EUROPEAN
COMMISSION

Brussels, 14.7.2022
SWD(2022) 190 final

PART 2/3

COMMISSION STAFF WORKING DOCUMENT

IMPACT ASSESSMENT REPORT

Accompanying the document

Proposal for a Regulation of the European Parliament and of the Council

on standards of quality and safety for substances of human origin intended for human application and repealing Directives 2002/98/EC and 2004/23/EC

{COM(2022) 338 final} - {SEC(2022) 304 final} - {SWD(2022) 189 final} -
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ANNEX 1: PROCEDURAL INFORMATION

LEAD DG, DECIDE PLANNING/CWP REFERENCES

The Directorate for Health and Food Safety (DG SANTE) is the lead DG on the initiative on Revision of the Union legislation on blood, tissues and cells.

The initiative is in the European Commission's Work Programme for 2021, in Annex II: REFIT initiatives, under the heading Promoting our European Way of Life. The initiative has received the validation in the Agenda Planning on the 10 November 2020 (reference PLAN/2020/8495), and the Inception Impact Assessment was published on 17 November 2020.

ORGANISATION AND TIMING

An Inter-Service Steering Group was set up and met on 12 November 2020, 8 December 2020, 20 May 2021, 11 October 2021, and 13 December 2021. Along with the SG (Secretariat-General) and SJ (Legal Service), the following Commission services took part in the ISSG: BUDG (Budget), JUST (Justice and Consumers), RTD (Research and Innovation), CNECT (Communications Networks, Content and Technology), REFORM (Structural Reform Support), DIGIT (informatics) and the JRC (Join Research Centre). The members of the Inter-Service Steering Group were regularly informed on the progress of the initiative and invited to relevant meetings.

In addition, there were close contacts with the Consumers, Health, Agriculture and Food Executive Agency (CHAFEA) / Health and Digital Executive Agency (HADEA) on this file.

CONSULTATION OF THE RSB

The file benefited from an upstream meeting with the Regulatory Scrutiny Board on the 31 May 2021. The Regulatory Scrutiny Board received the draft version of the Impact Assessment Report on 10 November 2021. The Board meeting took place on 8 December 2021 upon which a positive opinion with reservations was issued (see findings below).

EVIDENCE, SOURCES AND QUALITY

The Impact Assessment has built on two studies:

- A study supporting the whole impact assessment, which gathered information on impacts and costs for stakeholders of the proposed measures and options, and further documented borderline case studies. The study also organised participatory workshops bringing stakeholders together to discuss various topics (see Annex 2). The study was guided by a steering group composed of three senior experts in the field of blood, tissues and cells, who supervised the process and validated the study findings.
- A feasibility study focusing specifically on the costs and benefits from the digitalisation of the sector.

Extensive stakeholder consultation was also organised, with inputs gathered through two online questionnaires, eleven workshops, 3 hearings and several bilateral meetings (For more information, see Annex 2). Stakeholders presented views which, although important and representing large organisations, are not the most robust source of evidence. However, they were also invited to present evidence and data during these events, much of which was used in the Impact Assessment.

A number of stakeholder organisations published position papers that often included relevant and good quality evidence and data. These presentations were used both by the Impact Assessment contractor for their study and by the Commission for the Impact Assessment report. In many cases, these were appended to their online consultation submissions and, in some cases, they were launched during meetings hosted by the European Parliament [1].

Many of the 448 references in the BTC Evaluation were articles published in scientific journals and included data and evidence that was still relevant for the Impact Assessment. In addition, a number of further scientific articles were published more recently and were also used as evidence sources for this exercise [2]. These represent high quality evidence, due to the peer review process included by the publishers.

Evidence on costs is particularly difficult to gather in this sector, due to the predominant role of public sector organisations. The contractor for the Impact Assessment study conducted a survey with key authorities and professionals and worked on the basis of a series of assumptions that were validated with key stakeholder organisations to ensure that assumptions were robust.

Findings of the Regulatory Scrutiny Board

RSB main findings	Modification of the IA report
(1) The report is not sufficiently clear on the scope of the initiative and how it interacts coherently with the other ongoing initiatives in the health area.	The scope of the initiative has been clarified in section 1, and interactions with ongoing initiatives in the health area updated in sections 1, 5 and 6.
(2) The report does not discuss the change of legal instrument and how this leaves sufficient room for Member States' choices.	The change from two Directives to one Regulation has been further described under section 5.3 and in section 8.
(3) The design of the three regulatory options is not sufficiently clear. It does not integrate well enough the various measures	The description of the policy options in section 5.2 has been revised, to be clearer on the common aspects, and the ones that

[1] Examples of organisations that held European Parliament events with the support of MEPs included the European Federation for the Care of Newborn Infants, the European Blood Alliance and the Plasma Protein Therapeutics Association.

[2] Recent examples included articles on the EuroGTP II Risk assessment tool that are referenced in the section on innovation, a number of articles on the regulatory classification of faecal microbiota transplants, an article on the regulation of cord blood, a survey of haematopoietic stem cell transplant activity in the EU and a survey on medically assisted reproduction and intra-uterine insemination in European countries. These articles are fully referenced in the relevant sections of this report.

and does not link well to the objectives.	differ by policy options. the description also emphases the role of each key actors (NCAs, BE/TE, expert bodies, EU law).
RSB adjustment requests	Modification of the IA report
(1) The report should be clearer about the scope of this initiative, its relations with the other on-going revisions of related legislation, and whether, and where, all assumptions and definitions are streamlined across the health legislation.	The interactions with ongoing initiatives in the health area and the fact that this initiative is not modifying the delineation criteria between the BTC framework and other health frameworks (which are the ones defining the delineation criteria) has been added in sections 1, 2 and 5.
(2) The report should explain more convincingly why there is a need for harmonised measures at EU level (beyond the current EU standards). It should include the cross border dimension in the legal basis for the preferred options. The report should better explain why a different legal instrument ('regulation') has been chosen and it should demonstrate clearly that this choice still respects the subsidiarity principle.	The report explains more clearly (section 2.222.3) why the Member States are implementing more stringent national measures, and that to facilitate cross-border exchange of BTC (hence patients' access), there is a need for updated, and harmonised BTC safety and quality requirements. The options for the legal basis have been clarified (section 3.1) and discussion on the choice of a Regulation included (sections 5.3 and 8).
(3) The report should better explain how the three regulatory options would function in practice. It should better connect them with the respective measures and the objectives. All measures (e.g. voluntary and unpaid donations, and digital tools) should be well reflected throughout the report (in the problem section and objectives). The discarded options should be better justified.	The section 5 explains better how the options will work, in relation with the set objectives. It also describes comprehensively the elements for which there were no alternative options (for example on the VUD principle). The contribution of digital tools to the initiative has been made clearer in the problems, objectives, options, impacts and preferred option sections.
(4) The report should better present the methodology of the multi-criteria analysis (using the SOCRATES tool) and its results. It should be clearer about the underlying assumptions and drivers and how it integrated stakeholder views in the analysis. More generally, it should also reflect stakeholders' diverse opinions throughout the report.	The methodology of the multi-criteria analysis has been revised in the Annex 4, to explain better how it has been applied in practice to this IA. Stakeholders views, gathered during the process (via public consultations, workshops, dedicated surveys, interviews etc…) are described in Annexes 2 and 18. It should be noted that there was often a high level of consensus among stakeholders but when divergences were observed, those are better reflected in the report and its annexes. The annex 4 also describes more clearly how the stakeholders' judgements were used for the

	equity analysis.
(5) The report should be more transparent about the status of the planned data system and what choices are still left for this initiative.	The report has been updated and includes the Annex 19, summarising the initial findings from the feasibility study on the implementation of a SoHO-X data system. Such study is still ongoing and the requirements for the set-up of the SoHO-X platform are currently being defined by this study (clarified in section 8).

ANNEX 2: STAKEHOLDER CONSULTATION

2.1 CONSULTATION STRATEGY

Stakeholder consultation was a key step in the Impact Assessment for the revision of the legislative framework on blood, tissues, and cells (BTC). Consultation activities aimed to assess stakeholders' views and opinions (i) about whether the findings of the evaluation (2019) were still valid [3], (ii) on the three proposed policy options described in the Inception Impact Assessment (IIA) [4], (iii) on the extent to which they would address the shortcomings identified in the evaluation, and their likely impacts.

Relevant stakeholders [5] to be consulted were identified in the IIA. The list reflects the particularities of the BTC sector, including a strong role of networks between professional communities and public authorities and a limited role of industrial actors. BTC donors and patients were proactively encouraged to participate. To collect all relevant views and engage with stakeholders as much as possible, different consultation methods were combined.

2.1.1 Consultation Activities undertaken by DG SANTE

DG SANTE consulted with stakeholders via (i) the IIA publication for feedback, (ii) online surveys, (iii) hearings with national competent authorities and stakeholders and (iv) bilateral meetings with stakeholder organisations. Because of the COVID-19 pandemic, all meetings were held in virtual format.

The IIA was open for feedback between 17 November 2020 and 14 December 2020. Feedback was provided in an open text format and was taken into account in the design of further consultation activities.

Two surveys were designed and run in parallel: One addressed any interested stakeholder or citizen (Public Consultation), while the other addressed stakeholder organisations only (Targeted Consultation). Those addressed by the Targeted Consultation were encouraged also to submit an answer to the Public Consultation, and to limit their answers in the targeted questionnaire to the fields in which they had relevant experience in working with the current framework. The Public Consultation was available on the 'Have your Say' Portal and the Targeted Consultation was available on the DG SANTE webpage; both were available to respondents for 12 weeks, from 21 January to 15 April 2021. In addition to the views and opinions gathered by these surveys, respondents were free to submit supporting documents to their response. As a result, outcomes of the stakeholder consultation also include peer-reviewed scientific papers.

Three virtual half-day Hearings were organized in the first week of May 2021, to allow stakeholders to present relevant positions to National Competent Authorities and gather their reactions. These stakeholder presentations were pre-selected based on experience relevant to each Hearing topic and aimed to represent as many of the identified stakeholder groups as possible (such as patients, donors, manufacturers, and blood and

[3] https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/swd_2019_376_en.pdf.

[4] IIA: https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12734-Blood-tissues-and-cells-for-medical-treatments-&-therapies-revised-EU-rules_en.

[5] See Annex 4, Section 4.3, Figure 4.11.

tissues establishments representation). Summary reports, including list of attendees, were published on the DG SANTE webpages [6].

Finally, DG SANTE participated in 40 meetings with external stakeholders, usually organised at their initiative. These included eight meetings with Member State competent authorities (Germany, Spain, Austria, Poland, Croatia, and the Netherlands), eight with relevant EU agencies (EMA, ECDC, or subgroups thereof, e.g. the Committee for Advanced Therapies) and three with the Council of Europe (EDQM). In addition, some stakeholders organised meetings at the European Parliament to raise particular issues, where DG SANTE was also invited to attend. The outcomes of those discussions were taken into account during the impact assessment.

2.1.2 Consultation Activities conducted in the study supporting the Impact Assessment

In the context of the study, a series of 11 three-hour online participatory workshops based on topics suggested by DG SANTE was conducted between 27 April and 9 June 2021. These were open to one representative of each National Competent Authority and invited stakeholders with experience relevant to the topics to be discussed [7]. Summaries of those workshops, including main conclusions, were prepared by the External Study for the BTC Impact Assessment and published on the DG SANTE webpages [8]. In addition, online questionnaires addressed to competent authorities, and representatives of all stakeholder categories were used to fill remaining gaps in the evidence base.

The Impact Assessment study also involved some specific stakeholders through other activities. These included semi-structured interviews with 44 relevant experts from 25 organisations including blood and tissue establishments, competent authorities, a manufacturer and other organisations[9] to gather evidence on 15 case studies illustrating regulatory issues at the borderlines between the BTC framework and other health frameworks. In addition, 6 semi-structured interviews with professional representations of blood and tissue establishments were conducted as follow-up from the online questionnaires

2.2 Stakeholder Participation

The IIA received 82 responses. The Public and Targeted Consultation surveys received 214 and 159 responses, respectively. Respondents were well distributed geographically, across the EU and beyond, and replies were provided by the different stakeholder categories. The analysis by field of activity showed that a vast majority of respondents were active in blood transfusion and tissue and cell transplantation, with a large overlap

[6] Hearing on "Regulating for Sufficiency – Blood and blood components": https://ec.europa.eu/health/sites/default/files /blood_tissues_organs/docs/ev_20210504_mi_en.pdf; Hearing on "Regulating for Sufficiency – Tissues and cells": https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/ev_20210505_mi_en.pdf; Hearing on "Setting Technical Rules for BTC" https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/ev_06052021_mi_en.pdf

[7] Participation of stakeholders is described in more detail in Annex 6, section 6.2.

[8] https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/icf_summarynotes_stakeholder-workshops_en.pdf

[9] Including EMA Committee on Advanced Therapies, International Society for Extracellular Vesicles, NHSBT (we classified this once as international organisation, but that is still super vague

between both sub-sectors [10]. There were between 37 and 105 participants at the participatory Workshops and the Hearings were attended by 98 to 147 participants [11]. Response rates to the online surveys conducted by the External Study for the BTC Impact Assessment were generally lower, possibly reflecting the more granular nature of their consultation activities or a shorter timeframe for response [12].

Stratification by geographical location, sectors, and roles reflected the realities of the sector. There were fewer respondents categorised as donors, patients, and ethics bodies; however, this was expected, given that only blood donors and certain groups of blood-product-dependent recipients have established associations in the EU and the number of ethics bodies focusing on this field is low. It should also be kept in mind that the respondents for patients and donors were usually organisation representing larger groups. All other groups, including competent authorities, were considered satisfactorily represented.

2.3 Results of Stakeholder Consultation Activities

As all consultation activities were inclusive to all stakeholder categories, results are summarized by topic rather than by activity, or stakeholder group. Where relevant differences were expressed between stakeholder groups, those are reported.

Analysis of the results from the Public Consultation identified a coordinated response by 15 participants of the cord blood sector [13]. Some other respondents had also, evidently, coordinated their responses, but were represented by lower numbers (usually less than 10). These views usually related to considerations on specific sub-sectors (such as medically assisted reproduction or faecal microbial transplants), and tended not to have significant impacts on the choice between policy options or on the reference to specific measures.

2.3.1 Validity of Evaluation Findings

The feedback given to the IIA generally welcomed the revision of the legislation and supported the proposed objectives. It further highlighted the potential impacts of the revision on fundamental rights of EU citizens, such as the need to protect donors from discrimination and ensure universal access to high-quality treatments. These implications were taken into account when designing the two surveys.

The Public Consultation widely confirmed the validity of the evaluation findings [14].

[10] For more detailed analysis of the respondents, see Annex 18.
[11] Full documentation of the participant lists is provided in the External Study for the BTC Impact Assessment, ICF, Annex 14.
[12] Further details can be found in the final report of the External Study for the BTC Impact Assessment, ICF.
[13] See the public consultation factual summary report available at https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12734-Blood-tissues-and-cells-for-medical-treatments-&-therapies-revised-EU-rules/public-consultation_en
[14] https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12734-Blood-tissues-and-cells-for-medical-treatments-&-therapies-revised-EU-rules/public-consultation_en

2.3.2 Protecting patients

To ensure that patients receiving treatments based on substances of human origin are effectively protected from any risks, the revision aimed (i) to refine the scope of the framework to cover any gaps identified in the evaluation and (ii) to improve the setting of up-to-date technical rules.

SCOPE

Through formal consultation activities as well as ad-hoc contributions, stakeholders active in the fields of faecal microbial transplants and donated human breast milk repeatedly highlighted the increasing importance of their respective field and advocated for their inclusion within the future legislation. In the targeted consultation, 79 of 155 respondents agreed that the future framework should cover substances of human origin that do not meet the current definitions of blood, tissues, or cells, but are applied to patients, while 17 disagreed. Moreover, a majority of participants indicated that substances processed at bedside or during surgery should be included in the future framework. Less stringent requirements were preferred by 52 and 67 respondents respectively, while a majority of 67 respondents indicated that substances processed during surgery but outside of the surgical room should be subject to the full requirements.

On the other hand, some requirements proposed for the future legal framework were seen by stakeholders active in those fields as inappropriate for these potential new sub-sectors, prompting them to call for the development of separate sub-sets of legislation. This was also reflected in position papers submitted during the revision process. Some National Competent Authorities reported having developed own national guidelines to mitigate the current gaps and expressed concerns that they could be undermined. The support for a refined scope of the revised legislation, with a risk-based approach, was mirrored in the related Workshop [15].

Beyond suggesting specific substances to include, some competent authorities and establishments suggested clarifying that the scope includes all substances of human origin (10 mentions), or all substances of human origin intended for human application (9 mentions), while 3 stakeholders from the pharmaceutical industry and establishment representations in the transplant field advocated for keeping the scope of the legislation as is. Two authorities suggested allowing Member States to apply the framework to cover any gaps they observed in their jurisdiction.

Especially on the topic of the scope of the future framework, stakeholders repeatedly took the initiative to raise their proposals. This happened firstly through 3 bilateral meetings with a patient representation (breast milk) and a healthcare provider and a manufacturer (faecal microbial transplant), and secondly through 7 position papers from establishments and patient organisations (breast milk or faecal microbial transplants) and one authority (speaking on faecal microbial transplants).

[15] See summary of the workshop "Refining the Scope of the BTC Legislation" in https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/icf_summarynotes_stakeholder-workshops_en.pdf.

The related issue of definitions that stakeholders considered to be unclear was discussed in a workshop that resulted in a list of definitions that stakeholders wanted to be revised [16]. It was also discussed specifically in a meeting with a plasma industry stakeholder.

TECHNICAL RULES

To improve the protection of patients and donors, the revision proposes three policy options to ensure that technical rules are updated and kept flexible to reflect scientific and technological advances. In the Workshops and Hearings, blood and tissue establishments suggested to combine principles in EU legislation with the rule-setting by expert bodies, thus combining policy options 2 and 3. This combination was widely supported by National Competent Authorities and also brought up in the consultation surveys (4 mentions from public authority, tissue establishment and a professional representation thereof, and a standards setting organisation). Representatives from the cord blood sector, however, expressed (in the consultations and in a bilateral meeting) their view that policy option 3 was the most appropriate due to its harmonizing effect and the resulting predictability. In the IIA, some establishments indicated that option 3 was likely to maintain the current situation with its observed limitations, while authorities and establishments, and an academic body outlined that option 1 also holds limited promise to effectively address the objectives.

In the responses to the Public Consultation, a majority (112 to 145 out of 214 respondents, differing by sub-question on specific issues) indicated rule setting by expert bodies as the most effective option for patient protection. This option was also considered most cost-effective, with 123 out of all 214 respondents considering it 'very' or 'quite' cost-effective, as opposed to 109 respondents for policy option 1 and 76 for policy option 3. Blood and tissue establishments were notably a little more divided on this issue, with 45 selecting professionals (policy option 1) and 49 selecting expert bodies (policy option 2) as their preferred rule-setting level. This group was also slightly more inclined to consider rule setting by professionals very or quite cost-effective than other groups. No further explanation was provided. In a dedicated bilateral meeting, representatives of blood establishments expressed their support for policy option 2. In addition, topics related to Joint Actions in which Member States had been involved over the last years [17] were brought up in bilateral meetings and submitted documents, providing evidence in support of their application in the future framework.

Various consultation activities highlighted that a key challenge of the new approach to technical rules lies in reconciling the expected benefits of improved harmonization with concerns from National Competent Authorities that their currently applicable national rules may be undermined. National Competent Authorities as well as establishment representations, industry, and patient representations expressed high levels of interest in the procedures to be followed for the process of rule setting by Expert Bodies. In 148 free text comments, these groups mentioned success factors including transparency (29 mentions), clear references to the evidence base (24 mentions), and the need for adequate opportunities for stakeholder consultation (21 mentions, particularly from

[16] See the summary of the workshop "Key Definitions - Improvements and Additions" in https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/icf_summarynotes_stakeholder-workshops_en.pdf .

[17] For example Facilitating the Authorisation of Preparation Process for blood, tissues and cells (GAPP): https://www.gapp-ja.eu/ and EURO Good Tissue Practice II (EUROGTPII): http://goodtissuepractices.eu/.

academic/research institutions and industry stakeholders). Interestingly, respondents were divided on the importance of geographical representation of the experts included in rule setting. While 6 respondents indicated the need to ensure a balance, 5 responses indicated this should be of secondary importance to ensuring expertise on the topics at hand; no differences between stakeholder categories were observed.

Some concerns were expressed that will need to be considered, in particular regarding the status of EDQM, part of the Council of Europe, as an expert body that is not part of the EU. These concerns came largely from industry stakeholders, but also from a patient association, an establishment representation and 2 public authorities. Concretely, 4 participants highlighted that "the ECDC is an independent agency of the EU, and thus bound by its codes of practice, including transparency and accountability. The EDQM is not bound by the same principles." Eight highlighted that the Member States part of the Council of Europe, and of the EU, differ. One participant expressed concern that the reference to EDQM guidance may intensify observed competition between EU projects and EDQM for the limited number of experts in the field [18]. Additionally, 3 industry stakeholders highlighted that time for implementation by blood and tissue establishments needed to be ensured, and 3 authorities advocated that vigilance activities should remain under the guidance of the Commission instead of expert bodies.

The topic was also raised by authorities, healthcare providers, industry representations, and establishments through various position papers, submitted either ad hoc or in the context of the consultations. An authority stakeholder advocated for better harmonization and the healthcare providers and establishments suggested specific rules based on their experience.

Some specific issue within the wider realm of patient protection were brought up by stakeholders. Some industry stakeholders highlighted the potential role of Pathogen Inactivation technologies in addressing the problems tackled by the revision; this topic should also be addressed within wider discussions on technical rules. More importantly, the evaluation had identified innovative processing techniques taking place at the bedside of patients as an important topic of discussion for the revision process [19]. A dedicated workshop attended by public administrations, manufacturers, donors, establishments, and others concluded that patient protection could be achieved by an authorisation of the preparation process to remain proportionate to the risks patients are exposed to [20].

2.3.3 Protecting donors and children born from medically assisted reproduction

Although similar concerns apply to the protection of donors or children born from medically assisted reproduction, some specific stakeholder views were gathered and analysed. Consultation respondents from all categories expressed more granular views on rules for donor protection. From the three proposed options for rule-setting, EU legislation emerged as the most preferred option for donor protection and follow-up and consent rules (63 out of 149 and 73 out of 148 answers, respectively), while expert

[18] Participant's quote: "the problem of competition with EU-projects have been identified in the work with the EDQM-guide. The time and number of experts and health care professionals are limited. The risk of delaying EDQM revision must be considered before starting new EU-projects."

[19] https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/swd_2019_376_en.pdf.

[20] See details in the summary of the workshop "Regulating Point-of-Care BTC Processing (bedside and same surgical procedure)" in https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/icf_summarynotes_stakeholder-workshops_en.pdf .

bodies were most seen as the best source of rules for donor age limit and medical/behavioural history screening (70 and 100 out of 150 answers, respectively).

In a workshop on ethical issues of the revision attended by public administrations, establishments, patients, manufacturers, healthcare providers, academia, ethics bodies and others, most participants expressed agreement with the introduction of donor protection rules. Further details for implementation were discussed during dedicated workshops. Consensus was reached regarding mandatory reporting of donor reactions, internationally harmonised definitions, evidence-based donor selection criteria, and proportionate donor follow-up. Representatives of the non-reproductive tissue and cell sector specified donors of bone marrow and peripheral blood stem cells, as well as psychological impacts on donors, as important starting points/categories for donor follow-up.

In submitted position papers, two establishments active in the field of medically assisted reproduction called for the implementation of donor registries for sperm donors, while a healthcare provider from the medically assisted reproduction sector argued against this based on limited benefits observed in their national experience. A registry for children born from medically assisted reproduction was discussed in a workshop attended by public administrations, establishments, patients, and others and seen critically considering its limited expected benefit to individual children and a potentially misleading association between certain conditions and children born from medically assisted reproduction. An EU level list of minimum requirements for genetic testing was considered, but participants raised concerns that this may create disincentives and reduce the gamete donor pool.

2.3.4 Oversight

The evaluation found oversight practices in the sector to vary significantly across the EU. Support for increased harmonization was expressed by stakeholders from BTC establishments' representatives and industry. Stakeholders from industry and authorities also expressed their support for mutual recognitions of inspections (8 mentions in free text comments to the consultation surveys). Of the 214 respondents to the public consultation, the majority throughout all categories expressed support for the proposed measures to strengthen oversight and all four main measures received positive average ratings with limited critical ratings (expected positive impacts below 5 on a scale of 1-10 [21]) which are following:

(1) Regarding the 'introduction of oversight principles in EU legislation', 3 stakeholders from the medically assisted reproduction and organs sectors gave critical ratings. Overall, participants throughout all categories indicated agreement with the proposed oversight principles [22]; industry and authorities expressed support for their introduction in free text comments as well (5 mentions).

[21] https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12734-Blood-tissues-and-cells-for-medical-treatments-&-therapies-revised-EU-rules/public-consultation_en

[22] Further details in Annex 18: skills and competence of inspectors and other authority officials (122 agreed), lack of personal conflicts of interest of inspectors at each inspection (108 agreed), transparency to citizens (93 agreed), adequate administrative capacity (91 agreed), independence from the regulated sector (76 agreed), legal mandates to inspectors (60 agreed).

(2) For the 'introduction of EU audits', 14 negative ratings were given by authorities, business and industry stakeholders, research institutions and blood and tissue establishments.
(3) Different measures suggested for improving the 'cooperation among National Competent Authorities', such as joint inspections or peer audits, were rated low 15 times, by business/industry stakeholders, blood and tissue establishments, some authorities as well as a patient representation and a donor association. Some additional concerns regarding their practical implementation were identified in the workshop [23].
(4) Finally, an 'EU programme for training of staff in the competent authorities' received 6 critical ratings from tissue establishments, a patient organisation and an industry stakeholder.

From the 87 free text comments submitted on possible concerns regarding strengthened oversight measures, blood and tissue establishments, authorities, and healthcare providers expect an increase in costs (14 mentions), administrative burden (13 mentions), complexity (4 mentions), increased resource usage and workload (3 mentions respectively). Concerns regarding the availability of resources were underlined again by competent authorities and establishments in dedicated workshops attended by competent authorities and blood and tissue establishments. One healthcare provider indicated that these added costs may fall onto patients. Six comments from industry and public authorities also stressed the importance of risk-based approaches to oversight, while 4 comments from blood and tissue establishments highlighted the need for effective coordination between inspections at the EU level and at regional/local levels to ensure an added value.

When criticism was expressed, this usually referred to the scope of oversight rules. This included a coordinated response from 12 stakeholders active in the medically assisted reproduction sector, who cautioned that new EU measures may be incompatible with existing requirements at national level. Some stakeholders active in the ATMP field expressing the preference to keep their products regulated under the ATMP framework, and stakeholders active in faecal microbial transplants and human breast milk advocating for reduced requirements in their sectors to allow for differences in clinical use (perinatal tissues) and the persistence of existing national frameworks (faecal microbial transplants). In addition, 3 stakeholders (establishments and an authority) raised concerns that common EU measures may lower the quality of oversight in some countries.

2.3.5 Innovation

In response to the findings of the evaluation, the revision aims to support the development and supply of BTC that are processed or used in new ways, as long as they are demonstrated to be safe and effective. The measures defined are (i) improving regulatory advice and cross-sector collaboration at the borderlines with related health frameworks and (ii) ensuring that any therapy offered to patients is safe, of high quality, and effective.

BORDERLINES

[23] Concerns were raised in two workshops with establishments and competent authorities that some inspectors may be used to more stringent measures already in place in their Member States. Moreover, both operators and public authorities indicated risks of misinterpretation by the public if inspection reports were published.

Regulation of substances at the borderlines between the current framework for blood, tissues, and cells and related health frameworks (especially those for ATMPs, Medical Devices, and Medicinal Products [24]) may differ between Member States or be insufficient overall [25]. In the consultations, stakeholders were asked whether they were aware of cases in which they either (i) consider the criteria according to which substances are regulated to be unclear (104 replies out of 214 respondents), and/or (ii) consider that some substances could be regulated under a more suitable legal framework (54 replies out of 214 respondents). Examples given came from all stakeholder groups, but mainly from industry and Competent Authorities from the different frameworks. Respondents gave up to three examples each from a range of substances, focusing particularly on substances collected for a different future use, on microbiota, or on serum eye drops [26].

The problem of unclear borderlines was highlighted particularly by representatives of the pharma industry through a dedicated meeting as well as three position papers submitted within the consultations or the general revision process. A patient organisation representing patients with rare diseases raised related concerns in a bilateral meeting, flagging the increasing commercialization in the sector, mainly in the related ATMP field.

The 15 borderline case studies indicated that such problems led to geographical inequalities in access to novel therapies for patients, intentional circumvention of regulation by opportunistic innovators, decreased quality of processing techniques, and decreased patient access to innovative treatments as a result of disincentives to research and development [27].

