation in the US, where allogeneic islet transplants are regulated under the drugs regulations, illustrates that there may be a causal link between the regulatory framework into which a product is placed and the on-going availability and affordability of the product.

In the final analysis, even where there is regulatory certainty there is not necessarily consensus or a good understanding of how a classification has been arrived at when viewed alongside other seemingly similar products that have been classified differently. Having a cross sector mechanism tasked with providing guidance on the regulatory status of novel or complex BTCs is viewed by many respondents to the consultation as well experts interviewed as part of this study, as a way of exploring and addressing many of these on-going discussions around classifications and the rationale that underpins them.

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A9.15 – Platelet-rich plasma

The stakeholders consulted for this case study were a group of representatives from the industry (medical device companies), as well as experts from an EU institution.

Part A: Definition of the borderline issue

Description of the borderline substance/product/application

Platelet-rich plasma (PRP) is derived from a medical procedure normally performed in an operating theatre or other clinical setting whereby blood is collected from a patient and the PRP is separated out through centrifugation. The PRP is then re-injected into the same patient at site of treatment e.g. for orthopaedic use into the muscles or tendons[1]. It is an autologous point of care/bedside treatment that does not involve a blood establishment as defined in Directive 2002/98/EC. The cost of treatments in the EU could not be found, but it has been indicated in the US that the cost of a PRP treatment was between $500–$2500[2].

Uses of PRP

PRP is used for a wide range of indications, including in cosmetic treatment and sports medicine (orthopaedics). It has been noted that the goal of PRP treatments are not always clearly defined[3] and as a result, treatment outcomes are not always clear.

It has been estimated that PRP is used most in **Orthopaedics (40%)**, 19% in **General Surgery**, 3% in **Neurosurgery**, 18% in **Other** cases, and 10% in **Cosmetic** procedures[4]. Within orthopaedics, a survey among the German "Working Group for Clinical Tissue Regeneration" of the German Society of Orthopaedics and Traumatology[5], indicates that the most common indications for PRP were **tendon pathologies**, **osteoarthritis**, **muscle injuries** and **cartilage damage**.

Platelet-rich fibrin (PRF) is a second-generation platelet concentrate whereby fibrin matrix is polymerised in a tetra molecular structure, with incorporation of platelets, leucocytes, cytokines, and circulating stem cells. It is commonly used in **dentistry**[6]. PRF is also of interest to the present case study as it is derived from PRP. In terms of cosmetic use, PRP has been used in a "vampire facial" or "vampire lift" whereby PRP is injected to improve the texture and regeneration of the skin[7]. One industry stakeholder interviewed for this case study also reported that PRP is starting to be used for improving hair regrowth, without much if any evidence of efficacy. This is being done in clinics in i.a. France, Latvia, UK and the US[8].

2016 research from Transparency Market Research[9] indicated that Europe was the second largest share of the PRP market, following North America. The authors stated that key trends in PRP were a rise in demand for non-invasive cosmetic procedures, changing reforms and regulations in the cosmetic surgery industry in Europe, and the changing face of the cosmetic surgery industry in Asia Pacific. The top two drivers of these trends were increasing incidences of orthopaedic and sports injuries, and a rising number of cosmetic surgical procedures, and the top two restraints were the high cost of products and therapy, and the threat of therapy failure in some cases. A presentation by a key expert from the industry suggested that some key countries in Europe in which PRP is used are the Republic of Ireland, followed by the UK , Germany, Italy, and Spain[10].

The German Working Group for Clinical Tissue Regeneration regarded therapeutic PRP application as useful (89%), possibly even more important in the future (90%), although qualitative explanations of why this will be the case were not provided[11].

An analysis from 2019 estimated the global PRP market would reach $540.31mn by 2025, driven by sports injuries, androgenic alopecia patients, and the increasing use of PRP[12] for

these and other indications. A more recent analysis estimated the global PRP market at $476.1mn in 2020 and suggested it would expand at a compound annual growth rate of 12.0% from 2021 to 2028[13].

Overview of the regulatory issue

There are three main drivers of legal uncertainty related to PRP: the scope of the blood legislation, interplays with medical devices, and the lack of clarity about eventual use.

The scope of the current blood legislation has caused some issues related to PRP, as it may be too strict. The blood legislation only includes blood intended for transfusion, and excludes procedures which are part of the same surgical procedure. PRP is produced in hospitals or medical settings using a medical device, but there is legal uncertainty in terms of which legislation(s) should apply. In a meeting of Competent Authorities on Blood in 2012[14], the attendees discussed the question Ireland had raised at the previous meeting about if the safety and quality standards set up by Directive 2002/98/EC should be applied to this procedure, in particular regarding collection and testing. The relevant characteristics of PRP were that it is not intended to replace a lost volume of blood, it is a single-step autologous procedure without storage, yet the final product could be considered to have undergone processing. At this meeting, most Member States felt PRP does not fall under EU blood legislation.

At a subsequent meeting in 2012[15], the Commission indicated that PRP could fall under the scope blood directive as it applies "to the collection and testing of human blood and blood components, whatever their intended use…", however Member States replied it would be difficult in practice to ensure PRP complied with the 2002 blood legislation. This was reiterated at a meeting in 2013[16]. In a meeting in 2016[17], Denmark noted that PRF falls on a borderline, as it is a blood component that is used for purposes other than transfusion. In this meeting, it was determined that the collection and testing of PRF is covered by the EU blood legislation, however it was unclear which legal requirements apply “for the rest of the process”, presumably meaning the stages or processing and preparation following collection and testing. PRP is autologous, and is excluded from Tissues and Cells regulations through the same surgical procedure exemption. At a later meeting in 2019[18], a delegate from Denmark noted that due to divergent national approaches, the subject should be addressed further. An interviewee reported that the main regulatory issue with PRP is that it falls between regulatory gaps due to the confusion over the “whatever their intended use” clause in Article 2 of the Blood Directive and it is therefore an issue of scope.

The second driver of uncertainty is the interplay or potential overlap with medical devices, as PRP may represent a combination of a blood product and a medical device. The previous BTC evaluation study noted that in general for bedside devices which manipulate BTC, it is not clear whether the use of these medical devices is subject to the EU blood legislation and/or the EU Medical Device Regulation (Regulation 2017/145) as Directive 2002/98/EC only defines standards for collection and testing, whatever the intended purpose[19]. Further, the medical device regulation does not ensure the quality and safety (and indeed efficacy) of the BTC product produced. Another interviewee reflected that another area of difficulty is where the responsibility for classification falls, e.g. for medical devices classifications are put forward by the industry. Stakeholders reported that classification methods for BTC are not clear.

Finally, uncertainty related to PRP stems from confusion about off-label and other eventual uses of PRP. The use of substances of human origin in cosmetic products is prohibited by Commission Directive 95/34/EC of 10 July 1995, as well as the Cosmetics Regulation. Therefore, PRP’s cosmetic use provides regulatory difficulties as the cosmetic “vampire lifts” are not standardised and their cosmetic use is not covered by the BTC legislation[20]. The Blood Directive (2002/98/EC) also does not state anything about cosmetic use. Thus, consulted experts in the field reflected that currently, PRP largely falls outside of regulatory oversight. However, if PRP were fully brought under the blood legislation, it would be difficult

to apply collection and testing rules to all orthopaedic surgeons and facilities offering cosmetic procedures. In the US, the FDA has cleared PRP to be used for various orthopaedic indications[21], and PRP is often brough to market through a 510(k) application which implies that the device is 'substantially equivalent' to another previously cleared device[22]. However as clearance does not confer approval, PRP is often offered "off-label" in the US, whereby the professional providing PRP is liable rather than the manufacturers of the device[23].

Current regulatory status of PRP

Due to the lack of clear regulation described above, Member States regulate PRP in varied ways. At the Meeting of the Component Authorities for Human Blood and Blood Components of June 2019[24], the Danish competent authorities presented a short, partial survey indicating divergent national approaches to regulating PRP and PRF: three Member States regulated them under the EU tissues and cells legislation, five under the EU blood legislation, two under the EU pharmaceutical legislation, and three under other regulatory frameworks. Six Member States did not regulate such products. Two journal articles[25,26] and a paper[27] from the Health Council of the Netherlands indicate some further info on different approaches taken at national level:

- In **Italy** (as of 2015[28]), blood components for topical use are considered blood products and are under the responsibility of the Blood Transfusion Service, regardless of the amount, type, and protocol processing of clinical use.
- In **the Netherlands** (as of 2019[29]), autologous PRP does not fall under the regulations for the quality and safety of body materials and blood products, but can be regarded under complex regulations for so-called special need medicine. As a medical procedure, PRP treatment is currently covered by the Special Medical Procedures Act. The Health Council of the Netherlands did not consider this appropriate as PRP is not a case of cell transplantation.
- In **Spain** (as of 2019[30]), PRP was elevated to a pharmaceutical product for human use, which are more strictly regulated than blood-derived products. The Spanish Agency of Medicines and Health Care Products noted however that there is some confusion with this type of autologous product between the pharmaceutical production procedures and the pharmaceutical itself.
- An interviewed expert from the medical devices industry further elaborated that in **Germany** such decisions are taken at a regional level, contributing to poor harmonisation.

In a paper from 2015, Fiorentino et al stated that for PRP, "this lack of homogeneity in the European legal landscape regarding the management of the product obtained from whole blood processing will probably lead the Community legislature to intervene in the near future".

Current consequences of the regulatory issue

In the view of interviewees, the lack of clear regulation means that it is easy for a wide range of practitioners to extract PRP and inject it in various places without much control, which in itself affects the safety and quality of the applications. An expert from the medical devices industry reported that patient safety is not ensured when there is a lack of harmonisation in the application of regulation, as well as off-label use, across the EU. The same expert also reported that if the current regulatory status continues, it could lead to companies pulling out of the market in Europe as it is too difficult and complex to navigate.

Part B: Potential impact of measures proposed to resolve regulatory issues

The following sections discuss the impacts of the proposed measures being considered as part of the revision of the BTC legislation on different issues relating to PRP. Specifically, this study refers to: several measures under Objective 4: M4.1 concerning the same surgical procedure exclusion, M4.2-M4.4 concerning strengthened clarification processes, M4.5-M4.6 concerning strengthened authorisation processes, M4.7 for requiring clinical evidence for innovations/new claims and M4.8 concerning sharing of data on authorisations between Member States. It also considers M1.2 under Objective 1 (change in scope of the blood legislation).

In relation to the measures proposed in the current study, experts reported that compared to the baseline, the measures proposed would support resolution of the borderline issue of PRP (as long as they were enacted in a pragmatic way), as the current framework is not sufficient. The experts felt that resolution must be supported by a combination of various measures, including addressing the same surgical procedure exclusion, improved definitions, improved preparation process authorisation, and establishment of a classification mechanism. It was also considered by expert stakeholders that, for all measures, Option 2 (expert body regulation model) would give more reassurance, ensure flexibility, and drive harmonisation. However, it was noted that this would impose a lot of rigidity on working procedures, and it would be crucial to ensure there are experts available to advise. Issues seen with Option 1 (decentralised regulatory model) included that NCAs may use guidance not originally conceived for a new technology, and that it would impede harmonisation. Option 3 (centralised model was seen as not being dynamic enough, and would restrict innovation.

In addition to the measures and policy options proposed by the current impact assessment, some stakeholders proposed other changes which would facilitate resolution of the borderline issues around PRP, e.g.:

- The Health Council of the Netherlands has recommended “encouraging solid, scientifically founded guidelines for the application of PRP so that quality monitoring can take place” and addressing shortcomings in legislation at the EU level[31]. Note that PRP is at present included in the EDQM Tissues and Cells Guide[i]. This is linked to M4.5-4.6, which under Option 2, could see the GAPP Joint Action methodology implemented (use of EDQM monographs to strengthen preparation processes).
- A group of representatives from the medical device industry recommended that there should be a standard whereby if a substance or product containing cells is potentially borderline, it should by default fall under one legislation: the BTC legislation, which would provide the initial and basic quality and safety needs. A product should only be assigned to another piece of legislation when it can be clearly fitted there, which can be clarified through the implementation of bettering coordination measures (M4.2-M4.4).

Safety and quality

Some interviewees reflected that any sort of control measure, such as those proposed as part of the impact assessment, will only be to the benefit of control and safety for patients, as long as they do not restrict access. Specifically, removing the same surgical procedure exemption (M4.1), implementing risk assessments on novel processes (M4.5-M4.6), and requiring clinical evaluation of high risk novel products (M4.7) were seen by an expert

[i] A stakeholder interviewed for this case study noted that PRP was originally going to be covered in the EDQM Blood Guide, however, at some point it was taken on by the Tissues and Cells Guide. The stakeholders reported that this may have been because the clinical applications of PRP such as cosmetic use and for knee injuries are more under the competence of the Tissue and Cell Guide experts.

stakeholder from an EU institution as having scope to positively impact the QA and safety aspects – as long as a proportionate approach was taken with patient safety in mind.

Some expert stakeholders were concerned about the measures relating to the development of advisory committees or mechanisms to make regulatory clarifications and decisions (M4.2-M4.6). It was explained that if there are multiple such committees across the pharmaceutical and BTC fields, there will need to be an overarching structure which clarifies which committees supersede the others, or alternatively there could be one single committee with diverse backgrounds which could cover all the topics in the area. Another expert from the medical devices industry also felt an overarching committee could be useful, however it would be crucial to ensure that there are equal inputs from the relevant fields. Also related to the committees, it was reflected by several experts across bodies that a mechanism which could provide a binding decision as is the case with medical devices rather than solely advice would be preferable.

An expert recommended that as the EU Medical Device Regulation 2017/745 regulates both contact lenses for vision and contact lenses for cosmetic purposes (coloured contacts), the BTC legislation should do something similar and include cosmetic indications to ensure the safety and control of cosmetic and aesthetic uses of BTC products such as PRP[32]. However other experts from an EU institution reflected that it could be difficult to apply control measures or measure and control efficacy in cosmetic settings.

Costs and affordability

Costs often relate to administrative burdens of implementing new BTC requirements, therefore it could be expected that when a product moves from being an unregulated BTC to a regulated one, there will be associated costs. The cost of regulatory requirements needs to be justified by the benefits. Regulatory measures need to be chosen carefully to not overburden actors and it is important to recycle/build on what already exists.

An interviewee stated that the package of proposed measures related to Objective 4 hopefully would not decrease affordability of PRP, and that although increasing regulation may impact the cost to patients, enhancing quality and safety is to the benefit of the healthcare system.

Other expert stakeholders from the medical devices industry reflected that measures to strengthen preparation processes (M4.5-M4.6) would increase costs as each establishment will have to evaluate products in their setting. This would be particularly an issue under Option 1 as not all EU countries have a centralised blood establishment organisation, therefore each fragmented establishment would have to create their own sets of validation data. As such the sharing of preparation process authorisations between Member States was strongly supported.

Interviewees reported the direct compliance costs of the measures is difficult to quantify. They replied that administrative burdens and costs to regulators to implement the rules would depend on the policy option adopted. Potential other indirect costs include advisory meetings.

An expert stakeholder from an EU institution reported that if the legislation changes such that registration and inspection is necessary, the NCAs' portfolios will become very large, and this will have large implications from a capacity and regulatory point of view.

Expert stakeholders were supportive for the measures to strengthen the preparation process authorisation, recognising this would be beneficial in improving BTC knowledge by NCAs and applying the same rules and principles across Member States. However, some questioned whether facilities would be required to be BEs in order to have a preparation process authorisation, or if smaller facilities such as beauticians or orthopaedic surgeons (who also make use of PRP products) could have the authorisation without being a BE. It was suggested that the requirements on sites of clinical application could be proportionate to the work they do, while still including some reporting obligations or registration to ensure

vigilance, quality, and safety, including reporting of serious adverse reactions and serious adverse events.

Patient access

Expert stakeholders reflected that introducing a requirement for clinical data (M4.7) should be considered cautiously, as strict requirements for measuring efficacy could impact on patients' access to product such as PRP. The stakeholders were cautious about the ability of smaller paediatric cases of PRP being used to adhere to clinical trial guidelines. It was also reflected that the meaning of the terms such as "novel", "innovative", and "major changes in existing processes" (used to define when a clinical data requirement should be applied) needed to be well-defined in order to ensure a standardised approach to implementing clinical evaluations.

Separately, a group of expert representatives from the industry felt that the IT platform (M4.8) proposed to share information across Member States on preparation process authorisations, as well as other data and/or experiences between BEs would be a huge benefit and lead to greater transparency, especially if it were mandatory and could be publicly consulted. This in turn may lead to improvements in patient access as a result of more products being deemed safe for use and efficient based on the experiences of other Member States.

Considering the measures more widely, an interviewee reflected that the measures may not increase access, but would rather ensure that appropriate access with proven efficacy is ensured as the ultimate goal, as opposed to uncontrolled or unproven access (as is currently the case). This would therefore lead to better outcomes for patients.

Innovation, research and development

Expert stakeholders from an EU institution felt that if a correct balance were struck, the proposed measures would not discourage innovation. It will be important to ensure that measures aren't over-burdensome such that responsible innovation is ensured. The experts reflected that there is always increased burden when those who were not previously regulated are brought under regulations, for example with registration requirements and possibly increased reporting requirements. However, when burdens have increased due to regulation in other areas, the expert reported that over time the level of effort required becomes accepted and considered "commonplace". Another expert from the medical devices industry felt that expert consultation in the establishment of the advisory mechanisms (M4.2-M4.4) is key in ensuring innovative products are placed on the market. Another expert from the medical devices industry reflected that any new legislation in this area should fall under the public health and internal market competencies of the EU, rather than solely public health. This would help open up commercial activities and ensure innovation in the future.

A consulted expert from an EU institution reported that if registration and inspection became necessary, a downstream consequence is that the measures could lead to increased growth and jobs in Europe, presumably due to the need to employ staff to oversee registration and inspection. However, consulted experts also reflected that introducing a requirement for clinical data could negatively impact innovation.

Some expert stakeholders felt that it would be a good initiative to set up an internal BTC advisory mechanism (M4.2), as it would allow the industry to seek advice on the appropriate legislative framework for innovative products in the early stage of their development. It would also be important to involve experts and stakeholders in this advisory task for bringing the expertise and the competency to specific cases. This has reportedly been a strength of the Medical Device Coordination Group (MDCG) and the working groups for the MDR and medical devices.

Conclusions

There is support for including products such as PRP (and ECP) under the scope of a revised BTC legislation. It was agreed that the measures proposed in the revision of the BTC legislation would improve the quality and safety of these products (when compared to the current situation) while still ensuring adequate patient access and innovation. It was acknowledged that special consideration should be given to these 'bedside' or 'point of care' products, with the establishment of a registry and proportionate clinical efficacy requirements (M4.7) being favourable options. It was also agreed that Option 2 would ensure appropriate regulation of these products by involving appropriate experts in setting standards through an authoritative body such as the EDQM.

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A9.16 – Serum eye drops

The stakeholders interviewed for this case study were from a national special health authority in the UK and a regional eye bank. The health authority was selected as it had been providing serum eye drops since 2003 and therefore representatives from this authority were extremely familiar with the regulatory history and context in the EU.

Part A: Definition of the borderline issue

Description of the borderline substance/product/application

Serum, the portion of plasma remaining after coagulation of blood, can be used to formulate eye drops. Unlike artificial tears, blood-derived serum eye drops (SED) contain the biological nutrients found in natural tears to support the maintenance of the tear film[1]. SEDs contain a large number of properties that are present in real tears (e.g. antibodies, albumin, Vitamin A and growth factors), as well as a ten-fold higher total concentration of protein[2]. Serum eye drops can be derived from the patient's own blood (autologous) or from a donor (allogenic). Allogenic sources include adult blood as well as umbilical cord blood (collected from mothers during birth)[3].

The preparation of SEDs begins with the processing of whole blood collected from the patient or donor to separate the serum (via centrifugation). This can be provided undiluted or diluted in saline and added to dropper bottles for the patient to use at home. In the European Union, the blood collected must meet the standards of quality and safety specified in Commission Directive 2004/33/EC of 22 March 2004, which implemented Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components.

The use of autologous SEDs as a treatment was first described in a paper in the 1970s[4] as a method to treat chemical burns of the eye[5]. Its usefulness as a treatment for dry eye disease, specifically related to Sjögren's syndrome, was explored a decade later (with the first paper on this published in 1984)[6] and was increasingly introduced in day-to-day ophthalmic practice alongside other blood-derived products[7]. Over the last 20 years, an increasing number of peer-reviewed papers have been published highlighting the usefulness of SED for other indications including persistent epithelial defect, ocular graft-versus-host disease, recurrent corneal erosion, neurotrophic keratitis, and limbal stem-cell deficiency[8]. However, although interest in and demand for serum eye drops has increased, according to a paper published by Rauz et al (2017), current access to SED is restricted in several countries due to factors such as licensing status and cost[9].

The use of allogenic SEDs as a treatment is more recent, driven by innovation and several other factors negatively affecting the success of autologous SED treatment including: some patients not being able to donate enough of their own blood (e.g. children, those in poor health, those who are unable to donate blood) and requirements for patients in emergencies[10]. A group of interviewed stakeholders representing the UK blood and transplantation service explained that allogenic SEDs were introduced in 2014 (11 years after autologous SEDs began to be provided to patients), with blood collected from male, and regular A or AB donors (to ensure antigen matching between donor and recipient).

Using serum eye drops to treat dry eye disease

Serum eye drops are primarily used to treat dry eye disease. Dry eye disease is characterised by a loss of the tear film and accompanied ocular issues. It is a common disease among the general population; global dry eye disease prevalence is estimated to range from 5% to 50%, with estimates in Europe ranging from 10% to 30%[11].

The occurrence of dry eye diseases increases with age, with one source estimating that prevalence increases from 9% in patients aged 40 and over to 15% in the those aged 65 and over[12], though estimates are higher for women compared to men.

The market for dry eye disease treatments is growing due to the increasing global ageing population and advances in drug delivery techniques: in 2015 the global market was valued at €1bn ($1.2bn)[13] and current market estimates (GlobalData)[14] suggest the dry eye market will reach $11.1bn in 2028 in nine major countries[i].