Respondents to the consultations generally agreed that an EU-level structure for advice on whether a substance falls under the BTC framework would have positive impacts (rated with an average of 7 on a scale of 1 to 10) [28]. From 214 responses, 7 low scores of under 5, signalling an expected negative impact, came from industry/business stakeholders as well as blood and tissue establishments and one academic/research institution. An overwhelming majority of 164 out of 214 respondents from all categories indicated that this structure should coordinate with equivalent committees in related fields, a single negative response was made by a patient organisation. This overall conclusion was also mirrored in the workshop attended by competent authorities, establishments, donors, patients, manufacturers, healthcare providers, and academia. During the workshop, representatives of the Committee on Advanced Therapies (CAT) expressed concerns on and the need to consider efficiency for such coordination processes between different sector authorities. Respondents to the public and targeted consultations also agreed that the resulting advice should be publicly available (with one dissenting view from an industry stakeholder, out of a total of 148 responses) and that its work should be based on criteria set out in legislation (with five dissenting answers from public authorities and healthcare providers).

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[24] ATMP: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32007R1394&from=EN; Medical Devices: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745; Medicinal Products: https://eur-lex.europa.eu/legal-content/en/ALL/?uri=CELEX%3A32004L0024

[25] For detailed analysis of case studies, see Annex 11.

[26] For further details, see Annex 18.

[27] For detailed case studies, see Annex 11.

[28] https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12734-Blood-tissues-and-cells-for-medical-treatments-&-therapies-revised-EU-rules/public-consultation_en

PREPARATION PROCESS AUTHORISATION

For novel preparations of substances of human origin, the provision of legal requirements for demonstrating safety, quality, and efficacy were supported by a majority of stakeholders in all subcategories (155 out of 214 respondents). Twenty-six dissenting views came mainly from industry and blood and tissue establishments, referring to concerns regarding over-regulation or overlaps with existing requirements in the frameworks for Medical Devices or Medicinal Products.

2.3.6 Supply

The problem of supply sufficiency was specifically highlighted in the IIA feedback, a bilateral meeting with representatives from the pharma industry (PDMP manufacturers) and through statements from blood and tissue establishments as well as patient and donor organisations. Donor representatives argued that harmonized rules to ensure supply were needed to reduce the risks of over-donation and thus improve donor protection. European self-sufficiency was advocated for by a patient organisation and an establishment representation. On the other hand, one standard setting organisation expressed that supply in its Member States would be intermittently threatened if the revision implied drastic changes to existing national frameworks. In the IIA, some respondents indicated that they did not see the envisaged measures around data monitoring as tackling the root source of the problem.

Respondents to the Targeted Consultation indicated both a positive expected impact and a high or significant increase in administrative burden of the measures on which views were collected [29]. Especially promotional donation campaigns and measures that could increase trust, collaboration, and exchange between Member States were seen as an appropriate way to support supply of BTC (115 and 97 out of 143 respondents agreed, respectively). Each measure had two dissenting views coming from a healthcare provider, a blood establishment, and a public authority. While the majority of stakeholders supported investments into establishment equipment and staff (95 out of 142 respondents) as well as EU platforms for exchange of substances of human origins between Member States (81 out of 142 respondents agreed, dissenting views came mainly from industry), respondents throughout all stakeholder groups considered these would be associated with a considerable burden. The more granular measures of monitoring, reporting, preparedness planning, and improved exchange of substances of human origin to protect supply were also well received when presented by invited stakeholders from industry and blood and tissues establishment representations to the National Competent Authorities at the two Hearings on this topic.

Although largely considered helpful, especially by National Competent Authorities, some levels of concern were expressed regarding the introduction of contingency plans. Concerns were brought up by three plasma industry stakeholders that these may disrupt the flow of plasma between Member States. Four stakeholders (patient and donor organisations, an industry stakeholder and a blood establishment) questioned the general effectiveness of contingency plans. In addition, the measure proposing provisions to allow export bans was less supported across all stakeholder groups (52 out of 140 respondents indicated that this would not be appropriate).

[29] For the full list and further details, see Annex 18, Section II.

Participants throughout all categories repeatedly referred to the measures proposed in other areas of the revision to support a sustainable supply, such as for example those improving donor protection and harmonizing oversight. Moreover patients, donors, establishments and authorities underlined the importance of voluntary unpaid donation principle as a foundation of the sector. In the IIA feedback, arguments for reinforcement of voluntary unpaid donations in the future frameworks were made, while others saw it as a limiting factor for plasma collection in particular. Bilateral meetings and the annexes submitted to the consultations also referred to ethical considerations around the principles of voluntary unpaid donation. The workshop on ethical considerations, attended by competent authorities, ethics bodies, industry, establishments, patient representations, healthcare providers, academia, and others, underlined again the need for a sustainable supply of substances of human origins, on the basis of the prohibition of financial gain from the human body and its parts [30].

Beyond the suggested measures, repeated support was expressed for the introduction of Patient Blood Management [31] recommendations by stakeholders from pharmaceutical industry and research as well as a patient representation and a healthcare provider [32]. This was also brought up in two additional documents submitted by industry and a tissue establishment.

2.4 CONCLUSIONS

The consultation activities complemented each other to achieve a balanced evidence base with different types of responses and data collection activities. From all the stakeholder consultation activities organised, a preference for policy option 2 emerged. Analysis of quantitative data from the online consultation using Socrates [33] confirmed that the degree of conflict among stakeholders was low, as this preference was widely agreed between all stakeholder categories, and remained stable even when applying different weights to individual categories. Moreover, the consultation highlighted important concerns and elements for further discussion. Those were discussed in bilateral meetings with the relevant expert bodies during the revision process. When these concerns could not be satisfactorily addressed within the realm of policy option 2, flexibilities and links to other options were introduced in the form of a ‘cascade approach’ in the legal drafting. In addition, the analysis of respondents to the consultations highlighted once again the strong links between the blood sector on the one hand and the tissue and cell sector on the other, thus supporting the decision to combine both Directives into a single legal act on substances of human origins [34].

Analysis of the Public and Targeted Consultation results indicated support from National Competent Authorities for a strengthened role of ECDC and EDQM, considering that firstly, guidance from ECDC was appreciated as a lesson learnt from COVID-19, that

[30] In the workshop, most participants agreed that reference should be made to the guide developed by the Council of Europe (DH-BIO): https://rm.coe.int/guide-financial-gain/16807bfc9a.

[31] The European Commission has published guidance on the implementation of Patient Blood Management in 2017, based on the WHO definition of Patient Blood Management as "patient-focused, evidence based and systematic approach for optimising the management of patients and transfusion of blood products to ensure high quality and effective patient care". Further details: https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/2017_eupbm_authorities_en.pdf.

[32] For more details, see Annex 18

[33] For more details in the analysis with Socrates (social multi-criteria assessment of European policies), see IA SWD Section 8 and Annex 4

[34] Organs being excluded.

secondly, concerns regarding the scope and working methods from EDQM tended to come from other stakeholder categories, and that thirdly, preference for other options tended to be expressed by other stakeholder categories. Blood and Tissue Establishments, on the other hand, tended to express favour for rule-setting by professionals (policy option 1) in the Public Consultation, while making limited use of other consultation opportunities to specify any concerns.

Donors and patients as well as ethics bodies tended to raise important points to be taken into consideration during the implementation phase of the new legal framework, regarding for example voluntary unpaid donation principles or the use of new training opportunities for inspectors to ensure non-discrimination of donors based on their fundamental rights. Finally, National Competent Authorities and blood and tissues establishments expressed concerns regarding some specific measures would increase their costs or administrative burden. Consideration of EU level measures to provide support was taken into account when preparing the legal proposal.

ANNEX 3: WHO IS AFFECTED AND HOW?

3.1 PRACTICAL IMPLICATIONS OF THE INITIATIVE

3.1.1 Professionals working on any step of the chain from donor recruitment to clinical application of BTC

This legislation has an impact on the routine work of organisations in the public, non-governmental and private sectors that organise donation, banking and use of substances of human origin (excluding organs) for application to patients [35]. A transition period of 2 years is assumed, however, this could be modified during the negotiating and drafting phase of the legal proposal.

The technical provisions described in the cascade (M1B) will continue to address recipient protection but will be updated more frequently and will, therefore, be easier to apply at the entity level. Technical rules will be extended in scope to address donor protection and the protection of children born from medically assisted reproduction (M2B). This will impact on entities that organise donor recruitment and collection of BTC, as they will have to comply with new rules for donor selection and donor health monitoring. Most establishments have policies for donor selection and follow up that aim to ensure donor health, and adverse incidents are usually recorded in some way locally (M2A). Some centres working to international standards ensure that donor health is monitored even in the long term. But the approach to this varies considerably, with differing data elements, monitoring frequency and eligibility criteria applied. The added burden for this requirement will mostly involve adaptation to a common standard and data submission to registries and to the authority. The most significant additional administrative burden and cost will be the registration of all those donors where there is some risk to their health, i.e. they are pre-treated with hormones, subjected to an invasive procedure or they donate frequently over a period of time. The EU will invest in one or more EU-level registries to support donor registration and follow up so that these tools will not have to be put in place in each Member State or each entity.

With regard to strengthened oversight and extension of the scope to substances of human origin and certain steps affecting BTC safety and quality not currently addressed by the legislation, a number of entities will have new regulatory obligations (M1A). Health service providers that process BTC at the bedside or in surgery will have to register this activity with the competent authority. Donor registries, testing laboratories, commercial distributors and clinical users will also need to register their activities with the authority. The registration will be a simple process, online, re-using data submitted for multiple purposes and including a statement of compliance with any relevant provisions of the legislation. The EU-wide registration tool for professionals to authorities will be hosted and maintained by the European Commission. Existing blood and tissue establishments (including those in the EU Tissue Establishment Compendium) will be incorporated into this register.

All registered entities will have an obligation to submit an annual activity report and, in case of adverse incidents, to notify those to the competent authority without delay. Activity reporting will be a new obligation for many entities and for all those entities that

[35] For further description of the sectors, including the numbers of stakeholders and the scope of activities, see Annex 8.

are not within the scope of the current legislation. Nonetheless, all of these entities currently record their collection, processing, storage and distribution activities so the additional task will only be to submit it. Again, an EU-tool will be developed to facilitate reporting from professionals to their authorities and this tool could be used to replace the recording currently done at the entity level. Guidance for entities on reporting of data activity and adverse incident reporting will be provided and updated by EDQM and the Commission. Entities that do not process and store BTC will not be automatically inspected although the competent authority will have the power to conduct an inspection if it considers that to be necessary. A number of currently inspected establishments that carry out certain steps but do not process and store BTC can be moved to this less burdensome regulatory process. This could relieve administrative burden from some collection centres, testing laboratories, intra-uterine insemination centres and other entities. All those establishments that are authorised under the current legislation will be automatically included in the register of entities.

All entities that *process* BTC will need to apply to their competent authorities for a preparation process authorisation (M4B). Tissue establishments already have this requirement, although it is implemented in diverse ways, and in some Member States this has already been implemented for all BTC at a national level, with requirements for clinical studies to demonstrate safety and efficacy. There will now be a standardised approach to this authorisation process and the BTC entity will need to demonstrate safety, quality and also efficacy, when the degree of risk and/or novelty of the process indicates the need for clinical data/studies. This burden will be significant, particularly for those entities that are currently not required to have an authorisation for their preparation processes or where that authorisation is currently based exclusively on laboratory process validation. The need for clinical outcome data will be most common for those entities that are most active in the development of new technologies and BTC processes, or that support novel clinical uses of BTC. However, those particularly research and development oriented entities tend to be located in those Member States where more stringent requirements for preparation process authorisation are already in place. In the latter cases, the burden will involve adapting systems on a once-off basis to the common EU procedure.

The burden associated with the authorisation of new preparation processes will be significantly reduced by a provision that will allow for the recognition of EDQM monographs as an indication of established safety, quality and efficacy. Thus, when the preparation process and the clinical indication are already described in an EDQM monograph, the entity will need only to demonstrate compliance with the technical criteria in that monograph and the authorisation process will be considerably simplified. When this is not the case, the entity will be obliged to conduct a risk/novelty assessment and make a proposal for a study that is proportionate in extent and depth to the identified risk/novelty. It will be possible for entities to reduce the burden of conducting a risk assessment by using an existing online tool that has been developed and made available by an EU-funded project [36]. The authority will evaluate and, where appropriate, approve the proposal before any study is launched and the final results will be assessed before a full authorisation is granted. The conduct of studies that include clinical data collection will be one of the more significant costs associated with the new provisions. However,

[36] Trias E et al.; EuroGTP II Study Group. EuroGTP II: a tool to assess risk, safety and efficacy of substances of human origin. Int J Qual Health Care. 2020 Apr 21; 32(1):80-84.

the possibilities for sharing the evidence emerging from such studies, a practice that is typical in this sector, will reduce that burden.

Those entities that *process* and *store* BTC (i.e. BTC banks) will continue to be regulated as BTC establishments and will be regularly inspected, although the scheduling of those inspections will change from a fixed 2-yearly frequency to a risk-based scheduling approach (M3A). A number of establishments that are currently inspected every 2 years but represent low risk may move to less frequent inspections. A number of centres across the EU that currently collect and bank substances such as breast milk and faecal microbiota will now be subject to the provisions of this legislation and will need to be authorised and inspected as BTC establishments.

Where the regulatory pathway to follow for a newly developed preparation process is not clear to the entity, they will be able to refer their query to their authority who will in turn, be able to request advice from expert new EU-level BTC expert advisory group (M4A). This communication channel will also be available to SME/developers/manufacturers that are unsure regarding the applicability of this legislation to the substance/product that they are developing.

Those establishments that supply BTC for clinical use from the 'critical BTC' category [37] will be required to alert their authority when the supply of the substance falls below a pre-defined threshold and they will be obliged to have preparedness plans in place for any emergency that might threaten the supply of such substances. The burden associated with this obligation will not be significant as the process will be simple and will need to be used infrequently. Nonetheless, a common EU IT-tool will be developed to facilitate this reporting from professionals to their authorities.

3.1.2 Public authorities overseeing BTC activities

Member States will need to ensure that their competent authorities comply with the newly defined principles of independence and competence as defined in the new legislation (M3A). While many Member States currently have 2 or 3 authorities overseeing BTC and some have fully regional systems, they will all need to ensure that there is one co-ordinating BTC authority or contact point for all communication with other Member States and with the Commission. In many Member States, the authorities for blood and for tissues and cells are in fact the same organisation so this will not have a significant impact. In a small number, the authorities are entirely separate and they will need to co-ordinate with each other to comply with this.

Their work on inspection and preparation process authorisation will need to comply with Commission guidance that has been developed by working groups in which they are represented. Much of this work is already ongoing on a voluntary basis in EU-funded projects and in Expert Sub-groups. The new legislation will clearly define how such work among authorities should be developed as Commission guidance for common implementation. Authorities will be able to register their inspectors, assessors and vigilance officers in training programmes provided by the Commission (M3B). When

[37] 'Critical BTC' will be defined in legislation and will include those substances where, in case of a supply shortage or interruption, patient treatment would be delayed or cancelled and patient health would be compromised significantly. The category would include blood for transfusion, haematopoietic stem cells, heart valves, corneas and skin.

conducting inspections and process authorisations, the authority personnel will need to ensure that establishments and other entities apply correctly the provisions of the legislation as well as the technical standards defined by ECDC and EDQM as referenced in legislation. The authorities will be actively engaged, through their nominated experts in reviewing and giving feedback on the technical standards developed by EDQM (M1B and 2B).

The authorities will need to ensure that all relevant entities working with substances of human origin that were not previously within the scope of the legislation have registered their activities on the new EU register (M1A). Establishments authorised under the current framework will have their details registered automatically in the new register. The authorities will need to review those registrations to assess which entities comply with the establishment definition and need to be inspected. They will be able to access and download aggregated activity and vigilance data from the new register hosted by the Commission. A common EU IT-tool will be developed to facilitate this work.

Their process authorisation work will increase in volume, including blood as well as the current tissues and cells and extending to processes being applied by entities at the bedside or in surgery. It will also increase in complexity due to the new provision for including, when proportionate to the assessed risk, an evaluation of clinical outcome data and possibly even clinical trials (M4B). However, the reference to EDQM monographs and the sharing of process authorisation details of other Member States in the new EU digital tool will significantly reduce the amount of administrative burden associated with this obligation as competent authorities will be able to accept the valid authorisations carried out in other Member States. In some cases, the authority work in process authorisation will reduce as they will have access to the authorisations of other Member States on the EU register and will be able to recycle tis information and accept the use of those processes in their Member State without repeating the assessment process. For example, many of the processes applied at the bedside or in surgery involve the use of a medical device and their performance is standardised in the device instructions. A single authorisation of such a process can be re-used multiple times across the EU as long as the process is carried out identically in all sites.

The inspection work of authorities will continue with similar resources but they will have more freedom to schedule the inspections according to risk and to focus on those that are most necessary (M3A). Commission guidance for this assessment will be issued, in consultation with the Member States. They will be able to access the expertise of other Member States when needed for the conduct of a Joint Inspection. The legislation will define the conditions in which Joint Inspections can be requested. The authority will receive notifications from establishments when the supply of any critical BTC falls below a pre-defined threshold and policy action is needed to protect the supply for patients. The authority will also have access to EU-wide activity data so will be able to better understand the flow of BTC between Member States and with third countries (M3B). In this way, they will be equipped to inform policy makers, e.g., of the need to launch donation promotion programmes or to establish agreements with other Member States to better balance out shortages and surpluses.

Where the regulatory pathway to follow for a newly developed preparation process is not clear to the authority or where more than one framework applies to a substance/product, the authority will be able to refer its query to an EU-level expert committee for advice.

That committee, in turn, will be able to liaise with the equivalent expert committees of other adjacent frameworks to ensure a coherent advice and oversight (M4A).

This impact assessment took account of differences between Member States. In particular the size of Member States plays a role, with 4 large Member States (DE, FR, IT and ES) counting for 63% of all establishments and having already many of the proposed measures in place. This impacts the baseline, and consequent extra costs for measures. An EU budget is foreseen for technical assistance to help offset extra costs for those countries that do not have equivalent national measures already in place, as they are often smaller and central and Eastern European Member States. Some measures, allowing for sharing of information and joint working on inspections and preparation process authorisations, might even entail a saving for countries that have more stringent systems already in place (fall under the baseline). These are not included in the cost model, but listed as potentials for simplification.

3.1.3 Citizens

Obligations on citizens will be minimal and mostly associated with compliance with technical standards defined by expert bodies and relating to providing an accurate medical and behavioural history when donating BTC. However, such obligations are already implied in national legislation. However, transparency to citizens will increase as a result of the measures proposed. Notably, they will be able to consult the new EU-wide digital platform to see where donation and supply programmes are adequate to meet patient needs and where there is reliance on import or exchange with other Member States. Donor health will be better monitored and donors will have the possibility to report adverse outcomes directly to their authorities if they consider it necessary.

3.2 SUMMARY OF COSTS AND BENEFITS

I. Overview of Benefits (total for all provisions) – Preferred Option		
Description	***Amount***	***Comments***
Direct benefits		
Graded oversight approach allows to oversee some establishments with lighter approach and less resources than today (related to measure M1A)	EUR 4 m	750 establishments eligible, mainly saving on inspection costs for authorities and for themselves
Common IT-platform to share assessments of novel BTC technologies reduces duplications (related to measure M4A)	>EUR 2 m	Conservative estimate; Requests to authorize same new technologies are introduced and assessed in parallel across EU; Sensitive to unit cost of assessments and authorisations
Risk-based schedule allows to inspect same	Not quantified	Model has rather assumed this to be a cost-neutral measure as the same number of

activities/establishments more efficiently (targeting high-risk activities) (related to measure M3A))		resources (inspectors) allow for more oversight on most complex activities
Greater harmonisation of technical standards, through legal references to common rules set by expert bodies and joint Member State inspections will allow recognition of authorisations in other Member States, reducing the need for ad-hoc import authorisations in different Member States (M1B and 2B)	EUR 0.5 m / year	Applicable for almost 1,000 imports per year of blood stem cells (from bone marrow or peripheral blood) though central registry (WMDA registry, could be subject to one joint authorisation)
Deleting obsolete tests and screening measures (related to measure M1B)	EUR 2 m (example – West Nile Virus NAT tests)	Very high potential, given that every saving is multiplied by number of donations Example: West Nile Virus (WNV) can be tested for by individual NAT test or by pooled NAT test, which is EUR 7 cheaper per tested donation. Applicable to around 300,000 blood donations per year in countries affected by WNV
Employment /skills		The investment in the digitalisation and future-proofing of the sector will increase the sector specific expertise (e.g. inspectors) and digital skills in an innovative, knowledge-intensive sector
Digitalization allows for more efficient administrative processes in authorities and establishments	To be further quantified	The SOHO IT platform, financed by the Commission will facilitate local administration including registration and reporting by professionals as well as authorizations and oversight by authorities. E.g., annual reporting costs are estimated to go down from current 5,000-15,000EUR to 200-2000EUR with an automated reporting tool.

Indirect benefits		
EU patients	Not quantified	Access – streamlined and harmonized legal framework improves (cross-border) access to matching BTC and early access to safe new therapies
EU citizens donating BTC	Not quantified	Trust and willingness to donate – more donations by citizens that can trust their own health is well protected
Public health budget holders	Not quantified	Improved affordability - more and new therapies with high value, but typically offered at cost-price by public actors. Access to standardized data to help assess real value of therapies.
Medical device companies	Not quantified	Market increase - increase of BTC activities required equipment and continuous supply of devices and diagnostics.
Manufacturers of medicinal products	Not quantified	Market increase - streamlined and harmonised BTC framework facilitating access to starting materials for BTC-based medicinal products (plasma derivatives, advanced therapies)

Table 3.1 Overview of Benefits (total for all provisions) – Preferred Option

(1) Estimates are relative to the baseline for the preferred option as a whole (i.e. the impact of individual actions/obligations of the preferred option are aggregated together);

II. Overview of costs – Preferred option								
Over 10 years, 1000 EUR		EU		Businesses (incl. BE/TEs and healthcare)		National Administrations	
		One-off	Recurrent	One-off	Recurrent	One-off	Recurrent
Obj 1 – Patient protection	Direct costs	1 474.6	1 343.3	25 109.1	9 441.3	1 760.7	1 402
	Indirect costs						
Obj 2 – donors & offspring protection	Direct costs	1 224.6	1 057.6	28 475	12 241.3	-	722
	Indirect costs						
Obj 3 - Oversight	Direct costs	4 918.3	3 051.7	-	-	5 000	49.6
	Indirect costs						
Obj 4 - Innovation	Direct costs	2 846.1	1 944.3	992.3	4 137.8	2 810.7	667.5
	Indirect costs						
Obj 5 – supply monitoring	Direct costs	1 699.2	1 258.1	28 402.7	2 563.7	213.2	327.1
	Indirect costs						

Table 3.2 Overview of costs for the preferred option – by Objective.

(1) Estimates provided with respect to the baseline;

II. Overview of costs – Preferred option									
Over 10 years, 1000 EUR				Businesses (incl. BE/TEs and healthcare)		National Administrations		EU	
Objective	Measure			One-off	Recurrent	One-off	Recurrent	One-off	Recurrent
Patient protection	**M1A** - Fill regulatory gaps (e.g. FMT, breast milk)	M1.2: EU law incorporates definitions ensuring that safety and quality provisions apply to all SOHO/BTC for which the Treaty give competence to the EU.	Direct costs	2 553.6	1 212.9	632.9	421.9	73.8	71.6
			Indirect costs						
		M1.9: "Same surgical procedure" exclusion for point of care preparations is refined/removed - hospitals, healthcare providers are required to register their activities and report.	Direct costs	22 555.5	4 702.5	1 127.8	477.1	375.6	231.6
			Indirect costs						
	M1B – up-to-date technical rules	M1.3: EU law requires MS to publish more stringent rules in an accessible format.	Direct costs				17.4	122.2	111.6
			Indirect costs						
		M1.7: EU law requires establishments to take into account ECDC/EDQM rules on quality & safety requirements.	Direct costs		3 525.8		485.5	787.8	928.7
			Indirect costs						
Donor & offspring protection	**M2A** - Set donor and offspring protection principles in law	M2.1: EU law on donor safety amended to regulate donor eligibility, protect donor health, protect donor personal data and ensure donor ad	Direct costs	18 903.4	8 542.8		548.1	497.8	343.1
			Indirect costs						

		verse outcomes are reported and investigated.							
	M2B - Up-to-date technical standards for donor and offspring protection	M2.7: EU law requires establishments to take into account ECDC/EDQM rules on quality & safety requirement for donors and offspring from MAR.	Direct costs	9 571.5	3 698.5		173.9	575.6	7145
			Indirect costs						
Oversight	**M3A** - Set principles for oversight in legislation (e.g. independence of authority, risk-based inspections)	M3.1: EU law incorporates oversight principles for the organisation and for staff	Direct costs			5 000		90.7	171.7
			Indirect costs						
		M3.2: EU law obligates NCAs to base their inspection regimes on a risk-based approach.	Direct costs				-118.7	90.7	171.7
			Indirect costs						
		M3.5: EU law provides legal framework for Joint Member State inspections of blood and tissue establishments	Direct costs				154.7	987.9	669.9
			Indirect costs						
		M3.4: Commission audits of national control systems, accompanied by MS experts	Direct costs				13.6	987.9	669.9
			Indirect costs						
		M3.6: EU Support for training & IT	Direct costs					2 307.4	1 368.3
			Indirect costs						

Innovation	**M4A** - Create BTC mechanism to advise on applicability of BTC legislation and liaise with equivalent MD and (AT)MP mechanisms	M4.1 & M4.3: Establishment of EU level advisory mechanism to recommend/advise MS on when/what BTC requirements should be applied in part or in full. And: 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 MP (EMA innovation task force, EMA CAT) and MD frameworks (Borderlines and Classification Working Party).	Direct costs					362.9	686.9
			Indirect costs						
	M4B - Risk-based authorisation BTC processed or used in new ways, including clinical data when justified, with guidance	M4.4-5-6-7: 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 data demonstrating safety and benefit for patients that justifies any risks associated with treatment with BTC prepared in innovative	Direct costs	992.3	4 137.8	2 810.7	667.5	2 029.6	1 257.4
			Indirect costs						

		ways. And EU law obligates BE/TEs to conduct risk assessments on novel processes in compliance with technical guidance from expert bodies as referred to in EU legislation							
Supply monitoring	**M5A** – introduce supply monitoring and notification rules	M5.3: EU law is amended to require mandatory emergency plans, for critical BTC, at the level of the blood and tissue establishments, and national competent authorities.	Direct costs	11 752.7	-523.8	0.1	306.1	276.2	429.1
			Indirect costs						
	M5B – Require emergency preparedness plans with guidance	M5.5-6-7-8: EU law is amended with references to guidance from expert bodies for rules on sufficiency data reporting (incl monitoring and notifications) and on emergency preparedness/contingency.	Direct costs	16 650	3 087.5	213.1	20.9	1 120.6	829.1
			Indirect costs						

Table 3.3 Overview of costs for the preferred option – by Measure.

(1) Estimates provided with respect to the baseline;

ANNEX 4: METHODOLOGY - MULTI-CRITERIA DECISION ANALYSIS METHODOLOGY

This section describes the analysis of the impacts with the Social Multi-criteria Evaluation (SOCRATES) model developed by the Joint Research Centre.

4.1 Basic description of Social Multi-Criteria Evaluation (SMCE) methodological framework and software tool

SOCRATES (**SO**cial multi **CR**iteria **A**ssessmenT of **E**uropean policie**S**) is a new multiple criteria assessment software tool, explicitly designed for *ex-ante* Impact Assessment (IA) problems [38].

Quantitative evidence plays an important role in many IAs, but also qualitative data such as stakeholder input, conclusions of evaluations, as well as scientific and expert advice are frequently used. This generates a multitude of criteria, which should be consistently integrated and evaluated when comparing policy options. The most widespread multidimensional approach to ex-ante IAs is multi-criteria decision analysis, which forms the basis for SMCE [39], which has been explicitly designed for public policy. SMCE allows taking into account a wide range of assessment criteria, such as the impact on SMEs, the degree of protection of fundamental rights, consumer protection, etc. while all the multidimensional profiles of the problem remain in their original scales of measurement. Indeed, the latter is the main difference with traditional cost-benefit analysis (CBA), which grounds on steps like monetizing all social, environmental, and human rights aspects. In this respect, CBA and SMCE are not conflictual but complementary, as CBA can be utilised as component of a SMCE framework, dealing with the economic dimension.

Overall, the objective of SOCRATES and the underlying SMCE methodology is not to substitute policy-makers through a mathematical model, but to improve their understanding of the main features of the problem at hand, such as key assumptions, degree of uncertainty, robustness of results and overall technical and social defensibility of options chosen. While SMCE has already been applied in a multitude of policy problems, its recent technical implementation SOCRATES is now applied for this Impact Assessment.

SMCE proceeds on the basis of the following main concepts: dimensions, objectives, criteria, weights, criterion scores, impact matrix and compromise solution.

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[38] Ownership details: The software has been developed in the context of the European Commission's Competence Centre on Modelling (Non free license).

[39] Munda, G., A social multi-criteria framework for ex-ante impact assessment: Operational Issues, EUR 28752 EN, Publications Office of the European Union, Luxembourg, 2017, ISBN 978-92-79-72293-6, doi:10.2760/909528, JRC107899.; Munda, G., Dealing with Fairness in Public Policy Analysis: A Methodological Framework , EUR 28751 EN, Publications Office of the European Union, Luxembourg, 2017, ISBN 978-92-79-72292-9, doi:10.2760/75185, JRC107843.; Munda, G., On the use of Cost-Benefit Analysis and Multi-Criteria Evaluation in ex-ante Impact Assessment, EUR 28768 EN, Publications Office of the European Union, Luxembourg, 2017, ISBN 978-92-79-73213-3, doi:10.2760/311199, JRC107900.

- **Dimension** is the highest hierarchical level of analysis and indicates the scope of objectives, criteria and criterion scores. In IA studies, the general categories of economic, social and environmental impacts are dimensions.
- **Objectives** indicate the direction of change desired, e.g. growth has to be maximized, social exclusion has to be minimized, and carbon dioxide emissions have to be reduced.
- A **criterion** is a function that associates alternative actions with a variable indicating its desirability.
- **Weights** are often used to represent the relative importance attached to dimensions, objectives and criteria. The idea behind this practice is very intuitive and easy, that is, to place the greatest number in the position corresponding to the most important factor.
- A **criterion score** is an assessment of the impact consistent with a given criterion with reference to a policy option. Criterion scores can be both qualitative and quantitative.
- The **impact matrix** presents in a structured way, the information on the various criterion scores, i.e. each element of the matrix represents the performance of each option according to each criterion.

In general, in a multi-criterion problem, there is no solution (ideal or utopia solution) optimizing all the criteria at the same time, and therefore **"compromise solutions"** have to be found.

In summary, a SMCE approach can supply a methodological framework where the hierarchical structure of the option comparison step of a typical ex-ante IA (including dimensions, objectives and evaluation criteria) is clarified as much as possible by means of well-established concepts in the decision theory literature. This might help in increasing the degree of homogeneity across IA studies. The SOCRATES software helps structuring such a methodological framework.

A typical SOCRATES input requires the definition of policy options (called alternatives) dimensions, objectives and criteria. This information leads to the construction of an impact matrix, which may include crisp, stochastic or fuzzy measurements of the performance of an alternative with respect to an evaluation criterion. Qualitative information can be introduced too (in the form of linguistic or ordinal criterion scores). Weights as importance coefficients, may also be introduced. They can be attached to dimensions or criteria. Indifference and preference thresholds can also be introduced when needed. Generally a social conflict matrix is also constructed, where the impacts of each policy option on each social group are presented in a transparent way.

In our Impact Assessment study, first policy options were generated, and then entered in SOCRATES.

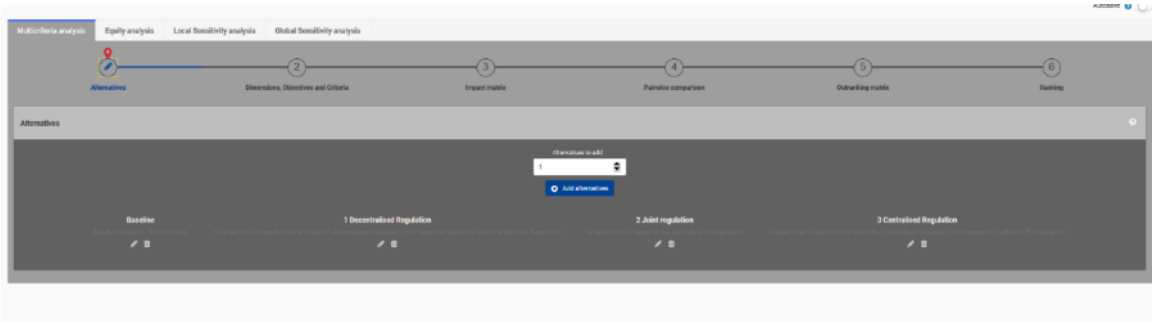


Figure 4.1: screenshot Socrates entry page

For a searchable overview of the individual measures, see the Policy Option tab on the dashboard.

As a next step, impacts and evaluation criteria were identified according to the Better Regulation Guidelines. These are presented in the following Table 4.1.

Dimension	Impact type	Specific Objective	Agreed criterion	Scoring	BL	PO1	PO2	PO3
Social	Public health	1 - patient protection	Agility of the regulatory system to respond to avoidable risks - time required for updates: Minimum time required to update/issue technical guidance in an emergency situation on safety and quality by the relevant experts in all MS (months)	**Minimum** time required to update/issue technical guidance **in an emergency situation** on safety and quality by the relevant experts in all MS (months)	6-12	1-36	1-6	6-12
Social	Public health	1 - patient protection	Agility of the regulatory system to respond to avoidable risks - time required for updates: Typical time required (end to end) to revise rules and bring them into force (months)	**Typical** time required (end to end) to revise rules and bring them into force (months)	180	1-36	12	48
Social	Public health	1 - patient protection	Availability of timely information for risk management on serious adverse events for patients	0 some information is available for risk management (BE/TE, clinicians, publish health authorities, researchers) on certain high risk events; not consistent across MS, no possibilities for advanced analytics + data available for all MS + consistent, structured, single reporting - data available on high risk events allowing advanced analytics	=	++	++	++
Social	Public health	1 - patient protection	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) baseline = consistency across some MS - possible inconsistency within countries +++ consistency across all MS	=	-	+++	+++

Social	Public health	1 - patient protection	Ability of the regulatory system to respond to avoidable risks -mobilising relevant scientific and technical knowledge in the BTC sectors	baseline = Engagement of experts with the relevant expertise and resources for the updates/issuing technical guidance on safety and quality - inconsistent; across MS and BE/TE s depending on their size and available resources + high quality expertise available to all MS	=	-	+++	+
Social	Public health	1 - patient protection	Mobilising relevant scientific and technical knowledge in the BTC sectors for the updates of guidance	baseline = Engagement of experts with the relevant expertise and resources for the updates/issuing technical guidance on safety and quality - inconsistent access to expertise; across MS and BE/TE s depending on their size and available resources + high quality expertise available to all MS	=	-	+	+
Social	Public health	1 - patient protection	Stakeholder confidence on the effectiveness of options in achieving patient protection from all avoidable risks	table 6.1 baseline = no impact + partially solve ++ more than partially solve +++ substantially solve	=	+	+++	++
Social	Public health	2 - protection of BTC donors and offspring	Agility of the regulatory system to respond to avoidable risks - time required for updates: Typical time required (end to end) to revise rules and bring them into force (months)	**Typical** time required (end to end) to revise rules and bring them into force (months)	180	1-36	12	48

Social	Public health	2 - protection of BTC donors and offspring	Availability of timely information for risk management, e.g. on issues with specific donors and with children born to donated gametes and embryos - a comprehensive, prompt reporting of serious adverse events (including self-reporting by donors)	baseline = some information is available on certain high risk events for risk management (BE/TE, clinicians, publish health authorities, researchers); not consistent across MS, not comparable + structured, comprehensive and consistent information is available on high risk events + information is consistently available across MS + information is available on all adverse events	=	++	++	++
Social	Public health	2 - protection of BTC donors and offspring	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) baseline = consistency across some MS - possible inconsistency within countries +++ consistency across all MS	=	=	+++	+++
Social	Public health	2 - protection of BTC donors and offspring	Ability of the regulatory system to respond to avoidable risks -mobilising relevant scientific and technical knowledge in the BTC sectors	baseline = Engagement of experts with the relevant expertise and resources for the updates/issuing technical guidance on safety and quality - inconsistent; across MS and BE/TE s depending on their size and available resources + consistent expertise available to all MS +++ high quality expertise available to all MS	=	-	+++	+

Social	Public health	2 - protection of BTC donors and offspring	Agility of the regulatory system to respond to avoidable risks - time required for updates : Minimum time required to update/issue technical guidance on safety and quality by the relevant experts in all MS (months)	**Minimum** time required to update/issue technical guidance on safety and quality by the relevant experts in all MS (months)	6-12	1-36	1-6	7-12
Social	Public health	2 - protection of BTC donors and offspring	Stakeholders' confidence that the options will achieve a stronger level of protection for OFFSPRING	Summary of stakeholder preferences baseline = no impact + partially solve ++ more than partially solve +++ substantially solve	=	=	+	+
Social	Public health	2 - protection of BTC donors and offspring	Stakeholders' judgement on the options' expected performance in protecting donors from avoidable risks that the options will achieve a stronger level of protection for DONORS	baseline = no impact + partially solve ++ more than partially solve +++ substantially solve	=	+	+++	++
Fundamental rights	Transparency/ access to data	2 - protection of BTC donors and offspring	Consistent application of privacy provisions for personal data in the BTC framework. Offering secure infrastructure, technical assistance and GDPR advice will ensure that this data is secure and GDPR provisions are respected to ensure the protection of personal data. (Charter of Human rights article 5)	= a high level of protection is guaranteed with a scope for improvement on consistent application of privacy provisions + improvements in the consistency (through legal advice, technical alignment)	**=**	**+**	**+**	**+**

Fundamental rights	Transparency/ access to data	2 - protection of BTC donors and offspring	Donors confidence that the measures would improve fundamental rights	0 no change + partial improvement ++ improvement +++ significant improvement				
Fundamental rights	Transparency/ access to data	2 - protection of BTC donors and offspring	Improving the level of human health protection for children born from donated sperm, eggs or embryos by reducing the risks of inherited genetic conditions (Charter of Human rights article 35)	= some provisions exist to prevent that children born from donated gametes are born with genetic conditions + improved roles on donor testing; reducing the probabilities of children to be born with certain genetic conditions	=	+	+	+
Fundamental rights	Transparency/ access to data	2 - protection of BTC donors and offspring	Revising discriminatory terms and provisions (e.g. consistency in the term 'partner'; deferral from donation must be proportional to risk) (Charter of Human rights article 21)	= a high level of protection is guaranteed with a scope for improvement + provisions reduce discrimination; no discriminatory terms used	=	+	+	+
Fundamental rights	Transparency/ access to data	2 - protection of BTC donors and offspring	Stakeholder confidence that the measures would improve fundamental rights	baseline = no change + partial improvement ++ improvement +++ significant improvement	=	+	++	++

Fundamental rights	Transparency/ access to data	2 - protection of BTC donors and offspring	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. Transparent access for the public and experts to information on the use of donated BTC (through aggregated indicators from activity data: public health indicators, descriptions of standards, processes, excluding personal health data)	+ transparent access to data as appropriate to public and professionals + possibility for donors to directly report serious adverse events	=	+	+	+
Fundamental rights	Transparency/ access to data	2 - protection of BTC donors and offspring	Transparency: Strengthening Patients and donors' informed consent: right to know what will happen with the donations / information about the potential risks of the therapy. Transparent access for the public and experts to information on the use of donated BTC (open data and open processes on the SOHO-X platform on aggregated indicators from activity data: public health indicators, descriptions of standards, processes, excluding personal health data) The possibility of self-reporting of adverse events by donors improves participation		=	+	+	+
Economic	Internal market	3 - oversight	Stakeholders' judgement on the expected effectiveness of options in achieving Objective 3 (strengthening and harmonisation of oversight)	baseline = no impact + partially solve ++ more than partially solve +++ substantially solve	=	+	+++	+++

Economic	Public health systems - sustainability	3 - oversight	Efficiency of the oversight - the extent to which the inspections are proportionate to the risks of activities	Number of MS using a consistent risk-based approach in overseeing blood, tissues and cells establishments	12	27	27	27
Social	Public health	4 - Innovation	Impact on patients' access to therapies using BTC processed or used in new ways with proven added value	baseline = certain innovative substances public sector entities are not able to develop/provide, 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)	=	+	+	+
Social	Public health systems	4 - Innovation	Safety of BTC processed or used in new ways - evidence on the safety and efficacy is available demonstrating the clinical efficacy outweighs the risk. E.g. Stamina (Italy)	Baseline = in the authorisation procedure only safety and quality is taken into account. There is no evidence on the efficacy + evidence on efficacy is requested for authorisation in proportion to the risk; + consistent application across MS (clinical evidence required in proportion to the risk) + authorisation data is shared to facilitate reuse, efficiency and consistency across MS	=	+++	+++	+++

Economic	Innovation and research	4 - Innovation	Impact on innovation in the BTC sector: 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 ;)	= 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	+	++	++	++
Economic	Innovation and research	4 - Innovation	Impact on innovation in the BTC sector: public sector innovation	Baseline = certain innovative substances public sector entities are not able 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. There is improved, but still transparency; as some elements remain confidential and proprietary information (e.g. in bone cleaning technologies) + open innovation model (e.g. clinical societies sharing studies in blood sector)	=	++	++	++

Economic	Innovation and research	4 - Innovation	More consistent and better improved national process authorisations: number of MS sharing data on national authorisations	baseline = under 10 + over 10, under 20 ++ over 20, but not all MS +++ all MS	=	++	++	++
Economic	Innovation and research	4 - Innovation	Regulatory coherence 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)	baseline = some BTCs are not regulated; for others, inconsistent application of the adjacent legal frameworks across MS + 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	=	++	++	++

Economic	Innovation and research	4 - Innovation	Regulatory coherence the extent to which there is consistent/comparable regulatory requirements for BTC, including coherence across legal frameworks (BTC, pharma, med tech):	baseline = the regulatory requirements for demonstrating quality, safety and efficacy are substantially different depending on the framework + consistency the level of evidence required to for demonstrating quality, safety and efficacy are comparable 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	=	++	++	++
Economic	Innovation and research	4 - Innovation	Stakeholder confidence that the proposed measures would result in a strengthened and consistent preparation process authorisation system that is outcome based	table 6,4 baseline = no impact + partially solve ++ more than partially solve +++ substantially solve	=	+	+++	++
Economic	Internal market	4 - Innovation	Stakeholder confidence that the measures would improve internal market and competition situation	baseline = no change + partial improvement ++ improvement +++ significant improvement	=	+	++	++

Economic	Public health systems - sustainability	4 - Innovation	Efficiency of authorisation - the extent to which the authorisations are proportionate to the risks of activities	baseline = some MS +++ all MS	=	=	+++	+++
Economic	Public health systems - sustainability	4 - Innovation	Sustainability of health budgets. The extent to which evidence is available for national/local decision for the effective use of healthcare budget (i.e. identifying the cost-effective BTC) - including the availability of scientific evidence for treatment protocols and guidelines; pricing and procurement or more formalised health technology assessment process	0 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	=	++	++	++
Social	Public health	5 - Supply Sufficiency	Resilience of the BTC supply: **availability of information** to predict and manage shortages/risks of interruption including emerging infectious health threats	0 information is available in some MS, 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 MS +timely availability	=	+	+++	+++

Social	Public health	5 - Supply Sufficiency	Resilience of the BTC supply: **preparedness** to effectively and timely management to react to and manage shortages/risks of interruption including emerging infectious health threats - Comment - This will facilitate the integration of this sector in broader EU initiatives (EU Partnerships on Pandemic Preparedness)	= permanent cooperation allows MS to coordinate crisis response + Strengthened capacities in MS to intervene to control and adjust supply, contingency plans are available but are not consistent across the EU ++ Strengthened capacities in MS to intervene to control and adjust supply, consistent, high quality contingency plans are available in all MS 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)	=	+	++	++
Social	Public health	5 - Supply Sufficiency	Stakeholder judgement on the expected effectiveness of options in achieving Objective 5 (avoiding shortages of critical BTC therapies)	baseline = no impact + partially solve ++ more than partially solve +++ substantially solve	=	+	++	++

Economic	Competitiveness	all	Stakeholder confidence that the measures would improve competitiveness, trade and investment flows	0 no change + little improvement ++ some improvement +++ significant improvement	=	+	++	++
Economic	costs of implementation	all	Cost of implementation EU budget	1000 EUR. NPV per year over 10-year period	350 000	6 411	6 986	8 519
Economic	costs of implementation	all	costs of implementation Range (cone of uncertainty at this phase of development) 25%- 400%	see Annex 19	=	139 200	738 000	1 089 000
Economic	costs of implementation	all	Costs of implementation for the BTC sector - BE-TE and healthcare providers	1000 EUR. NPV per year over 10-year period	125 667	171 887	156 281	156 363
Economic	costs of implementation	all	Costs of implementation for the BTC sector -Public Administrations	1000 EUR. NPV per year over 10-year period	15 473	18 761	18 524	18 524
Digital	Digitalisation	all	Data management: the extent to which the system can ensure data quality	see Annex 19	=	=	+	++
Digital	Digitalisation	all	Easiness in evolution: technology and scalability	see Annex 19	=	+	+	++
Digital	Digitalisation	all	Interoperability: the extent to which the system allows a consistent and integrated view of all the relevant data	see Annex 19	=	=	+	++
Digital	Digitalisation	all	Resilience: the extent to which the system can react to critical situations.	see Annex 19	=	=	=	+

Table 4.1: construction of the multi-criteria impact matrix

At this stage, impacts were assessed (cf. Report from the External Study for the BTC Impact Assessment) and validated with three BTC sector senior experts. Then, impacts were entered in SOCRATES. For a searchable overview of the criteria/impacts/methodological notes, as well as the impacts for baseline and the three policy options, see the SOCRATES Impacts tab on the dashboard.

4.2 Application of the SOCRATES mathematical procedure

The importance of mathematical approaches in SMCE is their ability to allow a consistent aggregation of the diverse information. Otherwise, even if everybody would agree on the multidimensional nature of an IA study, the implementation in a real-world assessment exercise would be impossible. The standard objection might be that the aggregation of apples and oranges is impossible. Multi-criteria mathematics does answer to this objection in a definitive way. When using mathematical rules, consistency between the problem structuring and the ranking of policy options is guaranteed, this makes the overall IA study much more defensible.

SOCRATES makes all required computations very quick. From a mathematical point of view, the information contained in the impact matrix useful for solving the so-called multi-criterion problem is:

- Intensity of preference (when quantitative criterion scores are present).
- Number of criteria in favour of a given alternative.
- Weight attached to each single criterion.
- Relationship of each single alternative with all the other alternatives.

Combinations of this information generate different aggregation conventions, i.e. manipulation rules of the available information to arrive at a preference structure. The aggregation of several criteria implies taking a position on the fundamental issue of compensability. For example, in evaluating a policy option that presents a very bad environmental impact and a very good economic impact, it is clear that allowing or not for compensability and to which degree is the key assumption.

An aggregation rule that is simple, non-compensatory and minimises the rank reversal phenomena is the Kemeny rule. Its basic idea is that the maximum likelihood ranking of policy options is the ranking supported by the maximum number of criteria (or criterion weights) for each pair-wise comparison, summed over all pairs of options considered. There is agreement in the literature that the Kemeny method is “the correct method” for ranking options, and that the only drawback of this aggregation method is the difficulty in computing it when the number of options grows. A numerical algorithm solving this computational drawback in an efficient way has been developed recently at JRC and it has been implemented in SOCRATES.

Various authors have argued that the presence of qualitative information in evaluation problems concerning socio-economic issues is a rule, rather than an exception. Thus there is a clear need for methods that are able to take into account information of a "mixed" type (both qualitative and quantitative criterion scores). Moreover, ideally, this

information should be precise, certain, exhaustive and unequivocal. Nevertheless, in reality, it is often necessary to use information which does not have those characteristics so that one has to face the uncertainty of a stochastic and/or fuzzy nature present in the data. Therefore, multi-criteria methods able to tackle consistently the widest types of mixed information should be considered as desirable ones in the IA framework.

From a mathematical point of view, SOCRATES deals with two main issues:

1. The problem of equivalence of the procedures used in order to standardize the mixed criterion scores;
2. The problem of comparison of fuzzy numbers typical of all fuzzy multi-criteria methods.

These two issues are dealt with a new semantic distance that is useful in the case of continuous, convex membership functions also allowing a definite integration.

Overall, the objective of SOCRATES is NOT substitution of policy-makers through a mathematical model, on the contrary, the objective is to improve their understanding of the main features of the problem at hand, such as key assumptions, degree of uncertainty, robustness of results and overall technical and social defensibility of options chosen. The philosopher Socrates said: "*I cannot teach anybody anything. I can only make them think.*" This is the main inspiring principle of the SOCRATES software too.

The SOCRATES software offers a measurement framework where the various criterion scores can assess impacts by using both quantitative (e.g. as result of simulation models) and qualitative (e.g. results of participatory techniques) information, and the mathematical aggregation rule guarantees consistency and transparency of results.

Three main components constitute the core of SOCRATES: multi-criteria, equity and sensitivity analyses. **Multi-criteria analysis** requires the definition of relevant dimensions, objectives and criteria. It uses weights as importance coefficients and clarify their role in the hierarchical structure. The impact matrix may include quantitative (including also stochastic and/or fuzzy uncertainty) and qualitative (ordinal and/or linguistic) measurements of the performance of an alternative with respect to an evaluation criterion. It supplies a ranking of the alternatives according to the set of evaluation criteria (i.e. the technical compromise solution/s).

In our study, from the 59 criteria considered, there are 9 (one per impact type) that are based on stakeholder views while the other 50 are based on objective and expert assessment.

By applying SOCRATES to the information contained in the impact matrix, the following ranking, shown in Figure 4.2, is obtained (under the assumption that all criteria have the same weight, see Figure 4.3).

Rank	1°	2°	3°	4°
4.77	🏆 2 Joint regulation	3 Centralised Regulation	1 Decentralised Regulation	Baseline

Figure 4.2: preferred option

The ranking is very clear: option ***2*** is the best choice followed by option ***3.*** The set composed by options ***1*** and the ***baseline*** is clearly the worst one.

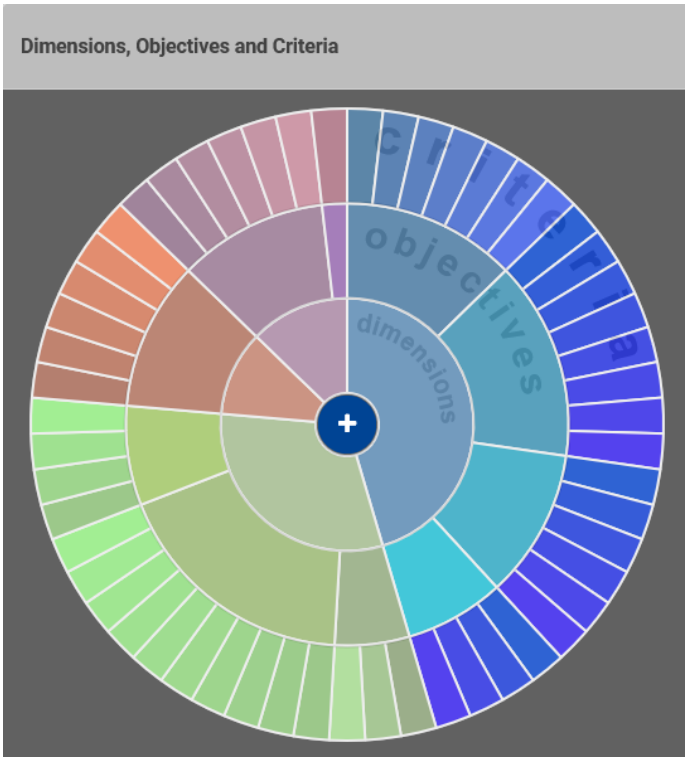


Figure 4.3: Equal criterion weighting assumption

By assuming that all dimensions have the same weight (see Figure 4.4), the ranking stays the same, thus both basic weighting schemes produce the same result. This result robustness will be further checked by means of local and global sensitivity analyses.

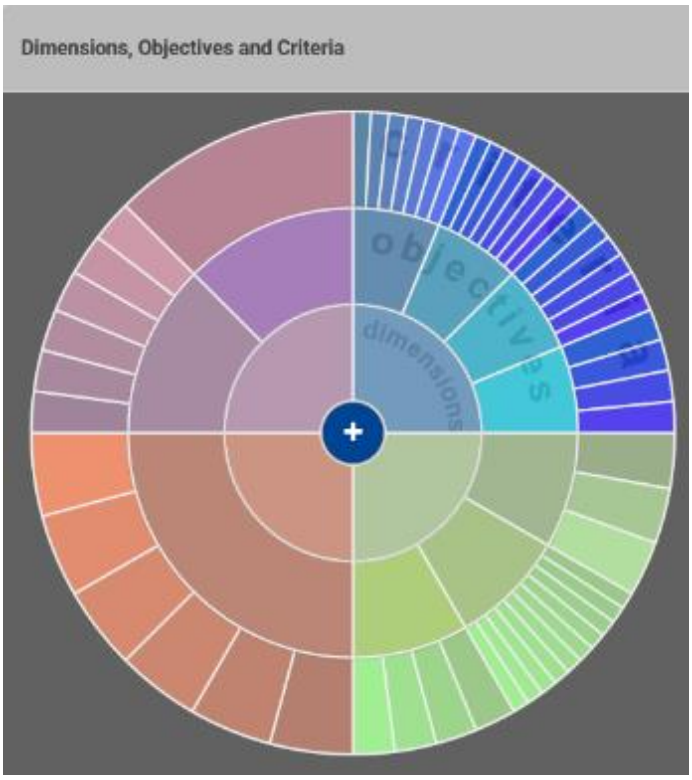
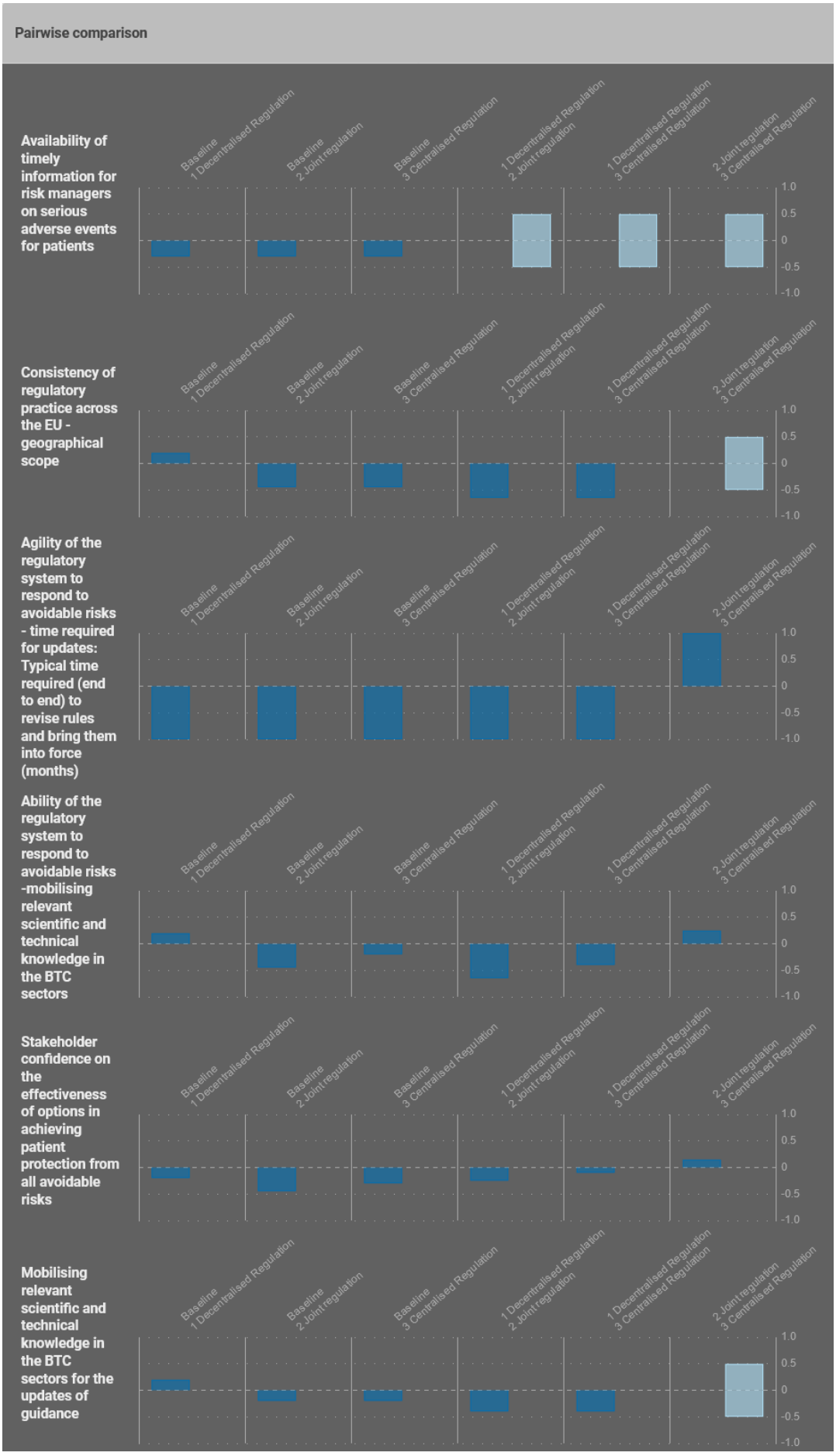
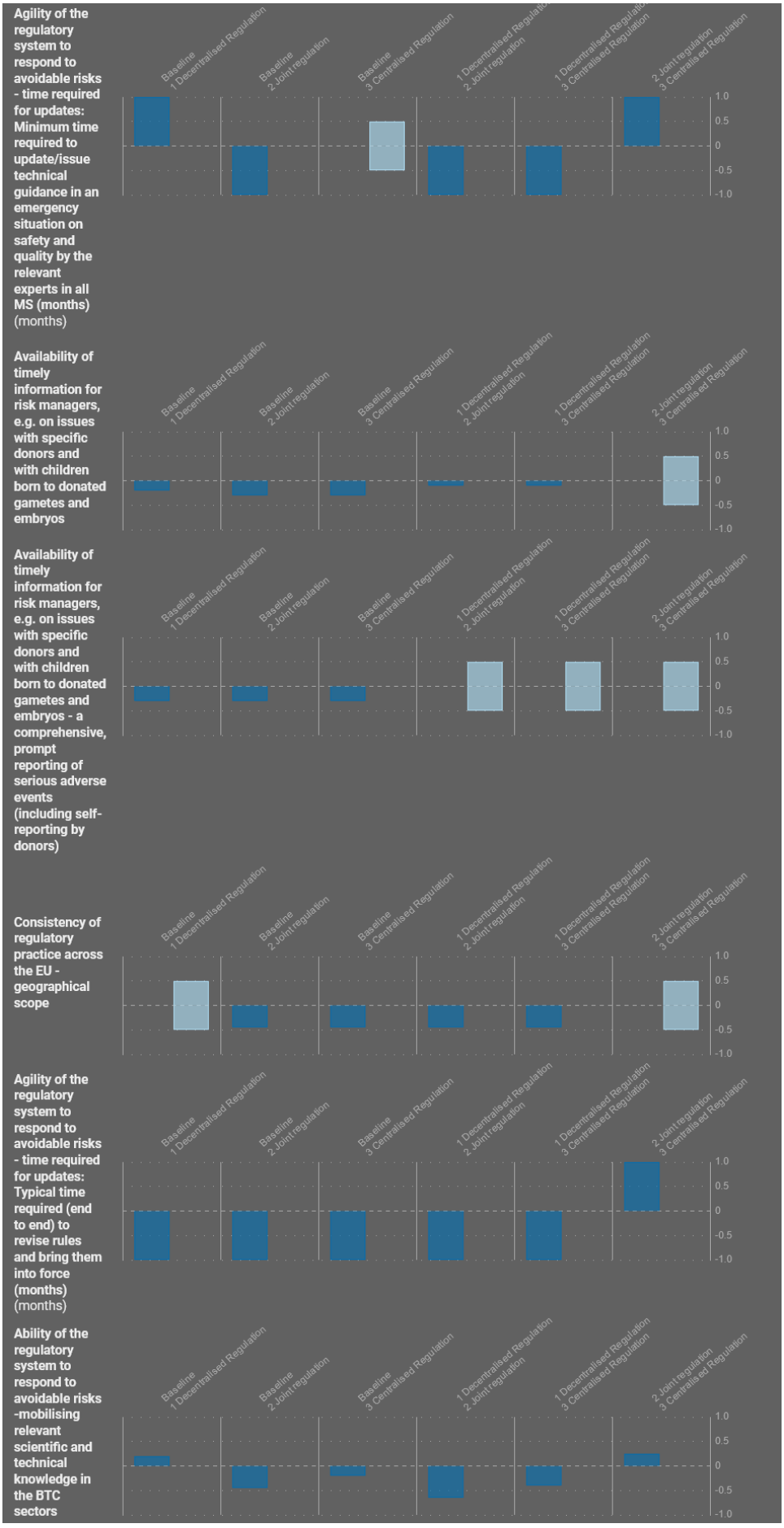