Treatments for dry eye disease is based on the stage/severity of the disease, and different treatments are available from over-the-counter pharmaceutical eyedrops, to ocular lubricants and contact lenses developed specifically to maintain hydrated eyes, and possibly even surgical solutions (e.g. punctual occlusion) for severe symptoms[15]. The prescription of serum eye drops is recommended for treatment of moderate-severe dry eye disease patients, as they have been proven to support ocular surface renewal, improve mixological defence restore tear film homeostasis[16].

Overview of the regulatory issues

The evaluation of the BTC legislation highlighted that SEDs (both autologous and allogeneic) fall outside the scope of the blood directives (2002/98/EC, 2004/33/EC, 2005/61/EC, 2005/62/EC) (except for collection and testing) as products that are not 'intended for transfusion'[17]. This has led to diverging practices in the EU Member States[18] and variable degrees of restrictions – from SEDs being classified as an unlicensed ("special") medicinal product to "simple" blood component[19] to no clear regulation at all. Results of a survey conducted by the Commission for the evaluation of the BTC legislation (to which 21 Member States responded) confirmed divergence in the regulation of serum eye drops. One participant suggested that products like serum eye drops which are obtained from blood and intended for a purpose other than transfusion (e.g. non-homologous use) falls outside any regulatory framework at EU level as blood cells are completely excluded from the Medicinal Products Directive (2001/83/EC)[20] and Directive 2004/23/EC.

This issue was first raised in a meeting of Competent Authorities on Blood in October 2012, where Finland presented information on a new procedure to manufacture eye drops from whole blood, and further discussed during a meeting of Competent Authorities on Tissues and Cells in December 2012. Uncertainty among Member States had been driven by the:

- **Timing of use:** If blood-derived products are used immediately after centrifuging and separating the blood components e.g. during surgery, they can be considered as part of a clinical act 'or same surgical procedure'. However, in the case of SEDs, the eye drops are generally stored in hospital laboratories for a few weeks before being handed over to the patient for autologous use.
- **Preparation process:** For SED treatments, the preparation process is sometimes performed outside the blood establishment and hospital blood bank (or blood transfusion laboratory) and cannot be easily integrated as a blood establishment or hospital blood bank procedure. Blood is collected in a clinic, transported and may be centrifuged in a hospital pharmacy, then delivered to the patient for (30) daily doses. The patient then stores the doses in a private home freezer.

[i] US, France, Germany, Italy, Spain, the United Kingdom, Japan, China and India

During the meeting of Competent Authorities on Blood in October 2012[21], three Member States explained they regulated these products as pharmaceuticals: UK and Ireland apply GMP Certificate requirements, but a marketing authorisation is not required[ii], whilst Austria has a similar approach. Other Member States take different approaches: according to one stakeholder interviewed for this case study (and as verified by the literature), Germany[22] regulates SED treatment under the medicine's regulation[iii], whereas in the Netherlands it is considered part of the BTC regulations (as the blood banks handle blood-derived products)[iv].

In the following year, during a meeting of Competent Authorities on Blood in April 2013, the Commission stated that eye drops manufactured from whole blood could fall under the Directive as it applies to "the collection and testing of human blood and blood components, whatever their intended use …". However, as described in the minutes of this meeting, the Commission set out it may be difficult in practice to ensure that these procedures comply with the provisions of EU blood legislation, and that changes (to Article II of Directive 2002/98/EC) could be considered during a future revision of the legislation[23]. According to a group of stakeholders interviewed as part of this study and who provide SED treatments in the UK, there has been continued uncertainty since this discussion as the EU law has not been modified to include SEDs within the scope of the BTC legislation – and so Member States continue to have diverging practices.

They also stressed that, from their perspective, SED treatments are not 'borderline substances' – the confusion is about how this is covered by the BTC regulatory framework and the subsequent interpretation of the blood legislation by Member States, as opposed to there being an issue regarding different regulatory frameworks. In this case, the main aspect to resolve is outlining what steps are covered by the BTC legislation beyond collection and testing and whether a product such as SED should fall (in its entirety) within the scope of the future BTC legislation In the remainder of this section, the impacts of having an unclear regulatory pathway for SED treatments is explored.

According to one paper by Bernabei et al. (2017) very few cases of adverse events related to contamination during production or autologous SED treatment have been reported in the literature[24]. However, diverging interpretations of the legislation across Member States can impact the quality and safety of SED treatments due to differences in preparation standards. For example, experts in SED treatments interviewed for this study from the UK explained that the classification of the SEDs as an unlicensed ('special') medicine requires that establishments follow guidelines for good manufacturing practice (GMP), hold a manufacturing license, issued and inspected by the national medicine regulator at two-yearly intervals, and the serum must be prescribed on a patient specific basis by a doctor. However, due to the uncertainty in interpreting the legislation for SED treatments, this approach is not taken uniformly across the EU – and the processing largely depends on the experience of single blood centres according to national or regional BEs[25].A survey of international production methods used to produce serum eye drops organised by the Biomedical Excellence for Safer Transfusion (BEST) Collaborative also highlighted a global lack of consensus on the technical details (e.g. maximal storage time, dilution of the serum, and temperatures) that influence the quality and characteristics of the final dispensed product[26].

[ii] An exemption from the need to obtain marketing authorisation is granted if a physician manufactures or prescribes a specific medical product to treat his own patient on a named basis.

[iii] Both the German Medicines Act (AMG) and the Blood Transfusion Act regulate production, distribution and application, unless it is carried out by one person under controlled conditions in a hospital setting.

[iv] An article by van der Meer et al. from 2015 stated the Dutch blood bank organisation was looking into the possibilities to move to using more allogeneic SEDs, as (GMP) regulations become stricter, making it for hospitals more difficult to provide autologous SEDs.

In a separate paper, one of interviewed stakeholders from the UK writes that "the 'unlicensed' status of serum eyedrops severely restricts how the service can be promoted", impacting patient's access to the SED treatment[27]. Additionally, in a paper by Rauz et al. (2017), it was reported that in the UK (and likely other Member States), under existing regulation there is an absence of robust systems for recording of outcomes or for implementing withdrawal/stopping strategies, which has led to variation in practice and geographical inequity in access to treatment.

Impact of the current regulatory issues on patient access was also discussed during an interview with one expert representing a regional eye bank in Italy. This stakeholder described how they tried to previously set up the option of autologous SED treatments for their patients but had to discontinue this service. Specifically, this was because – under existing national legislation – the serum had to be processed in a blood transfusion centre, rather than the eye bank itself. The stakeholder explained this affected the quality of the product: despite training transfusionists to produce eye drops, they were still not produced in the same way the eye bank would have produced them. The interviewed expert also described the impact on patient access where such an arrangement between an eye bank and transfusion centre has to be in place: a patient with severe medical issues seeing an ophthalmologist would have to make several appointments at a transfusion centre for the donation and collection of the eye drops, each costing the patient time/money. The expert suggested a multi-disciplinary team model (which exists in other countries e.g. The UK) would be more suitable, but this is often not possible to implement in some areas.

Future innovation in this field may be hampered if regulatory issues in this area are not resolved. For example, one interviewed stakeholder noted how currently it would be easier to regulate SED treatments if they were paired with a medical device (e.g. a contact lens or gel as a carrier for the SEDs). Although it was understood by the stakeholder that this would depend on whether the device plays a primary/ancillary role or alters the active properties of the substance, it was argued that this could be open to interpretation by some competent authorities if the fundamental and existing regulatory issues were not resolved.

Part B: Potential impact of measures proposed to resolve regulatory issues

The following sections discuss how the range of measures proposed to revise the BTC legislation may impact on the regulation of serum eye drops. This case study refers to: Measure 1.2 (to bring SEDs under the competence of BTC legislation) and Measures 1.6-1.8 (regarding the definition of rules on safety and quality); the six related measures promoting oversight under Objective 2; and several measures under Objective 4 (M4.1 relating to the same surgical procedure exclusion, M4.2-M4.4 concerning strengthened clarification processes, M4.5-M4.6 concerning strengthened authorisation processes).

Safety and quality

During workshop sessions organised for the study to inform the impact assessment for revising the BTC legislation, stakeholders were asked whether the scope and/or definitions of a revised legislation should include blood products like SEDs that are used for clinical purposes other than transfusion. As Figure 1 highlights below, most respondents (N=84) suggested that the scope of the legislation should be widened so that in addition to donation, collection/procurement and testing, all other steps up to clinical use and vigilance should also be included in the BTC scope (M1.2). An additional comment made during the workshop by a participant was that this would help to reduce existing costs created by needing two authorisations (a BE authorisation for donation and collection and a GMP certificate for processing).

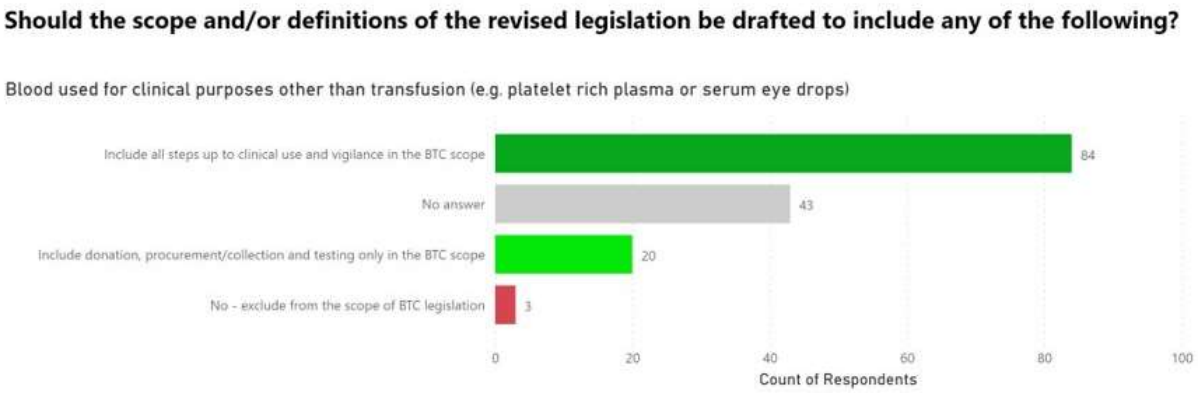

Figure 1: Responses to a workshop question on the scope of the revised BTC legislation

Additionally, workshop stakeholders were asked whether technical rules for safety and quality for SEDs should be included in the scope of the BTC legislation (M1.6-M1.8). From those that responded (N=95), nearly three-quarters (72%) more in favour of such a change for all aspects (from donation to distribution) whilst 27% suggested rules should only be included for donation and testing. Representatives from the UK delivering SED treatments agreed that a joint regulation model (Option 2) for implementing these rules (which was dynamic and informed by experts) would be the best option *"as long as it is in one guide with some monographs, so then we know that it is an accepted BTC product and… so it has input from experts and competent authorities, and it will be clear what it is regulated under".*

In terms of the potential impacts this might have for quality and safety, the same stakeholders pointed out that it would be linked to increased standardisation across services in different Member States – but that in general there would not be a huge change given that the immediate/first steps (donation and testing) are covered under the BTC regulation and SED treatments are well-established. However this could support the tracing of adverse reactions and events associated with the blood component collected (Objective 2).

Costs and affordability

One stakeholder interviewed for this case study explained that in some countries, the lack of clarity around regulating SED treatments means that there is no funding available. It is therefore possible to assume that revising the BTC legislation and clarifying the regulation of products like SEDs would change this, and make it possible to provide the service to more patients.

Interviewed stakeholders from the UK recognised that measures that might increase requirements for pre-clinical work or evaluation will generate a cost (which will need to be paid by the end-users). They provided an example of a clinical follow-up system they are implementing for SEDs; their modelling shows that although this increases the cost of the product by a small percentage (~3%), this increase would be proportionally higher for a smaller service with a lower volume of activity (as they are having to do the same amount of work).

Patient access

As set out earlier, current access to SED is restricted in several countries due to factors such as licensing status and cost. Measures to bring SED treatments under the scope of the BTC legislation (M1.2) and associated measures that can support the clarification of the regulatory pathway for blood-derived products like SEDs (e.g. Those being proposed under M4.2-M4.4) can increase patient access as more services are likely to be able to offer such treatments.

No further information on the impact the measures have on patient access to SED treatments is available.

Innovation, research and development

Feedback provided by the SoHO Vigilance Expert Sub-Group suggests that in general terms all types of substances of human origin should fall under the BTC framework, until they are classified otherwise by an overarching borderline committee or other designated agency.

Interviewed stakeholders from the UK also felt measures to introduce such an overarching body would help to improve transparency and innovation. According to one of the interviewees, in the case of SED treatments, this 'one-stop-shop' model (whereby a developer could a question on regulation to one body and all the relevant advisory bodies could comment and agree on the outcome) would be particularly beneficial as SED treatments become combined with medical devices. However, one interviewee also suggested that some measures might stifle innovation due to increasing barriers to entry (e.g. with the requirement for clinical evaluation and risk assessments) and therefore measures had to be proportionate. There were also additional costs and funding needs to consider, for example, costs of setting up clinical trials and registries.

The measure to clarify the point of care exclusion would also support innovation in novel SED treatments, such as using finger-prick autologous blood to derive eye drops28. In this procedure there are no production steps, and the patient is responsible for obtaining their own blood through pricking their finger with a lancet.

Conclusions

Stakeholders interviewed for this case study felt that, although SED treatments cannot be considered as 'borderline issue', if the measures being considered as part of the revision of the BTC legislation come in place , they will help avoid/resolve some of the long-standing questions on SED treatment regulation that Member States have been struggled with. In particular, the measures relating to the creation of advisory bodies and moving to taking a risk-based approach for authorisation (rather than a definition-based one) will help to avoid the issues some Member States have faced. In conclusion, it is appropriate to say that overall there is support for including SEDs in the scope of the future BTC legislation.

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Annex 10: Monitoring and evaluation framework – indicator tables

Table 1 – Monitoring indicators

#	Specific Objective	Impact type	Indicator		Who would collect the date	Source	Suggested method
1	Increase patient protection from all avoidable risks	Social – public health	Outcome	Public confidence in the safety of BTC system	European Commission	Survey evidence (e.g. panel survey with representative sample at Member State level)	New contract research – citizen survey at agreed frequency (e.g. biennial)
		Social – public health	Outcome	Number of BTC patients recorded as suffering adverse outcomes	European Commission	SARE reporting	Existing NCA reporting mechanisms
		Good governance	Intermediate outcome	Stakeholders (NCAs, BE/TEs) agree that they have access to up-to-date information on quality and safety requirements for patients allowing access and timely updates	European Commission	Survey evidence of relevant stakeholders	Contract research
		Social – public health	Output	Average elapsed time required to update rules/guidance	European Commission	Administrative data + consultations (EU institutions)	Commission analysis
		Social – public health	Output	Frequency of update of rules/guidance (only if Option 2 or Option 3 is adopted)	European Commission	Administrative data + consultations (EU institutions)	Commission analysis
		Social – public health	Output	Source of guidance used by BE/TEs in preparation of risk assessments Frequency of update of risk assessments by BE/TEs (only if Option 1 is adopted)	European Commission	Survey evidence (BE/TEs) Potential use of NCA administrative data	Contract research
		Social – public health (M1.2)	Output	Number of establishments brought into the scope of EU's BTC legislation (e.g. breast milk, FMT)	NCAs / European Commission	Administrative data (NCAs)	Extension to NCA reporting to Commission

#	Specific Objective	Impact type	Indicator		Who would collect the date	Source	Suggested method
		Social – public health (M1.3)	Output	Number of rules that go beyond EU standards which are published by NCAs in an accessible format	NCAs / European Commission	Administrative data (NCAs)	Extension to NCA reporting to Commission
2	Strengthening and harmonisation of oversight among Member States	Social – public health	Outcome	NCA confidence that system provides consistently robust oversight of BTC in all Member States	NCAs / European Commission	NCA survey (ideally repeat survey)	Contract research or extension to NCA reporting to Commission
		Social – public health	Intermediate outcome	NCA independence (institutional, inspector)	NCAs / European Commission	NCA survey	EU audits
		Social – public health	Intermediate outcome	Scale of exchange of BTC among Member States	European Commission	BE/TE survey	Contract research Potential from Objective 5 supply data system
		Social – public health (M2.2)	Output	Number of inspections completed per year for each risk category, for each NCA / Member State For Option 1 only: qualitative research on how NCAs have accommodated the variation on guidance used by BE/TEs and their judgement on risk assessment quality/consistency and implications for harmonisation of standards of patient safety.	NCAs / European Commission	Administrative data (NCAs)	Survey of NCAs or extension to NCA reporting to Commission[247]
		Social – public health (M2.2)	Intermediate outcome	Distribution of BTC establishments by risk category, for each NCA / Member State (and basis of categorisation)	NCAs / European Commission	Administrative data (NCAs)	Survey of NCAs or extension to NCA reporting to Commission

[247] Potentially available from Tissue Compendium for TEs, if data reporting is improved

#	Specific Objective	Impact type	Indicator		Who would collect the date	Source	Suggested method
		Social – public health (M2.3)	Intermediate outcome	NCA judgement on the utility of Commission guidance on oversight	NCAs / European Commission	NCA survey	Survey of NCAs or extension to NCA reporting to Commission
		Social – public health (M2.4)	Output	Number of audits of Member State systems completed by Commission services Outcome of audits of Member State systems completed by Commission services (recommendations)	European Commission	Administrative data (EU institutions)	annual audit report from Commission?
		Social – public health (M2.5)	Output	Number of Member State joint inspections of establishments completed; risk category + authorisation BTC of inspected establishments	NCAs / European Commission	Administrative data (NCAs)	Survey of NCAs or extension to NCA reporting to Commission
		Social – public health (M2.6)	Intermediate outcome	Usage statistics for IT platform launched by Commission (by functional module / function / origin)	European Commission	Application data generated by the IT platform	Commission review
3	Increase protection of BTC donors, and children born from donated sperm, eggs or embryos, from specific risks	Social – public health	Outcome	Number of donor adverse events reported (absolute and compared to number of donors)	NCAs / European Commission	Administrative data (NCAs/ EU)	Use of existing reporting system
		Social – public health	-	Number of MAR procedures / patients Number of children born as a result of MAR and followed-up	European Commission	BTC establishments	Contract research – BE/TE (repeat) survey
		Social – public health	Output	Average elapsed time required to update rules/guidance on donor safety and protection of children born from assisted reproduction	European Commission	Administrative data + consultations (EU institutions)	Commission review or contract research
		Social – public health	Output	Frequency of update of rules/guidance on donor safety and protection of children born from	European Commission	Administrative data + consultations (EU institutions)	Commission review or contract research

#	Specific Objective	Impact type	Indicator		Who would collect the date	Source	Suggested method
				assisted reproduction (only if Option 2 or Option 3 is adopted)			
		Social – public health	Output	Source of guidance used by BE/TEs in preparation of risk assessments on donor safety and protection of children born from assisted reproduction (only if Option 1 is adopted)	European Commission	BTC establishments Potential use of NCA administrative data	Contract research – BE/TE survey
4	Facilitate innovation of safe BTC therapies	Innovation and research	Intermediate outcome	Number of novel BTC applications approved per year by Member State authorities	European Commission	Administrative data	Survey of NCAs or extension to NCA reporting to Commission
		Innovation and research	Intermediate outcome	Number of novel BTC applications approved per year based on evidence available via other Member States	European Commission	Administrative data	Survey of NCAs or extension to NCA reporting to Commission
		Social – public health	Intermediate outcome	Number of therapies/products /establishments impacted by removal of same surgical procedure	European Commission	BE/TE operational data	Contract research
		Social – public health	Intermediate outcome	Number of decisions by new mechanism to advise on interface between BTC and other systems	European Commission	Administrative data	Commission review
		Social – public health	Intermediate outcome	Survey evidence on level of R&D investment and R&D activity in BTC (e.g. citations).	European Commission	Primary research on research activity data (research sector, developers, BE/TCs)	Contract research

#	Specific Objective	Impact type	Indicator		Who would collect the date	Source	Suggested method
		Social – public health	Outcome	Number of patients benefiting from innovative BTC authorised after the legislation was adopted	European Commission	BE/TE operational data	Contract research
		Social – public health	Intermediate outcome	NCA and BE/TE judgement on the clarity of the borderlines to the BTC legal framework	European Commission	Primary research with NCAs, BE/TEs	Contract research
		Social – public health	Intermediate outcome	Number of items raised for discussion among regulators in different regulatory areas	European Commission	Administrative data	Commission review
		Innovation and research (M4.1)	Output	Number of risk assessments conducted on novel processes by BE/TEs	European Commission	BE/TE operational data	Contract research – BE/TE survey
5	Avoid the risk of shortages due to insufficient or unreliable BTC supply	Social – public health	Intermediate outcomes	Number of shortage 'events' per year / Member State / type of BTC	European Commission	Reporting data	Commission review
		Social – public health	Intermediate outcomes	NCA, BE/TE, other stakeholders' confidence in the resilience of the BTC system to supply shocks	European Commission	Stakeholders	Contract research
		Social – public health	Intermediate outcomes	Quantity of BTC exchanged among Member States	European Commission	NCA & BE/TE data	Contract research
		Social - public health	Output	Number of support measures taken by European Commission and NCAs Qualitative research into the impact of the support measures	European Commission	EU / NCA administrative data	Commission review or contract research

Table 2 – Research required to quantify costs

#	Specific Objective	Impact type	Indicator		Source	Method
1	Increase patient protection from all avoidable risks	Economic	Output	Cost to BE/TEs of risk assessment conforming to revised EU legislation	BE/TE research	Qualitative and quantitative research with BTC establishments, during and after implementation
		Economic (M1.2)	Output	Cost to BE/TEs brought into the scope of EU's BTC legislation	BE/TE research	Qualitative and quantitative research with BTC establishments, during and after implementation
		Economic (M1.2)	Output	Cost to NCAs of change in scope of EU legislation	Administrative data (NCAs)	Contract research or extension to NCA reporting to Commission in the period during and after legislation comes into force
		Economic	Output	Change in costs to NCAs of obligation to evaluate BE/TE risk assessments.	Administrative data (NCAs)	Contract research or extension to NCA reporting to Commission in the period during and after legislation comes into force
		Economic (M1.7)	Output	Costs incurred by EU institutions in development and maintenance of rules on quality and safety (only if Option 2 adopted)	Administrative data (EU institutions)	Commission review
2	Strengthening and harmonisation of oversight among Member States	Economic (M2.2)	Output	Change in costs incurred by NCAs in development, application and operation of risk-based approach to inspections	Administrative data (NCAs)	Qualitative and quantitative research with NCAs, during and after implementation Research with NCAs. Data from Member States switching to risk-based approach could be compared to those that already have a risk-based approach.