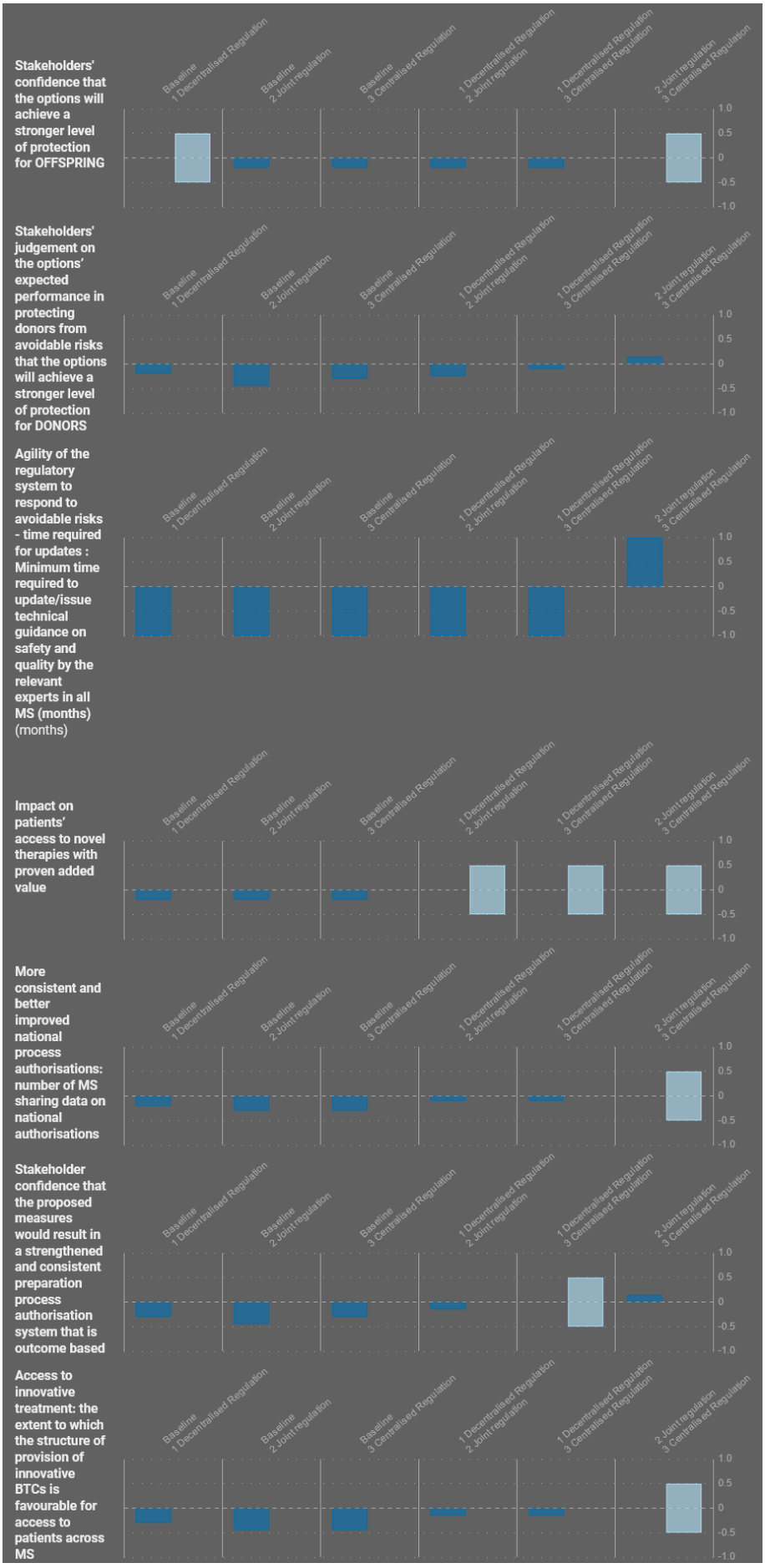
Figure 4.4: Equal dimension weighting assumption

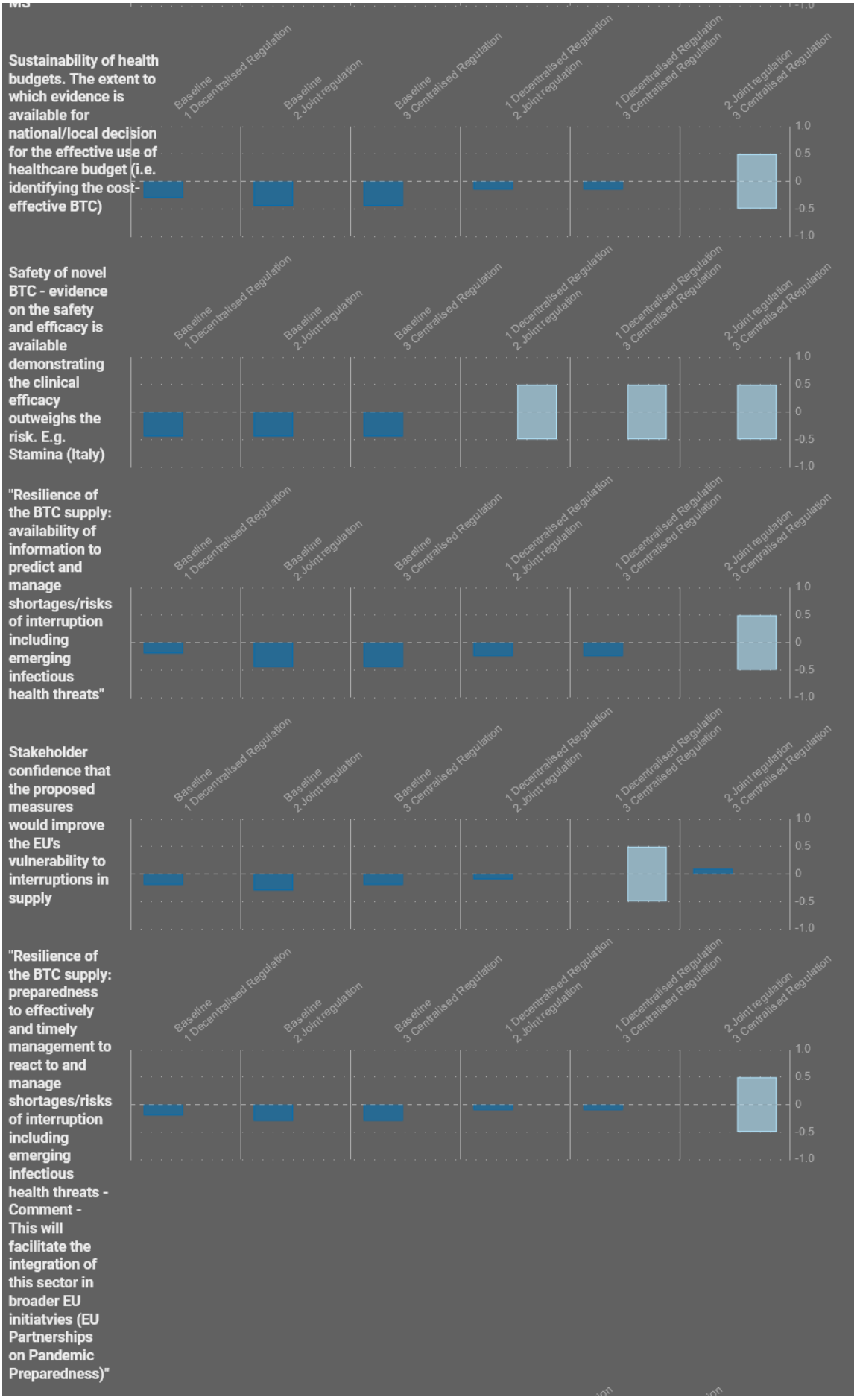
More information can be obtained by checking the pairwise comparisons, which allow one to be fully aware of the mutual weaknesses and strengths on each single evaluation criterion. This information is summarised graphically in the following Figure, where the degrees of credibility that any option is preferred or indifferent with respect to another one on each single criterion are illustrated. From this Figure it is possible to deduce that options ***2*** and ***3*** are indeed very similar, although there is a preference towards option ***2***. In fact if one looks at the performance on each of the single criteria, it is possible to see immediately that only the digital criteria are weakly in favour of option ***3***, while all the other criteria evaluate these two options as indifferent or are strongly in favour of option ***2***. On the contrary, when comparing one of these two top options with the other options the preference relation is very clear.

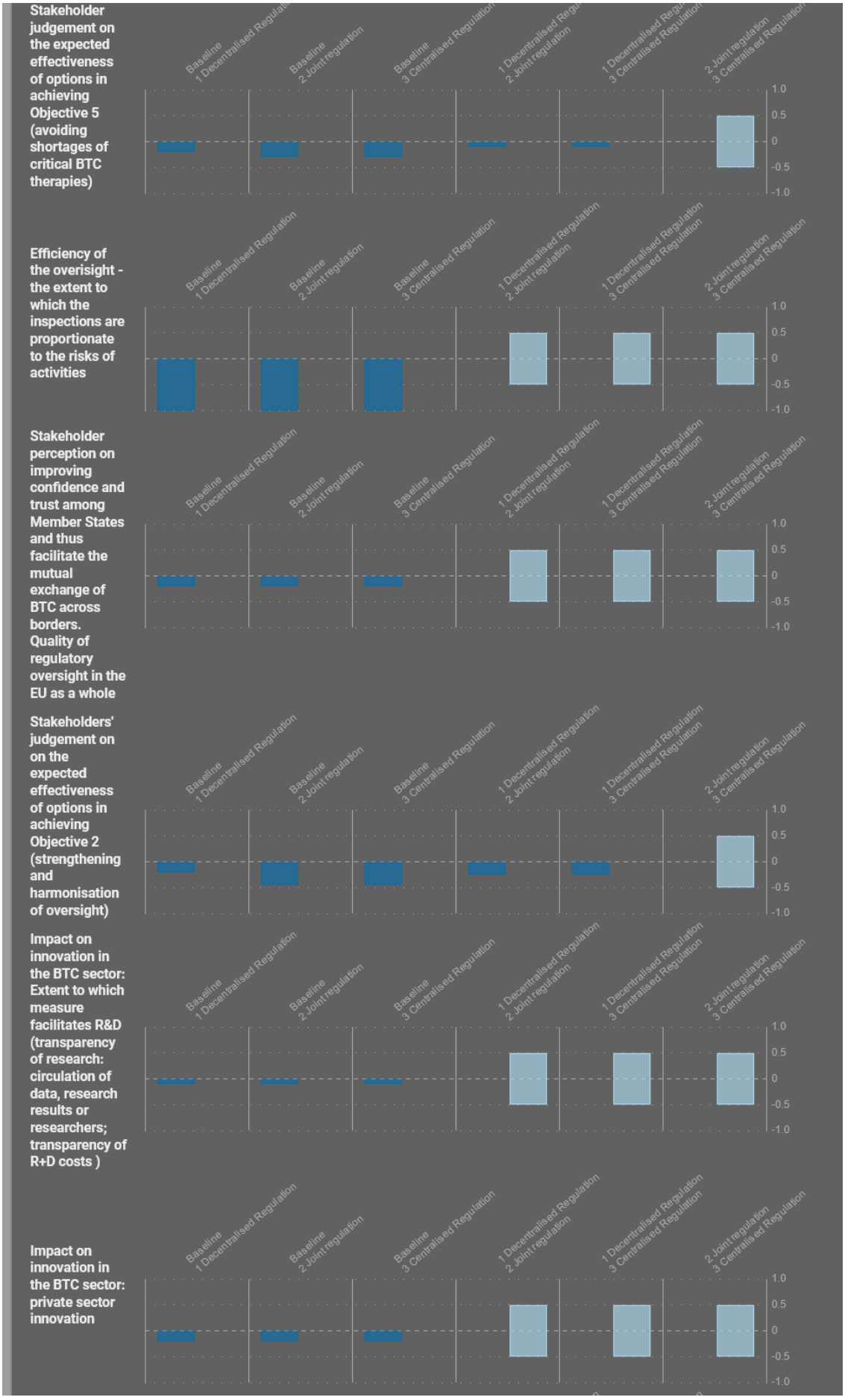
Data on the pairwise comparison within each criterion is provided in the following Figure 4.5.

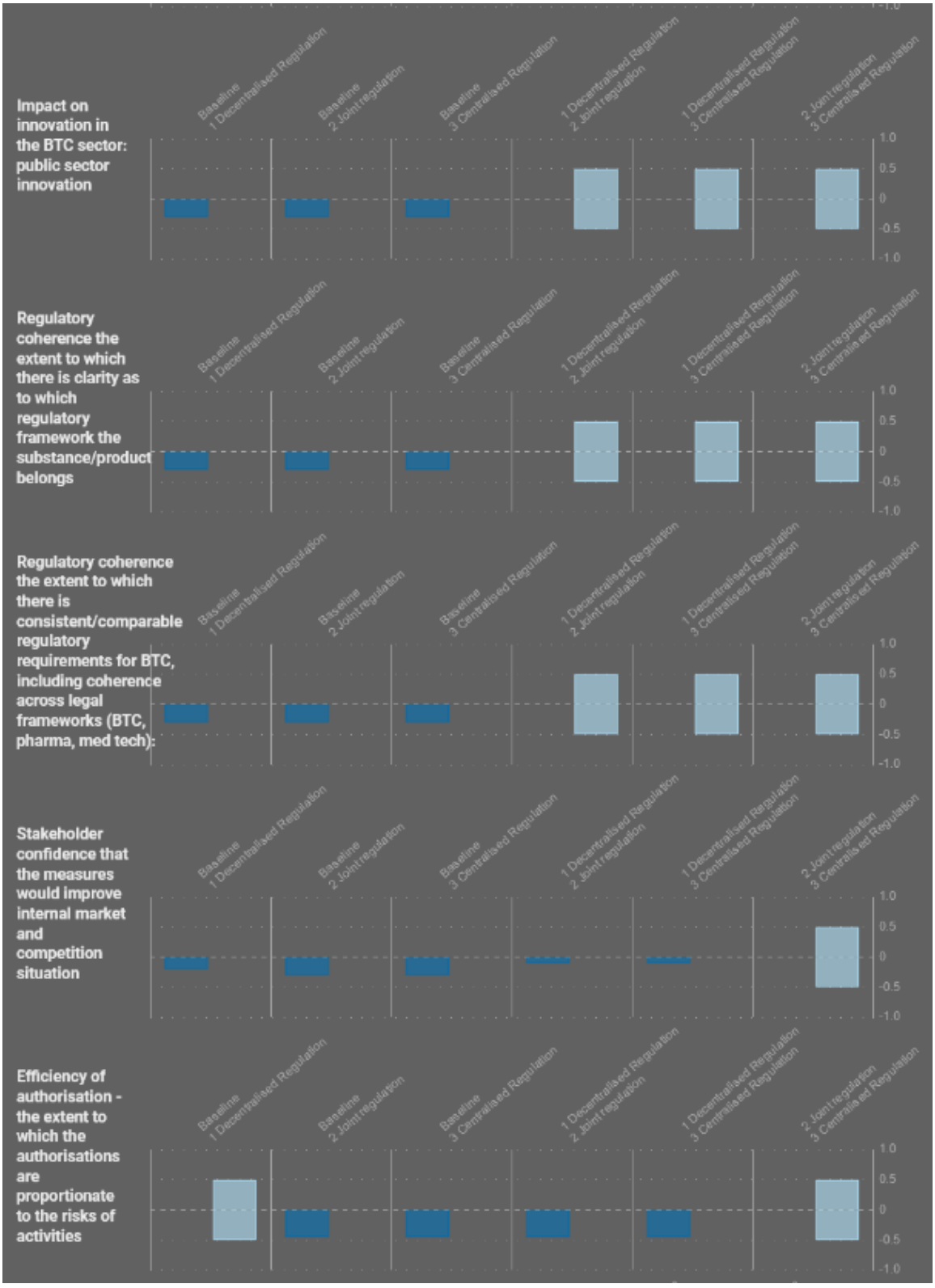

Pairwise comparison
Availability of timely information for risk managers on serious adverse events for patients
Consistency of regulatory practice across the EU - geographical scope
Agility of the regulatory system to respond to avoidable risks - time required for updates: Typical time required (end to end) to revise rules and bring them into force (months)
Ability of the regulatory system to respond to avoidable risks -mobilising relevant scientific and technical knowledge in the BTC sectors
Stakeholder confidence on the effectiveness of options in achieving patient protection from all avoidable risks
Mobilising relevant scientific and technical knowledge in the BTC sectors for the updates of guidance
Baseline
1 Decentralised Regulation
Baseline
2 Joint regulation
Baseline
3 Centralised Regulation
1 Decentralised Regulation
2 Joint regulation
1 Decentralised Regulation
3 Centralised Regulation
2 Joint regulation
3 Centralised Regulation
1.0
0.5
0
-0.5
-1.0

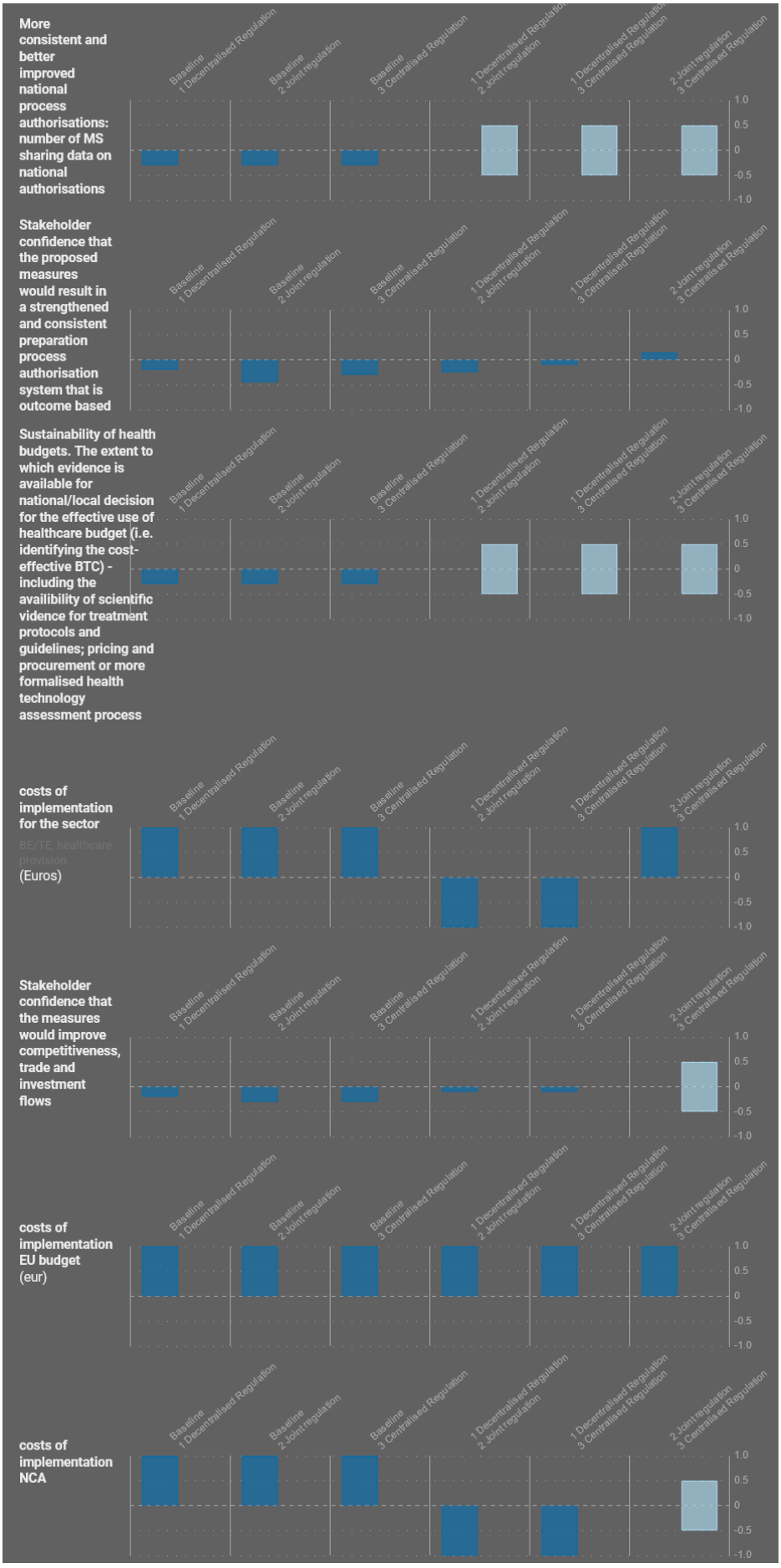

Agility of the regulatory system to respond to avoidable risks - time required for updates: Minimum time required to update/issue technical guidance in an emergency situation on safety and quality by the relevant experts in all MS (months) (months)
Availability of timely information for risk managers, e.g. on issues with specific donors and with children born to donated gametes and embryos
Availability of timely information for risk managers, e.g. on issues with specific donors and with children born to donated gametes and embryos - a comprehensive, prompt reporting of serious adverse events (including self-reporting by donors)
Consistency of regulatory practice across the EU - geographical scope
Agility of the regulatory system to respond to avoidable risks - time required for updates: Typical time required (end to end) to revise rules and bring them into force (months) (months)
Ability of the regulatory system to respond to avoidable risks -mobilising relevant scientific and technical knowledge in the BTC sectors
Baseline
1 Decentralised Regulation
Baseline
2 Joint regulation
Baseline
3 Centralised Regulation
1 Decentralised Regulation
2 Joint regulation
1 Decentralised Regulation
3 Centralised Regulation
2 Joint regulation
3 Centralised Regulation
1.0
0.5
0
-0.5
-1.0

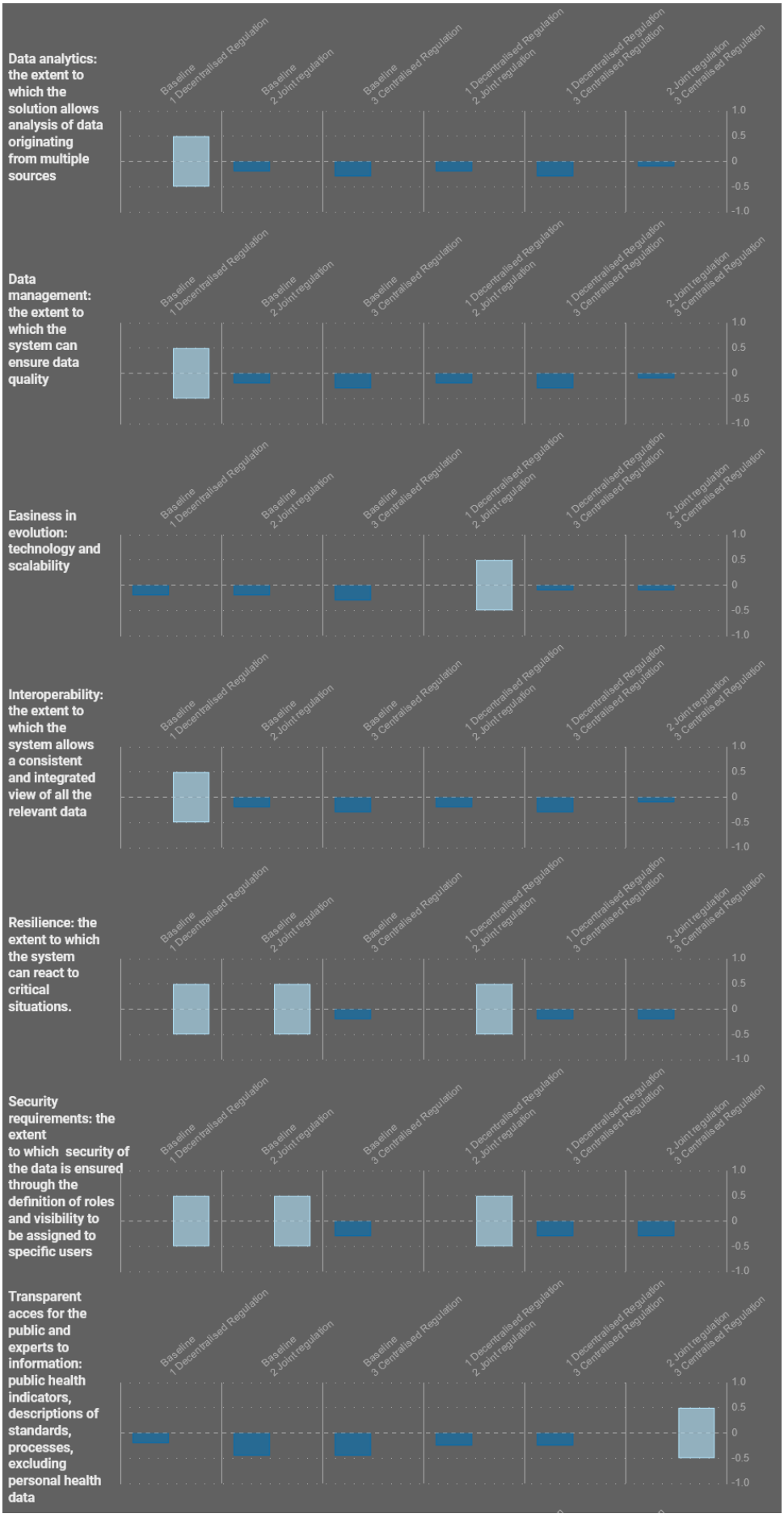

Stakeholders' confidence that the options will achieve a stronger level of protection for OFFSPRING
Stakeholders' judgement on the options' expected performance in protecting donors from avoidable risks that the options will achieve a stronger level of protection for DONORS
Agility of the regulatory system to respond to avoidable risks - time required for updates : Minimum time required to update/issue technical guidance on safety and quality by the relevant experts in all MS (months) (months)
Impact on patients' access to novel therapies with proven added value
More consistent and better improved national process authorisations: number of MS sharing data on national authorisations
Stakeholder confidence that the proposed measures would result in a strengthened and consistent preparation process authorisation system that is outcome based
Access to innovative treatment: the extent to which the structure of provision of innovative BTCs is favourable for access to patients across MS
Baseline
1 Decentralised Regulation
Baseline
2 Joint regulation
Baseline
3 Centralised Regulation
1 Decentralised Regulation
2 Joint regulation
1 Decentralised Regulation
3 Centralised Regulation
2 Joint regulation
3 Centralised Regulation
1.0
0.5
0
-0.5
-1.0