#	Specific Objective	Impact type	Indicator		Source	Method
		Economic (M2.2)	Output	Change in costs incurred by BE/TEs under risk-based approach to inspections (for each risk category, authorisation type, size of establishment, public/private/not-for-profit status)	BE/TE research	Qualitative and quantitative research with BTC establishments, during and after implementation
3	Increase protection of BTC donors, and children born from donated sperm, eggs or embryos, from specific risks	Economic	Output	Cost to BE/TEs in the MAR sector of risk assessment conforming to revised EU legislation	BE/TE research	Contract research in the period after legislation comes into force.
		Economic (M3.7)	Output	Costs incurred by EU institutions in development and maintenance of rules on quality and safety of donors and children born from MAR (only if Option 2 adopted)	Administrative data (EU institutions)	Commission review
4	Facilitate innovation of safe BTC therapies	Economic	Output	Change in costs incurred by BE/TEs arising from obligation to conduct risk assessments on novel processes	BE/TE research	Qualitative and quantitative research with BTC establishments, during and after implementation
		Economic	Output	Expenditure on clinical trials and other evidence gathering for novel BTC applications	BE/TE & developer research	Qualitative and quantitative research with BTC establishments & developers
		Economic	Output	Revenues / value derived from novel applications assessments	BE/TE & developer research	Qualitative and quantitative research with BTC establishments & developers
		Economic	Output	Change in costs incurred by NCAs arising from the obligation to evaluate BE/TE risk assessments on novel processes	Administrative data (NCAs)	Contract research or extension to NCA reporting to Commission in the period during and after legislation comes into force
		Economic (M4.11)	Intermediate outcome	Public healthcare system expenditure on BTC applications	Public health system data	Contract research

#	Specific Objective	Impact type	Indicator		Source	Method
		Economic (M4.11)	Output	Changes in costs incurred by EU institutions in developing and maintaining guidance on risk assessment for novel processes (Option 2 only)	Administrative data (EU institutions)	Commission review
5	Avoid the risk of shortages due to insufficient or unreliable BTC supply	Economic (M5.2)	Output	Incremental cost to BE/TEs of supply reporting obligations, including set-up costs	BE/TE operational data	Qualitative and quantitative research with BTC establishments, during and after implementation
		Economic	Output	Incremental costs to BE/TEs of contingency planning obligation, including set-up costs Qualitative research with BE/TEs on impact of greater visibility of supply data.	BE/TE operational data	Qualitative and quantitative research with BTC establishments, during and after implementation

Annex 11: Workshop summaries

Eleven workshops were organised between the 27th of April and the 10th of June 2021. The topics of the workshops and dates were agreed with DG SANTE. These events hosted 751 participants in total (including project team and Commission representatives).The workshops attracted a lot of interest from the different impacted/ interested stakeholder groups. Each workshop gathered several stakeholder groups, depending on their interest for the topic being discussed. In some workshops, given the high number of participants/ the nature of topics being discussed, stakeholders were divided in two or more breakout rooms. A complete list of stakeholders can be retrieved from the tables in Annex 6.

Table 1 – Stakeholder workshops: title and objectives

No.	Workshop title	Objectives
1	Refining the Scope of the BTC Legislation	To explore Article 2 of Directive 2002/98 and Article 2 of Directive 2004/23 and any definitions in Article 3 of the same Directives that contribute to the definition of scope. To explore the impact of including, in the scope of the revised legislation, BTC for different intended purposes (transfusion only, any therapeutic purpose, nutritional purposes, cosmetic purposes, autologous /family/partner use, product manufacture under another framework, in vitro research use, biobanking etc.). To make proposals for a scope that would feasibly improve the protection of donors and citizens.
2	Key Definitions - Improvements and Additions	To review the existing definition lists in the basic acts and the implementing Directives and consider any gaps or improvements needed. Participants will be asked to come to the workshop with proposals for discussion. [Note: the VUD definition will not be discussed here but in another workshop. Those definitions defining scope will also be excluded as they will have been discussed in the first workshop.].
3	Strengthening Blood and Plasma Donor Protection	To explore the measures that could be introduced to protect blood and plasma donors more effectively, looking at measures for eligibility for donation, donor health monitoring and long term follow up (if appropriate). To explore the principles that should be defined in legislation and the mechanism for keeping technical level donor protection rules up to date.
4	Better Protection of Donors for Non-Reproductive Tissues and Cells	To explore the measures that could be introduced to better protect donors of bone marrow, peripheral blood stem cells, cord blood and any relevant replacement tissues donated during life. To look at measures for eligibility for donation, donor health monitoring and long term follow up (where appropriate), considering special donation circumstances such as related or paediatric donation. To explore the principles that should be defined in legislation and the mechanism that should be adopted for keeping technical level donor protection rules up-to-date.
5	Better Protection of MAR Donors and Children Born from MAR	This workshop will explore the measures that could be introduced to protect donors more effectively, looking at measures for eligibility for donation, donor health monitoring and long term follow up (if appropriate). The possible impact on donors of genetic testing will be explored. Possible measures to monitor the health of children born from MAR will be explored, looking at feasibility and effectiveness. The participants will explore the principles that should be defined in legislation and the mechanism that should be adopted for keeping technical level donor protection rules up to date.
6	Strengthening Oversight (Inspection, Authorisation, and Vigilance) – Authorities	To explore the oversight principles that should be defined in EU legislation to ensure that oversight is independent, free of conflict of interest, effective and transparent. To examine issues such as national vs regional oversight systems, regulation of EU distribution, import, export, online distribution, promotional activities, 'brokering' services etc. Importantly, it will evaluate the measures proposed in the policy options, including the possibility of introducing an EU level auditing system of Member State oversight systems.

No.	Workshop title	Objectives
		It will also address the legal status of inspector and vigilance officer training, joint inspections, inspection guidance etc.
7	Strengthening Oversight (Inspection, Authorisation, and Vigilance) - Operators	To explore the oversight principles that should be defined in EU legislation to ensure that oversight is independent, free of conflict of interest, effective and transparent. It will examine issues such as national vs regional oversight systems, regulation of EU distribution, import, export, online distribution, promotional activities, 'brokering' services etc. Importantly, to evaluate the measures proposed in the policy options, including the possibility of introducing an EU level auditing system of Member State oversight systems. To address the legal status of inspector and vigilance officer training, joint inspections,
8	Authorising Novel BTC	To assess different dimensions of authorisation procedures for novel BTC to find an appropriate balance between risk mitigation and regulatory burden. Discussions will address, for example, the role of conditional process authorisations, the proportionality of clinical evidence requirements, and the roles of different actors (such as clinical outcome registries, professionals and their associations, authorities, EDQM, and DG SANTE). The deliverables of the GAPP Joint Action will be key workshop inputs.
9	Borderlines with Other Regulated Frameworks: Classification Advice and Interplay	Review of a series of borderline case studies to elucidate the problems and will explore the likely impact of the introduction of an advisory mechanism for classification within the BTC framework. It will also consider how interplay can be improved for the regulation of those substances/products that fall in the scope of more than one framework. This workshop will not address bedside or 'same surgical procedure' BTC as these will be addressed in a dedicated workshop.
10	Regulating Point-of-Care BTC Processing (bed-side and same surgical procedure)	To explore whether existing oversight (medical device certification, hospital governance) is adequate to ensure the safety and effectiveness of these processes. It will consider how to achieve the optimal protection of the recipients of SoHO transplants or transfusions when point-of-care technologies are employed. Some prepared case studies may also be discussed. The Impact of the removal of the 'same surgical procedure' exclusion from the tissues and cells legislation will be assessed.
11	Ethical Principles (Voluntary Unpaid Donation, Prohibition of Profit from the Human Body and BTC Allocation)	To discuss the EU level approach to voluntary unpaid donation, prohibition of profit from the human body and appropriate use of BTC. It will explore the current definition of VUD and the potential for a harmonised definition (considering the recommendations of DH-BIO, Council of Europe and the Nuffield Council of Bioethics). There could be further discussions on ethical concerns in the SoHO sector, addressing themes around priority supply of substances as well as the impact of commercialisation. A focus will be on what could be in EU level legislative principles and whether current definitions should be improved.

A11.1. Authorising Novel BTC – 27 April 2021

The BTC evaluation identified a high level of innovation in the BTC sector and concluded that current requirements for the authorisation of new BTC processes and clinical uses are not adequate. A particular concern was the lack of clear rules for the demonstration of efficacy.The workshop aimed to explore different dimensions of authorisation procedures for novel BTC including the application and authorisation process, the role of stakeholders, the proportionality of clinical data collection requirements and the possible role of clinical outcome registries.

The event was attended by 80 participants from invited organisations, including NCAs (CAs), professional societies representing BTC establishments and clinical users, patient representative organisations and representatives from EU institutions (DG SANTE, HaDEA,

EDQM). The scene was set in plenary by a presentation by the GAPP Joint Action (an EU-funded action with the full title *Facilitating the Authorisation of Preparation Process for blood, tissues and cells*). The 3-year action, involving a large number of Member States, BTC CAs, was coming to the completion of its work. The co-ordinators provided an update on the work carried out to support CAs in improving the assessment and evaluation of novel BTC preparation processes and reflected in Commission policy options for revision of the legislation. Following the presentation, participants were split into 2 breakout groups, one focused on questions related to the authorisation process and the role of stakeholders and the other focused on questions related to the proportionality of clinical data collection requirements and the role of clinical outcome.

The key messages arising from the workshop discussions were the following. There was strong support for (i) referring to the EQQM BTC monographs as an indication that a specific preparation for a specific clinical application is not novel; (ii) requiring the use of a risk assessment tool such as that developed by the EU-funded Euro-GTP II project and (iii) applying the authorisation process and clinical study proposals of the GAPP Joint Action when a preparation process is not covered by an EDQM monograph. Specifically, the GAPP concepts of Minimum Information Preparation Process Dossier, Clinical Follow-up Plan and Clinical Investigation Plan should be reflected in legislation. Clinical outcome registries were seen as useful resources to gather evidence of efficacy, although they can be costly to run. Mixed views were expressed on whether the Clinical Trial Framework (Regulation 536/2014) should be applied for the most novel and highest risk BTC. There was also strong support for having a central IT platform at EU level where information on the authorisation of BTC preparation processes could be shared with, and used by, other Member States.

Participants agreed that strengthening the authorisation of novel BTC processes would bring standardisation, more possibilities for inter-Member State mutual recognition, greater trust and confidence and increased availability for patients to novel preparations with demonstrated efficacy. This outcome would also stimulate further innovation in the BTC field. Concerns were expressed on the level of technical expertise needed for assessment at the CA level, the length of the process and its resource-intensive nature.

A11.2. Regulating Point-of-Care BTC Processing (bed-side and same surgical procedure) – 12 May 2021

Many new ways of processing autologous blood, tissues and cells have been developed for use in hospital, both at the bedside and during surgery, often using medical devices. These procedures are generally not subject to the current BTC legislation and the approaches to ensuring their safety and efficacy vary across the EU. This workshop explored whether existing oversight (medical device certification, hospital governance) is adequate to ensure the safety and efficacy of these treatments. During this workshop, the potential impact of the removal of the tissue and cell ‘same surgical procedure’ exclusion from the EU legislation was considered, along with the potential impact of inclusion of autologous blood components collected and administered at the ‘point of care’.

The event was attended by 58 representatives from invited organisations including NCAs, professional associations, the medical devices industry, hospitals and patient organisations the European Commission and the Council of Europe (EDQM). The plenary scene was set by three presentations of point of care BTC treatments that are increasingly applied: autologous platelet rich plasma used in a wide range of procedures including cosmetic applications, extracorporeal photopheresis carried out with ‘open’ and ‘closed’ devices and autologous fat prepared and used in a variety of ways. Consequently, the participants were split into breakout groups for discussion based on a series of questions.

There was a clear view among participants that BTC used in surgery, or next to the patient, should be regulated by the BTC legislation for both therapeutic and non-therapeutic preparations, if the BTC are processed in any way. The provisions should not, however, be

equivalent to full blood or tissue establishment authorisation requirements but, rather, be limited to an authorisation of the preparation process, with a focus on efficacy. The authorisation requirements should be proportionate to the risks associated with therapy, in line with the proposals of the GAPP Joint Action, although the action had not specifically considered point of care BTC. A suggestion of introducing mandatory registration of such point of care processes was also discussed. It might include activity data and vigilance reporting obligations, along with desk-based preparation process authorisation. It was noted that some of these processes also move the BTC under the Advanced Therapy Medicinal Product legislation and that close regulatory collaboration would be important.

A11.3. Strengthening Blood and Plasma Donor Protection – 17 May 2021

An important shortcoming of the existing legislation is the limited degree of protection afforded to donors, defining only limited donor protection provisions. In both BTC basic acts, reporting of donor reactions is mandated, as part of vigilance, but only when the safety or quality of the donated substance itself has been compromised. This workshop explored the measures that could be introduced to protect blood and plasma donors more effectively. During this workshop, potential measures for eligibility for donation, donor health monitoring and long term follow up were considered, along with the principles that should be defined in legislation and the mechanism for keeping donor protection rules up to date.

The event was attended by 49 representatives from invited organisations including representatives from NCAs for blood and blood components, professional societies representing blood services and clinical users, public and private plasma fractionators and their representative organisations, donor associations, EDQM (Council of Europe) and DG SANTE. The scene was set in plenary by two presentations on how vigilance can help to strengthen blood and plasma donor protection, as well as on donor adverse events and how those should be identified and reported. Following this introduction, participants were split into two breakout groups for discussion based on a series of questions. The groups were divided according to participant interest in either the field of blood for transfusion or plasma for medicinal product manufacture.

There was an overall agreement that measures to strengthen blood and plasma donor protection should be introduced in revised legislation. Monitoring and reporting of donor reactions should be mandated, irrespective of the impact of the reaction on the quality of the donated substance. Policy Option 2 was considered the most appropriate approach to ensuring comprehensive, up-to-date provisions for donor care, while it was felt that high level principles needed to be defined in the legislation (i.e. combination of Policy Options 2 and 3).

There was also a strong support to adopt internationally harmonised definitions for donation eligibility and reactions. Participants considered that donor eligibility criteria should be evidence-based and should be defined to optimise donor care. For plasma in particular (which crosses EU borders at high frequency) harmonisation of donor eligibility ability criteria is desirable, although it was highlighted that local epidemiological differences should be taken into account. Participants felt there should be some form of long-term follow-up undertaken for donors, and that follow-up measures should be evidence based, while respecting the principle of proportionality.

A11.4.– Better Protection of Donors for Non-Reproductive Tissues and Cells – 17 May 2021

An important shortcoming of the existing legislation is the limited degree of protection afforded to donors. This workshop aimed to explore the measures that could be introduced to better protect donors of bone marrow, peripheral blood stem cells, cord blood and any

relevant replacement tissues donated during life. During this workshop, potential measures for eligibility for donation, donor health monitoring and long term follow up were considered (taking into account special donation circumstances such as related or paediatric donation). The workshop also explored the principles that should be defined in legislation and the mechanism that should be adopted for keeping technical level donor protection rules up-to-date.

The event was attended by 60 representatives from invited organisations including representatives from NCAs for tissues and cells, professional societies representing TEs and clinical users, donor associations, EDQM (Council of Europe) and DG SANTE. The scene was set in plenary by two presentations on the reporting of serious adverse reactions and events and its consequences on donors, as well as on how to safeguard cell donors (examining differences between family and unrelated donors). Subsequently, the participants were split into breakout groups for discussion based on a series of questions, depending on whether they were more interested in the tissues sector or the cells sector.

There was an overall agreement among participants that measures that can help strengthen donor protection should be included in revised EU legislation. Reporting of donor reactions should be mandated, irrespective of whether the quality or safety of the donated substance was impacted. Participants considered that there should be a risk-based assessment approach for donors in terms of eligibility. Harmonised eligibility criteria were considered as desirable although participants added that local epidemiological differences need to be taken into consideration.

Participants agreed that it would be more practical to have the high-level donor protection principles in the legislation (Policy Option 3). However, Policy Option 2 was seen as the preferable approach to setting donor care technical standards, allowing for agility and responsiveness and for inclusion of the professional bodies in setting standards. There was considerable discussion on long-term follow-up and health monitoring. It was considered that this should include all types of bone marrow and peripheral blood stem cell donors, and take into consideration the psychological impact on donors as well as the number of donations (to the extent possible – for some types of donations, long-term follow-up might be difficult). Participants also agreed that common approaches for donor care should be evidence-based and specified in the legislation.

A11.5. Better Protection of MAR Donors and Children Born from MAR – 18 May 2021

The current BTC legislation contains important shortcomings affecting the protection afforded to gamete donors as well as children born from MAR (MAR). This workshop aimed to explore the possible measures that could be introduced to improve donor protection, especially for oocyte donors. These measures related to rules on eligibility for donation, donor health monitoring and long term follow up, particularly for oocyte donors and children born from donated gametes or embryos. In addition, the workshop aimed to explore the feasibility and effectiveness of the establishment of donor registries and/or registries to monitor the health of children born from MAR. The principles that should be defined in the legislation and the mechanism through which technical donor and child protection rules should be kept up to date were identified as topics for the discussion.

The event was attended by 51 representatives from stakeholder organisations including tissue and cell competent authorities, the European Society for Human Reproduction and Embryology (ESHRE), the Commission's Vigilance Expert Subgroup r, gamete banks, MAR patient associations including Fertility Europe and paediatric society representatives. DG SANTE was also represented. The workshop was opened with a summary of the proposed policy options and a presentation by DG SANTE of a selection of preliminary results from the online consultations for the Impact Assessment of the BTC legislation. This was followed by three stakeholder presentations to set the scene. The first two, from ESHRE and Fertility Europe, presented recommendations to improve protections for donors and for children

born from donated gametes or embryos from the perspectives of professional and patient associations, respectively. These were followed by a presentation from the Vigilance Expert Subgroup, detailing the most recent vigilance data before presenting steps the Vigilance Expert Subgroup is recommending to improve the vigilance reporting on serious adverse reactions and events and recommendations regarding reporting future reporting requirements.

The key messages emerging from the discussions were the following. There was strong support for a range of measures to improve the protection afforded to oocyte donors (it was clarified that the use of term 'donor' in the context of these discussions applied , including limits on the frequency and number of donations, donor age, and donor compensation. The participants highlighted the need for improved traceability of donations to allow monitoring the number and frequency of donations. A proposal for an EU-level gamete donor registry was supported as a measure to improve protection of both donors and of children born from donated gametes and embryos. There was less support for a registry of children born from donated gametes and embryos, with concerns raised regarding whether this would provide benefits for individual children and might drive misleading associations between children born from MAR and certain conditions. There was a preference for integrating information on the health of these children into broader paediatric registries as an alternative. It was noted that high quality genetic testing of donors is the measure that gives the most effective protection to children born from donated gametes or embryos. There was support for defining a minimum list of genetic tests for donor screening at EU level, although ethical concerns regarding donors' right not to know were also raised. The group offered a range of suggestions to ensure genetic screening did not reduce the donor pool more than necessary, such as testing for conditions based on a threshold of prevalence in a given population and using genetic matching to allow donors with recessive conditions to remain eligible.

A11.6. Strengthening Oversight (Inspection, Authorisation, and Vigilance) – Authorities – 25 May 2021

The evaluation of the BTC legislation identified a need to strengthen the oversight of the BTC sector so that rules are implemented more uniformly, in order that inter-Member State confidence is improved and the cross-border exchange of BTC can take place more smoothly. This workshop aimed to explore the oversight principles which might be defined in EU legislation to ensure that oversight is independent, free of conflicts of interest, effective and transparent. Other measures, that might be taken to improve and standardise the approach to oversight in Member States, and described in the policy options, were also to be explored, including the proposed measure of an EU-level auditing system of BTC competent authorities and a possible move to risk-based inspection scheduling. This workshop aimed to explore these topics from the perspective of the competent authorities. A separate workshop explored the same topics from the perspective of the establishments regulated by this legislation.

The event was attended by 58 representatives from BTC competent authorities and representatives from EU institutions. The workshop was opened with a summary of the proposed policy options and a presentation by DG SANTE of a selection of preliminary results from the online consultations for the Impact Assessment of the BTC legislation. The scene was set by presentations from members of the Vigilance Expert Subgroup and the Inspections Expert Sub-group (both sub-groups of the Commission's SoHO Competent Authorities Expert Group), highlighting where they saw improvements needed. Participants were divided in two break-out groups, one on blood and one on tissues and cells, to discuss the topics in more detail.

The key messages that emerged from the discussions were the following. Policy Option 2 was seen as the approach that would be most effective for achieving strengthened oversight. There was strong support among the participants for referencing Commission

guidance for the conduct of oversight activities in the revised legislation. The guidance would be developed by the competent authority expert sub-groups. Common training activities were also seen as being of key importance. In an online poll of participants, most indicated that the proposed oversight principles should be set out in the revised BTC legislation and would contribute to the aim of strengthening oversight, although a significant number were not sure if this measure would be effective. Participants indicated strong support for the EU to conduct audits of national control systems, and for joint compliance inspections between two or more Member States (as proposed in Policy options 2 and 3). Making inspection reports publicly available was not strongly supported, due to concerns regarding risks of misinterpretation by the public although it was suggested to publish summaries. . The most important concern expressed by the participants was the risk that resources might not be made available to allow them to effectively implement the strengthened oversight provisions likely to be included in revised legislation.

A11.7. Strengthening Oversight (Inspection, Authorisation, and Vigilance) – Operators – 26 May 2021

The evaluation of the BTC legislation identified a need to strengthen the oversight of the BTC sector so that rules are implemented more uniformly, in order that inter-Member State confidence is improved and the cross-border exchange of BTC can take place more smoothly. This workshop aimed to explore the oversight principles which might be defined in EU legislation to ensure that oversight is independent, free of conflicts of interest, effective and transparent. Other measures, that might be taken to improve and standardise the approach to oversight in Member States, and described in the policy options, were also to be explored, including the proposed measure of an EU-level auditing system of BTC competent authorities and a possible move to risk-based inspection scheduling. This workshop aimed to explore these topics from the perspective of the establishments regulated by this legislation. A separate workshop explored the same topics from the perspective of the competent authorities.

The event was attended by 37 representatives from organisations including BTC professional associations, the medicinal product manufacturing industry, patient organisations and the European Commission. The workshop was opened with a summary of the proposed policy options and a presentation by DG SANTE of a selection of preliminary results from the online consultations for the Impact Assessment of the BTC legislation. The scene was set by presentations from representatives of the European Association of Tissue and Cell Banks and the Plasma Protein Therapeutics Association, highlighting where they saw improvements needed. The need for common oversight definitions and for streamlining inspection/audit activities for greater efficiency were raised. Participants were divided in two break-out groups, one on blood and one on tissues and cells, to discuss the topics in more detail.

There was a strong indication from participants that policy Option 2 would best achieve the goal of improving cross-border exchange of BTC. Participants felt that the measures in this policy option would help to improve harmonisation and trust between Member States, although there were some caveats to this. While there was widespread support both for joint inspections by Member States and for a system of EU audits of national oversight systems, concerns were raised about how inspectors from different Member States might expect to see the more stringent requirements applied in their Member State, when inspecting in another Member State. There was broad support for including the proposed principles on independence, transparency in revised legislation, although some doubts were expressed concerning how the implementation of these principles would be ensured. There was generally little support for publishing inspection reports in full due to concerns this would be misinterpreted by the public; however, there was some support for publishing aggregated inspection data.

A11.8. Key Definitions: Improvements and Additions – 1 June 2021

Various developments since the adoption of the BTC legislation have rendered certain definitions (Article 3 of both 2002/98 and 2004/23, as well as definitions in the implementing legislation) unclear, or out-of-date. Other necessary definitions are missing. In other cases, definitions differ between the blood and the tissue & cell Directives without a clear justification. The workshop aimed to review the existing definition lists in the basic acts and the implementing Directives, and to consider any gaps or improvements needed.

The event was attended by 69 participants including the study team, representatives from EU institutions (DG SANTE, EDQM) pharmaceutical industry representatives, medical devices representatives' organisations, NCAs (NCAs for BTC, pharmaceutical products, ATMP, medical devices), BTC establishment representatives (banking and collection of BTC), and representatives of patients/donors' organisations. The scene was set in plenary by a series of short presentations made by a number of stakeholders on key definitions needing improvement or additions: the European Society of Human Reproduction and Embryology (ESHRE), the European Plasma Alliance (EPA), the International Plasma and Fractionation Association (IPFA), the European Eye Bank Association (EEBA) and the European Blood Alliance (EBA). Following the presentations, participants were split into two breakout groups, one with a focus on the tissues and cells sector, and the other on the blood sector.

In both breakout groups, participants raised concerns concerning a number of current definitions, noting for instance that these definitions are either too broad and do not reflect the current reality, or that they need to be either expanded or further clarified. Definitions that were discussed in the group focusing on the tissues and cells sector included: 'tissue establishment', 'tissues for human application', 'processing', 'quality assurance', 'altruistic donation', 'partner donation', 'non-partner donor of gametes' and 'responsible person'. Definitions that were discussed in the group focusing on the blood sector included: 'distribution and transport', 'plasma fractionation', 'manufacturing', 'therapeutic', 'transfusion', 'blood component', 'blood product', 'recovered plasma', 'serious event', haemovigilance', 'inspections', 'establishment' and 'hospital blood banks'.

Participants noted that definitions should be expanded to ensure that they capture all substances of human origin intended for human application.

Participants agreed that there is a need for greater harmonisation. Different Member States use different definitions in their transposed legislation. Participants explained that there are already definitions from the Council of Europe, WHO, etc. That could be used as guidance.

A11.9. Refining the Scope of the BTC Legislation – 2 June 2021

There are several substances of human origin that are not included in the scope of the BTC legislation because of the wording of the definitions included there, even though the EU Treaty provides a mandate to regulate their safety and quality. Examples include human breast milk and intestinal microbiota. There are other substances for which it is unclear which regulations apply (blood or tissues & cells), such as serum eye drops. This workshop aimed to explore Article 2, and any definitions in Article 3, in Directives 2002/98 and Directive 2004/23 that contribute to defining the legislation's scope. It aimed to explore the impact of expanding the scope of the legislation to include substances of human origin for different intended purposes (including transfusion only, nutritional purposes, cosmetic purposes, etc., with the aim of improving protection for donors and citizens to whom these substances are applied.

The event was attended by 86 representatives from organisations including professional and patient associations, BTC and pharmaceutical competent authorities, the medical devices industry, as well as DG SANTE and EDQM (Council of Europe). The scene was set in plenary by two presentations in which the case was made for expanding the scope of the legislation to include new substances, namely faecal microbiota transplantation (FMT) and donor human milk. In both cases, speakers pointed to the need for an EU-wide framework for safety and quality for these substances and to the appropriateness of the BTC framework where donor and recipient safety are the focus. The noted, however, the need to take into account the specificities of these fields and to ensure proportionate regulatory measures. Following this, the participants were split into breakout groups for discussion based on a series of questions.

The key messages emerging from the discussions were the following. There was strong support among participants for expanding the scope of the legislation to include new substances and therapies. FMT, donor human milk and serum eye drops were all seen as substances to be included in the revised legislation, along with several other substances such as platelet rich plasma prepared and used in hospitals . While there was support for expanding the legislation's scope, several participants noted that any new measures for such substances should be proportional to the risks associated with their use and some suggested graded approaches to oversight activities. Participants also supported extending to scope of the legislation to the authorisation of further key players such as donor registries. To better address borderline substances going forward, suggestions were made by participants for the legislation to explicitly reference other frameworks so that ambiguity over which framework covers novel treatments can be avoided. It was clearly shown that for the fields of FMT and breast milk, for instance, there would be new borderlines with the pharmaceutical framework and the food supplements framework when certain processes are applied. In this context, there were calls for refining the definition of "industrially manufactured" to make this term clearer, and to ensure that it is understood in the same way across EU legislation.

A11.10. Ethical Principles (Voluntary Unpaid Donation, Prohibition of Profit from the Human Body and BTC Allocation) – 8 June 2021

Given that all BTC start as a donation from an individual, there are inevitable ethical issues to consider. While these issues fall largely under Member State competence, some impact on safety, quality and sufficiency of supply and are relevant to the EU Charter of Fundamental rights. As such, some ethical principles are mentioned in existing EU legislation. The workshop aimed to discuss the EU level approach to voluntary unpaid donation, prohibition of profit from the human body, appropriate use of BTC and other issues impacting on fundamental rights in the BTC legislation. The focus was put on what could be in EU level legislative principles and whether current definitions should be improved.

The event was attended by 98 participants including the study team, representatives from EU institutions (e.g., DG SANTE, DG JUST), EDQM (Council of Europe) and other organisations active in standards setting, pharmaceutical industry representatives, advanced therapy medicinal products representatives and medical devices representatives organisations, NCAs (NCAs for BTC, Pharmaceutical products, ATMP, Medical devices), BTC establishments representatives (banking and collection of SoHO) and representatives of patients/donors organisations. The scene was set in plenary by a presentation by DG Justice on the EU Charter of Fundamental rights and the need for all new EU legislation to be assessed against the principles in that Charter. This was followed by a DG SANTE presentation on how fundamental rights may be affected by the future update of the BTC legislation. The Council of Europe delivered a presentation on the "Guide on prohibition on financial gain" developed by their DH-BIO Committee. This was followed by a series of short

presentations by stakeholders on their priorities and views on ethical issues related to BTC donation. The European Foundation for the Care of Newborn Infants (EFCNI), Bone Marrow Donors Worldwide, European Blood Alliance (EBA), European Plasma Alliance (EPA), European Patient Organisation for patients with Inflammatory Neuropathies (EPODIN), Fertility Europe and CORESoHO presented positions during this session.

The key messages arising from the workshop discussions were the following. Most participants were in favour of introducing provisions for donor protection, and of ensuring up-to-date and evidence-based BTC technical rules safety and quality; aspects they saw as impacting on fundamental rights. They agreed that introducing measures that support a sustainable supply of critical BTC, as well as increasing harmonisation of BTC safety and quality rules would also increase protection of fundamental human rights of EU citizens. Most participants agreed that the prohibition of making the human body and its parts a source of financial gain as described in the Council of Europe (DH-BIO) recommendation should be specifically referenced in EU's BTC legislation. Participants also agreed that the revision of the legislation should include the principle of informed consent and that donors should be aware of the potential uses of their donations.

A11.11. Borderlines with Other Regulated Frameworks: Classification Advice and Interplay – 9 June 2021

The workshop explored the borderlines between the BTC framework and other EU regulatory frameworks; specifically, the borderline with medicinal products (non-ATMP), the borderline with ATMPs (Advanced Therapy Medicinal Products) and the borderline with medical devices. Online stakeholder consultation had confirmed a finding of the BTC Evaluation that a lack of clarity at the borderlines with other regulated substances represents a hurdle to innovation in the BTC sector. Stakeholders had indicated that this was one of the 3 highest priority issues to be addressed in the revision of the legislation. All three policy options for the revision include a mechanism for improving classification advice.

The event was attended by 105 representatives from: EU institutions, organisations in charge of standards setting, pharmaceutical industry, advanced therapy medicinal products and medical devices organisations, NCAs (NCAs), BTC establishments representatives (banking and collection of SoHO), patient/donor organisations, with a predominance of stakeholders and authorities from the pharmaceutical sector. The scene was set in plenary by two presentations. One on the new EU regulatory framework for medical devices and provisions it includes to promote interaction between authorities in different frameworks for combination products/substances. The second on the European Medicines Agency experience with borderline products, including their collaboration with Heads of Medicines Agencies in the EU-Innovation Network Borderline Classification Group (BLCG). This new informal initiative discusses borderline cases, some of which involve substances of human origin. The participants were then split into 3 breakout groups for discussion on the borderlines between BTC and pharmaceuticals (non-ATMP), between BTC and ATMPs and between BTC and medical devices.

Key messages emerging from these discussions were:

(i) Establishing a BTC advisory mechanism will promote a common approach between BTC authorities. It should work according to clear and agreed inclusion criteria, defined in the revised BTC legislation. While some dissenting views were expressed during the break-out discussion on classification criteria, the majority of participants considered ensuring safety and quality and patient access as the most important considerations when setting these criteria. The BTC advisory mechanism should be multi-disciplinary, with access to a pool of experts across different BTC sub-sectors.

(ii) Clear definitions and good collaboration across regulatory frameworks will be the most effective measures to improve classification mechanisms, particularly given that the number of novel therapies at the borderlines are likely to increase. The new BTC mechanism could

interact with established EU advisory mechanisms in other frameworks. It was suggested that the parallel revision of the BTC and the pharmaceutical legislation offered a rare opportunity to put in place a cross-sectoral EU level mechanism for discussion on the regulatory status of novel substances at the borderlines between regulatory frameworks. Although deciding regulatory status is ultimately a Member State competence, all stakeholders shared the wish to see common guidance made across the EU.

(iii) When substances fall under more than one regulatory framework (e.g. BTC are the starting material for the manufacture of a medicine or a medical device), effective communication on donor requirements for starting materials, traceability, vigilance, etc. between the relevant authorities was seen as essential.

Annex 12: Document and data log

Name of source	Authors / organisation	Date of source
ten years of Co-operation between the European Commission and the EDQM/Council of Europe (contains Blood Transfusion: A Life Saving Measure infographic).	EDQM	2021
20 years of the European IVF-monitoring Consortium registry: what have we learned? A comparison with registries from two other regions	Ch De Geyter et al	2020
2013 Report on the Rapid Alert system for Human Tissues and Cells (RATC)	European Commission	2014 (Data from 2013)
A prospective time-course study on serological testing for human immunodeficiency virus, hepatitis B virus and hepatitis C virus with blood samples taken up to 48 h after death	C Edler et al	2011
A sustainable blood and blood components provision in the EU – Revision of the EU Blood Directives. Position Statement	European Blood Alliance	2021
Additional background information to the Human Fertilisation and Embryology Authority's consultation response to the revision of the EU legislation on blood, tissues and cells (unpublished)	Human Fertilisation & Embryology Authority	2021
Additional Statement of the German Ministry of Health (MoH) and the Paul Ehrlich Institute to the consultation on the Revision of the EU BTC legislation (unpublished)	German Ministry of Health (MoH) and the Paul-Ehrlich	2021
Adequacy of the National Blood Supply: Report to Congress 2020	U.S. Department of Health and Human Services	2020
An EU-wide overview of the market of blood, blood components and plasma derivatives focusing on their availability for patients	Creative Ceutical	2015
Applications for Approval of Clinical Trials per Year (unpublished)	Paul-Ehrlich-Institut	Accessed 2021
ART in Europe, 2016: results generated from European registries by ESHRE	C Wyns et al	2020
Assisted Reproductive Technology Surveillance (CDC) – United States	S Sunderam et al	2020
AVIS statement on the revision of the BTC legislation (unpublished)	Associazione Volontari Italiani Sangue	2021
Banking of corneal stromal lenticules: a risk-analysis assessment with the EuroGTPII interactive tool	E Trias et al	2020
Bioethics Briefing Note: Egg freezing in the UK	Nuffield Council on Bioethics	2020
Blood donor deferral: time for change? An evidence-based analysis	V Borra et al	2016
Blood use in Europe: learning from the impact of COVID-19 - A Blood and Beyond policy briefing	Blood and Beyond	2021
Blood, Tissues and Cells from Human Origin	European Blood Alliance	2013
Blood/plasma activity dataset – preliminary project description February 2021 (unpublished)	J Wiersum-Osselton	2021
Bulgarian Tissue Bank Position paper regarding the tissues and cells legislation (unpublished)	Bulgarian Association of Tissue Banks / European Association of Tissue Banks	2012

Name of source	Authors / organisation	Date of source
Call to Action – Position Paper on ensuring access to plasma derived medicinal products for patients across European Union (unpublished)	EPODIN	Accessed 2021
Challenges of the EU 'tissues and cells' directive	G M Hartshorne	2005
Changing dynamics in the world of plasma: Is Europe ready? Event Report (unpublished)	Friends of Europe	2020
Claims surrounding cord blood stem cells (unpublished)	Office of Compliance and Biologics Quality, Centre for Biologics Evaluation and Research, FDA	2020
Clinical development of ATMPs: hospitals as an exemption?	M Hildebrandt	2019
Commission Staff Working Document on the application of Directive 2002/98/EC on setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC	European Commission	2016
Commission Staff Working Document on the implementation of Directives 2004/23/EC, 2006/17/EC and 2006/86/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells	European Commission	2016
Commission Staff Working Document on the implementation of the principle of voluntary and unpaid donation for human blood and blood components as foreseen in Directive 2002/98/EC on setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC	European Commission	2016
Commission Staff Working Document on the implementation of the principle of voluntary and unpaid donation for human tissues and cells.	European Commission	2016
Compilation of Community Procedures on Inspections and Exchange of Information	European Medicines Agency	2010
Cryos Position Paper on the revision of the Union legislation on blood, tissues and cells (unpublished)	Cryos International	2021
Data on the number of clinical trials authorised (including BTC trials)	Paul-Ehrlich-Institut	Accessed 2021
Database content analysis	Notify Library	Accessed 2021 (live search tool)
DEHP plasticizer and blood bags: challenges ahead	M Lozano and J Cid	2013
Do Egg Donors Face Long-Term Risks?	J E Brody (New York Times)	2017
Donor Selection Criteria Report	SaBTO	2017
EBMT Transplant Activity Survey 2018	European Group for Blood and Marrow Transplantation	2018
Ebola Virus Disease and Substances of Human Origin	SaBTO	2014
ECDC Meeting Report: Assessing the risk of communicable diseases transmissible through substances of human origin	ECDC	2011
ECDC Special Report: HIV and men who have sex with men	ECDC	2017

Name of source	Authors / organisation	Date of source
ECDC Technical Report: Risk of transmission of Ebola virus via donated blood and other substances of human origin in the EU	ECDC	2014
Economic landscapes of human tissues and cells for clinical application in the EU: Final Report	European Commission	2015
E-course on CAR-T Cells (slidepack) (unpublished)	European Society for Blood and Marrow Transplantation	Accessed 2021 (no publication date)
ECP Survey Results on regulating point-of-care processing (unpublished)	ANSM	2021
EDQM survey (B-SCEP Survey Results Anonymised) (Unpublished)	EDQM	Accessed 2021
EEBA letter on 24 hrs testing requirements (unpublished)	EEBA	2010
EEBA statement on stem cell applications in the treatment of ocular disorders	EEBA	2018
ESHRE position paper on the revision of the European Union legislation on Blood Tissues and Cells	ESHRE	2021
EU CCP Platform: COVID - 19 convalescent plasma collection and transfusion	European Commission	Accessed 2021 (live database)
EU market authorisation strategy: lessons from the first 22 ATMP submitted to the EMA	O Ball et al	2019
Europe Platelet-Rich Plasma Market will grow at 7.1% CAGR, to be valued at US$ 75.8 Million By 2027 | Coherent Market Insights	Medgadget	2020
European Blood Alliance - Interactive Map of Bloodbanks	European Blood Alliance	Accessed 2021 (live search tool)
European Health Information Gateway Indicators - Number of hospitals	European Health Information Gateway	2019
European pregnancy rates from IVF and ICSI 'appear to have reached a peak'	ESHRE	2019
European Sperm Bank: 8 recommendations to create a more secure approach to non-partner donation in the EU (unpublished)	European Sperm Bank	2020
Evaluation of the Union legislation on blood, tissues and cells	European Commission	2019
Extracorporeal Photo Chemotherapy (ECP) procedures – Survey on national authorisation practices regarding bed-side procedures in the EU (unpublished)	SANTE	2021
Facilitating the Authorisation of Preparation Process For Blood, Tissues and Cells (various deliverables)	GAPP Consortium	Deliverables dated from 2020-2021
Feedback from the National Marrow Donor Program/Be the Match and Be The Match BioTherapies regarding revision of EU rules	National Marrow Donor Program (NMDP)	2021
For profit bone banks – a contribution to the revision of the BTC legislation from eNOTE (unpublished)	eNOTE	2021
Fortification of Human Milk for Preterm Infants: Update and Recommendations of the European Milk Bank Association (EMBA) Working Group on Human Milk Fortification	S Arslanoglu et al	2019

Name of source	Authors / organisation	Date of source
General Monograph: Phage Active Pharmaceutical Ingredients	MDPI	Accessed 2021
Guide for the implementation of the principle of prohibition of financial gain with respect to the human body and its parts from living or deceased donors	Council of Europe	2018
Hematopoietic cell transplantation and cellular therapy survey of the EBMT: monitoring of activities and trends over 30 years	J R Passweg et al	2020
Hepatitis E and blood donation safety in selected European countries: a shift to screening?	D Domanović et al	2017
Horses for courses: an approach to the qualification of clinical trial sites and investigators in ATMPs	M Hildebrandt	2020
IFBDO-FIODS Position on the revision of the BTC legislation	International Federation of Blood Donor Organisations	2021
Inception Impact Assessment Underlines the Need for Timely Action to Decrease the Reliance on Third Countries for Plasma	Plasma Protein Therapeutics Association	2021
Influence of embryo culture medium (G5 and HTF) on pregnancy and perinatal outcome after IVF: a multicenter RCT	S H M Kleijkers et al	2016
Infographic on organs, blood, tissues and cells in the EU	European Commission	Accessed 2021
Introduction to the Plasma Industry	Marketing Research Bureau	2018
IPFA Position Paper on ZIKA virus and the safety of plasma-derived medicinal products	IPFA	2018
Keratinocyte Production And Use (Queen Astrid Military Hospital, Brussels, Belgium)	Queen Astrid Military Hospital	2019
Key Economic and Value Considerations for Plasma-Derived Medicinal Products (PDMPs) in Europe	T Kluszczynski, S Rohr and R Erns	2020
Key Ethical issues of Donation (unpublished)	Cyros International	2021
Key findings: An EU-wide overview of the market of blood, blood components and plasma derivatives focusing on their availability for patients	Creative Ceutical / European Commission	2015
Letter to the EMA on MSM donor policy (unpublished)	Platform of Plasma Protein Users	2016
Maintaining human milk bank services throughout the COVID-19 pandemic: A global response	Shenker et al.	2021
Making Human Milk Matter: The need for regulation in the European Union Policy Recommendations	European Foundation for the care of newborn infants (EFCNI)	2020
Manifesto for European action on Patient Blood Management (PBM)	International Foundation for Patient Blood Management	2020
Minutes from call about ESHRE project oocyte donor protection (unpublished)	ESHRE CDPTO	Accessed 2021
Minutes from call about EU Research projects on oocyte donor protection (unpublished)	ESHRE CDPTO	Accessed 2021
Monitoring of blood transfusion operations in EU-countries	Erik Stenholm	2015
More than 8 million babies born from IVF since the world's first in 1978	ESHRE	2018