MS
Sustainability of health budgets. The extent to which evidence is available for national/local decision for the effective use of healthcare budget (i.e. identifying the cost-effective BTC)
Safety of novel BTC - evidence on the safety and efficacy is available demonstrating the clinical efficacy outweighs the risk. E.g. Stamina (Italy)
"Resilience of the BTC supply: availability of information to predict and manage shortages/risks of interruption including emerging infectious health threats"
Stakeholder confidence that the proposed measures would improve the EU's vulnerability to interruptions in supply
"Resilience of the BTC supply: preparedness to effectively and timely management to react to and manage shortages/risks of interruption including emerging infectious health threats - Comment - This will facilitate the integration of this sector in broader EU initiatvies (EU Partnerships on Pandemic Preparedness)"
Baseline
1 Decentralised Regulation
Baseline
2 Joint regulation
Baseline
3 Centralised Regulation
1 Decentralised Regulation
2 Joint regulation
1 Decentralised Regulation
3 Centralised Regulation
2 Joint regulation
3 Centralised Regulation
1.0
0.5
0
-0.5
-1.0


Stakeholder judgement on the expected effectiveness of options in achieving Objective 5 (avoiding shortages of critical BTC therapies)
Efficiency of the overisight - the extent to which the inspections are proportionate to the risks of activities
Stakeholder perception on improving confidence and trust among Member States and thus facilitate the mutual exchange of BTC across borders. Quality of regulatory oversight in the EU as a whole
Stakeholders' judgement on on the expected effectiveness of options in achieving Objective 2 (strengthening and harmonisation of oversight)
Impact on innovation in the BTC sector: Extent to which measure facilitates R&D (transparency of research: circulation of data, research results or researchers; transparency of R+D costs)
Impact on innovation in the BTC sector: private sector innovation
Baseline
1 Decentralised Regulation
Baseline
2 Joint regulation
Baseline
3 Centralised Regulation
1 Decentralised Regulation
2 Joint regulation
1 Decentralised Regulation
3 Centralised Regulation
2 Joint regulation
3 Centralised Regulation
1.0
0.5
0
-0.5
-1.0


Impact on innovation in the BTC sector: public sector innovation
Regulatory coherence the extent to which there is clarity as to which regulatory framework the substance/product belongs
Regulatory coherence the extent to which there is consistent/comparable regulatory requirements for BTC, including coherence across legal frameworks (BTC, pharma, med tech):
Stakeholder confidence that the measures would improve internal market and competition situation
Efficiency of authorisation - the extent to which the authorisations are proportionate to the risks of activities
Baseline
1 Decentralised Regulation
Baseline
2 Joint regulation
Baseline
3 Centralised Regulation
1 Decentralised Regulation
2 Joint regulation
1 Decentralised Regulation
3 Centralised Regulation
2 Joint regulation
3 Centralised Regulation
1.0
0.5
0
-0.5
-1.0


More consistent and better improved national process authorisations: number of MS sharing data on national authorisations
Stakeholder confidence that the proposed measures would result in a strengthened and consistent preparation process authorisation system that is outcome based
Sustainability of health budgets. The extent to which evidence is available for national/local decision for the effective use of healthcare budget (i.e. identifying the cost-effective BTC) - including the availibility of scientific vidence for treatment protocols and guidelines; pricing and procurement or more formalised health technology assessment process
costs of implementation for the sector
BE/TE, healthcare provision
(Euros)
Stakeholder confidence that the measures would improve competitiveness, trade and investment flows
costs of implementation EU budget
(eur)
costs of implementation NCA
Baseline
1 Decentralised Regulation
Baseline
2 Joint regulation
Baseline
3 Centralised Regulation
1 Decentralised Regulation
2 Joint regulation
1 Decentralised Regulation
3 Centralised Regulation
2 Joint regulation
3 Centralised Regulation
1.0
0.5
0
-0.5
-1.0


Data analytics: the extent to which the solution allows analysis of data originating from multiple sources
Data management: the extent to which the system can ensure data quality
Easiness in evolution: technology and scalability
Interoperability: the extent to which the system allows a consistent and integrated view of all the relevant data
Resilience: the extent to which the system can react to critical situations.
Security requirements: the extent to which security of the data is ensured through the definition of roles and visibility to be assigned to specific users
Transparent acces for the public and experts to information: public health indicators, descriptions of standards, processes, excluding personal health data
Baseline
1 Decentralised Regulation
Baseline
2 Joint regulation
Baseline
3 Centralised Regulation
1 Decentralised Regulation
2 Joint regulation
1 Decentralised Regulation
3 Centralised Regulation
2 Joint regulation
3 Centralised Regulation
1.0
0.5
0
-0.5
-1.0

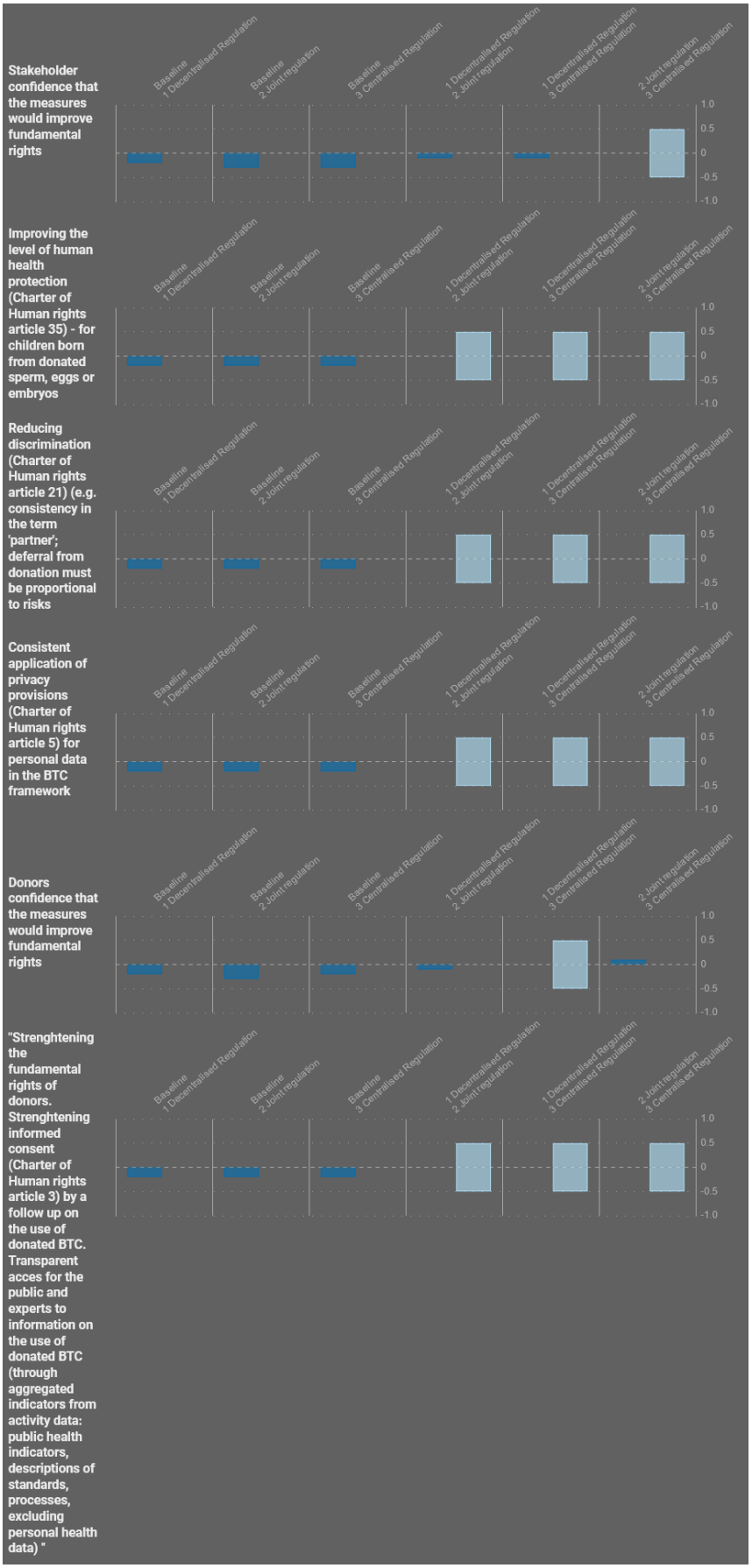


Figure 4.5: pairwise comparison

4.3 Sensitivity and robustness analysis

To further clarify the preference structure, it is advisable to perform a *sensitivity analysis.* In the framework of SOCRATES, the objective of sensitivity analysis is to check if the rankings provided are stable and to determine which of the input parameters influence more the model output. Local sensitivity analysis looks at the sensitivity of results to a) the exclusion/inclusion of different criteria and dimensions; and b) dimensions and criterion weights change; all parameters are changed one per time. Global sensitivity analysis focuses on all the possible combinations of criterion weights; all parameters are changed simultaneously. The whole information produced by local and global sensitivity analyses is synthesised into simple graphics.

Let us then first look at the influence of the exclusion of the various criteria and dimensions, one per time and at the effect of using the subset of criteria belonging to one dimension only (i.e. first one criterion per time is eliminated and the corresponding ranking is obtained later a whole dimension with all its criteria is eliminated and the effect on the final ranking is checked).

The results of this exercise are presented in the following Figure 4.6, where it is indicated how many times each option is present in any rank position, and the percentage each rank position is occupied by each single option. In this way, it becomes clearer and clearer that option ***2*** is the most desirable one, in fact it occupies the first position in the ***93 per cent*** of all the rankings obtained.

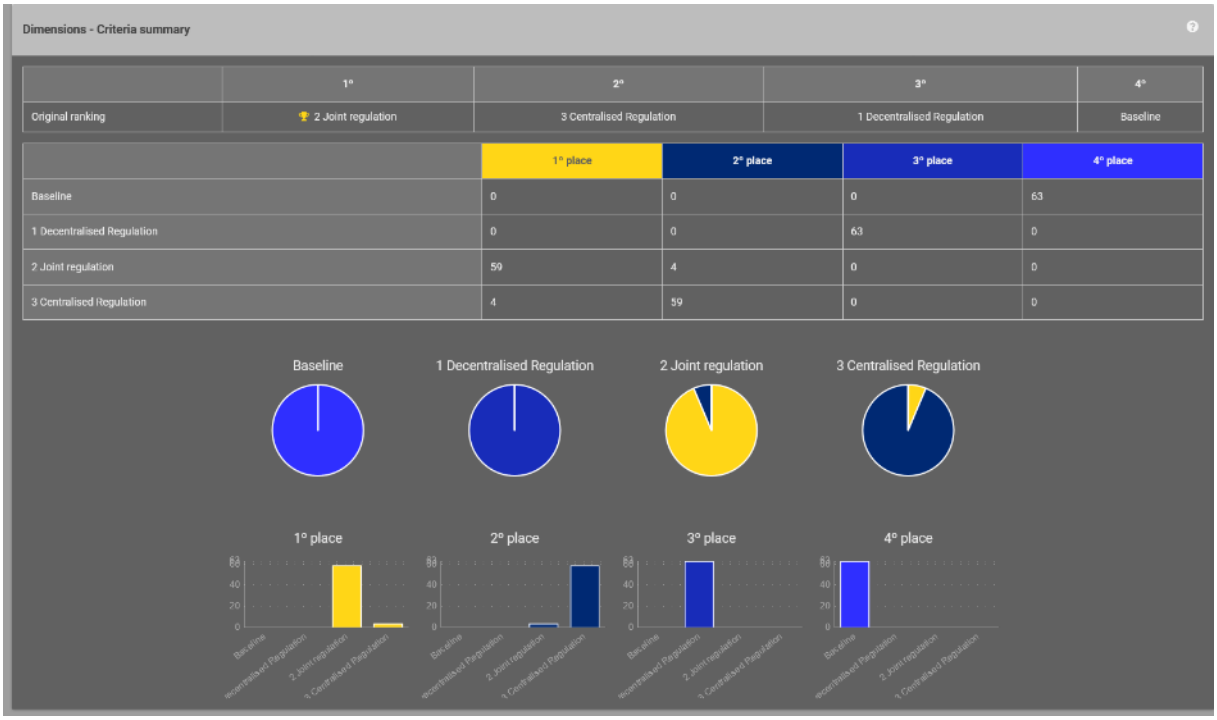


Figure 4.6: Dimensions – criteria summary

In particular, by excluding one criterion per time, results never change, while the only change is due to the very special case where the digital dimension only is used, while if the digital dimension is excluded no change in the result is produced (see Figure 4.7). From a policy point of view, the situation where the only relevant dimension is the digital one is irrelevant, thus we can safely state that option 2 is the most desirable option.

~ Digital	🏆 2 Joint regulation	3 Centralised Regulation	1 Decentralised Regulation	Baseline
Digital	🏆 3 Centralised Regulation	2 Joint regulation	1 Decentralised Regulation	Baseline

Figure 4.7: Ranking without the digital dimension and considering the digital dimension only

Finally, the issue of robustness of results with respect to weights is particularly relevant. Since we have already computed the rankings according to the equal criterion and dimension weighting assumptions, let us now see what happens if all possible combinations of criterion weights are considered. This exercise is carried out by means of the global sensitivity analysis.

As shown in the Figure 4.8, the results are very stable, in fact, whatever weight set we use, ***option 2 is always the top ranked one.***

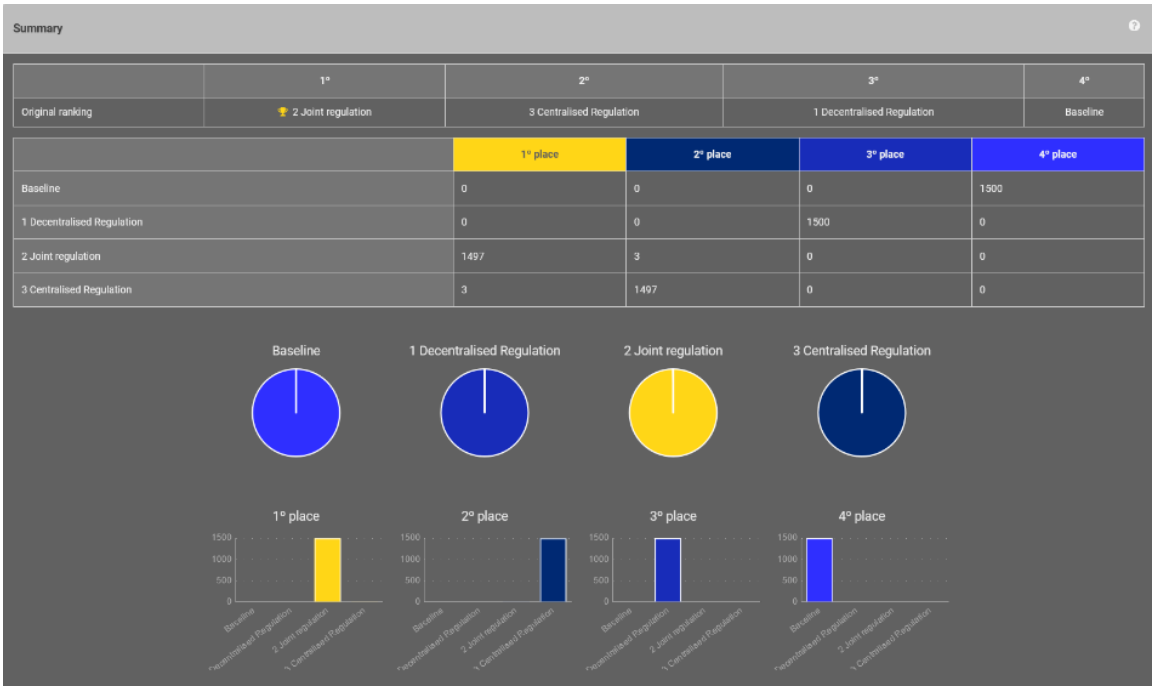


Figure 4.8: Summary

4.4 Stakeholder preferences

Equity analysis requires as input a set of social actors and their qualitative evaluation of the alternatives considered in the multi-criteria analysis, in this case, by questions from the online public consultation (questions 5-6, 10-11-12, 15 and 25 for objectives 1-2, 3, 4 and 5 respectively). The organised consultations gathered a high number of replies (214 respondents); all stakeholders categories as well as the major organisations identified previously were represented (namely, authorities and stakeholders, from BTC sectors as

well as from related pharma and device sectors, patients and donor organisations…). While the survey – and so the equity matrix - is not representative, it gives an accurate picture of the views of the sector. The fact that these criteria show subjective stakeholders views and preferences is clearly indicated.

These were summarized in the equity matrix – by stakeholder type – a summary is available on the dashboard.

The equity analysis starts from the following social impact matrix (Figure 4.9) where the position of the various stakeholders towards the set of the policy options have been summarised by using qualitative scores. Overall there is a clear stakeholder preference for Option 2. The negative score in the baseline (--) expresses the stakeholder's assessment of the (evolution of) the situation in the next 10 years.

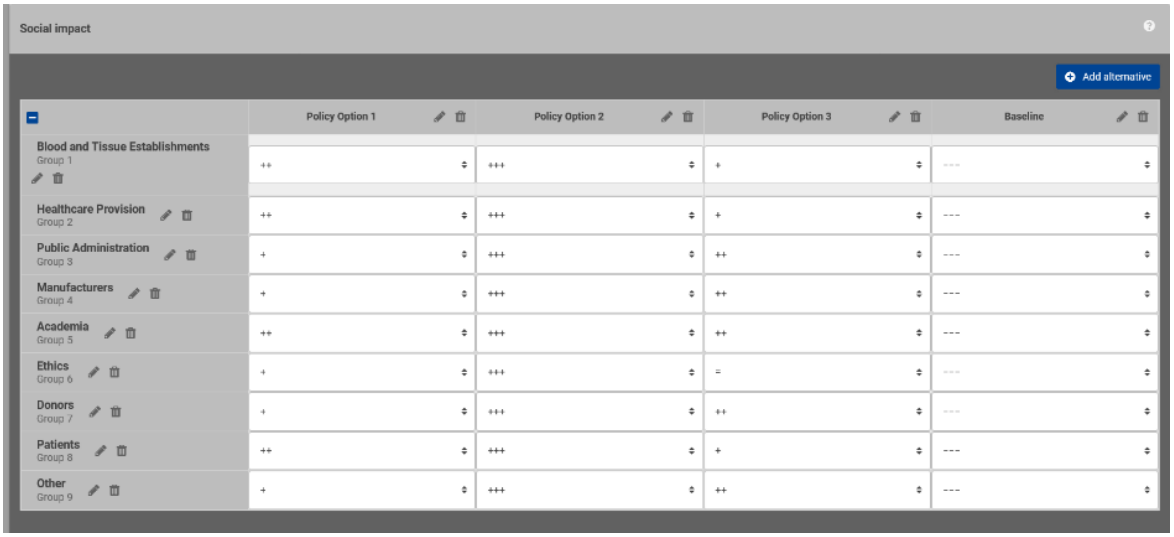
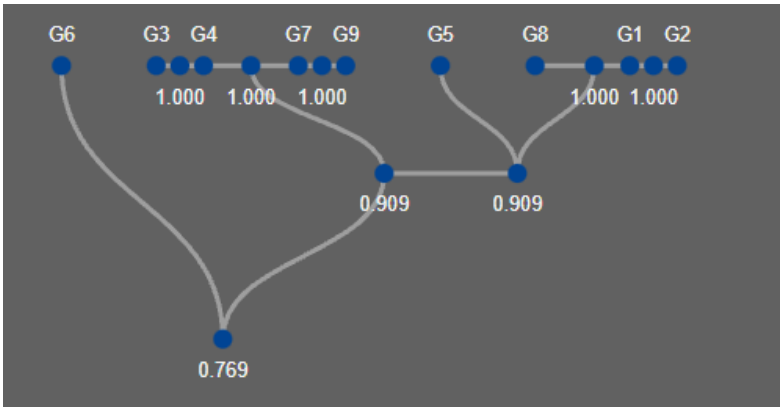


Figure 4.9: Social impact matrix

SOCRATES supplies the following information:

- Indications of the distance of the positions of the various social groups (i.e. possibilities of convergence of interests or coalition formations). This information is summarized in the form of a dendrogram, where the credibility of their convergence is also indicated.
- Ranking of the policy options according to actors' impacts or preferences (as presented in the social impact matrix).
- Vetoed options, that is according to the minority principle, all coalitions, however small, should be given some fraction of the decision power. One measure of this power is the ability to veto certain subsets of outcomes. The main idea is that it is not prudent to implement policy options whose degree of conflict is too high (and thus the decision taken might be very vulnerable).

In our study, the SOCRATES equity analysis produces the following information:



Credibility	Coalition	1°	2°	3°	4°
1.000	G3: Public Administration, G4: Manufacturers	Policy Option 2	Policy Option 3	Policy Option 1	Baseline
1.000	G7: Donors, G9: Other	Policy Option 2	Policy Option 3	Policy Option 1	Baseline
1.000	G3: Public Administration, G4: Manufacturers, G7: Donors, G9: Other	Policy Option 2	Policy Option 3	Policy Option 1	Baseline
1.000	G1: Blood and Tissue Establishments, G2: Healthcare Provision	Policy Option 2	Policy Option 1	Policy Option 3	Baseline
1.000	G8: Patients, G1: Blood and Tissue Establishments, G2: Healthcare Provision	Policy Option 2	Policy Option 1	Policy Option 3	Baseline
0.909	G5: Academia, G8: Patients, G1: Blood and Tissue Establishments, G2: Healthcare Provision	Policy Option 2	Policy Option 1	Policy Option 3	Baseline
0.909	G3: Public Administration, G4: Manufacturers, G7: Donors, G9: Other, G5: Academia, G8: Patients, G1: Blood and Tissue Establishments, G2: Healthcare Provision	Policy Option 2	Policy Option 3	Policy Option 1	Baseline
0.769	G6: Ethics, G3: Public Administration, G4: Manufacturers, G7: Donors, G9: Other, G5: Academia, G8: Patients, G1: Blood and Tissue Establishments, G2: Healthcare Provision	Policy Option 2	Policy Option 1	Policy Option 3	Baseline

Figure 4.10: Dendogram

As one can easily see, ***option 2*** is also the less conflictual one, no stakeholder is against its implementation. This is not true for all the other options considered. In fact, if we look at the grand coalition, which has a high degree of credibility (0.769), option 2 is top ranked and all other options are vetoed.

ANNEX 5: COST CALCULATIONS

The cost calculations are based on the External Study for the BTC Impact Assessment. A calculator was developed based on the **standard cost calculation method**. Unit costs and calculations from the External Study for the BTC Impact Assessment were verified.

The **following adjustments** were made:

- Reordering the measures: Donor protection is objective number 2 (it was objective number 3 in the External Study for the BTC Impact Assessment). Removing the "same surgical procedure" exemption was moved under objective 1 (patient protection) – it was under Objective 4 innovation in the External Study for the BTC Impact Assessment.
- The allocation of EU costs across the policy objectives was refined – including the costs of the EU platform. However, given the horizontal nature of these tasks, this allocation to various objectives remains somewhat artificial.
- For the quantification, the standard cost model from the external study supporting the IA was complemented with input from the feasibility study [40] focusing specifically on the costs and benefits from the **digitalisation** of the sector. Digitalisation aspects were in particular considered for existing measures (e.g. reporting) that cause undue administrative burden as well as newly proposed measures (e.g. to improve crisis management) that allow for more **efficiency in the healthcare systems.** All policy options include costs for central investment in common data infrastructure and services as well as technical support and capacity building for local data owners. The IA adjusted the reporting costs used by the External Study for the BTC Impact Assessment to more consistently refer to the SOHO-X cost calculations. These unit costs were cross-checked with the comparable costs of the EHDS IA and the ranges are similar.
- The one-off costs for the measure on same surgical procedure use the following assumption to assess the baseline on the digitalisation of the sector: 'Administrative patient data were stored electronically in 80% of the EU27 GP practices. In some countries, usage rates were below the 50% level (Greece, Romania, Lithuania), going down as far as 26% (Latvia). The highest use rates were found in Finland and Hungary (100%), Estonia (98%), Denmark and the Netherlands (97%) and Sweden (96%)' from the EHDS IA.

This BTC cost calculator shows the unit costs and breaks down the costs by measures, stakeholder as well as policy options. The calculator is available on the interactive dashboard; a small excerpt is provided in the following Figure 5.1.

[40] For further details, see Annex 19.

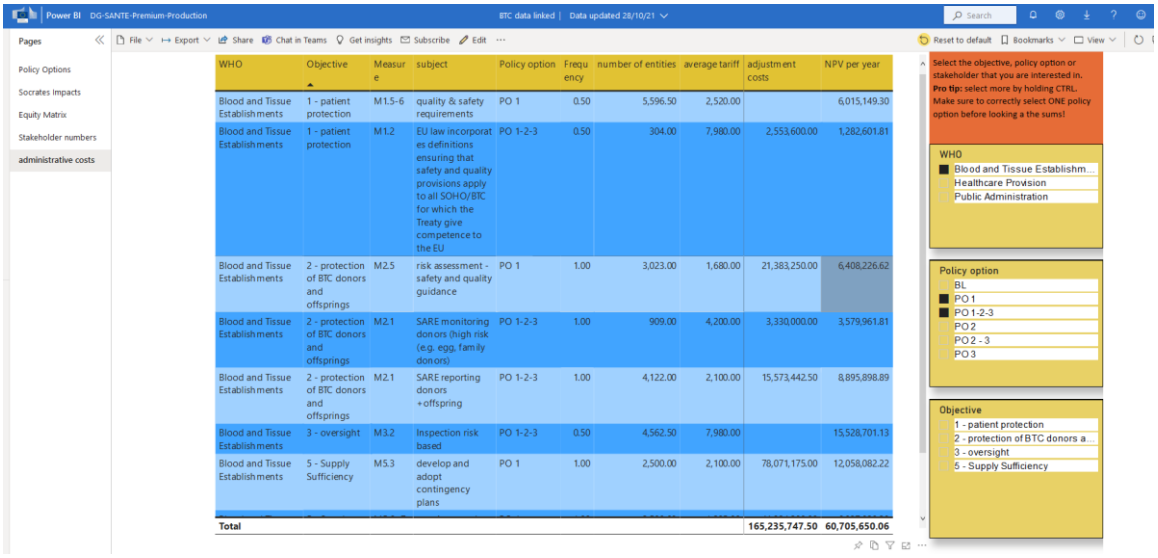


Figure 5.1: Screenshot of interactive dashboard

5.1 Relevant information provided by the External Study for the BTC Impact Assessment

5.1.1 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, including analysis of data from the European Commission's EU Coding Platform: Reference Compendia for the Application of a single European Coding System for Tissues and Cells;
- Cost inquiry for Establishments. The online inquiry targeted to representative organisations and establishments included a set of questions on the costs incurred by establishments for complying with the current regulations and practices. It provided 40 (partial) replies from establishments from 14 countries [41]. Approximately half of the replies came from tissue establishments (20), while only a few from blood establishments (3), and establishments treating both blood and tissues (6). The remaining replies came from milk banks (5) and other organisations, including blood and tissue banks, stool 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 included micro and small organisations (11 and 10 respectively), medium-sized (12) and, to a lower extent (7), large organisations.
- Cost inquiry for Regulators. A cost inquiry targeted to regulators (National Competent Authorities) was designed to collect information on the status of

[41] 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 14 of the External Study for the BTC Impact Assessment, ICF.

implementation of measures data on the costs incurred by regulators. It provided (partial) replies from regulators in 12 Member States [42].

- Follow-up activities for Regulators: after receipt of information from the surveys and cost inquiries, follow-up activities were used to collect supplementary information. Follow-up interviews were conducted with NCAs in four Member States (Austria, Italy, the Netherlands, Spain) to gather additional details and better quality the information provided via the cost enquiry. In addition, emails were sent to 23 NCAs to have confirmation of the status of implementation of key measures. 15 replies were received, which allowed collecting information from additional Member States (compared to the replies to the cost enquiry) and consolidating the mapping, improving the accuracy of the assessment of the baseline [43].
- Information from other stakeholder's consultation carried out as part of the study, in particular from workshops.

5.1.2 General Assumptions

5.1.2.1 Dimension of the BTC sector

The desk research and the analysis of the Compendium data 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.

The analysis of the BTC establishments showed that 63% of all Tissue and Cells establishments 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 absence of specific data, the same geographical distribution was assumed for blood establishments as for Tissue and Cells ones.

Based on the analysis of the Compendium data, the current total number of establishments operating in the T&C sector is 3258. Amongst those, 1716 are specifically authorised for MAR activities.

The estimation of the number of BTC/SOHO establishments 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, we estimated that there are currently about additional 300 establishments impacted (approximately 6% of the total BTC sector), covering breast milk and FMT. However, no source was identified to help estimating the number of establishments cosmetics for non-therapeutic use. Therefore, the estimates for these measures are quite conservative.

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[42] These include Austria, Bulgaria, Denmark, Estonia, France, Germany, Ireland, Italy, Netherlands, Slovenia, Spain, Sweden.

[43] 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).

The study mapped the national competent authorities for blood, tissue and cells and MAR establishments in the Member States. It is, on this basis, estimated that there are 50 [44] such authorities. In some countries regional health authorities are directly involved in the implementation of the BTC regulatory framework. These were not excluded from the mapping exercise and the cost estimations because they are not directly responsible for the transposition of EU legislation in the BTC sector, or for the design of national measures necessary for its implementation.

5.1.2.2 Labour costs

The NCAs and establishments cost enquiries asked for the average salary costs of staff involved in the implementation of measures.

The ratio of the annual salary costs of relevant staff on the real GDP per capita [45] 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 GDP per capita was then calculated for those Member States in which data from establishments and NCAs were made available.