Name of source	Authors / organisation	Date of source
NBF-BIS Letter on 24 hours testing requirement (unpublished)	NBF-BIS Foundation	2010
Newsletter Transplant: International figures on donation and transplantation 2019	EDQM/Council of Europe	2020
Not a crystal ball: Mapping opportunities and threats for the future demand of red blood cells in the Netherlands using a scenario approach	P Sasongko et al	2021
Note des autorités françaises (position statement on BTC revision) (unpublished)	République Française	2021
Notice to stakeholders withdrawal of the united kingdom and EU rules in the field of substances of human origin (blood, tissues and cells, and organs)	European Commission	2018
Notify Library: Adverse Occurrence Search	Notify Library	Accessed in 2021 (live search tool)
Number of BEs (EU27) (unpublished)	ICF (data derived from EDQM, 2015 and Member state population figures)	2021
On the critical assessment of the impact of the recent European Union Tissues and Cells Directive	P M Bhargava	2005
Oocyte donor risks and protective measures – results of a systematic review and document analysis (unpublished)	J Block	2020
Plasma Flows On A Global Level – Impact And Realities In Europe	Marketing Research Bureau	2020
Plasma Supply Management Symposium proceedings. Strasbourg, 29 and 30 January 2019.	European Directorate for the Quality of Medicines & HealthCare (EDQM)	2021
Platelet-Rich Plasma Market: Global Industry, Size, Share, Growth, Trends, and Forecast, 2018–2026	Report Buyer	2018
Position paper on BTC consultation (unpublished)	CERUS	2021
Position Paper: Europe Needs to Collect More Plasma	PPTA	2021
Position statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products	EMA Committee for Medicinal Products for Human Use (CHMP)	2010
Prioritising of bacterial infections transmitted through substances of human origin in Europe	D Domanovic et al	2017
Rapid Alert system for Blood and Blood Components (RAB) Summary of 2015 activities	European Commission	2016 (Data from 2015)
Rapid Alert system for Blood and Blood Components (RAB) Summary of 2016 activities	European Commission	2017 (Data from 2016)
Rapid Alert system for Blood and Blood Components (RAB) Summary of 2014 activities	European Commission	2015 (Data from 2014)
Rapid Alert system for human Tissues and Cells (RATC) and for human Blood and Blood Components (RAB) Summary of 2017 activities	European Commission	2018 (Data from 2017)
Rapid Alert system for human Tissues and Cells (RATC) and for human Blood and Blood Components (RAB) Summary of 2018 activities	European Commission	2019 (Data from 2018)

Name of source	Authors / organisation	Date of source
Rapid Alert system for human Tissues and Cells (RATC) and for human Blood and Blood Components (RAB) Summary of 2020 activities	European Commission	2021 (Data from 2020)
Rapid Alert system for human Tissues and Cells (RATC) Summary of 2014 activities	European Commission	2015 (Data from 2014)
Rapid Alert system for human Tissues and Cells (RATC) Summary of 2015 activities	European Commission	2016 (Data from 2015)
Rapid Alert system for human Tissues and Cells (RATC) Summary of 2016 activities	European Commission	2017 (Data from 2016)
Rapid Alert system for human Tissues and Cells (RATC) and for human Blood and Blood Components (RAB) Summary of 2019 activities	European Commission	2020 (Data from 2019)
Recent market status and trends of fractionated plasma products	M Hotchko, P Robert	2018
Recommendation CM/Rec(2020)6 of the Committee of Ministers to member States on establishing harmonised measures for the protection of haematopoietic progenitor cell donors	Committee of Ministers; Council of Europe	2020
Regulation (EU) 2017/625 of the European Parliament and of The Council of 15 March 2017 on official controls and other official activities performed to ensure the application of food and feed law, rules on animal health and welfare, plant health and plant protection products	European Parliament and the Council of the European Union	2017
Regulation of the European Parliament and of The Council amending Regulation No 851/2004 establishing a European Centre for disease prevention and control	European Commission	2020
Reliance: a smarter way of regulating medical products - The IPRP survey	P Doerr et al	
Report from the Commission to the European Parliament, the Council, the European Economic and Social Committee And The Committee of The Regions 2nd Report on Voluntary and Unpaid Donation of Tissues And Cells	European Commission	2011
Report From the Commission to the European Parliament, the Council, the European Economic And Social Committee and the Committee of The Regions 2nd Report on Voluntary and Unpaid Donation of Blood and Blood Components	European Commission	2011
Report on the Rapid Alert system for human Tissues and Cells (RATC) (2010 – 2012)	European Commission	2014 (Data from 2010-2012)
Report on voluntary and unpaid donation of tissues and cells (2011/2193(INI)) [European Parliament plenary sitting]	European Parliament	2011
Response to article – 'A critical assessment of the impact of the European Union Tissues and Cell Directive (2004) on laboratory practices in assisted conception' by David Mortimer	Saunders, Douglas, and Adrianne Pope	2005
Responsible implementation of expanded carrier screening	L Henneman et al, on behalf of the European Society of Human Genetics (ESHG)	2016
Rethinking blood use in Europe to improve outcomes for patients	Blood and Beyond	July 2020 (updated January 2021)
Revision of the Union legislation on blood, tissues and cells Public consultation factual summary report	European Commission	2021

Name of source	Authors / organisation	Date of source
Risk proportionate approaches in clinical trials: Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use	Expert Group	2017
Roadmap consultation response from Aarhus University Hospital available on the Have Your Say Portal	Aarhus University Hospital	2020
Roadmap consultation response from Agence de la biomedicine available on the Have Your Say Portal	Agence de la biomedecine	2020
Roadmap consultation response from Alliance for Regenerative Medicine available on the Have Your Say Portal	Alliance for Regenerative Medicine	2020
Roadmap consultation response from Anonymous Cord bank available on the Have Your Say Portal	Anonymous Cord bank	2020
Roadmap consultation response from ANSM available on the Have Your Say Portal	ANSM	2020
Roadmap consultation response from Associazione Volontari Italiani Sangue (AVIS) available on the Have Your Say Portal	Associazione Volontari Italiani Sangue (AVIS)	2020
Roadmap consultation response from Associzione Farmaceutici Industria - Working Group on Biotech available on the Have Your Say Portal	Associzione Farmaceutici Industria - Working Group on Biotech	2020
Roadmap consultation response from Blood Transfusion Association available on the Have Your Say Portal	Blood Transfusion Association	2020
Roadmap consultation response from Bristol Myers Squibb available on the Have Your Say Portal	Bristol Myers Squibb	2020
Roadmap consultation response from Bulgarian Drug Agency available on the Have Your Say Portal	Bulgarian Drug Agency	2020
Roadmap consultation response from CD-P-TS / GTS / EDQM available on the Have Your Say Portal	CD-P-TS / GTS / EDQM	2020
Roadmap consultation response from Centrul pentru Inovatie in Medicina available on the Have Your Say Portal	Centrul pentru Inovatie in Medicina	2020
Roadmap consultation response from CNPMA available on the Have Your Say Portal	CNPMA	2020
Roadmap consultation response from Committee for Advanced Therapies (the CAT) available on the Have Your Say Portal	Committee for Advanced Therapies (the CAT)	2020
Roadmap consultation response from Common representation of Substances of Human Origin's (CoRe SoHO) available on the Have Your Say Portal	Common representation of Substances of Human Origin's (CoRe SoHO)	2020
Roadmap consultation response from Cord Blood Association available on the Have Your Say Portal	Cord Blood Association	2020
Roadmap consultation response from CSL Behring available on the Have Your Say Portal	CSL Behring	2020
Roadmap consultation response from Danish Patient safety Authority available on the Have Your Say Portal	Danish Patient safety Authority	2020
Roadmap consultation response from Danish Sperm Bank Alliance available on the Have Your Say Portal	Danish Sperm Bank Alliance	2020
Roadmap consultation response from DON DU SANG LA POSTE ORANGE available on the Have Your Say Portal	DON DU SANG LA POSTE ORANGE	2020
Roadmap consultation response from Dutch Transplant Foundation (NTS) available on the Have Your Say Portal	Dutch Transplant Foundation (NTS)	2020

Name of source	Authors / organisation	Date of source
Roadmap consultation response from ECA ATMP Interest Group available on the Have Your Say Portal	ECA ATMP Interest Group	2020
Roadmap consultation response from EFPIA (European Federation of Pharmaceutical Industries and Associations) available on the Have Your Say Portal	EFPIA (European Federation of Pharmaceutical Industries and Associations)	2020
Roadmap consultation response from Etablissement français du sang available on the Have Your Say Portal	Etablissement français du sang	2020
Roadmap consultation response from EU citizen / patient advocate available on the Have Your Say Portal	EU citizen / patient advocate	2020
Roadmap consultation response from EUCOPE available on the Have Your Say Portal	EUCOPE	2020
Roadmap consultation response from EuropaBio available on the Have Your Say Portal	EuropaBio	2020
Roadmap consultation response from European Association of Hospital Pharmacists (EAHP) available on the Have Your Say Portal	European Association of Hospital Pharmacists (EAHP)	2020
Roadmap consultation response from European Association of Tissue and cell Banks available on the Have Your Say Portal	European Association of Tissue and cell Banks	2020
Roadmap consultation response from European Blood Alliance (EBA) available on the Have Your Say Portal	European Blood Alliance (EBA)	2020
Roadmap consultation response from European Eye Bank Association (EEBA) available on the Have Your Say Portal	European Eye Bank Association (EEBA)	2020
Roadmap consultation response from European Haemophilia Consortium (EHC) available on the Have Your Say Portal	European Haemophilia Consortium (EHC)	2020
Roadmap consultation response from European Hospital and Healthcare Federation (HOPE) available on the Have Your Say Portal	European Hospital and Healthcare Federation (HOPE)	2020
Roadmap consultation response from European organisation for Rare Diseases (EURODIS) available on the Have Your Say Portal	European organisation for Rare Diseases (EURODIS)	2020
Roadmap consultation response from European Patient Organisation for Dysimmune and Inflammatory Neuropathies (EPODIN) available on the Have Your Say Portal	European Patient Organisation for Dysimmune and Inflammatory Neuropathies (EPODIN)	2020
Roadmap consultation response from European Society for Blood & Marrow Transplantation available on the Have Your Say Portal	European Society for Blood & Marrow Transplantation	2020
Roadmap consultation response from European Society of Human Reproduction and Embryology (ESHRE) available on the Have Your Say Portal	European Society of Human Reproduction and Embryology (ESHRE)	2020
Roadmap consultation response from EURORDIS-Rare Diseases Europe available on the Have Your Say Portal	EURORDIS-Rare Diseases Europe	2020
Roadmap consultation response from Fédération Française pour le Don de Sang Bénévole available on the Have Your Say Portal	Fédération Française pour le Don de Sang Bénévole	2020
Roadmap consultation response from Finnish Red Cross Blood Service available on the Have Your Say Portal	Finnish Red Cross Blood Service	2020

Name of source	Authors / organisation	Date of source
Roadmap consultation response from FRANCE - Secrétariat général des Affaires européennes available on the Have Your Say Portal	FRANCE - Secrétariat général des Affaires européennes	2020
Roadmap consultation response from Frauenmilchbank-Initiative (Human Milk Bank Initiative) available on the Have Your Say Portal	Frauenmilchbank-Initiative (Human Milk Bank Initiative)	2020
Roadmap consultation response from Grifols, S.A. available on the Have Your Say Portal	Grifols, S.A.	2020
Roadmap consultation response from ICCBBA available on the Have Your Say Portal	ICCBBA	2020
Roadmap consultation response from ILGA-Europe (the European Region of the International Lesbian, Gay, Bisexual, Trans and Intersex Association) available on the Have Your Say Portal	ILGA-Europe (the European Region of the International Lesbian, Gay, Bisexual, Trans and Intersex Association)	2020
Roadmap consultation response from Inspectie Gezondheidszorg en Jeugd available on the Have Your Say Portal	Inspectie Gezondheidszorg en Jeugd	2020
Roadmap consultation response from International Federation of Blood Donor Organisations (IFBDO/FIODS) available on the Have Your Say Portal	International Federation of Blood Donor Organisations (IFBDO/FIODS)	2020
Roadmap consultation response from International Patient Organisation for Primary Immunodeficiencies available on the Have Your Say Portal	International Patient Organisation for Primary Immunodeficiencies	2020
Roadmap consultation response from International Plasma and Fractionation Association available on the Have Your Say Portal	International Plasma and Fractionation Association	2020
Roadmap consultation response from ISCT EU Legal and Regulatory Affairs Committee available on the Have Your Say Portal	ISCT EU Legal and Regulatory Affairs Committee	2020
Roadmap consultation response from Jagiellonian University available on the Have Your Say Portal	Jagiellonian University	2020
Roadmap consultation response from Johanna Kostenzer available on the Have Your Say Portal	Johanna Kostenzer	2020
Roadmap consultation response from MedTech Europe available on the Have Your Say Portal	MedTech Europe	2020
Roadmap consultation response from Ministerio de Sanidad available on the Have Your Say Portal	Ministerio de Sanidad	2020
Roadmap consultation response from Ministry of Health, Welfare and Sports of The Netherlands available on the Have Your Say Portal	Ministry of Health, Welfare and Sports of The Netherlands	2020
Roadmap consultation response from Ministry of Social Affairs and Health available on the Have Your Say Portal	Ministry of Social Affairs and Health	2020
Roadmap consultation response from Netherlands Donor Feces Bank available on the Have Your Say Portal	Netherlands Donor Feces Bank	2020
Roadmap consultation response from Norwegian Medicines Agency available on the Have Your Say Portal	Norwegian Medicines Agency	2020
Roadmap consultation response from Organización Nacional de Trasplantes (ONT) available on the Have Your Say Portal	Organización Nacional de Trasplantes (ONT)	2020

Name of source	Authors / organisation	Date of source
Roadmap consultation response from Paul-Ehrlich-Institut, Federal Institute for Vaccines and Biomedicines available on the Have Your Say Portal	Paul-Ehrlich-Institut, Federal Institute for Vaccines and Biomedicines	2020
Roadmap consultation response from Pharmabiotic Research Institute available on the Have Your Say Portal	PHARMABIOTIC RESEARCH INSTITUTE	2020
Roadmap consultation response from Plasma Protein Therapeutics Association available on the Have Your Say Portal	Plasma Protein Therapeutics Association	2020
Roadmap consultation response from Polski Bank Komórek Macierzystych S.A. available on the Have Your Say Portal	Polski Bank Komórek Macierzystych S.A.	2020
Roadmap consultation response from Public organisation Tissue Establishment available on the Have Your Say Portal	Public organisation Tissue Establishment	2020
Roadmap consultation response from Regina Maria Banca Centrala de Celule Stem available on the Have Your Say Portal	Regina Maria Banca Centrala de Celule Stem	2020
Roadmap consultation response from Romanian Competent Authority (National Transplant Agency- Cells Department) available on the Have Your Say Portal	Romanian Competent Authority (National Transplant Agency- Cells Department)	2020
Roadmap consultation response from SEVIBE CELLS S.L. available on the Have Your Say Portal	SEVIBE CELLS S.L.	2020
Roadmap consultation response from Spanish Association of Tissue Banks available on the Have Your Say Portal	Spanish Association of Tissue Banks	2020
Roadmap consultation response from Spanish Society of Fertility available on the Have Your Say Portal	Spanish Society of Fertility	2020
Roadmap consultation response from Stichting Sanquin Bloedvoorziening available on the Have Your Say Portal	Stichting Sanquin Bloedvoorziening	2020
Roadmap consultation response from Takeda available on the Have Your Say Portal	Takeda	2020
Roadmap consultation response from Tampere University Regea Cell and Tissue Center available on the Have Your Say Portal	Tampere University Regea Cell and Tissue Center	2020
Roadmap consultation response from Tanya CASSIDY available on the Have Your Say Portal	Tanya CASSIDY	2020
Roadmap consultation response from Terumo BCT available on the Have Your Say Portal	Terumo BCT	2020
Roadmap consultation response from Thalassaemia International Federation available on the Have Your Say Portal	Thalassaemia International Federation	2020
Roadmap consultation response from The Human Milk Foundation available on the Have Your Say Portal	The Human Milk Foundation	2020
Roadmap consultation response from The National Blood Centre available on the Have Your Say Portal	The National Blood Centre	2020
Roadmap consultation response from University / university hospitals Leuven available on the Have Your Say Portal	University Hospitals Leuven	2020
Safety and Quality Standards for E.U. Regulation of Cord Blood and Perinatal Tissue Banking – Letter (unpublished)	Cord Blood Association	2021
Sample report: Blood Screening Market Estimates and Trend Analysis from 2016 to 2028	Grand View Research	2018

Name of source	Authors / organisation	Date of source
Shortage of medicines - how to address an emerging problem	European Parliament	2020
Should young women sell their eggs?	D D La Cruz (New York Times)	2016
SoHO-X feasibility study (currently unpublished)	SANTE	Accessed 2021
Spreadsheet containing info on blood donations per Member State (unpublished)	ICF (data derived from EBA)	Accessed 2021
Statement of the European Society of Human Reproduction and Embryology (ESHRE) on the European Commission proposal of viral screening in assisted reproduction treatments	ESHRE	2009
Statutory Cost Regulation for Official Duties of the Paul-Ehrlich-Institut pursuant to the German Medicinal Products Act (unpublished)	Paul-Ehrlich-Institut	Accessed 2021
Stool for fecal microbiota transplantation should be classified as a transplant product and not as a drug: letter to the editor	J J Keller et al	2019
Study supporting the evaluation of the EU legislation on blood and tissues and cells	ICF S.A. / European Commission	2019
Summary of EU Research projects on oocyte donor protection (unpublished)	ESHRE CDPTO	Accessed 2021
Summary of the 2011 annual reporting of serious adverse events and reactions (SARE) for blood and blood components (data collected from 01/01/2010 to 31/12/2010)	European Commission	2013 (Data from 2010)
Summary of the 2011 annual reporting of serious adverse events and reactions for tissues and cells (data collected from 01/01/2010 to 31/12/2010)	European Commission	2013 (Data from 2010)
Summary of the 2012 annual reporting of serious adverse events and reactions (SARE) for blood and blood components (data collected from 01/01/2011 to 31/12/2011)	European Commission	2013 (Data from 2011)
Summary of the 2012 annual reporting of serious adverse events and reactions for tissues and cells (data collected from 01/01/2011 to 31/12/2011)	European Commission	2014 (Data from 2011)
Summary of the 2013 annual reporting of serious adverse events and reactions (SARE) for blood and blood components (data collected from 01/01/2012 to 31/12/2012)	European Commission	2014 (Data from 2012)
Summary of the 2013 annual reporting of serious adverse events and reactions for tissues and cells (data collected from 01/01/2012 to 31/12/2012)	European Commission	2014 (Data from 2012)
Summary of the 2014 annual reporting of serious adverse events and reactions (SARE) for blood and blood components (data collected from 01/01/2013 to 31/12/2013)	European Commission	2015 (Data from 2013)
Summary of the 2014 annual reporting of serious adverse events and reactions for tissues and cells (data collected from 01/01/2013 to 31/12/2013)	European Commission	2015 (Data from 2013)
Summary of the 2015 annual reporting of serious adverse events and reactions for tissues and cells (data collected from 01/01/2014 to 31/12/2014)	European Commission	2016 (Data from 2014)
Summary of the 2016 annual reporting of serious adverse reactions and events for tissues and cells (data collected from 01/01/2015 to 31/12/2015)	European Commission	2017 (Data from 2015)
Summary of the 2016 annual reporting of serious adverse reactions and events for blood and blood components (data collected from 01/01/2015 to 31/12/2015)	European Commission	2017 (Data from 2015)

Name of source	Authors / organisation	Date of source
Summary of the 2017 annual reporting of serious adverse reactions and events for tissues and cells (data collected from 01/01/2016 to 31/12/2016)	European Commission	2019 (Data from 2016)
Summary of the 2017 annual reporting of serious adverse reactions and events for blood and blood components (data collected from 01/01/2016 to 31/12/2016)	European Commission	2019 (Data from 2016)
Summary of the 2018 annual reporting of serious adverse reactions and events for tissues and cells (data collected from 01/01/2017 to 31/12/2017 and submitted to the European commission in 2018)	European Commission	2020 (Data from 2017)
Summary of the 2018 annual reporting of serious adverse reactions and events for blood and blood components (data collected from 01/01/2017 to 31/12/2017 and submitted to the European commission in 2018)	European Commission	2020 (Data from 2017)
Summary of the 2019 annual reporting of serious adverse reactions and events for tissues and cells (data collected from 01/01/2018 to 31/12/2018 and submitted to the European commission in 2019)	European Commission	2020 (Data from 2018)
Summary of the 2019 annual reporting of serious adverse reactions and events for blood and blood components (data collected from 01/01/2018 to 31/12/2018)	European Commission	2020 (Data from 2018)
Supply and demand for plasma-derived medicinal products - A critical reassessment amid the COVID-1 9pandemic	J Hartmann	2020
Survey on ART and IUI: legislation, regulation, funding and registries in European countries	C Calhaz-Jorge et al	2020
Technology forecast: advanced therapies in late clinical research, EMA approval or clinical application via hospital exemption	C Edler and C Wild	2019
The 2016 global status report on blood safety and availability	World Health Organisation	2017
The Barcelona Principles: An agreement on the human donated tissue for ocular transplantation, research, and future technologies	Global Alliance of Eye Bank Association	2018
The collection, testing and use of blood and blood components in Europe, 2011 report	EDQM	2011
The collection, testing and use of blood and blood components in Europe, 2012 report	EDQM	2012
The collection, testing and use of blood and blood components in Europe. 2013 report	EDQM	2013
The collection, testing and use of blood and blood components in Europe, 2014 report	EDQM	2014
The collection, testing and use of blood and blood components in Europe. 2015 report	EDQM	2015
The collection, testing and use of blood and blood components in Europe. 2016 report	EDQM	2016
The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies	EBMT	2019
The impact of plasma derived therapies in Europe	Copenhagen Economics	2021
The International Haemovigilance Network Database for the Surveillance of Adverse Reactions and Events in Donors and Recipients of Blood Components: technical issues and results	C. Politis et al	2016

Name of source	Authors / organisation	Date of source
The ISSCR Comments on Public and Stakeholder Consultations for the Revision of the EU's BTC legislation	International Stem Cell Society - ISSCR	2021
The Magistral Preparation of Advanced Therapy Medicinal Products (ATMPs)	Gilbert Verbeken et al	2020
The Plasma Proteins Market in Europe — 2017	Marketing Research Bureau	2017
The Revision of the EU Blood Directive: How to enhance plasma collection by getting more donors via increased regulatory efficiency? Meeting Report	PPTA	2021
The use of Faecal Microbiota Transplantation (FMT) in Europe: A Europe-wide survey	S Baunwall et al.	2021
Tissue establishment compendium dataset (see Annex 13.3 for analysis)	European Commission	Accessed 2021
Transfusion-associated infections: 50 years of relentless challenges and remarkable progress	Herbert A. Perkins and Michael P. Busch	2010
TS100 Sexual Risk Behaviours of Donors impacting Transfusion Safety (unpublished)	EDQM	2017
Unproven stem cell therapy subject to FDA regulation -11th Circular	FDA	2021
Value creation in the cell therapy industry: The role of regulation	T Nunes Agostinho	2016
Vigilance Expert Subgroup input to impact assessment on reforms to EU legislation on BTC (unpublished)	Vigilance Expert Subgroup	2021
Vigilance: lessons learned from the tissue and cell experience in the European Union. Part 1: reporting and communication	D Fehily et al	2013
Vigilance: lessons learned from the tissue and cell experience in the European Union. Part 2: investigation	D Fehily et al	2014
Virus NAT for HIV, HBV, and HCV in Post-Mortal Blood Specimens over 48 h after Death of Infected Patients – First Results	T Meyer et al	2012
Voluntary Non-Remunerated Donors – Summary	European Blood Alliance	2016
Webpage: Brexit blood product plans revealed	British Society for Haematology	2018
Why Are There Only 11 Cell and Gene Therapies in Europe?	Timothé Cynober	2020
Workshop with Stakeholders and Blood, Tissue and Cell Competent Authorities Substances of Human Origin Expert Group (CASoHO E01718) 6 May 2021, 09:30-13:00	European Commission	2021
World Blood Donor Day 2020 "Safe blood saves lives" (unpublished)	European Blood Alliance	2020

Annex 13: Description of the sector

A13.1. Sector snapshot

Table 1 – Overview of the BTC sector

Variable	Data point type	Data point	Source	Data Coverage	Other notes on data
Blood collection and/or preparation for transfusion	Number of establishments	1400 EU BEs	European Commission. (n.d.). Blood. Available from: https://ec.europa.eu/health/blood_tissues_organs/blood_en	EU	Understood to be sourced from Creative Ceutical (2013), An EU-wide overview of the market of blood, blood components and plasma derivatives focusing on their availability for patients
Blood collection and/or preparation for transfusion	Other information on the sector	Blood screening market (Europe): Revenue in 2020: $755.27 Mn; Notable markets: UK, Germany, France. Italy, Spain, Russia	Sample report: Blood Screening Market. (2018). MARKET ESTIMATES & TREND ANALYSIS FROM 2016 TO 2028. Not available online.	Europe	
Blood collection and/or preparation for transfusion	Other information on the sector	1,400 EU BEs collect and process 20 million blood donations every year, enabling around 25 million transfusions to patients.	European Commission. (n.d.). Blood. Available from: https://ec.europa.eu/health/blood_tissues_organs/blood_en	EU	Understood to be sourced from Creative Ceutical (2013), An EU-wide overview of the market of blood, blood components and plasma derivatives focusing on their availability for patients
Blood collection and/or preparation for transfusion	Other information on the sector	More than 5 million patients in Europe receive approximately 25 million units of blood annually	International Foundation for Patient Blood Management. (2020). Manifesto for European action on Patient Blood Management (PBM). Available from: https://www.ifpbm.org/images/EU%20PBM%20Manifesto%20February%202020%2024.pdf	Europe	
Blood collection and/or preparation for transfusion	Other information on the sector	Partial data reported by 19 countries indicated that over 3.3 million patients were transfused.	DG SANTE. (2020). Summary of the 2019 annual reporting of serious adverse reactions and events for blood and blood components.	EU	Data collected from 01/01/2018 to 31/12/2018

Variable	Data point type	Data point	Source	Data Coverage	Other notes on data
		The same report shows number of recipients transfused each year ranging from 3.1 and 4.2 million between 2013 and 2018 , for 18-20 countries (so not the entire EU).	Available from: https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/2019_sare_blood_summary_en.pdf		
Blood collection and/or preparation for transfusion	Other information on the sector	An estimated 4.6 million patients are transfused in EU27 Member States annually.	European Commission (2020). Summary of the 2019 Annual Reporting of Serious Adverse Reactions And Events For Blood and Blood Components. Manifesto for European action on Patient Blood Management (PBM) (2020)	EU27	EU27 estimate calculated using figures in the Summary of the 2019 Annual Reporting of Serious Adverse Reactions And Events For Blood and Blood Components (Data Collected From 01/01/2018 To 31/12/2018) and Manifesto for European action on Patient Blood Management (PBM) (2020) and population data.
Blood collection and/or preparation for transfusion	Other information on the sector	Nearly 10.4 million donors annually	EDQM. (2016). The collection, testing and use of blood and blood components in Europe. Available from: https://freepub.edqm.eu/publications/PUBSD-90/detail	EU27	EU27 estimate calculated using figures in the EDQM 'The collection, testing and use of blood and blood components in Europe – 2016 Report' and Member State population data.
Blood collection and/or preparation for transfusion	Other information on the sector	21 EU Member States reported a total of 9.4 donors	EDQM. (2016). The collection, testing and use of blood and blood components in Europe. Available from: https://freepub.edqm.eu/publications/PUBSD-90/detail	EU21	
Plasma collection for the manufacture of medicinal products.	Number of establishments	European Plasma Alliance has 11 private sector members with 137 plasma collection centres in four European countries: Germany, Austria, Czech Republic, and Hungary	PPTA. (n.d.). Boards of Directors. Available from: https://www.pptaglobal.org/about-us/boards-of-directors	Europe (DE, AT, CZ, HU)	

Variable	Data point type	Data point	Source	Data Coverage	Other notes on data
Plasma collection for the manufacture of medicinal products.	Number of establishments	There are more than 150 IQPP certified plasma donation centres in Europe	European Commission. (2020). Organs, blood, tissues & cells in the EU. Available from: https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/infographic_obtc_en.pdf	Europe	
Plasma collection for the manufacture of medicinal products.	Other info on the sector (turnover etc.)	8.6 million litres of plasma per year is used for manufacturing medicines in the EU	European Commission. (2020). Organs, blood, tissues & cells in the EU. Available from: https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/infographic_obtc_en.pdf	EU+UK	
Plasma collection for the manufacture of medicinal products.	Other info on the sector (turnover etc.)	Plasma volumes currently collected in Europe fulfil only around 62% of the clinical need. 38% of plasma is imported from the United States.	Roadmap consultation response from Plasma Protein Therapeutics Association [Business Association] (2020)	Europe	
Plasma collection for the manufacture of medicinal products.	Other info on the sector (turnover etc.)	On average, 6.3 L of plasma per 1,000 inhabitants was collected by plasmapheresis in 27 Member States. Austria, the Czech Republic and Germany have considerably more extensive plasmapheresis programmes (>10L of plasmapheresis plasma per 1,000 inhabitants per annum[248]).	EDQM. (2016). The collection, testing and use of blood and blood components in Europe. Available from: https://freepub.edqm.eu/publications/PUBSD-90/detail	EU	
Plasma collection for the manufacture of medicinal products.	Other info on the sector (turnover etc.)	2,759,324 litres of plasma were collected in 2002 from 146 IQPP certified donation centres in Europe	Factsheet on EU Collections (litres) & Number of centres (unpublished)	Europe	

[248] The volume of plasma collected by apheresis per 1 000 inhabitants reflects the capacity of national plasmapheresis programmes.

Variable	Data point type	Data point	Source	Data Coverage	Other notes on data
Hospital blood banks, preparing for transfusion of blood and blood components	Number (of establishments)	1,295 hospital-based blood centres	WHO. (2016). 2016 Global Status Report on Blood Safety and Availability. Available from: https://apps.who.int/iris/bitstream/handle/10665/254987/9789241565431-eng.pdf	WHO European Region	
All BEs	Number (of establishments)	1,400 BEs in the EU collect millions of blood donations each year.	European Commission. (2019). Commission staff working document: Evaluation of the Union legislation on blood, tissues and cells. Available from: https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/swd_2019_376_en.pdf	EU	
All BEs	Number (of establishments)	387 stand-alone and 1,295 hospital-based blood centres reported by countries in the European region (includes countries outside of the EU).	WHO. (2016). 2016 Global Status Report on Blood Safety and Availability. Available from: https://apps.who.int/iris/bitstream/handle/10665/254987/9789241565431-eng.pdf	WHO European Region	
All BEs	Number (of establishments)	3741 reporting establishments (including hospital blood banks)	European Commission data, supplied 16/8/21.	EU	
Tissue collection, preparation or banking for transplantation	Number (of establishments)	ICF analysis of the Tissue Compendium data gives 3,258 establishments[249] across Member States. The Member State with highest number of establishments is Germany (29%) followed by Spain (15%) and France (10%)	ICF analysis of Compendium data supplied by the Commission (see Annex 13.3)	EU	
Tissue collection, preparation or banking for transplantation	Other info on the sector (turnover etc.)	The overall number of reported tissues and cells distributed in 2018 amounted to 995,407 units (501,103 non-reproductive, reported by 25 countries, and 494,304 reproductive tissues and cells, reported by 18 countries).	DG SANTE. (2020). Summary of the 2019 annual reporting of serious adverse reactions and events for tissues and cells. Available from: https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/2018_sare_tc_summary_en.pdf	EU	Data collected from 01/01/2018 to 31/12/2018 and submitted to the European Commission in 2019

[249] The number of establishments has been calculated by the number of unique codes in the Compendium

Variable	Data point type	Data point	Source	Data Coverage	Other notes on data
Tissue collection, preparation or banking for transplantation	Other info on the sector (turnover etc.)	In 2019, 29,767 patients in 20 EU Member States received stem cell transplants to replace their own that had been destroyed.	Eurostat. (2019). Surgical operations and procedures performed in hospitals by ICD-9-CM. Available from: https://appsso.eurostat.ec.europa.eu	EU + EEA	
Haematopoietic stem cell (HSC) collection, preparation or banking for transplantation	Number of procedures	2019 data: Allogenic HSC: 12384 Autologous HSC: 19497 Total HSC: 31881	EBMT Activity Survey Data from 2019 (unpublished, raw data provided by the European Society for Blood and Marrow Transplantation).	EU26	No known transplant program in Malta.
Haematopoietic stem cell (HSC) collection, preparation or banking for transplantation	Number (of establishments)	As of 2018, there are 509 full centre members and 55 associate centre members, 122 individual, and 35 honorary members, from 65 different countries of EBMT. [250]	EBMT. (2019). The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies. Available from: https://www.ebmt.org/sites/default/files/2019-01/2019_Book_TheEBMTHandbook.pdf	"Europe and collaborating countries"	
Haematopoietic stem cell (HSC) collection, preparation or banking for transplantation	Other info on the sector (turnover etc.)	48,512 HCT in 43,581 patients, comprising 19,798 (41%) allogeneic and 28,714 (59%) autologous, reported by 700 centres in 51 countries during 2019.	Passweg, J.R., Baldomero, H., Chabannon, C., et al. (2019). Hematopoietic cell transplantation and cellular therapy survey of the EBMT: monitoring of activities and trends over 30 years. Bone Marrow Transplantation. 56. https://doi.org/10.1038/s41409-021-01227-8	"Europe and collaborating countries"	
Reproductive tissue or cell collection, preparation or banking for assisted reproduction	Number (of establishments)	1,716 establishments in the EU with at least one authorisation for MAR	ICF analysis of Compendium data supplied by the Commission (see Annex 13.3)	EU	
Reproductive tissue or cell collection, preparation or banking for assisted reproduction	Other info on the sector (turnover etc.)	There were 920 thousand assisted reproduction cycles within the EU in 2016 (including UK figures)	European Commission. (2020). Organs, blood, tissues & cells in the EU. Available from: https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/infographic_obtc_en.pdf	EU	

[250] Members mainly consist of centres active in the transplantation of haematopoietic stem cells.

Variable	Data point type	Data point	Source	Data Coverage	Other notes on data
Reproductive tissue or cell collection, preparation or banking for assisted reproduction	Other info on the sector (turnover etc.)	43 out of the 44 European countries are performing ART and IUI	Calhaz-Jorge, C., De Geyter, C.h., Kupka, M.S., et al. (2020). Survey on ART and IUI: legislation, regulation, funding and registries in European countries: The European IVF-monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE). Human Reproduction Open. 2020(1). https://doi.org/10.1093/hropen/hoz044	Europe	
Reproductive tissue or cell collection, preparation or banking for assisted reproduction	Other info on the sector (turnover etc.)	The number of reproductive tissues and cells distributed in 2018 amounted to 494,304, reported by 18 countries).	DG SANTE. (2020). Summary of the 2019 annual reporting of serious adverse reactions and events for tissues and cells. Available from: https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/2018_sare_tc_summary_en.pdf	EU	Data collected from 01/01/2018 to 31/12/2018 and submitted to the European Commission in 2019
Reproductive tissue or cell collection, preparation or banking for assisted reproduction	Other info on the sector (turnover etc.)	Number of cycles with oocyte donation: 26 645 Aspirations 8 839 Frozen oocyte replacement 20 729 Frozen embryo replacement More than 21,000 fresh cycles with sperm donation	ESHRE. Data supplied to ICF 25 August 2021.	EU	Data related to 2017 and are likely to be an under-estimate due to incomplete reporting in some centres in certain Member States.
Clinical application of tissues –transplantation.	Other info on the sector (turnover etc.)	The main types of non-reproductive tissues and cells distributed were skeletal tissues (347,241 units), haematopoietic progenitor cells (HPC; 56,604 units) and ocular tissues (40,310 units).	DG SANTE. (2020). Summary of the 2019 annual reporting of serious adverse reactions and events for tissues and cells. Available from: https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/2018_sare_tc_summary_en.pdf	EU	Data collected from 01/01/2018 to 31/12/2018 and submitted to the European Commission in 2019
Clinical application of tissues – transplantation.	Other info on the sector (turnover etc.)	9,216 placental/amniotic membrane tissues were transplanted across 12 Member States in 2019	EDQM. (2020). Newsletter transplant: International figures on donation and transplantation 2019. Available from: https://freepub.edqm.eu/publications	EU	

Variable	Data point type	Data point	Source	Data Coverage	Other notes on data
Clinical application of haematopoetic stem cells (HSC) - transplantation	Other info on the sector (turnover etc.)	1,235 allogeneic transplants, mainly to treat relapse or graft failure and 3,696 autologous, the majority of which were likely to have been part of multiple transplant procedures such as tandem procedures, or as salvage autologous transplants for PCD. 819 of the allogeneic HCTs were reported as being given after a previous autologous HCT and were mainly for lymphoma or PCD.[	Passweg, J.R., Baldomero, H., Chabannon, C., et al. (2019). Hematopoietic cell transplantation and cellular therapy survey of the EBMT: monitoring of activities and trends over 30 years. Bone Marrow Transplantation. 56. https://doi.org/10.1038/s41409-021-01227-8	Europe and collaborating countries	
Clinical application of reproductive tissues or cells - assisted reproduction	Other info on the sector (turnover etc.)	Of the 494,304 units of reproductive tissues distributed, 249,353 sperm units were delivered for insemination and 244,357 embryos, following partner and non-partner donation, were delivered for transfer. 30 ovarian tissues and 564 testicular tissues were distributed for the preservation of fertility.	DG SANTE. (2020). Summary of the 2019 annual reporting of serious adverse reactions and events for tissues and cells. Available from: https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/2018_sare_tc_summary_en.pdf	EU	Data collected from 01/01/2018 to 31/12/2018 and submitted to the European Commission in 2019
Clinical application of reproductive tissues or cells - assisted reproduction	Other info on the sector (turnover etc.)	National registries of ART and IUI are in place in 31 out of the 43 countries contributing to ESHRE survey, and a registry of donors exists in 18 of them	Calhaz-Jorge, C., De Geyter, C.h., Kupka, M.S., et al. (2020). Survey on ART and IUI: legislation, regulation, funding and registries in European countries: The European IVF-monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE). Human Reproduction Open. 2020(1). https://doi.org/10.1093/hropen/hoz044	Europe	
Clinical application of reproductive tissues or cells - assisted reproduction	Other info on the sector (turnover etc.)	125779 ART infants were born in 24 EU Member States (2017 data) according to ESHRE, meaning infants born after IVF and ICSI cycles, which includes fresh and frozen cycles, cycles after preimplantation genetic	Calhaz-Jorge, C., De Geyter, C.h., Kupka, M.S., et al. (2020). Survey on ART and IUI: legislation, regulation, funding and registries in European countries: The European IVF-monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE). Human	Europe	Figure thought to be an under-estimate. Excludes MAR techniques, such as ovarian stimulation or intra-uterine insemination.

Variable	Data point type	Data point	Source	Data Coverage	Other notes on data
		testing, and cycles with donated oocytes.	Reproduction Open. 2020(1). https://doi.org/10.1093/hropen/hoz044		
TEs	Number (of establishments)	3,258 establishments	ICF analysis of Compendium data supplied by the Commission (see Annex 13.3)	EU	Based on unique identifiers
TEs	Number (of establishments)	Tissues and cells are handled by 3,700 TEs in the EU (includes figures from UK)	European Commission. (2020). Organs, blood, tissues & cells in the EU. Available: https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/infographic_obtc_en.pdf	EU	
Government oversight of blood or TEs (inspection, authorisation, vigilance)	Number (of establishments)	NCA blood: 37 NCA tissues and cells:34 Combined: 50	ICF estimate	EU	Regional health authorities were not included in the mapping exercise and in the cost estimations.
Pharmaceutical industry – manufacturers of plasma derived medicinal products	Other info on the sector (turnover etc.)	There are 7-8 large companies active in the EU (mostly from the private sector)	ICF consultation with PPTA		
FMT – collection and preparation	Number (of establishments)	24 hospital-based FMT centres from EU Member States reported a total of 1,095 FMT procedures (2019).	Baunwall, S.M.D. et al. (2021). The use of Faecal Microbiota Transplantation (FMT) in Europe: A Europe-wide survey. The Lancet Regional Health. https://doi.org/10.1016/j.lanepe.2021.100181	EU Member States	
FMT - application	Other info on the sector (turnover etc.)	The 24 centres referenced at left reported a total of 1,095 FMT procedures (2019)	Baunwall, S.M.D., Terveer, E.M., Dahlerup, J.F., et al. (2021). The use of Faecal Microbiota Transplantation (FMT) in Europe: A Europe-wide survey. The Lancet Regional Health.	EU Member States	
FMT - application	Other info on the sector (turnover etc.)	743 (68%) with Clostridioides difficile infection as indication, 346 (32%) with experimental indications, and 6 (0.5%) unaccounted for.	Baunwall, S.M.D., Terveer, E.M., Dahlerup, J.F., et al. (2021). The use of Faecal Microbiota Transplantation (FMT) in Europe: A Europe-wide survey. The Lancet Regional Health.	EU Member States	
Human breast milk – collection/preparation		Approximately 250 human milk banks are currently operating in	European Foundation for the Care of Newborn Infants. (2020). Making Human Milk	EU	

Variable	Data point type	Data point	Source	Data Coverage	Other notes on data
		more than 20 countries across Europe.	Matter: The need for regulation in the European Union. Available from: https://www.efcni.org/wp-content/uploads/2021/01/2021_01_21_EFCNI_MakingHumanMilkMatter_PolicyRecommendations_final-small.pdf		
Human breast milk - application	Other info	Globally more than one in ten infants – an estimated 15 million – are born preterm with an average preterm birth rate of 8.7% in Europe.	European Foundation for the Care of Newborn Infants. (2020). Making Human Milk Matter: The need for regulation in the European Union.	Global and Europe	
Sites concerned by bed-side / "same surgical procedure"	Number (of establishments)	The global platelet-rich plasma market is largely consolidated, with top five players accounting for around 80.2% share in 2015.	BCC Research. (2016). Platelet-Rich Plasma Market: Global Industry, Size, Share, Growth, Trends, and Forecast, 2016–2024.	Global	
Sites concerned by bed-side / "same surgical procedure"	Other info on the sector (turnover etc.)	Europe accounted for the second largest share of the platelet-rich plasma market (2015) and is expected to account for 24.4% market share and reach value of US$ 110.5 Mn by 2024 at a CAGR of 12.2% during the forecast period from 2016-2024.	BCC Research. (2016). Platelet-Rich Plasma Market: Global Industry, Size, Share, Growth, Trends, and Forecast, 2016–2024.	Europe	Figures include countries outside of the EU.
Sites concerned by bed-side / "same surgical procedure"	Other info on the sector (turnover etc.)	It has been estimated that PRP is used most in Orthopaedics (40%), 19% in General Surgery, 3% in Neurosurgery, 18% in Other cases, and 10% in Cosmetic procedures.	BCC Research. (2016). Platelet-Rich Plasma Market: Global Industry, Size, Share, Growth, Trends, and Forecast, 2016–2024.	Global	A survey of the Working Group for Clinical Tissue Regeneration (German Society of Orthopaedics and Traumatology) suggests the most common indications for PRP were tendon pathologies, osteoarthritis, muscle injuries and cartilage damage.