In those MS in which NCAs and establishments failed to provide data, we used the above percentage differences was 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 MS, 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 used by ICF previously in impact assessment support studies carried out by the contractor for the External Study for the BTC Impact Assessment and accepted.

The table below provides an overview of the key data points for labour costs used throughout the cost estimation.

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

Table 5.1 Labour cost factors – applied to all relevant measures

[44] The full list is provided in Annex 8. (Table 8).

[45] Available at: https://ec.europa.eu/eurostat/databrowser/view/sdg_08_10/default/table?lang=en.

**2x multiplier applied to salary costs, 220 working days assumed*

5.1.2.3 Other costs of implementation

The NCAs and establishments cost enquiries asked for 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 in impact assessment support studies carried out by the contractor for the External Study for the BTC IA 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 groups meetings: EUR 28 000 each;
- Expert fees (for preparatory work): EUR 400 per person/day.

5.1.2.4 10 year projections

The External Study for the BTC Impact Assessment had looked at the impact of the various measures over a 10 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 10 years.

The consultation also informed the study, providing assumptions about the growth of the BTC sector itself over the next 10 years.

The blood sector is expected to remain relatively stable. To estimate the number of blood establishments in 10 years, we looked at the population growth projection [46] in each Member State and apply the same growth factor to the number of establishments.

The T&C sector is expected to grow in the coming decade. This is particularly the case for the MAR sector. To estimate the number of T&C establishments in 10 years (excluding establishments operating in MAR activities), we applied the same logic than above, adding a factor of 1% on the top of the projected population growth percentage.

To estimate the number of MAR establishments in 10 years, we applied again the same logic, adding a factor of 2% on the top of the projected population growth percentage.

In addition, it is estimated that, as an effect of the provisions introduced, about 750 T&C establishments 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 and 150 in MAR) has been reflected into the projections over time.

[46] https://ec.europa.eu/eurostat/databrowser/view/tps00002/default/table?lang=en

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.

Type of establishments	Current population	Population in 10 years (projection)	Average over 10 years
Blood establishments	1,400	1,420	1,410
T&C establishments	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

Table 5.2 BTC sector – Current population and projections over 10 years

5.1.2.5 Discount rate

In accordance with the revised version of the Better Regulation Guidelines, a 3% social discount rate was applied.

5.1.2.6 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 5 identified gaps, a baseline scenario was determined to understand which Member States already implement what is proposed under each of the main areas covers by the proposed EU reform and to which extent these MS 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 obtain 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 measures under considerations. To assess the number of NCAs already implementing the measure (and thus the ones impacted by the provision), a simple proportion was applied to the overall number of NCAs identified (50). For establishments, we combined the results of the mapping exercise with data on the geographical distribution of BTC establishments.

For each of the 5 objectives covered by the study, we collected the following data points were collected:

from the 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 the establishments:

- current type of activities (e.g., processing one or several BTC products, Member State(s) of establishment)
- 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 5 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

NCAs:

{(Level of Effort (in person days) * Labour cost) + additional costs – in half of the cases} * estimated number of MS 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.

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 – 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 3 – 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	Stakeholder	Cost of the baseline (EUR thousand)	Source
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

Table 5.3 Baseline per objective (over 10 years)

5.1.3 Costs estimations of measures

5.1.3.1 Cost types included in the estimation

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 one-off 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. Monitor adverse events MAR/ follow-up for children under Objective 32, activities related to oversight under Objective 23 and activities related to supply monitoring under Objective 5) should be placed under this category, as opposed to administrative costs [47].

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) National Competent Authorities (NCAs), and 3) BTC establishments.

5.1.3.2 Estimations of costs for EU institutions

Costs for the EU institutions include costs incurred by the EU Commission and by European expert bodies (ECDC and EDQM) in the baseline scenario and under the measures under consideration.

[47] 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.

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 the ECDC.

The costs for the IT platform were supplied by the SoHO-X Feasibility Study [48]. Consistently 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, 2 and 5, therefore the related costs are presented only once (under Objective 1), to avoid double counting. The costs for this IT platform correspond to the costs of the platform defined as 'New single system' by the SoHO-X Feasibility Study (option M6C), while those for the IT platform under Objective 3 correspond to the platform defined as 'Upgrade and connect' (option M6B). Finally, the costs for the IT platform under Objective 4 were estimated by the GAPP project.

5.1.3.3 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 contingency plans in Member States that do not.

The calculation of **one-off 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

It was assumed that the one-off costs would be incurred by NCAs during a three-year period. One-off costs were therefore distributed over three years and discounted.

The calculation of **enforcement costs** for national competent authorities 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 previously in other impact assessment support studies carried out by the contractor for the External Study for the BTC IA and accepted.

5.1.3.4 Estimation of costs for establishments

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

[48] For further details, see Annex 19.

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 **one-off 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 one-off costs would be incurred by establishments during a three-year period. One-off 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 years period considered by the impact assessment. This approach has been used previously in other studies accompanying impact assessments and accepted.

5.1.4 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 measures are already in place in Member States, guidance is provided in national legislation and/or from NCAs and these is based on available scientific evidence and publications from 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 implementations of measures in option 1 and option 3, relatively to option 2.

5.1.4.1 Cost Estimation for Option 1

EU institutions

One-off 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 2, 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

One-off costs are assumed to be the same under all options for NCAs. It is likely that, under Option 3, especially, NCAs will have to carry out some legislative action to include the EU rules in the national legislative 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 in higher enforcement costs, having to familiarise themselves with different frameworks (potentially, each establishment inspected/regulated may a slightly different interpretation of the scientific evidence available).

Establishments

One-off 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 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 (the general objective of guaranteeing high levels of quality and safety will be maintained under option 1 as well).

5.1.4.2 Cost Estimation for Option x.2

EU institutions

One-off costs are mainly represented by the costs for the IT platform, assumed to be the same under options 1, 2 and 3.

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 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 the EDQM, it is assumed that guidance rules are revised three times over the 10 years period.

NCAs

In absence of data from the cost enquiry, one-off costs are assumed to amount to 2 or 3 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 three times over the 10 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, one-off costs are assumed to amount to 2 to 3 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 three times over the 10 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.

5.1.4.3 Cost Estimations of Option 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 Better Regulation guidelines), 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 guidance rules are revised twice over the 10 years period.

One-off 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, one-off 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 10-year 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 assumed to be the same as under Option 2.

Establishments

In absence of data from the cost enquiry, one-off costs are assumed to be 2 to 3 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 10-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.

5.1.5 Cost estimations per objective

The assessment of costs of measures under Objectives 1, 2 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.

Objective 1

Measure	Assumption
M1.2 - filling gaps in the scope of the framework	• Number of additional SoHO establishments in scope: 304 • Number of Member State (MS) impacted: all • One-off 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 – required publication of more stringent measures in MS	• Number of NCAs impacted: 26 (13 MS) • 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 evaluation of BE/TE risk assessments	• Number of MS impacted: all • Impact for NCAs: 1 extra person-day per inspection (based on risk-based inspection schedule, as per Objective 3) • 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 – BE/TE risk assessments	• One-off 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
M1.9 – Removal of same surgical procedure exemption	• Number of Member States impacted: 27 (50 NCAs); • Number of establishments impacted: 11,000 hospitals; • One-off costs for NCAs: 10 person-days; • Enforcement costs for NCAs: 2 hours per hospital per year; • One-off 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.

Table 5.4 Key assumptions adopted for measures under Objective 1

Additional elements related to the key assumptions for the measure M1.9 – Removal of 'Same surgical procedure' exemption

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 one-off and enforcement costs.

One-off costs: 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: 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.

Establishments

Scope of the measure: it was assumed that the measure would apply to hospitals (rather than to BTC establishments). The number of hospitals (11 000 hospitals) has been derived from secondary sources [49]. It is assumed that clinics would not be impacted.

One-off costs: it was assumed that these would be very limited, corresponding to the simple registration. 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: 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 [50].

Estimated: 'easy' reporting cost (automated process): EUR 374 per year per hospital

Objective 2

Measure	Assumption
M2.1 SARE reporting	**SARE Reporting:** • Number of MS impacted as a new measure: 8 (13 NCAs) • Number of establishments impacted: 3,250 (all blood establishments, sperm/oocyte banks (50), HSC (900)), • MAR establishments for offspring reporting (1,772) • Average effort for establishments impacted: 5 person-days (10 for one-off costs) • One-off 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 MS impacted as a new measure: 25 • Number of establishments impacted: 800 in impacted MS (blood establishments (plasma), sperm/oocyte banks HSC (family donors) MAR establishments sperm/oocyte banks, own donors)

[49] Available at: https://gateway.euro.who.int/en/indicators/hfa_471-5011-number-of-hospitals/

[50] For further details, see Annex 19.

Measure	Assumption
	• Enforcement costs for NCAs: 0.5 person-days (monitoring) • Enforcement costs for establishments: 10 person-days
M2.5-M2.7 – quality and safety requirements for donor/offspring protection	**Evaluation of rules for safety and quality for donors and offspring** • Number of MS impacted as a new measure: 7 (13 NCAs) • Number of establishments impacted: • One-off costs for NCAs: setting up the monitoring an 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 inspection in a given year: as per inspection schedule (2,282 using average frequency for risk-based inspection regime) • Number of establishments impacted: all • One-off costs for establishments: setting up safety and quality system: 30person-days (Option 2&3) • Enforcement costs for establishments: revising/updating safety and quality system: 20 person-days •

Table 5.5 Key assumptions adopted for measures under Objective 2

Objective 5

Measure	Assumption
M5.1 - mandatory monitoring obligations of critical BTC supplies	• Number of MS 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 MS 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); • One-off 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 MS impacted (implementing new measure): 21 (39 NCAs), new system based on EU platform; • One-off 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); • One-off 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

Table 5.6 Key assumptions adopted for measures under Objective 5

Measures under Objective 3

This Objective focuses on oversight measures and does not include measures that differs according to the policy options. Therefore, the estimations and options described in section 5.1.4 do not apply.

The table below provides an overview of the key assumptions used for the more important measures under this objective.

Measure	Assumption
M3.2 – Risk-based inspection	• Number of Member States impacted: 7 Member States (13 NCAs) implementing new measure. • Number of establishments impacted: all (including SoHO establishments as per Objective 1). • One-off costs for NCAs: 20-40 person-days; • One-off 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
M3.4 – 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 • Effort: 35 person-days per audit (including preparation, fieldwork and follow-up);
M3.5 – 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).

Table 5.7 Key assumptions adopted for measures under Objective 3

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.

Measures M4.1 to M4.3 – 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 M4.4 to M4.6 – 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 (covering 82% of all BTC establishments in the EU). The share of NCAs that would need to implement such measures entirely is estimated using the general assumptions described above.

The one-off 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).

One-off costs are expressed per establishment, estimated using the general assumptions described above. Given the uncertain correlation between authorisations and 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 preparation process. The information obtained via the cost enquiry for the high-risk novel BTC preparation processes 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 preparation process. They are assessed using available literature. 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: following discussions with the GAPP Joint Action, four categories of risk for novel BTC preparation processes have been identified, 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 [51]);
- 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 preparation processes carried out in France and Germany, applying the general assumptions described above. A lower boundary was built 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 M4.7 – IT platform

Costs for EU institutions to design and maintain the IT platform are estimated using the general approach and assumption described above.

Measures M4.8 to M4.11 – Risk assessment on novel Preparation Process

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.

Measure	Assumption
M4.4 – M4.6 – strengthened preparation process authorisations	• Number Member States impacted: 8 (15 NCAs); • Number of novel BTC processes per level of risk: o Negligible risk: (Complex reporting): 50% (909 – 1,271) o Low risk (Clinical evaluation): 25% (455 - 653);

[51] See Annex 19.

Measure	Assumption
	○ Moderate risk (Clinical investigation): 20% (364 - 508); ○ High risk (Clinical trials): 5% (91 - 127). • One-off 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: 25-40person-days; ○ High risk: 30-90 person-days; • One-off 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.

Table 5.8 Key assumptions adopted for measures under Objective 4

5.1.6 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 estimated.

The measures not quantified are the following:

- M1.1 (principles for safety and quality): 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);
- M2.2; the costs of this measure are assessed in conjunction with measure 2.1;
- M2.3 (new definitions): not feasible to estimate without knowing more about the content of the new definitions incorporated in EU legislation;
- M2.4 (IT platform): the costs of this measure are assessed in conjunction with measures M1.4 and M5.4
- M3.1(oversight principles): assessed only in a qualitative way, as data collected too unreliable to provide robust estimations;
- M4.4: Costs assessed in conjunction with measure M4.5;
- M4.8: costs for NCAs assessed in conjunction with measures M4.9-M4.11 (i.e., per each option);
- M5.3: costs of this measure are assessed in conjunction with measures M5.6-M5.8 (i.e. per each option)
- M5.5: not feasible to estimate without knowing more about the content of the measure;

5.2 Understanding of key factors in the calculations

Measure	using the standard list of measures
Stakeholders	using the standard stakeholder categories
One-off costs	Minimum maximum values per entity.
Frequency	Annual
Unit cost	(time required *daily rates)
Affected entities	See number of stakeholders. Includes projections for 10 years. For one-off costs, the entities already fulfilling the requirement or conducting the activity were not counted.
Total one-off costs	Average of minimum maximum one-off costs * affected entities
Total administrative cost	Unit costs*frequency*affected entities
Time period	10 years. NB. Given the important investment in the digitalisation of the sector, the benefits are expected to extend for more than 10 years. The recommended 10 years' timeframe was used, but potentially a longer timeframe could better reflect the value of the investment.

Discount rate	3%, social discount rate
Net present value (annual)	Formula used: =NPV(0,03;Table368[@[total administrative costs (total entities 1y)]] + [@[one-off costs]]; [@[total administrative costs (total entities 1y)]] 1-10; 10

Table 5.9: Key factors in calculations

5.3 Inputting unit costs

Unit costs were defined in the cost calculator. The following table gives a summary of the key unit costs used as inputs in the model. These unit costs are described in detail in section above , including their relevance to the measures. In general, they are based on surveys with sector establishments and authorities. Where high variations were reported, standardized unit costs were defined subject to a validation with ICF experts. SANTE organised three further expert meetings to validate these unit costs with sector experts and authorities, where the proposed unit costs were confirmed.

adjustment_hig...	15.540	=' unit costs'!$F$12
adjustment_lo...	6.660	=' unit costs'!$C$12
adjustment_me...	11.100	=' unit costs'!$E$12
annual_load	2.220	=' unit costs'!$C$13
average_assess...	2.472,4	=' unit costs'!$J$179
average_eviden...	23.300,0	=' unit costs'!$G$202
BE_TE_average_...	4.563	='stakeholder numbers'!$E$5
BE_TE_critial_BTC	2.500	='stakeholder numbers'!$E$12
daily_rate_BTC	420	=' unit costs'!$C$4
daily_rate_IT	400	=' unit costs'!$C$5
daily_rate_IT_o...	250	=' unit costs'!$C$6
daily_rate_NCA	347	=' unit costs'!$C$3
entities	11.000	='stakeholder numbers'!$E$16
EU_audit_NCA_...	2.100	=' unit costs'!$E$126
EU_audit_unit_...	74.933	=' unit costs'!$E$115
EU_expert_fees...	400	=' unit costs'!$C$7
expert_group_2...	22.400	=' unit costs'!$C$20
expert_group_a...	28.000	=' unit costs'!$C$19
expert_group_a...	22.000	=' unit costs'!$E$19
hospitals	11.000	='stakeholder numbers'!$E$19
NCA_average_o...	50	='stakeholder numbers'!$E$2
new_establish...	304	='stakeholder numbers'!$E$7
novel_processi...	4084	=' unit costs'!$C$177
novel_processi...	4541	=' unit costs'!$C$178
single_load	250	=' unit costs'!$C$14
sub_expert_gro...	22.400	=' unit costs'!$C$20
sub_expert_gro...	16.000	=' unit costs'!$E$20

Figure 5.2: list of key unit costs

Note: working with an EU average overestimates the costs (monetised value of the effort) for Member States with lower price levels (lower GDP per capita). This can be considered more acceptable than underestimating the efforts needed, in particular for less well-resourced establishments/authorities. Furthermore, in the validation workshops with the sector it was also highlighted that for certain countries (of high GDP/capita) and certain profiles (bio-scientists in the sector, analysts) the daily costs are typically higher (EUR 100/hour)

5.4 Notes on the cost calculation – triangulation of most sensitive elements

A couple of measures are very important in the overall modelling as they entail the highest cost, and therefore also have the highest influence on the overall outcome. Moreover, they are particularly sensitive to input parameters. The following data points and calculations were used to triangulate and assess the robustness of the calculations by the External Study for the BTC IA.

5.4.1 Data reporting (various measures)

Generating evidence to assess the quality, safety and efficacy of BTC for the authorisation process is expected to be one of the most substantial costs of the measures proposed. This cost varies radically based on the extent of data collection (adverse events reporting, clinical investigations, clinical evaluations or clinical trials); the number of patients, as well as the data to be recorded.

A key factor is the **cost required for data input per patient** (time*hourly wage of data collector). The time varies depending on the complexity of the treatment (e.g. number of treatment episodes) but also on the data to be recorded (e.g. reporting on the quality of life of patients requires time, but its value is highly recognised by both patients and professionals). Practical examples show a data collection range between 15 minutes to over 5 hours per treatment episode (under EUR 5 – EUR 250 per treatment episode) [52].

Another important element are the **costs of developing and maintaining databases.** Depending on the complexity, such databases start from EUR 100 000 (convalescent plasma prototype).

On such technical elements, large economies of scale can be attained, through development of reusable components, provision of safe infrastructure, technical support and legal advice on GDPR.

5.4.2 Generating clinical evidence (measure M4.B)

An important component when assessing the measures the support innovation, is the **cost of clinicians input to the protocol, implementation and control; various administrative and site monitoring costs** [53]. This varies highly according to the extent of the data collection: clinical investigation require expert input to define the specific data and structured collection; clinical investigations imply even further costs related to

[52] The wages for data collector can also vary highly in the function of their profile and the salary levels in MS. In 2020, the average hourly labour cost was EUR 28.5 in the EU, ranging from EUR 6.5 in Bulgaria to EUR 45.8 in Denmark (Eurostat).

[53] Sertkaya, A., Wong, H.-H., Jessup, A., & Beleche, T., *Key cost drivers of pharmaceutical clinical trials in the United States*, Clin. Trials 13(2), 2016, DOI: 10.1177/1740774515625964.

ethical approval and observing Good Clinical Practices. At the end of the spectrum, the current gold standards of evidence collection, clinical trial cost on average around EUR 35 000, but can increase up to 10 times for certain diseases (e.g. blood diseases) - based on data from the pharma sector [54].

This magnitude is confirmed by other estimations from the pharma sector, such as the model of International association of mutual benefit societies (AIM), which estimates the amount of R&D for the treatment of a single patient would range from EUR 20 to EUR 1 200 (according to the amount of R&D spent) for a disease with a high prevalence. These research costs increase for rare and ultra-rare diseases (up to EUR 1 m) as well as life-long treatments (estimated at EUR 100 000 per year).

A large part of these costs is expected to occur in hospitals/ health care provider setting and impact the public health budgets. However, if this evidence is used well by decision-makers to identify the optimal therapeutic protocol / precise patient population who benefits from the treatment, the overall impact on the public budget is likely to be positive.

Costs vary highly in function of the quality of the evidence generated; therefore, it is essential to keep the regulatory requirements proportional. The risk based approach does exactly this: it requires only key information on low risk BTC, avoiding unnecessary reporting where it is of little added value. For high risk BTC, more substantial evidence is required - in these cases the higher costs are justified by avoiding adverse outcomes for patients or supporting innovative BTC with limited or no added therapeutic value.

A risk-based approach has the flexibility to accommodate innovative technologies in the future and assign the proportionate regulatory requirements.

Furthermore it is important to note that this cost is substantial in countries that need to start working with clinical evidence to authorise novel BTC preparation processes. However, in a large number of EU Members States, this is already current practice (baseline), and the proposed measure would allow for significant savings by sharing evidence and assessments. Savings therefore have the potential to be more significant.

This distribution has been verified and confirmed by an expert workshop(on authorisations). While it remains the one of the most volatile part of the calculations, the assumptions and ranges were confirmed.

5.4.3 Costs of inspections (M3A)

Inspections are a resource-intensive activity, one inspection takes several days both for authorities (8 days) and for establishments (19 days). Measures that change these inspection practices therefore can have a significant impact.

However, a cost-neutral assumption has been modelled for the most important measure, shifting the planning for inspections from rigid 2-year intervals to flexible risk-based interval (with at least one inspection every 4rd year).

[54] Moore, T.J., Heyward, J., Anderson, G., and Alexander, G.C., *Variation in the estimated costs of pivotal clinical benefit trials supporting the US approval or new therapeutic agents, 2015-2017: a cross-sectional study*, BMJ Open 10(6), 2020, DOI: 10.1136/bmjopen-2020-038863.

This modelling proved it possible to inspect the same number of establishments, with a similar number of inspectors (inspection m person days) as needed today to inspect each establishment every 2nd year (requiring 8 person days), following this distribution:

risk based inspection schedule	inspection per year	percentage of establishments	days per inspection NCA	days per inspection BE/TE
low risk	0,25	60%	6	13
medium risk	0,5	30%	9,5	25
high risk	2	10%	14	35

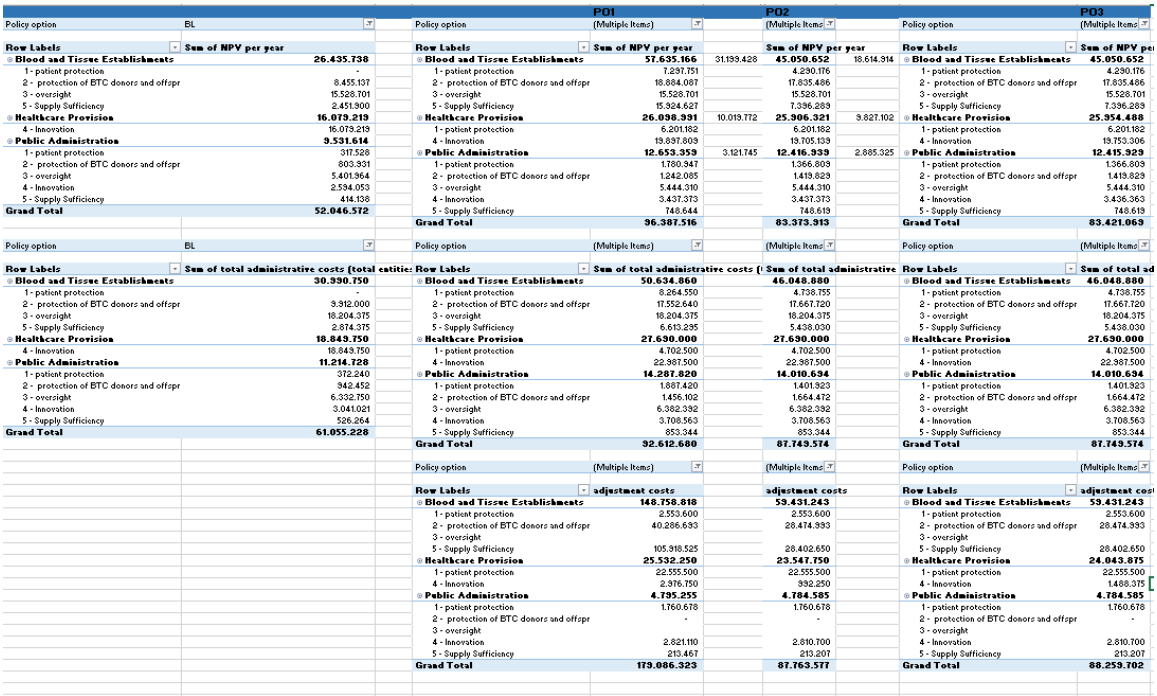
Table 5.104.3: costs of inspections

This distribution has been verified and confirmed by the Expert Subgroup on Inspection in the field of substances of human origin. The assumption to make this a cost-neutral measure was fully supported given that no immediate changes in staff levels for national authorities are to be expected.

The key unit costs were verified with sector experts in three workshops (on Oversight; on Authorisations; and on the Digital Platform). No major concerns were raised by the experts. Some unit costs were refined (days needed by BE/TE and NCA; number of expected BTC processed in new ways; distribution of expected authorisations by risk category)

5.5 Results

The calculated costs were aggregated in pivot tables by cost type, stakeholders, objectives and policy options. These were used to construct the overview tables in the IA.



Policy option	BL
Row Labels	Sum of NPV per year
Blood and Tissue Establishments	26.435.738
1 - patient protection	-
2 - protection of BTC donors and offspr	8.455.137
3 - oversight	15.528.701
5 - Supply Sufficiency	2.451.900
Healthcare Provision	16.073.219
4 - Innovation	16.073.219
Public Administration	9.531.614
1 - patient protection	317.528
2 - protection of BTC donors and offspr	803.931
3 - oversight	5.401.964
4 - Innovation	2.594.053
5 - Supply Sufficiency	414.138
Grand Total	52.046.572

	PO1		PO2		PO3
Policy option	(Multiple Items)		(Multiple Items)		(Multiple Items)
Row Labels	Sum of NPV per year		Sum of NPV per year		Sum of NPV per
Blood and Tissue Establishments	57.635.166	31.139.428	45.050.652	18.614.314	45.050.652
1 - patient protection	7.297.751		4.290.176		4.290.176
2 - protection of BTC donors and offspr	18.884.087		17.835.486		17.835.486
3 - oversight	15.528.701		15.528.701		15.528.701
5 - Supply Sufficiency	15.924.627		7.396.289		7.396.289
Healthcare Provision	26.098.991	10.013.772	25.906.321	9.827.102	25.954.488
1 - patient protection	6.201.182		6.201.182		6.201.182
4 - Innovation	19.897.809		19.705.139		19.753.306
Public Administration	12.653.359	3.121.745	12.416.939	2.885.325	12.415.929
1 - patient protection	1.780.347		1.366.809		1.366.809
2 - protection of BTC donors and offspr	1.242.085		1.419.829		1.419.829
3 - oversight	5.444.310		5.444.310		5.444.310
4 - Innovation	3.437.373		3.437.373		3.436.363
5 - Supply Sufficiency	748.644		748.619		748.619
Grand Total	96.387.516		83.373.913		83.421.069

Policy option	BL
Row Labels	Sum of total administrative costs (total cattie
Blood and Tissue Establishments	30.990.750
1 - patient protection	-
2 - protection of BTC donors and offspr	3.912.000
3 - oversight	18.204.375
5 - Supply Sufficiency	2.874.375
Healthcare Provision	18.843.750
4 - Innovation	18.843.750
Public Administration	11.214.726
1 - patient protection	372.240
2 - protection of BTC donors and offspr	942.452
3 - oversight	6.332.750
4 - Innovation	3.041.021
5 - Supply Sufficiency	526.264
Grand Total	61.055.226

Policy option	(Multiple Items)
Row Labels	Sum of total administrative costs
Blood and Tissue Establishments	50.634.860
1 - patient protection	8.264.550
2 - protection of BTC donors and offspr	17.552.640
3 - oversight	18.204.375
5 - Supply Sufficiency	6.613.295
Healthcare Provision	27.630.000
1 - patient protection	4.702.500
4 - Innovation	22.927.500
Public Administration	14.287.820
1 - patient protection	1.887.420
2 - protection of BTC donors and offspr	1.456.102
3 - oversight	6.382.392
4 - Innovation	3.708.563
5 - Supply Sufficiency	853.344
Grand Total	92.612.680

Policy option	(Multiple Items)
Row Labels	adjustment costs
Blood and Tissue Establishments	148.756.818
1 - patient protection	2.553.600
2 - protection of BTC donors and offspr	40.286.693
3 - oversight	
5 - Supply Sufficiency	105.916.525
Healthcare Provision	25.532.250
1 - patient protection	22.555.500
4 - Innovation	2.976.750
Public Administration	4.795.255
1 - patient protection	1.760.678
2 - protection of BTC donors and offspr	-
3 - oversight	
4 - Innovation	2.821.110
5 - Supply Sufficiency	213.467
Grand Total	179.086.323

	PO1		PO2		PO3
Policy option	(Multiple Items)		(Multiple Items)		(Multiple Items)
Row Labels	Sum of total administrative		Sum of total administrative		Sum of total ad
Blood and Tissue Establishments	46.048.880		46.048.880		46.048.880
1 - patient protection	4.738.755		4.738.755		4.738.755
2 - protection of BTC donors and offspr	17.667.720		17.667.720		17.667.720
3 - oversight	18.204.375		18.204.375		18.204.375
5 - Supply Sufficiency	5.438.030		5.438.030		5.438.030
Healthcare Provision	27.630.000		27.630.000		27.630.000
1 - patient protection	4.702.500		4.702.500		4.702.500
4 - Innovation	22.927.500		22.927.500		22.927.500
Public Administration	14.010.634		14.010.634		14.010.634
1 - patient protection	1.401.923		1.401.923		1.401.923
2 - protection of BTC donors and offspr	1.664.472		1.664.472		1.664.472
3 - oversight	6.382.392		6.382.392		6.382.392
4 - Innovation	3.708.563		3.708.563		3.708.563
5 - Supply Sufficiency	853.344		853.344		853.344
Grand Total	87.743.574		87.743.574		87.743.574