A13.2. List of NCAs for Blood, Tissues and Cells

Table 1 – National BTC NCAs for Blood, Tissues and Cells

COUNTRY	ORGANISATION
AUSTRIA	BASG
AUSTRIA	AGES MEA
BELGIUM	Agence fédérale des médicaments et des produits de santé (AFMPS)
BULGARIA	Executive Agency for Transplantation
BULGARIA	Bulgarian Drug Agency
CROATIA	Ministry of Health - Institute for Transplantation and Biomedine
CYPRUS	Ministry of Health of Republic of Cyprus
CZECH REPUBLIC	Thomayer Hospital, Prague
CZECH REPUBLIC	Ministry of Health of the Czech Republic
CZECH REPUBLIC	State Institute for Drug Control
DENMARK	Danish Patient Safety Authority
ESTONIA	Estonian State Agency of Medicines
FINLAND	Finnish Medicines Agency (Fimea)
FRANCE	Agence Nationale de Securite des Medicaments (ANSM)
FRANCE	Agence de la Biomedecine
FRANCE	Sous-direction de la politique des produits de santé et de la qualité des pratiques et des soins. Bureau de la bioéthique et des éléments et produits du corps humain (PP4) - Ministère des Solidarités et de la Santé - Direction générale de la Santé
GERMANY	Federal Ministry of Health
GERMANY	PEI
GREECE	ATTIKON General University Hospital
GREECE	Hellenic National Blood Transfusion Center
GREECE	Hellenic Ministry of Health
HUNGARY	Ministry of Human Capacities
HUNGARY	Hungarian National Blood Transfusion Service
SPAIN	Organización Nacional de Trasplantes - Director

IRELAND	Health Products Regulatory Authority
ITALY	Italian National Transplant Centre
ITALY	Italian National Blood Centre
LATVIA	State Agency of Medicines of Latvia
LITHUANIA	National Transplant Bureau, Ministry of Health
LITHUANIA	Lithuanian Ministry of Health
LUXEMBOURG	Ministère de la Santé
MALTA	Maltese Ministry of Health
NEDERLAND	Ministry of Health, Welfare and Sport
POLAND	Institute of Haematology and Transfusion Medicine (IHTM)
POLAND	Ministerstwo Zdrowia (Ministry of Health)
POLAND	NCK
PORTUGAL	CNPMA - National Council for Assisted Reproduction
PORTUGAL	The National Institute of Blood and Transplantation
PORTUGAL	Directorate General of Health
PORTUGAL	Institute for Blood and Transplantation Services
ROMANIA	National Transplant Agency
ROMANIA	Regional Blood Transfusion Centre
SLOVAKIA	Slovakian Ministry of Health
SLOVAKIA	SIDC
SLOVENIA	Agency for Medicinal Products and Medical Devices
SLOVENIA	Institute for transplantation of Organs, tissue and cell of the Republic of Slovenia
SPAIN	Spanish ART Competent Authority
SPAIN	Spanish Ministry of Health
SWEDEN	The National Board of Health and Welfare
SWEDEN	Health and Social Care Inspectorate (IVO)

A13.3. Analysis of Tissue Compendium data

This annex contains an analysis of data provided on the EU Coding Platform Reference Compendia for the Application of a single European Coding System for Tissues and Cells - EU Tissue Establishment Compendium.

This can be found online at https://webgate.ec.europa.eu/eucoding/reports/te/index.xhtml.

The main dataset was supplied to ICF by the Commission on 11 June 2021.

A13.3.1. Number of listed establishments by Member State

There are 3,258 establishments[251] across Member States. The Member State with highest number of establishments is Germany (29%) followed by Spain (15%) and France (10%).

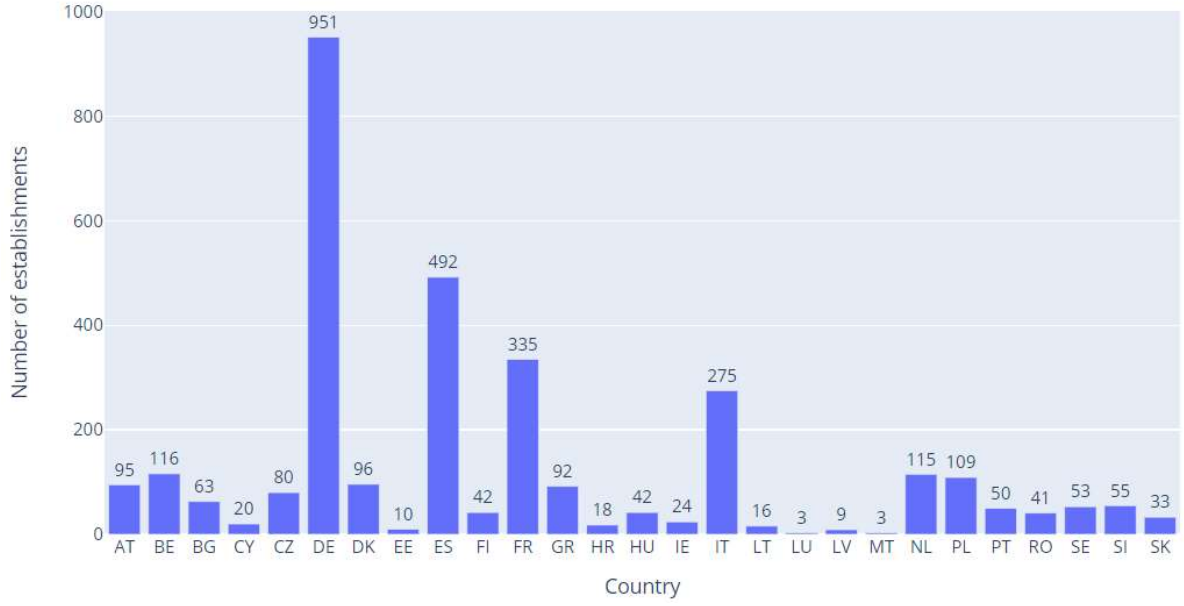

Figure 1: Number of establishments by Member State, ICF analysis

The map below provides an alternative representation of the number of establishments by Member State[252].

[251] The number of establishments has been calculated by the number of unique codes in the Compendium

[252] If the 'city' element of the establishment address could be provided then we should be able to provide a more detailed map.

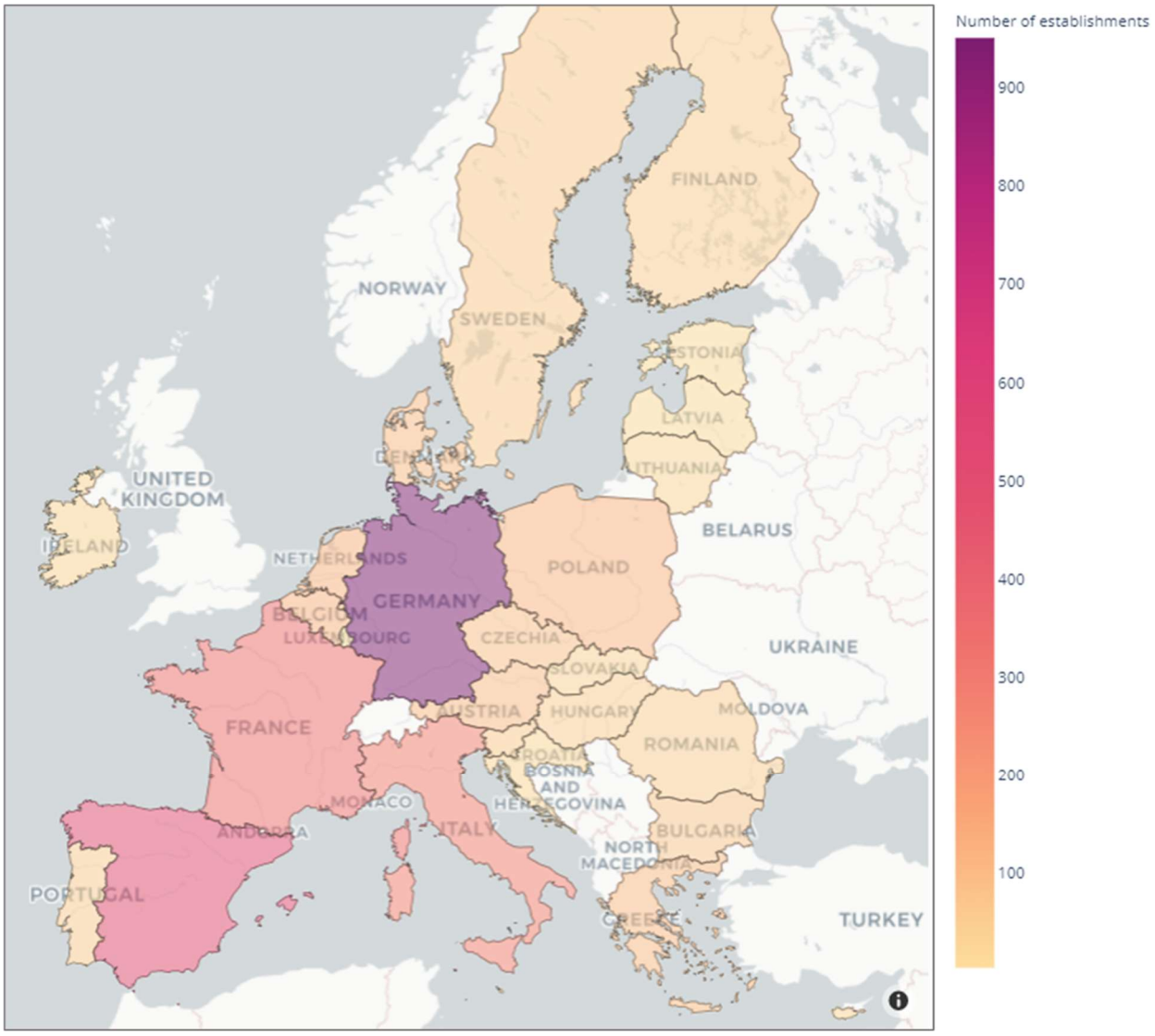

Figure 2: Distribution of establishments by Member State, ICF analysis

A13.3.2. Distribution by type of BTC authorised

The Compendium references 36 BTC categories. Figure 3 shows the number of establishments with authorisations in each of these categories. The *reproductive, sperm* category is the most referenced with 49% of establishments authorised in this category. This is followed by *reproductive, oocytes* (referenced by 36% of establishments) and *reproductive, embryos/zygotes* (31%).

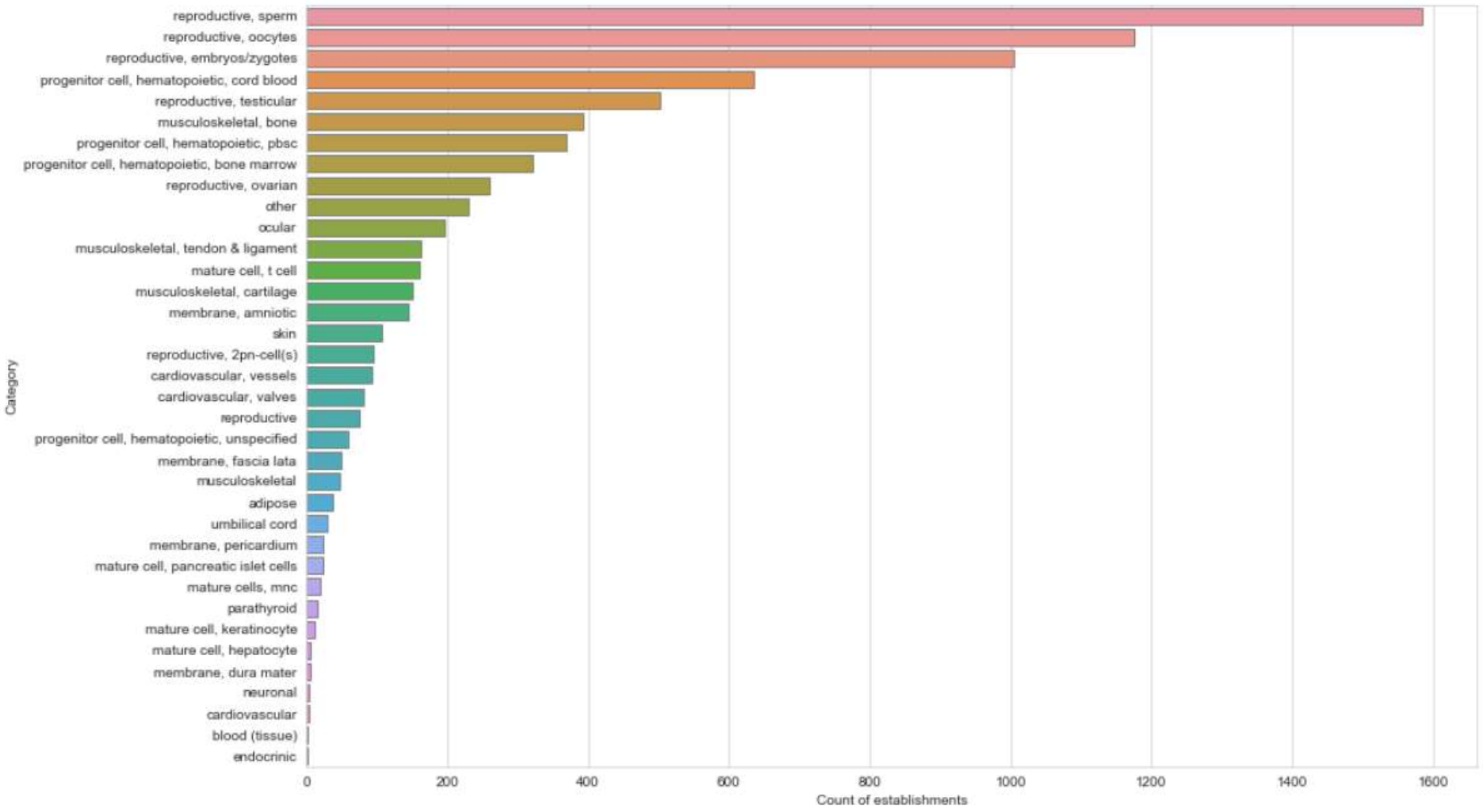

Figure 3: Number of establishments authorised by category, all EU, ICF analysis

A13.3.3. Distribution by category and Member State

Table 2 shows the number of establishments authorisations in each of the 36 Compendium categories by Member State. Germany and Spain have the highest number of establishments across all Member States, and this is reflected at individual category level as Germany has the highest number of establishments for 17 of the categories and Spain has the highest for 8 of the categories.

47% (17) of the categories have authorisations in 20 or more Member States. There are three categories (*reproductive, embryos/zygotes, reproductive, oocytes* and *reproductive, sperm*) where all Member States have at least 1 authorisation. Conversely, there are five categories (*blood (tissue)*, *cardiovascular*, *endocrinic*, *musculoskeletal*, *reproductive*) which have authorisations in only one Member State (Germany)[253].

For some categories, the number of establishments are concentrated in certain Member States. For example, the 36 EU establishments authorised for *'adipose'* are distributed across 14 Member States, but 10 are in Poland. 150 establishments across 22 Member States are authorised for '*musculoskeletal, cartilage'* BTC, of which 49 (33%) are in Spain. This is also the case for *musculoskeletal, tendon & ligament*. The most extreme example of concentration is found for the category '*progenitor cell, hematopoietic, cord blood'* where 55% (347) of the EU's establishments authorised for this BTC are found in Germany. There are established authorised for this in 24 other 25 Member States.

A13.3.4. Clustering of authorisations for different types of BTC

58% of all authorisations are in the seven reproductive categories. Two of the categories (*reproductive* and *reproductive, 2pn-cell(s)*) are only found in one and four Member States, respectively. The five other categories in this area (*embryos/zygotes, oocytes, ovarian, sperm, testicular*) however, are more clustered. 19 Member States[254] have establishments authorised in all five of these categories. Similarly, for the four *progenitor cell, hematopoietic* categories, 24 Member States[255] have establishments authorised in the three principal ones (*bone marrow, cord blood, pbsc*).

For the four *musculoskeletal* categories, one (*musculoskeletal*) only has authorisations in Germany. For the three others in this area, 20 Member States have establishments authorised in all three (*bone, cartilage, tendon & ligament*). For the *cardiovascular* categories, 20 Member States have establishments that are authorised in both *valves* and *vessels*.

[253] These identities may simply indicate idiosyncrasies or errors in BTC coding.

[254] These are Austria, Belgium, Czechia, Germany, Denmark, Estonia, Finland, France, Greece, Croatia, Lithuania, Latvia, Malta, Netherlands, Portugal, Romania, Sweden, Slovenia, Slovakia

[255] The three Member States which do not have establishments authorised in all three of these categories are Luxembourg, Latvia, Malta.

Table 2 – Authorised establishments by Member State by category

	AT	BE	BG	CY	CZ	DE	DK	EE	ES	FI	FR	GR	HR	HU	IE	IT	LT	LU	LV	MT	NL	PL	PT	RO	SE	SI	SK	Total
adipose		1	3		2	3	1		1		1			1		2	1					10	1			5	4	36
blood (tissue)						2																						2
cardiovascular						4																						4
cardiovascular, valves	4	1	1		4	16	1		14	1	9	1	1	3	2	5	1				1	3	1		2	8	2	81
cardiovascular, vessels	4	2	1		4	13	1	4	16	1	14	2	1	3	3	5	1					2	2		3	9	2	93
endocrinic						1																						1
mature cell, hepatocyte		1			2				1																1	1		6
mature cell, keratinocyte		3							1	2												2					3	11
mature cell, pancreatic islet cells		1			2	4			1		1					2					1	2			1	7		22
mature cell, t cell	6				12	15	1	1	2	10	32	7			4	48	1					9	5		6	2		161
mature cells, mnc	10	1			1		1		2	3																1		19
membrane, amniotic	5	4	4	1	8	24	1	2	22	2	19	5	2	3	2	11	2				4	4	2		7	5	6	145
membrane, dura mater					2											1						1	1					5
membrane, fascia lata	3	7	2		4	7	1		5		3	4			1	6		1			2	1	1				1	49
membrane, pericardium	1		3		2	3	2			2		1			1	1	1					3	1				2	23
musculoskeletal						46																						46
musculoskeletal, bone	21	18	5	2	15	94	24	4	54	12	25	25	2	4	2	8	1	1	1		18	6	3	2	21	19	5	392
musculoskeletal, cartilage	11	7	4		7	19	1	3	49	11	6			1	1	6		1	1		2	5	3	2	1	4	5	150
musculoskeletal, tendon & ligament	9	7	4		6	12	5	3	49	11	10	8		2	1	6	1				3	5	3	2	5	5	6	163
neuronal	1						1			1						1												4
ocular	7	4	7	3	6	39	1	2	34	2	17	4	1	5	2	13	2		3	1	5	7	8		5	12	5	195
other	11	12	7		18	73	7	1	7	5	1	4	1	1	1		1	1			14	18	5	1	9	24	8	230
parathyroid	1								11							2						1						15
progenitor cell, hematopoietic, bone marrow	10	14	6	3	12	64	4	1	21	11	29	7	1	3	4	65	2				10	25	5	4	7	7	6	321
progenitor cell, hematopoietic, cord blood	12	9	11	5	16	347	2	1	48	1	29	6	1	8	3	52	5		1		8	20	10	8	7	20	5	635
progenitor cell, hematopoietic, pbsc	14	14	5	2	14	83	6	2	24	11	34	7	1	5	6	75	2				10	26	5	5	7	7	4	369
progenitor cell, hematopoietic, unspecified	1				1		2		41			7									2	1					3	58
reproductive						74																						74
reproductive, 2pn-cell(s)	2					91																	1	1				95
reproductive, embryos/zygotes	34	18	40	8	42	8	25	5	262	12	141	54	15	19	10	140	8	1	6	2	16	46	26	26	22	5	13	1004
reproductive, oocytes	34	32	40	10	43	163	25	5	273	12	144	54	15	19	10	140	8	1	6	2	16	47	11	26	22	5	13	1176
reproductive, ovarian	6	32			8	19	1	5	7	5	65	50	2		1	1	8		1	2	6		2	26	7	3	2	259
reproductive, sperm	37	46	41	10	44	191	64	5	389	16	264	54	16	22	14	150	8	2	6	2	71	47	14	26	24	5	13	1581
reproductive, testicular	41	32			40	168	2	5		11	65	50	10	4			8		1	2	4		2	26	19	5	6	501
skin	10	3	4	1	5	20		1	11	1	11	9	1	1	1	5		1			4	3	2	1	3	6	3	107
umbilical cord	2		3	2	2	2		1	1		2						1					2		1	1	7	2	29
Total	297	269	191	47	322	1605	179	51	1346	143	922	359	70	104	69	745	62	9	26	11	197	296	114	157	180	172	119	8062

Source: ICF analysis

A13.3.5. Medically assisted reproduction 'sector' analysis

Within the MAR categories, *reproductive, sperm* has the most authorisations.

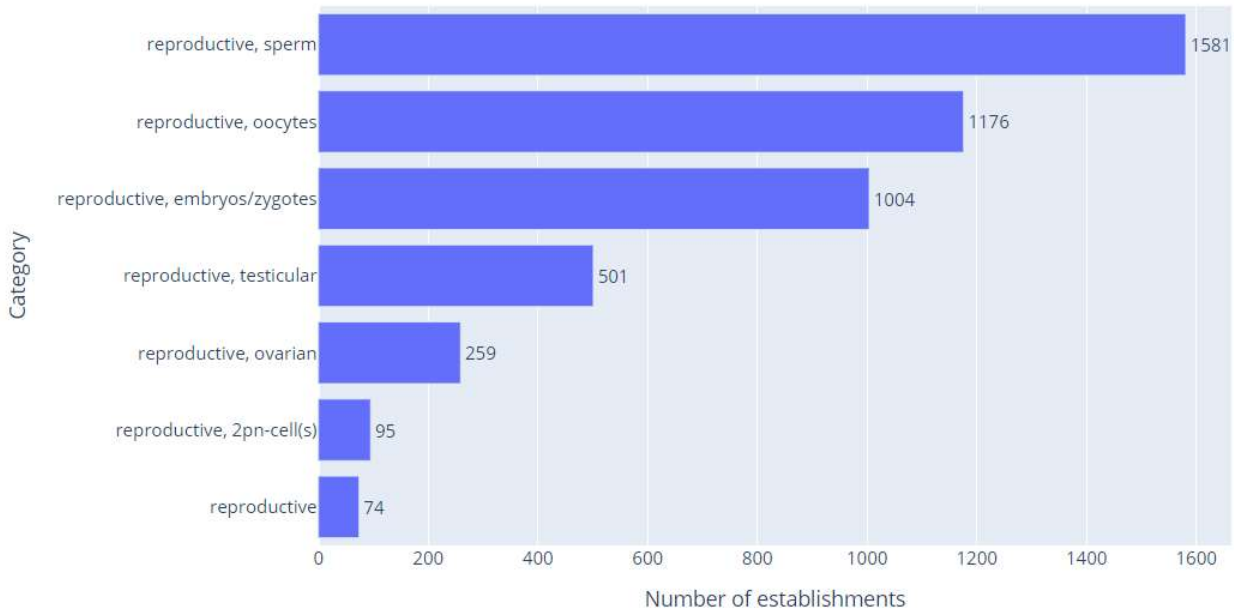

Figure 4: Number of establishments authorised for MAR, ICF analysis

Across Member States, Spain has the highest number of establishments with at least one authorisation within MAR (400). This is followed by Germany with 286 and France with 267 (Figure 5).