Policy option	(Multiple Items)
Row Labels	adjustment costs
Blood and Tissue Establishments	53.431.243
1 - patient protection	2.553.600
2 - protection of BTC donors and offspr	28.474.393
3 - oversight	
5 - Supply Sufficiency	28.402.650
Healthcare Provision	23.547.750
1 - patient protection	22.555.500
4 - Innovation	992.250
Public Administration	4.784.585
1 - patient protection	1.760.678
2 - protection of BTC donors and offspr	-
3 - oversight	
4 - Innovation	2.810.700
5 - Supply Sufficiency	213.207
Grand Total	87.763.577

Policy option	(Multiple Items)
Row Labels	adjustment cost
Blood and Tissue Establishments	59.431.243
1 - patient protection	2.553.600
2 - protection of BTC donors and offspr	28.474.393
3 - oversight	
5 - Supply Sufficiency	28.402.650
Healthcare Provision	24.043.875
1 - patient protection	22.555.500
4 - Innovation	1.488.375
Public Administration	4.784.585
1 - patient protection	1.760.678
2 - protection of BTC donors and offspr	-
3 - oversight	
4 - Innovation	2.810.700
5 - Supply Sufficiency	213.207
Grand Total	88.259.702

Figure 5.3: Total costs

ANNEX 6: STAKEHOLDER CONSULTATION METHODOLOGY

6.1 Stakeholder Mapping

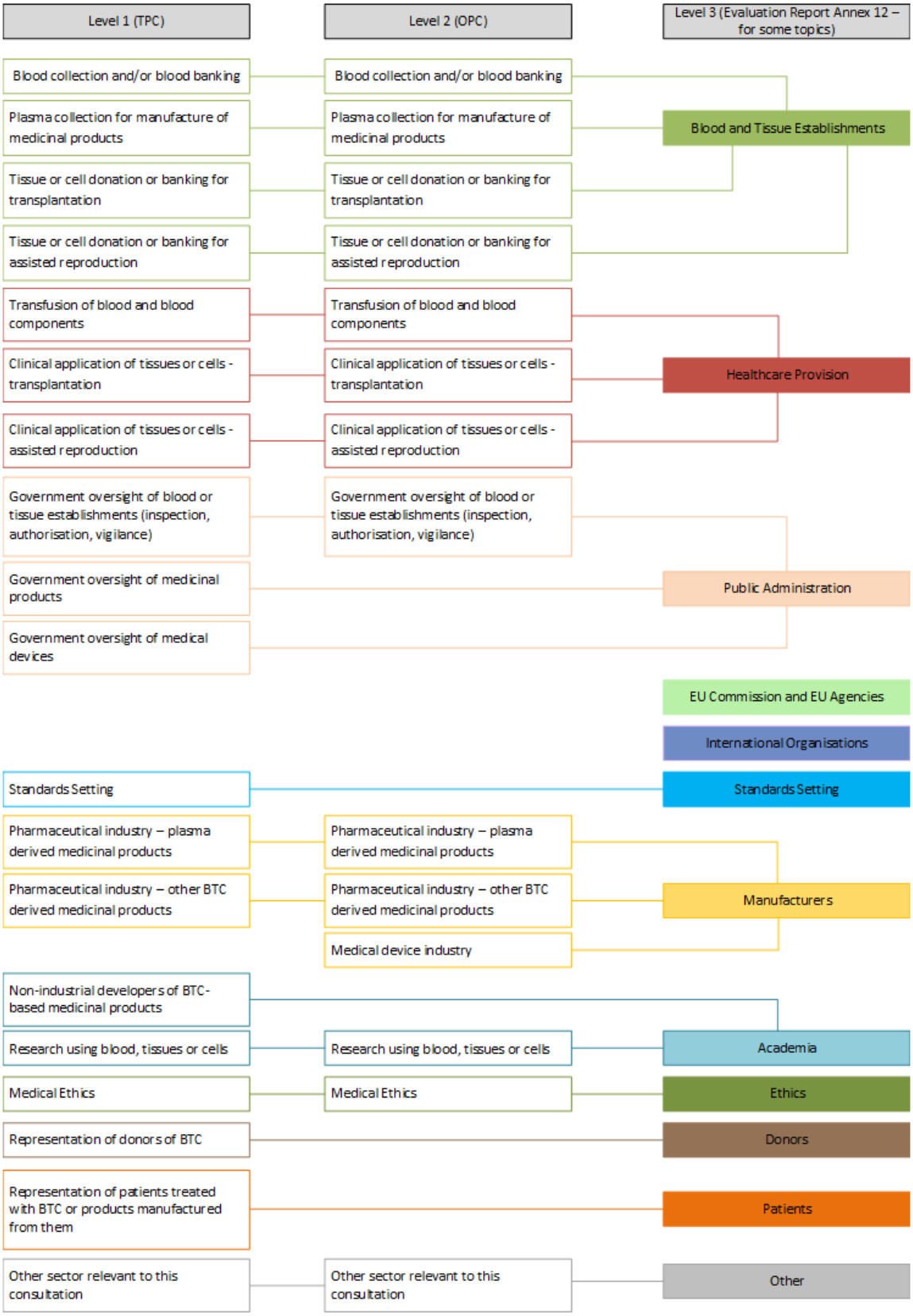


Figure 6.1: Stakeholder categories as used for design and analysis of stakeholder consultations

6.2 Workshops

A series of 11 Workshops on the following topics was conducted:

- Refining the Scope of the BTC Legislation
- Key Definitions - Improvements and Additions
- Strengthening Blood and Plasma Donor Protection
- Better Protection of Donors for Non-Reproductive Tissues and Cells
- Better Protection of MAR Donors and Children Born from MAR
- Strengthening Oversight (Inspection, Authorization, and Vigilance) - Authorities
- Strengthening Oversight (Inspection, Authorization, and Vigilance) - Operators
- Authorising Novel BTC
- Regulating Point-of-Care BTC Processing (bed-side and same surgical procedure)
- Borderlines with Other Regulated Frameworks: Classification Advice and Interplay
- Ethical Principles (Voluntary Unpaid Donation, Prohibition of Profit from the Human Body and BTC Allocation)

After National Competent Authorities were invited to register preliminary interest in participating, interest greatly exceeded what was considered ideal to achieve a balanced and collaborative discussion. Thus, participation was limited to one representative per Member State authority and the number of representatives per professional association was also limited in some cases. This restriction was lifted for the last two Workshops ('Ethical Principles' and 'Borderlines with Other Regulatory Frameworks') due to a particularly high demand for participation and an agreement with the contractor that more breakout groups could be organised for these workshops.

Views and opinions expressed were recorded in written minutes and summarised in the study to support the Impact Assessment process. Anonymous online polls were used to record general tendencies amongst participants. Their results provided indicative feedback on certain topics, and clear consensus in some cases, although it was not possible for participants to consolidate views within their own organisations before responding.

6.3 Data Collection and Analysis of Online Consultations

After evaluation of the IIA Feedback, two questionnaires were designed and published in EU-Survey. Although both questionnaires were publicly accessible, one (Public Consultation) addressed any interested stakeholder or citizen while the other (Targeted Consultation) addressed stakeholder organisations only, inviting those with experience of working in the current legal framework to respond. The Public Consultation was available on the "Have your Say" Portal and the Targeted Consultation was available on the DG Santé webpage. Those addressed by the Targeted Consultation were encouraged also to submit an answer to the Public Consultation, and to limit their answers in the targeted questionnaire to the fields in which they had relevant experience. Both surveys were structured according to the five key problems identified in the evaluation. Different types of questions were used, combining single choice questions, multiple choice questions, and scales of impact (1-10). When relevant, or whenever respondents selected "Other" as an answer option, they were prompted to provide clarification in an open question limited to 1000 characters. When questions were mandatory, a "no answer" option was included to allow respondents to focus on the questions relevant to them.

The quantitative data obtained by DG SANTE through the Public and Targeted Consultation surveys was analysed using Microsoft PowerBI (Version 2.91.383.0) and Microsoft Excel. Depending on the type of question asked, results were visualized in graphical form or summarized statistically. Stratification by sector and type of respondent was conducted and taken into account where relevant. Qualitative data was extracted from the open questions in the online questionnaires according to specific keywords (noting, for example, any positive/negative references to specific measures or policy options as well as any new concerns or suggestions raised) and recorded in Microsoft Excel.

ANNEX 7: THE BTC LEGISLATION

There are many commonalities between the Blood and Tissues and Cells Directives. They have the same legal basis [55], and similar generic oversight requirements; both lay down common (minimum) quality and safety standards at Union level for all stages from donation to distribution for clinical use in a patient and aim to facilitate increased exchange of BTC substances between Member States. Many professionals and authorities work across both sub-sectors [56].

Decisions and policies on the many ethical aspects (e.g., access to in vitro fertilisation (IVF) therapies) remain at a Member State level, except where they have an impact on safety and quality. Legal competence for issues related to the organisation of healthcare services (including BTC services) also remains at the Member State level [57].

7.1 Blood

Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 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

Commission Directive 2004/33/EC of 22 March 2004 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components

Commission Directive 2009/135/EC of 3 November 2009 allowing temporary derogations to certain eligibility criteria for whole blood and blood components donors laid down in Annex III to Directive 2004/33/EC in the context of a risk of shortage caused by the Influenza A (H1N1) pandemic

Commission Implementing Directive 2011/38/EU of 11 April 2011 amending Annex V to Directive 2004/33/EC with regards to maximum pH values for platelets concentrates at the end of the shelf life

Commission Directive 2014/110/EU of 17 December 2014 amending Directive 2004/33/EC as regards temporary deferral criteria for donors of allogeneic blood donations

Commission Directive 2009/135/EC of 3 November 2009 allowing temporary derogations to certain eligibility criteria for whole blood and blood components donors laid down in Annex III to Directive 2004/33/EC in the context of a risk of shortage caused by the Influenza A (H1N1) pandemic

Commission Directive 2005/61/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events

[55] Article 168(4)(a) of the Treaty on the Functioning of the European Union (TFEU).

[56] See Public consultation factual summary report, Section II, p. 4 available at https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12734-Blood-tissues-and-cells-for-medical-treatments-&-therapies-revised-EU-rules/public-consultation_en.

[57] See Article 168(7) TFEU.

Commission Directive 2005/62/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards Community standards and specifications relating to a quality system for blood establishments

Commission Directive (EU) 2016/1214 of 25 July 2016 amending Directive 2005/62/EC as regards quality system standards and specifications for blood establishments

7.2 Tissues and Cells

Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells

Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells

Commission Directive 2012/39/EU of 26 November 2012 amending Directive 2006/17/EC as regards certain technical requirements for the testing of human tissues and cells

Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells

Commission Directive (EU) 2015/565 of 8 April 2015 amending Directive 2006/86/EC as regards certain technical requirements for the coding of human tissues and cells

Commission Directive (EU) 2015/566 of 8 April 2015 implementing Directive 2004/23/EC as regards the procedures for verifying the equivalent standards of quality and safety of imported tissues and cells

Commission Decision of 3 August 2010 establishing guidelines concerning the conditions of inspections and control measures, and on the training and qualification of officials, in the field of human tissues and cells provided for in Directive 2004/23/EC of the European Parliament and of the Council

Commission Decision of 3 July 2015 establishing a model for agreements between the Commission and relevant organisations on the provision of product codes for use in the Single European Code

ANNEX 8: BTC SECTOR AND CROSS BORDER EXCHANGES

8.1 Numbers of stakeholders in the BTC Sector

Stakeholder name	Baseline numbers	Average number over period of 10 years [58]
Public Administration	**50**	**50**
NCA blood	37	37
NCA tissues and cells	34	34
Blood and Tissue Establishments	**4 658**	4 563
Blood and Tissue Establishments *(High S&Q Impact) WITHOUT MAR*	2 942	3 194
New establishments		304
New entities (former establishments)		750
Blood establishments - collection and/or preparation for transfusion	1 400	1 410
Tissue establishments	3 258	3 153
MAR establishments (part of tissue establishments)	1 716	1 369
Establishments with critical BTC		2 500
Establishments donor reporting	1 654	1 654
Establishments high risk donor monitoring	900	909
Offspring reporting	1 772	1 772
Hospital entities that process SoHO with immediate use (*Medium S&Q Impact*) [59]	11 000	11 000
Plasma collection centres for the manufacture of medicinal products.	150	150
Hospital blood banks, preparing for transfusion of blood and blood components	1 295	1 295
Hospitals	11 000	11 000

Table 8.1: Stakeholder overview

[58] For a detailed elaboration on the calculations used for the 10-year projections, see Annex 5, Section 5.1.2.4.

[59] This includes entities that process autologous SoHO at the bed-side or in surgery as well as IUI clinics. The number of hospitals is considered a good approximation – no BTC processing takes places in some hospitals, while BTC processing can also take place in some clinics (without hospitalisation)

8.2 List of BTC Competent Authorities by Member State

AUSTRIA	Federal Office for Safety in Health Care (BASG)
	Austrian Agency for Health and Food Safety (AGES)
BELGIUM	Agence fédérale des médicaments et des produits de santé (AFMPS)
BULGARIA	Executive Agency for Transplantation
	Bulgarian Drug Agency
CROATIA	Ministry of Health
	Institute for Transplantation and Biomedicine
CYPRUS	Ministry of Health of Republic of Cyprus
CZECH REPUBLIC	Ministry of Health of the Czech Republic
	Thomayer Hospital - Prague
	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 Sécurité des Médicaments (ANSM)
	Agence de la Biomédecine
GERMANY	German Federal Ministry of Health
	Paul-Ehrlich-Institut
GREECE	Attikon General University Hospital
	Hellenic Ministry of Health
	Hellenic National Blood Transfusion Centre (EKEA)
HUNGARY	Ministry of Human Capacities
	Hungarian National Blood Transfusion Service
IRELAND	Health Products Regulatory Authority
ITALY	Italian National Transplant Centre (CNT)
	Italian National Blood Centre (CNS)
LATVIA	State Agency of Medicines
LITHUANIA	National Transplant Bureau – Ministry of Health
	Ministry of Health
LUXEMBOURG	Ministère de la Santé, Direction de la Santé - division de l'inspection sanitaire
MALTA	Ministry of Health
THE NETHERLANDS	Ministry of Health, Welfare and Sport
POLAND	Institute of Hematology and Transfusion Medicine (IHTM)
	Ministerstwo Zdrowia (Ministry of Health)).
	National Blood Centre (NCK)
PORTUGAL	Directorate General of Health
	The National Institute of Blood and Transplantation
	Institute for Blood and Transplantation Services
	National Council for Assisted Reproduction (CNPMA)
ROMANIA	National Transplant Agency
	Regional Blood Transfusion Centre
SLOVAKIA	Ministry of Health

	State Institute for Drug Control (SIDC)
SLOVENIA	Agency for Medicinal Products and Medical Devices
	Institute of the Republic of Slovenia for the Transplantation of Organs and Tissues, Slovenija-transplant (ST)
SPAIN	Spanish ART Competent Authority
	Ministry of Health
	Organización Nacional de Transplantes
SWEDEN	National Board of Health and Welfare
	Health and Social Care Inspectorate (IVO)

Table 8.2: List of BTC Competent Authorities by Member State

8.3 Cross-border aspects of the BTC Sector

BTC	Volumes (Patients/donors affected)	Estimated value	Dynamics of the sector	Cross border aspects
Blood components for transfusion	20 million whole blood donations [60] made by almost 10.4 million donors every year [61] > 4.6 million patients transfused yearly [62]	EUR 2-4 billion, counting 25 million units transfused and EUR 80-160 per unit of blood components transfused [63]	Public or non-profit (e.g. Red Cross) blood services supply their local hospitals without competition from other blood establishments (1400 BEs).	Intra EU: Inter-Member State exchange of blood components for transfusion is **rare and is organised on a voluntary basis** in cases of shortage or when rare blood types are needed for specific patients (<1%) [64]. 3rd countries: to date, exchange of blood components for transfusion with third countries is extremely rare and is related to exchange of small numbers of rare blood types [65] or crisis response.
Plasma for manufacture of medicinal products (PDMP)	Around 10 million litres collected annually (39% as plasma in private centres [66], 24% as	EUR 2-3 billion, assuming a market value of the eventual PDMP of 200-300	Plasma is collected across the EU for this purpose. In four Member States (AT, CZ, DE, HU) the private sector plays a major role in this activity and those countries	Intra-EU: plasma **crosses borders to a high degree** to be manufactured in company plants (each company has plants in a few Member States) [69]. 3rd countries: about one fourth of plasma is imported from the US to manufacture PDMP for EU citizens [70].

[60] DG SANTE website: SoHO activity infographic, updated 2021 https://ec.europa.eu/health/blood_tissues_organs/blood_en

[61] 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. https://freepub.edqm.eu/publications/PUBSD-90/detail

[62] 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), available at https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/2019_sare_blood_summary_en.pdf, and Manifesto for European action on Patient Blood Management (PBM) (2020) and population data. available at https://www.ifpbm.org/images/EU%20PBM%20Manifesto%20February%202020%2024.pdf

[63] Creativ-Ceutical report - an EU-wide mapping exercise of the market for blood, blood components and plasma derivatives, focusing on their availability for patients, (2015), including data Market Research Bureau – available at https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/20150408_key_findings_cc_en.pdf

[64] Key findings of the Creative Ceutical Report, (2015) page 2. Creative Ceutical Report – An EU-wide overview of the market of blood, blood components and plasma derivatives focusing on their availability for patients (2015) https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/20150408_key_findings_cc_en.pdf, page 2.

[65] Nance S et al. (2015) International rare donor panels: a review Vox Sang 110 (3): 209-218

[66] A large part of the collection of plasma for PDMP is organised in the private sector in just 4 Member States: Austria, Czech Republic, Germany and Hungary (in those countries, the collection is shared among public and private centres).

	plasma in public centres and 37% recovered from whole blood donations [67]).	EUR/litre [68] and 10 million litres of plasma collected	collect significantly more than the other Member States that rely on blood services to do this as an additional activity.	
Haematopoietic stem cells (from bone marrow)	> 35.000 new patients treated with >40 000 HSCT [71] > 34.000 donors [72]	EUR 3 billion, assuming transplants with 40% autologous/family donations at EUR 50,000 per transplant and 60% allogenic donations at EUR 130,000 per transplant [73]	Distribution is based on the selection of the best matching donor for a patient, rather than on comparative cost criteria. Globally networked donor registries are needed to match donors with patients and are either public or independent but non-profit. There is some limited competition between them for donor recruitment.	Intra EU: **Around 50% of patients are transplanted with a donation from another country.** 14 donations cross an EU border every day, from a donor in one Member State for transplant to a patient in another[74] Third countries: significant share of units is imported from non EU donors/registries, due to need for genetic matching.
Medically assisted	165,000 babies born (from a total of more	EUR 2-3 billion, assuming an	Many public and private clinics treating patients, with a small	Intra-EU: Subject to **significant inter-Member State exchange, particularly of** sperm, shipped across

[69] Key findings of the Creative Ceutical Report, (2015) page 3 Creative Ceutical Report – An EU-wide overview of the market of blood, blood components and plasma derivatives focusing on their availability for patients (2015) https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/20150408_key_findings_cc_en.pdf, page 3.

[70] The EU-28 was importing around 40% of its plasma needs. As the UK, at one point, imported 100% of its plasma due to the risks associated with variant Creutzfeldt-Jakob disease in that country, the dependency now in EU-27 is reduced to around 25%; source: Marketing Research Bureau.

[67] Source: Marketing Research Bureau 2019, shared by PPTA

[68] Creativ-Ceutical report - an EU-wide mapping exercise of the market for blood, blood components and plasma derivatives, focusing on their availability for patients, including data Market Research Bureau – available on SANTE website

[71] The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies. (2019)(2019) https://www.ebmt.org/sites/default/files/2019-01/2019_Book_TheEBMTHandbook.pdf

[72] Source: Newsletter Transplant -International figures on donation and transplantation 2020 https://freepub.edqm.eu/publications/PUBSD-87/detail

[73] European Bone Marrow Transplant Society and Rathenau report - Economic landscapes of human tissues and cells for clinical application in the EU – available at https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/economiclandscapes_humantissuescells_en.pdf

[74] Summary minutes of BTC Impact Assessment Hearing on 5 May 2021 https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/ev_20210505_mi_en.pdf

reproduction	than 800,000 treatment cycles performed in 2016 [75] > 39.000 oocytes donors [76]	average fee of EUR 2,000-3,000 per cycle [77]	number of gamete banks providing sperm internationally generally competing on a for-profit basis.	borders. There is also significant travel of prospective parents going abroad to get access to IVF treatments which are not allowed in their own country (e.g., older women) [78]
Bone, skin, cornea and heart valves	Patients transplanted*: - Musculoskeletal tissues ~12.000 - Skin ~2.000 - Cornea ~14.500 - Heart valves ~700 *2020 data from AT, BG, HR, CZ, EE, FI, HU, IT , LT, NL, PT, RO, SK, SI, ES and SE [79]	Not quantified, expected to be below EUR 500 million	There are both public sector and private for-profit establishments, sometimes in competition with each other. Public sector establishments charge to recover their costs, but need to achieve certain volumes of activity to achieve this with fees that are competitive with the private sector. Private sector establishments usually act on a larger and more international scale than public establishments.	Intra-EU: A large part of this is **local collection for local needs**, mainly by public actors. For example, there are 400 establishments providing bone for transplantation; 87% of the bone they supply remains in its country of origin. Some larger establishments provide grafts to hospitals in multiple EU countries Private actors organise **inter-Member State and third country exchanges**, often importing tissues from the United States through subsidiaries established in the EU for this purpose. Surpluses of EU grafts with short expiry dates are shipped to hospitals in third countries to avoid discard [80]

[75] ESHRE statement: European pregnancy rates from IVF and ICSI 'appear to have reached a peak'. News release 25.06.2019 https://www.eurekalert.org/news-releases/543795

[76] ESHRE. "*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*". Source: ESHRE fact sheets 3 "Egg donation", January 2017. Available online at https://www.eshre.eu/Press-Room/Resources

[77] Rathenau report - Economic landscapes of human tissues and cells for clinical application in the EU – available at https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/economiclandscapes_humantissuescells_en.pdf

[78] Due to their high degree of specialisation, organisational or ethical factors, some BTC therapies are not available in all countries. Consequent cross-border movements of patients are subject to the cross-border Directive (Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare).

[79] Source: Newsletter Transplant -International figures on donation and transplantation 2020 https://freepub.edqm.eu/publications/PUBSD-87/detail.

[80] Economic landscapes of human tissues and cells for clinical application in the EU https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/economiclandscapes_humantissuescells_en.pdf

BTC therapies unregulated or regulated under different frameworks	Faecal Microbiotic Transplants : ~ 1100 recipients Human breast milk supplied for thousands of pre-term infants Routine processing of BTC at the bedside or in surgery	Not quantified – low current value expected (below EUR 100 million) though significant growth possible	Breast milk banks and FMT: ~300 establishments Most EU hospitals perform some processing BTC at the bedside or in surgery.	FMT **mostly collected, prepared and used locally** [81]. However, future industrial developments may involve centralised manufacturing of medicinal products, In this case, FMT might **cross borders as a starting material** for this manufacturing, in a manner analogous to plasma. [82] Similarly, breast milk banks have been established across the EU to **collect and supply locally.** [83] However, the potential for using large numbers of donations to prepare fortifiers industrially points to a **potentially high level of inter-Member State exchange as a starting material** in the future [84]. Bedside and in-surgery processing, by definition, does not involve cross-border exchange.

Table 8.3: Cross-Border Aspects

[81] Baunwall SMD et al. The use of Faecal Microbiota Transplantation (FMT) in Europe: A Europe-wide survey. The Lancet Regional Health - Europe (2021), https://doi.org/10.1016/j.lanepe.2021.100181

[82] Mikkelsen TA et al. Towards an EU-wide suitable regulatory framework for faecally derived, industrially manufactured medicinal products. Letter to the Editor, United European Gastroenterology 8(3):351-352. https://pubmed.ncbi.nlm.nih.gov/32213033/

[83] Kontopodi E, Arslanoglu S, Bernatowicz-Lojko U, Bertino E, Bettinelli ME, Buffin R, et al. (2021) "Donor milk banking: Improving the future". A survey on the operation of the European donor human milk banks. PLoS ONE 16(8): e0256435. https://doi.org/10.1371/journal.pone.0256435

[84] Arslanoglu S et al. (2019) Fortification of Human Milk for Preterm Infants: Update and Recommendations of the European Milk Bank Association (EMBA) Working Group on Milk Fortification. Frontiers in Pediatrics 7 pp.1-14. https://www.frontiersin.org/articles/10.3389/fped.2019.00076/full

ANNEX 9: HOW THE BTC SECTOR FACED THE COVID-19 PANDEMIC

9.1 Support to the BTC sector

On 9 January 2020, the Directorate General for Health and Safety (DG SANTE) issued an alert for the Member States concerning a new virus from Wuhan, China.

With an increasing sense of urgency, specific measures were taken *in the blood, tissues and cells sector* too, to respond to the novel coronavirus:

- The technical guidance on donor selection and testing, in the BTC legislation, could not be updated quickly enough in light of the rapidly evolving scientific evidence. The ECDC published, within 3 months, a guidance on donor testing and deferral to prevent the spread of COVID-19 through substances of human origin (SoHO) [85]. This guidance has been updated twice (month 4 and month 12) [86]. From the beginning, it confirmed that the risk of transmission of the virus by transfusion, transplantation and medically assisted reproduction was likely to be low; however, there are significant risks for patients of a possible decrease of BTC supply, given the measures limiting person to person contact. This guidance was non-binding for Member States and voluntary compliance with it was relied on to achieve a common level of donor and recipient protection from the risks of COVID-19 infection.
- In month 3, The European Commission published a clarification that Substances of Human Origin (SoHO) are considered to be essential goods/services, which allowed free cross-border circulation of life-saving substances even during strict border controls [87]. ECDC recommended that the supply of personal protective equipment be prioritised for blood collection centres, that blood donation be considered an essential activity to continue during lockdown and that there should be representation from the SOHO sector in national crisis committees [88].
- The first meeting to coordinate the responses of BTC national Competent Authorities was organised in month 4 by the Commission.
- A potential treatment for COVID-19 convalescent plasma is based on a substance of human origin (antibodies from the recovered patients). In month 4, the EC published a guidance document [89] and set up a database to collect evidence on its use, which started data collection in month 5 [90]. A Horizon 2020 project, Support-E, was funded to coordinate EU efforts to evaluate this potential therapy. The project grant was signed in month 9.

[85] Coronavirus disease 2019 (COVID-19) and supply of substances of human origin in the EU/EEA - Second update', European Centre for Disease Prevention and Control, December 2020, Stockholm, Sweden, 2020. https://www.ecdc.europa.eu/en/publications-data/coronavirus-disease-2019-covid-19-and-supply-substances-human-origin

[86] https://www.ecdc.europa.eu/sites/default/files/documents/COVID%2019-supply-substances-human-origin-first-update.pdf ; https://www.ecdc.europa.eu/en/publications-data/coronavirus-disease-2019-covid-19-and-supply-substances-human-origin

[87] https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/2020_soho_crossbordershipments_en.pdf

[88] https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-supply-substances-human-origin.pdf

[89] https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/guidance_plasma_covid19_en.pdf

[90] EU CCP Data Platform: https://www.euccp.dataplatform.tech.ec.europa.eu/. As of September 2021, 117 blood establishments from 21 countries have registered data on 150 000 Convalescent plasma donations and over 1 000 treated patients

- The European Commission used the Emergency Support Instrument (ESI) [91] in month 6 to launch a call of EUR 40 million to help public and non-governmental organisations across the EU to establish or increase their collection of plasma by apheresis [92]: in month 12, the funds were allocated [93]: the purchase of plasmapheresis machines alone will allow the collection of up to 500 000 extra litres of plasma per year, a 21% increase on the volume of plasma collected by the public/NGO sector currently, and the actual increase will be significantly greater than this, due to the purchase of additional plasma collection sets.

9.2 Lessons learnt from the pandemic

9.2.1 Supply

The COVID-19 crisis impacted the supply of BTC [94]; but National Competent Authorities did not report substantial deficits that would have obstructed access to life saving BTC to a large population. Existing local, national and EU structures and capacities allowed quick response, and reduction in healthcare activities reduced demand for some BTC (like blood for surgery) [95].

Still, in 2020, ad hoc surveys illustrated the trend in falling supplies and retrospective reports documented the cessation of transplant activity for some substances such as corneas, and the complete suspension of IVF services. For example, a survey by the European Blood Alliance for the period February to March 2020 indicated a 9% (median, range 1-27%) decrease in donations of blood and blood components compared to the same months in 2019 in the 15 national and regional blood services that responded. The decline in blood components distributed to hospitals was 12% (median, range 1-18%), however this did not lead to shortages due to the parallel decrease in demand [96]. Plasma collection was subject to significant declines; highlighting the strong dependence of the EU on non-EU plasma supply (primarily from the United States). Eventually, the availability of reserve stocks of plasma prevented major shortages and the supply of distributed PDMPs was not altered [97]; but given that the complex manufacturing of plasma-derived therapies can take 7-12 months, any

[91] 'Coronavirus: European Commission strengthens support for treatment through convalescent plasma', European Commission Press Release, July 2020: https://ec.europa.eu/commission/presscorner/detail/en/ip_20_1435

[92] The most efficient technology that allow frequent donation but a significant set-up equipment cost.