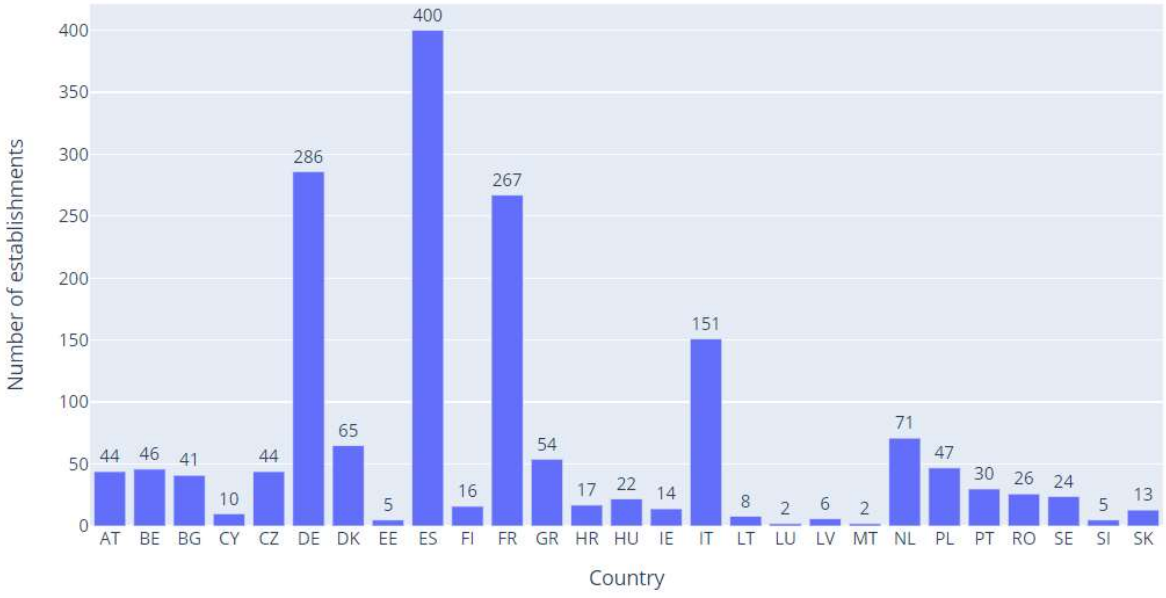

Figure 5: Number of establishments by Member State with at least one authorisation for MAR, ICF analysis

The distribution of authorisations for each of the MAR categories across Member States is shown in Figure 6. A single establishment may have multiple authorisations, for example, Spain has the highest number in this area with 931 authorisations across 400 establishments, although it is worth noting that the establishments in Spain are only authorised in four of the categories (*sperm, oocytes, ovarian, embryos/zygotes*). This contrasts with Germany (the Member State with second highest number of authorisations - 714 authorisations across 286 establishments) which has authorisations in all seven categories. It is also only one of four Member States (alongside Austria, Portugal and

Romania) which has authorisations in *2pn-cell(s)* where it has 91 of the 95 total authorisations.

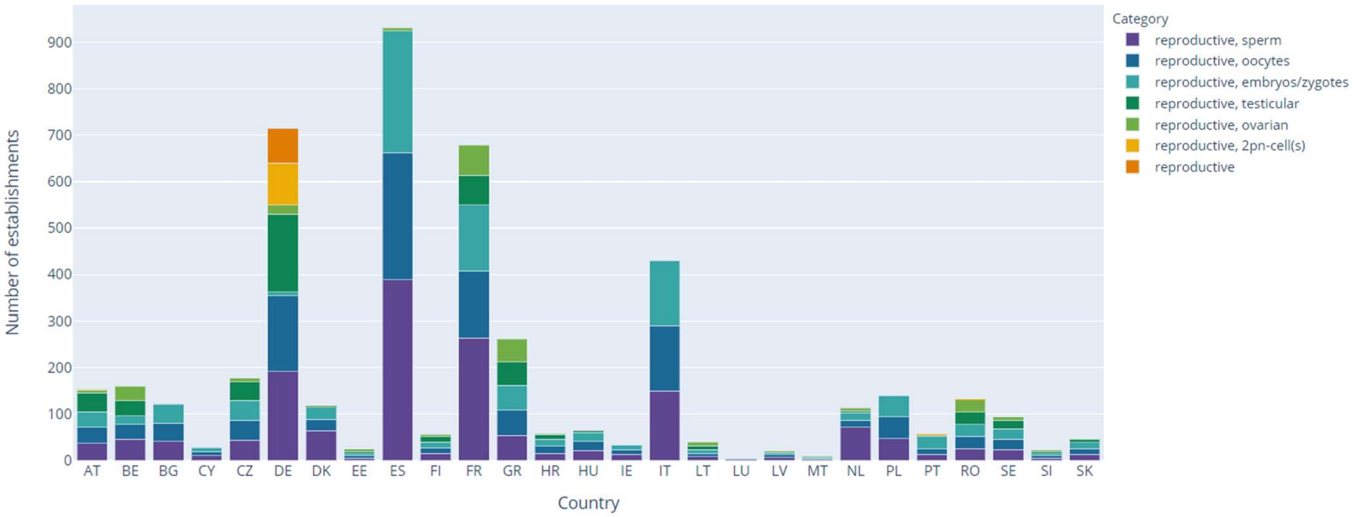

Figure 6: Number of authorisations for MAR by Member State, ICF analysis

A13.3.6. EDQM category matching – identification of establishments dealing with 'critical BTC'

Each of the Compendium categories were matched with those in the EDQM. Figure 7 shows a comparison, for each Member State, between the total number of establishments authorised under the Compendium categories and those under the EDQM categories.

The Compendium categories were matched using both EDQM category columns[256]. This was done to capture matches at the broader level, for example *Placental tissue*, and at the more granular level, for example *amniotic membrane*. To account for differences in spelling such as *haematopoietic* in the EDQM categories and *hematopoietic* in the Compendium, approximate string matching was applied for matches to column A (the broader category level). Approximate string matching is the process of locating strings that approximately match a pattern (in this case column A of the EDQM categories) rather than exactly match a pattern. The returned output is a ratio of similarity showing the likelihood that the pattern and the input string is a 'true' match. Matches were accepted that returned a ratio of 90 or higher as, at this level, differences in spelling could be accounted for but noise would be excluded. For matches with column B in the EDQM, where more granular descriptions are provided, exact matches for any of the terms were included[257].

Across Member States there are 1,469 establishments with at least one authorisation in the EDQM categories compared with 3,258 within the compendium categories. Germany remains the Member State with highest number (623) of establishments authorised under DQM 'critical' BTC categories. Italy has 124 establishments in the EDQM critical categories and Spain 99.

[256] In the Compendium, there is the category 'other' which could match on multiple EDQM column B categories. Due to the lack of specificity, it was excluded from the matching.

[257] Where the generic term 'membrane' was found in the Compendium, terms alongside it were used to ensure relevance and allocate matches. 'Membrane, amniotic', for example, was matched into the Placental category in the EDQM, however, 'Membrane, fascia lata' was not matched with the EDQM categories.

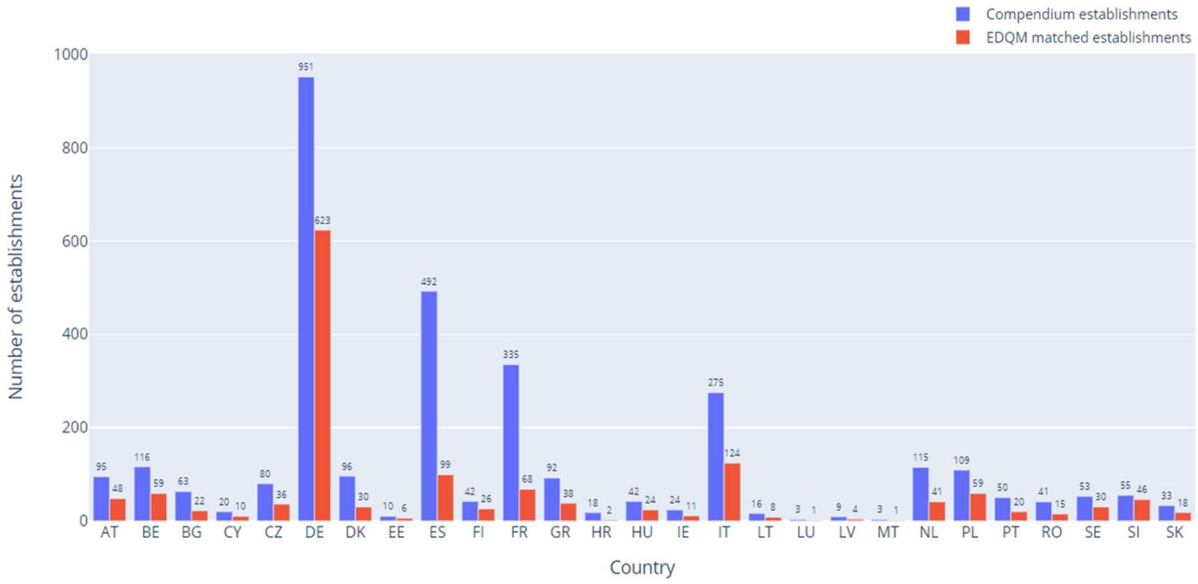

Figure 7: Number of establishments authorised in EDQM categories by Member State, ICF analysis

Table 3 (overleaf) shows, by Member State, the number of authorisations in each of the EDQM categories[258]. The category with the largest number of authorised establishments is *Haematopoietic* where 61% of all establishments with an EDQM match are authorised in this category. All Member States except Malta and Luxembourg have at least one establishment authorised in this category. The category that is the most represented across Member States is *Musculoskeletal* as all countries except Malta hold an authorisation. The category with the smallest number of authorisations is *Neuronal* (4) this is followed by *Hepatic* with six authorisations across four Member States.

[258] Single establishments may have multiple authorisations across categories. For example, Austria has 48 establishments and 69 authorisations as there are 9 establishments with 2 or more authorisations.

Table 3 – Number of establishments authorised in EDQM categories by Member State

	AT	BE	BG	CY	CZ	DE	DK	EE	ES	FI	FR	GR	HR	HU	IE	IT	LT	LU	LV	MT	NL	PL	PT	RO	SE	SI	SK	Total
Ocular	7	4	7	3	6	39	1	2	34	2	17	4	1	5	2	13	2		3	1	5	7	8		5	12	5	195
Placental	5	4	4	1	8	24	1	2	22	2	19	5	2	3	2	11	2				4	4	2		7	5	6	145
Cutaneous	10	6	4	1	5	20		1	12	2	11	9	1	1	1	5		1			4	5	2	1	3	6	3	114
Cardiac	1		3		2	3	2			2		1			1	1	1					3	1				2	23
Vessels	4	2	1		4	13	1	4	16	1	14	2	1	3	3	5	1					2	2		3	9	2	93
Muscoloskeletal	23	18	5	2	16	145	24	4	54	12	25	26	2	4	2	8	1	1	1		19	8	3	2	21	19	6	451
Neuronal	1						1			1						1												4
Adipose		1	3		2	3	1		1		1			1		2	1					10	1			5	4	36
Pancreatic		1			2	4			1		1					2					1	2			1	7		22
Hepatic		1			2				1																1	1		6
Parathyroid	1								11							2						1						15
Haematopoietic	17	22	15	6	19	442	8	3	66	11	36	11	1	12	6	93	7		1		17	34	11	12	8	25	9	892
Total	69	59	42	13	66	693	39	16	218	33	124	58	8	29	17	143	15	2	5	1	50	76	30	15	49	89	37	1996

Source: ICF analysis

Annex 14: Definitions of 'critical BTC' used in Objective 5 options

Table 1 – Tissues: Working definition of 'critical BTC' (tissues) adopted for the appraisal of Objective 5 measures on supply monitoring and reporting and contingency planning / emergency preparedness

Requirement:	**Mandatory monitoring obligation**	**Notification when sudden supply risk; BE/TE contingency plans**
Measure reference:	**M5.1**	**M5.2 , M5.3**
Cornea, full thickness (high endothelial cell density)	Yes	Yes
Cornea, full thickness (low endothelial cell density)	Yes	Yes
Cornea for Endothelial Keratoplasty (pre-cut/peeled in the Tissue Establishment)	Yes	Yes
Sclera	Yes	No
Other ocular	Yes	No
Amniotic membrane	Yes	No
Amniotic membrane eyedrops	Yes	No
Other placental	Yes	No
Skin	Yes	Yes
Acellular dermal matrix	Yes	No
Keratinocytes/melanocytes	Yes	No
Other cutaneous tissues	Yes	No
HV, aortic	Yes	Yes
HV, pulmonary	Yes	Yes
HV, aortic decellularised	Yes	Yes
HV, pulmonary decellularised	Yes	Yes
Non-valved patches and conduits	Yes	No
Pericardium	Yes	No
Other heart tissues	Yes	No
Vessels, arteries	Yes	No

Requirement:	**Mandatory monitoring obligation**	**Notification when sudden supply risk; BE/TE contingency plans**
Measure reference:	**M5.1**	**M5.2 , M5.3**
Vessels, veins	Yes	No
Whole or part of structural/supporting bone	Yes	No
Tendons (including with bony attachments)/ligaments/fascia	Yes	No
Osteochondral grafts	Yes	No
Bone filling material (excluding femoral heads)	Yes	No
Femoral heads	Yes	No
Demineralised bone matrix (including combined with a carrier)	Yes	No
Meniscus	Yes	No
Other musculoskeletal (e.g. ear ossicles, cranial bone, cartilage)	Yes	No
Nerves	Yes	No
Adipose Tissue	Yes	No
Pancreatic islets	Yes	Yes
Hepatocytes	Yes	No
Parathyroid tissue	Yes	No
HPC from bone marrow for transplantation	Yes	Yes
HPC from peripheral blood for transplantation	Yes	Yes
Peripheral blood mononuclear cells for transplant support (e.g. donor lymphocytes for infusion)	Yes	No
Peripheral blood mononuclear cells for other purposes, excluding ATMP (e.g. production of CAR-T cells, NK cells)	Yes	No
HPC from cord blood for transplantation	Yes	Yes
Other cells (e.g. bone marrow for other purposes), excluding ATMP	Yes	No

Table 2 – Blood: Working definition of 'critical BTC' (blood) adopted for the appraisal of Objective 5 measures on supply monitoring and reporting and contingency planning / emergency preparedness

Requirement:	**Mandatory monitoring obligation**	**Notification when sudden supply risk; BE/TE contingency plans**
Measure reference:	**M5.1**	**M5.2 , M5.3**
Whole blood	Yes	Yes
Red blood cells	Yes	Yes
Platelets	Yes	Yes
Fresh frozen plasma	Yes	No
Plasma for fractionation	Yes	Yes
Rare Red blood cells	Yes	No

Annex 15: Cross border exchanges

Note that some estimates are incomplete or estimated. Footnotes provide sources where possible; data without a footnote represents a Commission estimate.

Table 1 – Cross border exchanges

Category	EU volume	Intra-EU exchange	Import (I) / Export (E)	Drivers	Legal barriers (B) / Facilitators (F)
Blood components for transfusion	+20 million units (1400 BEs)	Occasional, less than 1%	N/A	Need for rare blood types Infectious disease outbreaks in a country	No standardisation (B)
Plasma for PDMP	9 million litres	Continuous, >75%	3 million litres US plasma to make PDMP for EU patients + Continuous import to EU plants (to re-export PDMP)	Many global manufacturing plants are based in EU (I/E) No plants in every Member States (Intra-EU)	Standardisation through PMF and GMP provisions, in pharma law (F)
Haematopoietic stem cells in bone marrow (collect to apply)	35 000 units	Continuous, 44% of all donations come from other EU Member States	Continuous, 16% of all donations come from 3rd country	Genetic match needed specific recipient Accreditation allows mutual recognition	Standardisation thanks to (non-legal) accreditation programme (F)) Provisions to facilitate emergency and direct import (F)
Haematopoietic stem cells in cord blood units (collect to store)	In 2012, worldwide over 640 000 cord blood units were stored in public banks, of these 196 997 cord blood units were registered in 23 Cord Blood Registries in 18 EU Member States[259].	Significant	N/A	National restrictions in some countries drive cross-border storage abroad. Brokers collecting locally send for storage in large facilities abroad	N/A

[259] Rathenau Instituut. (2015). Economic landscapes of human tissues and cells for clinical application in the EU: Final Report. (Accessed 17 August 2021). Available from: https://op.europa.eu/en/publication-detail/-/publication/5a0fd429-4a4e-11e6-9c64-01aa75ed71a1

Category	EU volume	Intra-EU exchange	Import (I) / Export (E)	Drivers	Legal barriers (B) / Facilitators (F)
Bone	400 TEs	Limited, 87% stays within country	I/+++ E/- 1/4th of all bone is imported	Commercially driven by (U.S.-based companies With partnerships with EU-based importing TEs	No standardisation, extra national safety and quality requirements (B) National admin burden, including for translations (B) Provisions to authorise importing TEs (F)
Heart valves	3 700[260] In 2012 in the European Union, a total of 77 cardiovascular TEs were active. In 2012, Member States reported the donation of 1 974 hearts, processing of 3,890 heart valves and discard of 1,008 heart valves, resulting in 2,882 heart valves issued for transplantation[261].	Informal networks of TEs for cross-border exchange Number of Tissues[262]: - Received from foreign countries (Intra EU): 85 - Distributed to foreign countries (Intra EU): 197	I/+ E/- Number of Tissues[263]: - Received from foreign countries (Extra EU): 129 - Distributed to foreign countries (Extra EU): 102	Local shortages/surpluses Price differences Mainly small scale public TEs Informal networks of TEs for cross-border exchange Need for size matching (general shortage of very small sizes for children/infants).	No standardisation, extra national safety and quality requirements (B) National admin burden, including for translations (B) National export restrictions in some Member States (B) Provisions to authorize importing TEs (F)
Cornea	40 000[264] In Europe, in 2012, 141 corneal TEs were active. 40 185 corneas were	Volume of corneas[266]: Distributed to other Member State: 1,321	I/+ E/+	Local shortages/surpluses Short shelf-lives Price differences	No standardisation, extra national safety and quality requirements (B) National admin burden, including for translations (B)

[260] Data compiled for previous evaluation study, based on Eurocet and Rathenau data.

[261] Rathenau Instituut. (2015). Economic landscapes of human tissues and cells for clinical application in the EU: Final Report. (Accessed 17 August 2021). Available from: https://op.europa.eu/en/publication-detail/-/publication/5a0fd429-4a4e-11e6-9c64-01aa75ed71a1

[262] Note not all Member States were represented in the data. EUROCET. (2019). Report 2019: Tissue Data Year 2018. (Accessed 17 August 2021). Available from: https://zdravlje.gov.hr/UserDocsImages/2020%20Transplantacija%20i%20biomedicina/EUROCET_Tissue_European%20data_2018.pdf

[263] Note not all Member States were represented in the data. EUROCET. (2019). Report 2019: Tissue Data Year 2018. (Accessed 17 August 2021). Available from: https://zdravlje.gov.hr/UserDocsImages/2020%20Transplantacija%20i%20biomedicina/EUROCET_Tissue_European%20data_2018.pdf

[264] Data compiled for previous evaluation study, based on Eurocet and Rathenau data.

[266] Rathenau Instituut. (2015). Economic landscapes of human tissues and cells for clinical application in the EU: Final Report. (Accessed 17 August 2021). Available from: https://op.europa.eu/en/publication-detail/-/publication/5a0fd429-4a4e-11e6-9c64-01aa75ed71a1

Category	EU volume	Intra-EU exchange	Import (I) / Export (E)	Drivers	Legal barriers (B) / Facilitators (F)
	recovered. From these, 30 428 corneas were distributed[265].	Received from other Member States: 643	Significant import from U.S - Informal networks of TEs for import/export	Mainly small scale public TEs	National export restrictions in some Member States (B) Provisions to authorize importing TEs (F)
Skin	Number of donations, total: 2,095[267] N° of Tissue retrieved, total: 4,090,519[268]	Number of Tissues[269]: - Received from foreign countries (Intra EU): 32,064 - Distributed to foreign countries (Intra EU): 52,491	I/- E/- Some international partnerships Number of Tissues[270]: - Received from foreign countries (Extra EU): 55,213 - Distributed to foreign countries (Extra EU): 24,915	Mainly small scale public TEs	Additional national safety and quality requirements (B) National admin burden, including for translations (B) National export restrictions in some Member States (B) Provisions to authorize importing TEs (F)
Gametes	Number of donations[271]: - Sperm collection: 137,575 - Oocytes collection: 25,758	Significant cross-border supply of gametes	Occasional – gametes imported/exported with families in/emigrating	National access restrictions, driving online ordering and direct supply sperm International recruitment of donors International brokers to offer IVF treatments abroad	

[265] Rathenau Instituut. (2015). Economic landscapes of human tissues and cells for clinical application in the EU: Final Report. (Accessed 17 August 2021). Available from: https://op.europa.eu/en/publication-detail/-/publication/5a0fd429-4a4e-11e6-9c64-01aa75ed71a1

[267] Note not all Member States were represented in the data. EUROCET. (2019). Report 2019: Tissue Data Year 2018. (Accessed 17 August 2021). Available from: https://zdravlje.gov.hr/UserDocsImages/2020%20Transplantacija%20i%20biomedicina/EUROCET_Tissue_European%20data_2018.pdf

[268] Note not all Member States were represented in the data. EUROCET. (2019). Report 2019: Tissue Data Year 2018. (Accessed 17 August 2021). Available from: https://zdravlje.gov.hr/UserDocsImages/2020%20Transplantacija%20i%20biomedicina/EUROCET_Tissue_European%20data_2018.pdf

[269] Note not all Member States were represented in the data. EUROCET. (2019). Report 2019: Tissue Data Year 2018. (Accessed 17 August 2021). Available from: https://zdravlje.gov.hr/UserDocsImages/2020%20Transplantacija%20i%20biomedicina/EUROCET_Tissue_European%20data_2018.pdf

[270] Note not all Member States were represented in the data. EUROCET. (2019). Report 2019: Tissue Data Year 2018. (Accessed 17 August 2021). Available from: https://zdravlje.gov.hr/UserDocsImages/2020%20Transplantacija%20i%20biomedicina/EUROCET_Tissue_European%20data_2018.pdf

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