[93] 'COVID-19: Commission supports blood services to increase COVID-19 convalescent plasma collection' European Commission Press Release, January 2021: https://ec.europa.eu/commission/presscorner/detail/en/ip_21_50. At the end of the grant on 15 October 2021, the EU has supported over 100 national, regional and local blood centres in 13 EU Member States and the UK strengthening their plasma collection capacity with 22.5 million EUR from the Emergency Support Instrument. Around 25% of the ESI funds are being used to purchase/lease about 300 plasmapheresis machines. Part of the remaining 75% of the funds is used for the purchase of additional plasma collection sets/equipment.

[94] Extraordinary COVID-19 meeting of the Competent Authorities for Blood and Blood Components (June 2020) https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/ev_20210603_sr_en.pdf

[95] Piteira, R., Bofill-Ródenas, A.M., Farinas, O., Tabera, J., and Vilarrodona, A. *Lessons Learned From SARS-CoV-2 Pandemic in Donation and Tissue Banking Activities: Key Takeaways*, Transplantation (2021), 105(7), pp.1398-1402. (submitted as supporting document to the Consultation surveys).

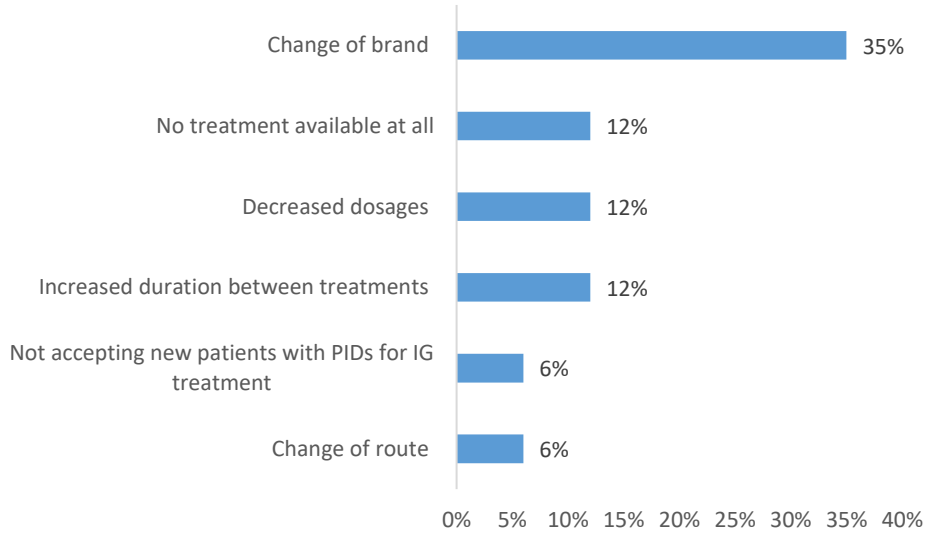
[96] Reported by the European Blood Alliance at a meeting of Blood Competent Authorities on 3 June 2020: https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/ev_20210603_sr_en.pdf.

[97] European Distribution Data by PPTA.

decline in plasma donations could potentially impact patients' ability to access their lifesaving therapies with delays [98].

Data collected by the External Study for the BTC Impact Assessment confirms that COVID-19 poses additional risks 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.

In response to the establishments survey by the External Study for the BTC Impact Assessment, a representative organisation for patients treated with products manufactured from BTC (PDMPs) [99] 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 (PIDs): 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%).



[98] There are reports on other BTCs affected, such as hematopoietic stem cells where a global report indicates an average fall of 16% in donations in the first months of the pandemic, and MAR where a study showed a complete suspension of services in most countries in the first period of the crisis. Activity data of this type is not routinely collected at the EU level.

[99] Stakeholder commentary on the IPOPI of immunoglobulins shortage survey.

Figure 9.1: Impact of immunoglobulins shortages during the COVID-19 pandemic on patients' treatment (Source: Stakeholder commentary on the IPOPI IG shortage survey).

The pandemic highlighted the challenge of not having mandatory activity data reporting requirements in place, but ad hoc survey by the European Blood Alliance and other professional organisations [100], indicated that the data is available at the establishment level [101]. Much experience was also gained during pandemic on the need for crisis preparedness and emergency plans and on the need for SoHO experts to participate in national crisis management bodies [102]. A survey of Member States by EDQM indicated that a majority already have a national emergency plan for the blood service [103], indicating that there is experience to be shared and built on in this area.

As a follow-up to the COVID-19 crisis, the Commission initiated a Structured Dialogue [104] to assess and address supply security for medicinal products. This exercise has looked into supply of plasma and PDMP, and further measures to ensure supply of these therapies will require initiatives both within the Structured Dialogue and within this initiative.

9.2.2 Innovative BTC therapies: new use of plasma

The COVID crisis brought the need to urgently assess whether COVID-19 Convalescent Plasma (CCP) (plasma from a donor who recovered from the infection) might prove a useful therapy to treat COVID-19 patients. To assess and authorize this potential therapy, Member States took very different approaches from no clinical evidence needed to requirements for full randomised controlled trials to demonstrate efficacy. This was a duplication of resources and efforts from establishments and National Competent Authorities [105]. When asked about lessons learnt from COVID-19 in the Public Consultation, stakeholders repeatedly expressed appreciation for the coordination efforts from the Commission and for the opportunity to share common data amongst actors and authorities across the EU [106]. In addition, valuable experience of sharing donation and clinical use data was gathered through the common EU database hosted by the Commission to support CCP collection and use. The experience demonstrated how an EU level platform that is fed with data from the blood establishment level can be used by authorities to monitor activity in their Member State, without the expense and burden of establishing their own national database.

[100] Summary minutes of the Hearing "Regulating for Sufficiency – blood and plasma" (May 2021): https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/ev_20210504_mi_en.pdf.

[101] In addition, article 21(5) of the Tissues and Cells Directive requires a sort of contingency arrangement for the TEs.

[102] This was specially recommended by ECDC in its guidance on Substances of Human Origin and COVID-19.

[103] 16 out of 20 Member States which replied to the survey from EDQM work programme on Blood Contingency and Emergency Planning.

[104] https://ec.europa.eu/health/human-use/strategy/dialogue_medicines-supply_en

[105] At least 48 EU clinical trials on CCP were registered in the "ClinicalTrials.gov" database as of October 2021; Search of: convalescent plasma | COVID-19 - Results on Map - ClinicalTrials.gov.

[106] Further details are provided in Annex 18.

ANNEX 10: BORDERLINE CONCERNS FOR BTC INNOVATION

The BTC sector is subject to significant and continuous innovation, both in the way that BTC are processed in establishments and the way they are used in patients. The majority of innovative developments in the BTC sector are driven by the public sector and are usually incremental in nature, evolving through small quality improvement steps rather than in single substantial changes [107].

As an indication of the pace of development of blood processing since the EU legislation was adopted, it is notable that in 2004, 18 blood component specifications were detailed in EU legislation [108], while the most recently published edition of the EDQM Blood guide (2020) specifies the quality criteria for 38 blood components [109] that are routinely used for patient transfusion across the EU today. When the tissue and cell legislation was adopted, corneas were always transplanted whole. Since then, processing techniques have developed and now eye banks across the EU routinely laser cut corneas to allow the supply of thin lamellar grafts, sometimes with more than one patient treated from one cornea [110]. Bone that was stored frozen without processing is now treated in a wide range of often complex ways, to remove cells, to remove minerals, to reduce or eliminate contaminants and to prolong preservation times [111]. Furthermore, some processing steps can now be carried out at the bed-side of the patient during surgery. In general, there is also a trend towards increased automation in BTC collection and processing, using devices as well as computerised systems incorporated during processing to ensure more consistent preparations and improved documentation and traceability. All these developments raise questions on what EU legal requirements are required to ensure safety and quality.

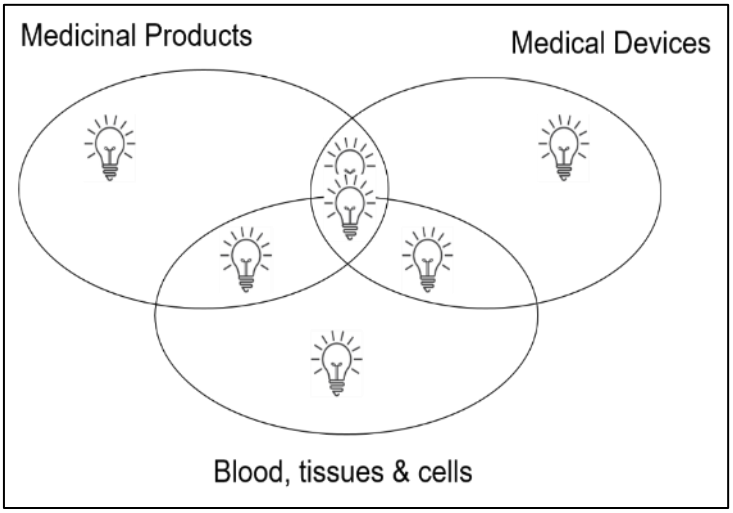


Figure 810.1: Innovation often occurs at the borderlines between the BTC sector, the medicinal product sector and the medical device sector.

10.1 Findings from the 2019 Evaluation

Developers (mainly academic/public sector) have highlighted that a **lack of legal clarity is a key concern that inhibits them from developing new BTC processes and uses**.

[107] For a description of the trends of innovation, see Evaluation {SWD (2019) 376 final}, Section 5.1.1.1, p. 29-31.

[108] Directive 2004/33/EC Annex II, reproducing the blood component monographs in the EDQM Guide to the preparation, use and quality assurance of blood components that was current at the time.

[109] https://www.edqm.eu/en/blood-guide

[110] Boynton GE and Woodward MA (2015) Evolving techniques in Corneal Transplantation. Curr Surg Rep. 3(2). Published online 1 Feb 2015.

[111] Osborne JC, Kurz A, Trias E et al. (2012) Skeletal Tissue: Specific recovery and processing issues. In: Tissue and Cell Processing: an Essential Guide Eds: Fehily D, Brubaker, S, Kearney J and Wolfinbarger L.

While most BTC based substances/products fall clearly into either the medicinal or BTC legal framework, the evaluation suggested that in some cases, it is challenging for Member States [112] to decide on classification [113]. Furthermore the use of devices and automation in BTC processing triggers questions regarding the applicability of the medical devices regulatory framework to BTC. While the EU has three separate legal frameworks for each of these sectors (substances of human origin, pharmaceuticals and medical devices) innovation often crosses these legal borders.

The 2019 evaluation report on the BTC legislation highlighted a lack of clarity on the interpretation of several definitions that delineate the regulatory borderlines with other frameworks [114], in particular:

- the term 'prepared industrially or manufactured by a method involving an industrial process', which is a determining factor for whether a product falls within the scope of the medicinal products legislation;
- the term 'substantial manipulation', relevant to determine whether the ATMP Regulation is applicable or not, has been subject to variable interpretation;
- the term 'used for the same essential function' has sometimes proved difficult to interpret and can result in identical substances prepared through similar or identical processes being subject to different safety and quality legal requirements in different Member States because of the way in which they are used clinically.

These definitions, and hence the scope of the BTC legislation, are not set within the BTC legislation, but in the Acts that regulate those other frameworks.

One response to the lack of clarity comes from the mandate entrusted to the Committee on Advanced Therapies at EMA by the ATMP Regulation. That committee provides non-binding scientific recommendations on whether the ATMP regulation is applicable to a particular product. The Committee responds to queries concerning specific products submitted by the substance/product developer, and advises on whether a specific medicinal product falls, on scientific grounds, within the definition of an ATMP. The Committee does however not assess whether a product falls in the scope of the pharmaceutical legislation (Directive 2001/83/EC) and does not provide indications of what the product is if it is not considered to meet the criteria of an ATMP.

Representatives of public [115] as well as private innovators [116] have called for more common clarity across these EU legal frameworks regarding when to apply which legal requirements. It is noted that those human substances that are not currently regulated under

[112] Classifying a substance/product as a BTC or as a medicinal product or establishing which of the respective legal framework applies is primarily a Member State responsibility, but bring very different legal requirements.

[113] Evaluation {SWD (2019) 376 final}, Annex 16, Table 2, p. 213.

[114] Evaluation {SWD (2019) 376 final}, p. 70-71.

[115] CoReSoHO submission evaluation *"T&C professionals and TEs/BEs require a clear definition of criteria for the classification of T&C under the EC Directive 2004/23. The same product can be considered a tissue/cellular therapy or ATMP, depending on the MS, and based on its final use. This leads to the requalification under ATMP of pre-existing cellular therapies, for example, bone marrow aspirate for orthopaedic use even though the production process remains the same (it is not more complex to produce)."*

[116] EFPIA submission 2019 BTC evaluation *"It seems that there is some room for clarification of borderlines between EU legislations on blood, tissues, cells, organs, medicinal products and medical devices".*

the BTC framework will bring further questions regarding these borderlines, in particular in relation to the 'industrial process' criterion [117].

Two key concerns have been raised as a consequence of this lack of clarity:

- **Under-regulation**: BTC-based therapies are offered on a commercial basis to, often desperate, patients without proof of their benefit and safety. Over the years, a series of cases have been reported where companies have offered such therapies without adequate oversight causing widespread concern, described in a position paper published by the Worldwide Network for Blood and Marrow Transplantation [118] and resulting in calls for a global response [119]. Several of these cases also received considerable media attention when authorities stepped in to stop treatments with unproven cell therapies, such as the X-cell case in Germany [120], the Stamina case in Italy [121]. More recently, the use of unproven stem cell therapies, regulated under the ATMP hospital exemption, in Polish hospitals raised concerns.
- **Over-regulation**: some safe and effective BTC-based therapies are considered to meet the criteria for ATMPs and are re-classified as such. The tissue establishments, that had developed and prepared them for many years, are asked to significantly invest to meet medicinal product manufacture requirements or to stop offering these established therapies. This re-classification does not always lead to commercial and affordable alternatives. As a consequence, it happens that patients no longer have access to these therapies. This scenario was reported by the Belgian Military Hospital [122] that had to stop providing and using autologous cultured keratinocytes to treat burn wound patients, although they had done this effectively for many years. Cultured keratinocytes are one of a number of borderline case studies conducted for this Impact Assessment that describe this scenario [123].

These concerns are typically raised in connection with hospital settings, particularly when more advanced technologies are being used to process BTC at the bedside or in surgery and where it is often difficult to know whether the pharmaceutical legislation and ATMP regulation, or BTC directives are, or should be, applicable.

10.2 Further evidence gathered in this Impact Assessment

Regarding the borderline issues, an objective of this Impact Assessment was to gather more evidence on the borderline problem, in particular in terms of the impacts of divergent

[117] At the stakeholder workshop on scope, 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 legislative frameworks where it defines scope.

[118] Position paper on Unproven Cell-Based Therapies: Current Global Status and Recommendations to the World Health Organization (2018) WBMT-Unproven-Therapies-2020.pdf

[119] Z Master et al. Unproven stem cell interventions: A global public health problem requiring global deliberation. Stem Cell Reports, Volume 16, Issue 6, 2021, Pages 1435-1445. https://doi.org/10.1016/j.stemcr.2021.05.004.

[120] Notorious stem cell therapy centre closes in Germany: News blog (nature.com).

[121] Abbott, A. Italian stem-cell trial based on flawed data. Nature (2013). https://doi.org/10.1038/nature.2013.13329.

[122] Verbeken, G., Draye, J-P., Fauconnier, A., et al. (2020). The Magistral Preparation of Advanced Therapy Medicinal Products (ATMPs). Journal of Surgery & Practice.

[123] Annex 11, sections 11.6, 11.7 and 11.8.

regulatory decisions between Member States, or of classification under one framework, on the safety and quality of those therapies, on patient access, price and affordability, and on research and innovation in general. It is acknowledged that the issue posed by innovation occurring at the borderlines between different frameworks can be fully addressed only when also considering how the legislation applicable to medicinal products, in particular, is currently functioning [124]. A comprehensive solution for this challenge will only be delivered in the future, jointly through this BTC initiative and the pharmaceutical strategy, as stakeholders active at the borderlines also underlined through their contributions to the revision process [125]. However, within this Impact Assessment exercise, options to clarify the scope of the legislation and to provide advice on the provisions from the BTC legislation applicable to innovative BTC is assessed (see annex 12).

This impact assessment has explicitly assessed the extent and consequences of these concerns, through dedicated questions in the consultations, the development of a series of dedicated borderline case studies and a dedicated workshop with authorities and stakeholders from the different legal frameworks to discuss the concerns and possible solutions [126].

This impact assessment identifies the wide extent of these concerns, which is recognised by stakeholders and authorities inside and outside the BTC sector, and confirms that lack of legal clarity regularly has significant consequences on safety, cost, availability and access.

10.2.1 Public consultation

There was a high level of response to the public consultation, with answers from 214 participants representing professionals as well as authorities, from the private as well as the public sector. This consultation confirmed that these borderline challenges are widely experienced. 49% of respondents from different groups, including in particular from industry and public administration, indicated that they are aware of cases where the regulatory classification of substances of human origin is unclear [127].

The 104 respondents that answered ‘yes’ were asked to describe the product/substance, name the framework with which BTC borders for that substance/product and describe the impact of the lack of clarity. Many respondents listed more than one product/substance. These are grouped into categories in the following list:

- Tissues and cells collected for a different future use

  The largest group was made up of 34 respondents from tissue establishments that described the collection of cells that might subsequently be used for a different function in the recipient. These substances lie mostly at the borderline with

[124] Revision of the EU general pharmaceuticals legislation: https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Revision-of-the-EU-general-pharmaceuticals-legislation_en.

[125] See the position papers from International Society on Stem Cell Research and a letter to the Commissioner from the Cord Blood Association.

[126] See the summary of the workshop “Borderlines with Other Regulated Frameworks: Classification Advice and Interplay”: https://ec.europa.eu/health/sites/default/files/blood_tissues_organs/docs/icf_summarynotes_stakeholder-workshops_en.pdf page 11.

[127] See also Annex 2: Stakeholder Consultation, Section 3.5.

medicinal products (both ATMP and non-ATMP), although one respondent each mentioned substances at the internal borderline between the blood and tissues Directives, at the borderline with medical devices, and at the borderline with Hospital/Healthcare Regulation in the Member States. Twenty of these respondents specifically described minimally manipulated cord blood and gave a coordinated response to indicate that regulation under the medicinal product framework would increase costs and reduce patient access. One respondent highlighted that innovation could be hampered by the application of the medicinal products framework for these substances. Regulation under hospital governance alone was seen to reduce oversight. Finally, respondents argued that the lack of regulatory clarity created difficulties and threatened access as well as quality/safety/efficacy.

A similar group of 19 respondents described the collection of cord blood or cord tissue for the subsequent separation of mesenchymal stem cells and pointed to a lack of clarity at the same borderline. All of these respondents indicated that classification as a medicinal product would threaten to increase costs and reduce patient access. One respondent specified that lack of clarity at the borderlines hampered innovation. In these cases also, it was evident that the responses had been co-ordinated in the manner of a 'campaign'.

- Isolated cells, exosomes and amniotic membrane

Nineteen respondents from industry, academia, public administration and others referred to specific tissue or cell types (keratinocytes, hepatocytes, chondrocytes, pancreatic islets, and other cells), as well as exosomes and amniotic membrane, as preparations that are at the borderline with medicinal products (ATMP). All referred to reduced access issues when these substances are regulated at ATMP. One also referred to access being less equitable and two mentioned higher costs. While one respondent expressed concern that the definition of "cell culture" was unclear and thus scientific evidence was at times lacking, another highlighted that efficacy could be more reliably proven under the ATMP framework.

- BTC as starting materials for medicinal products

Nine respondents, mainly from industry but also from a public administration and others, pointed to a lack of clarity at the borderline when BTC are used to manufacture medicinal products (ATMP and non-ATMP). Four of these described plasma for the manufacture of medicinal products, pointing to the impact of a lack of inter-Member State standardisation in plasma donor acceptance criteria, noting that it brings inefficiencies to the system.

The others referred to cells for ATMP manufacture, noting that the cells are regulated under the blood legislation in some countries and under tissues and cells in others, causing difficulties for ATMP manufacturers. One proposed that all such cells should fall under the tissue and cell legislation and two suggested that there should be dedicated rules for such cells.

- Adipose tissue/cells prepared in the hospital

Two public authorities noted that the preparation of autologous adipose tissue at the bedside/in surgery falls at a borderline with medicinal products (non-ATMP). Both expressed concern that the application of medicinal product legislation could limit patient access to the affected therapies. However, it was also suggested that quality and safety may increase from the application of medicinal products framework.

- Microbiota

Thirty two respondents that described microbiota (mainly faecal). These respondents, representing represented industry, public authorities, and other public organisations as well as individual citizens and academia, refer to the borderline with medicinal products (mostly non-ATMP) and, to a much smaller extent, medical devices, although many focused on the current absence of a clear legal framework. Three respondents each mentioned that regulation under the medicinal products framework reduces access and increases costs. On the other hand, six respondents mentioned that access was reduced by the absence of a clear framework. Similarly, 10 respondents saw quality/safety/efficacy threatened by the absence of a framework and three indicated that this could be improved by regulation as medicinal products or as BTC. Two respondents specifically criticized the lack of oversight in absence of a clear legal framework and one mentioned that the medicinal products or the BTC framework would provide clear guidance for businesses working in this field.

- Serum eye drops

Serum eye drops were listed by 20 respondents, mostly from public authorities and to a much smaller extent from industry, academia, and other organisations, indicating a borderline with medicinal products (mostly non-ATMP) and, to a much smaller extent, medical devices. Six mentioned concerns regarding patient access if regulation is under the medical devices or medicinal products frameworks; two more agreed that costs would increase in those cases. One respondent indicated that regulation as medicinal products hampers cross-border exchanges. On the other hand, three respondents indicated that regulation as medicinal products could help with quality/safety/efficacy, and one respondent indicated that regulation as blood may threaten access as well. Finally, four respondents criticized the current levels of regulatory ambiguity, limited standardisation and the confusion these create.

- Platelet-rich Plasma and related preparations

Nineteen respondents, mainly public authorities and to a much smaller extent individual citizens, academia, and industry, indicated that these substances lie mainly at the borderline with Medicinal Products (both ATMP and non-ATMP) and, to a smaller extent, at the borderline with Medical Devices. Two respondents mentioned the relevance of Hospital/Healthcare Regulation in the Member States. Respondents indicated that quality/safety/efficacy may be limited under the BTC framework, but also that regulation under the medicinal products framework would increase costs and potentially reduce patient access. Five answers focused specifically on the ambiguity resulting from lacking clarity and raised issues concerning harmonization, traceability, patient information, and quality.

- Placenta

Sixteen respondents, largely from industry, listed placenta as a substance at the borderline between BTC and Organs and between BTC and Medicinal Products (non-ATMP). All respondents indicated that the classification of placenta as an organ of the mother increased costs and limited patients' access.

- Human milk

Nine respondents, both individual citizens and organisations, listed human milk as a substance at the borderline with medicinal products (non-ATMP) as well as food legislation. Two indicated that these substances currently lacked any regulatory

framework. Concerns regarding the application of food legislation were raised in regards to reduced access, reduced clarity, and reduced evidence on quality and safety by one respondent each. One respondent criticized that the application of medicinal products legislation would threaten access to the substance, another raised the same concern regarding the application of the BTC framework. Finally, one respondent considered that the application of hospital/healthcare governance (i.e. non EU regulation) threatened adequate oversight.

- Acellular tissue and tissue extracts

Eight respondents from industry and academia listed substances without living cells as being at the borderline with medical device legislation. These included demineralised bone matrix and other tissues from which cells have been removed. Respondents raised concerns regarding a lower level of traceability under the medical device framework and the negative impact of a lack of regulatory clarity. Two respondents raised concerns that patients' access may be reduced when the medical devices framework is applied. However, one respondent indicated that innovation may be supported by application of the medical devices framework. Two respondents referred to this borderline for certified technologies used in BTC processing.

- Extracorporeal photopheresis

This autologous treatment of patient blood was raised by 4 respondents (from public administration, industry, and academia) as having an unclear borderline with medicinal products (ATMP) and with hospital/healthcare governance (i.e. non EU regulation). One respondent raised concerns that the lack of clarity as to which legal framework should apply may result in reduced patient access to treatment and another highlighted that oversight is lacking under hospital/healthcare governance.

- Novel blood components

Four respondents (three public authorities and one other organisation) listed novel blood components without a clear regulatory classification, the borderline being with medicinal products (non-ATMP) for chemically altered blood cells and for dried plasma and with medicinal products (ATMP) and medicinal products (non-ATMP) for cultured platelets. Two noted that the latter are sometimes unregulated at EU level.

Furthermore, 45% of respondents consider that there are substances/products being regulated under one legal framework but would be better regulated under another (54/119 with 95 ‘no answers’). There were slight variations between categories of respondents; notably, almost 40% of respondents from academia or patient organisations reported problems of this nature.

The 54 respondents that answered ‘yes’ were asked to describe the product/substance and to explain why they considered it to be inappropriately regulated. Their response are grouped by substance category in the following list:

- Cord blood and placental tissue.

Forty one respondents, largely private actors, referred to cord blood or umbilical cord tissue. Eighteen of these referred to the separation of mesenchymal stem cells (MSC) from cord blood, arguing that this should not be regulated as ATMP (one considered that enzymatic digestion should be regulated as ATMP while

other separation mechanisms should not) (7). Four respondents argued that "cord blood stem cells banked for allogeneic and non-homologous use should be classified as an advanced therapy medicine product (ATMP)." The other 19 argued against the classification of cord blood based on non-homologous use/substantial manipulation; some referred to a need for clarity regarding the collection of umbilical cord blood in/ex utero or called for the classification of placenta as waste product (8). A few of these also referred to gaps arising from the lack of clarity regarding whether the blood or tissues and cells Directive should apply.

- Processing of Starting Materials
  Seven referred to the application of the medicinal product framework for processing of starting materials for medicinal products (including plasma), pointing out that the definition of 'processing' needs to be clarified.

- Keratinocytes
  Four expressed the view that keratinocytes should be regulated as BTC, rather than ATMP, to improve access and efficacy and 4 considered that the regulatory framework for platelet-rich plasma needs to be clarified.

- Faecal Microbiota Transplantation
  Nine respondents referred to faecal microbiota transplantation, noting either a lack of regulatory framework or commenting that the application of the medicinal product framework is difficult for this substance. Seven argued it should be regulated as SoHO and 2 said it should be regulated as medicinal product.

- Serum Eye Drops
  Eight respondents referred to serum eye drops, arguing against what they perceive as over regulation when the medicinal product framework is applied and pointing out that it hampers access and cross-border exchanges. They argue for regulation as SoHO but note the need to allow distribution to the patient's home.

- Others
  The remaining 13 each referred to an individual substance/product. Five of them (chondrocytes, tissue extracts, human milk, and non-haematopoietic progenitor cells - not cultured, blood for transfusion in Germany that is currently regulated as a medicinal product) were cases where it was argued that the classification should be changed to BTC. For the others (placenta, white blood cells, adipose, cosmetic/aesthetic SoHO, donor lymphocyte infusions, extra-corporeal photopheresis, and HPC) it was argued that the classification needs to be clarified.

10.2.2 Targeted consultation

The public consultation was complemented by a targeted consultation with 160 respondents, including all the major associations of public and private stakeholders

working in the BTC sector. The targeted consultation highlighted the complexity of getting legal clarity as the main driver for this challenge [128]. 72 respondents indicated that they had experience of working at the borderlines with other regulated frameworks. From that experience, 79% responded that they find it complex, or very complex to apply the criteria that set the scope of the different legal frameworks and understand which framework(s) applies to their substance/product (56/71); 85% responded that it is (very) complex to obtain confirmation of the regulatory framework to be applied in their country (58/68); 93% find it complex, or very complex, to have the regulatory decision made in their Member State accepted in another Member State (54/58); and, most importantly at EU level, 89% responded that they find it complex, or very complex, to obtain guidance on the regulatory status from EU level expert groups/committees such as the Commission's SoHO Expert group of competent authorities, the Committee on Advanced Therapy Medicinal Products or the Medical Device Borderline and Classification working group of the Medical Devices Co-ordination Group (54/61).

10.2.3 Borderline case studies

To understand the impact of these widely reported concerns, the External Study for the BTC Impact Assessment organised an information and data collection exercise, exploring 20 borderline case studies, covering different scenarios. [129]

Each case study aims to describe the therapy and technology, including multiple types of manipulations or therapeutic indications, when relevant. They describe the regulatory situation (current as well as historical, central/EU as well as national) and the impact on safety, quality, cost, affordability, eventual patient access and innovation. The studies describe the current preparation and use of the substance or product in question, followed by an overview of the regulatory issue. They also provide an overview of the judgements made by 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.

Each case study is based on literature research, with, overall, hundreds of references to peer reviewed articles published in scientific journals included in the case studies [130]. These were complemented by interviews to add perspectives of leading experts in the therapy or technology each case focused on. These experts were often identified by and speaking on behalf of their European clinical societies [131].

Each case study has been revised in the light of comments by DG SANTE to the first drafts. Additionally, the consolidated case study that is linked to the ATMP classification process was been sent to EMA for review.

The case studies can be grouped according to the following scenarios:

1) Currently unregulated therapies (donated breast milk, faecal microbiota transplants, serum eye drops):

[128] For further details, see Annex 18
[129] For further details, see Annex 11.
[130] For further details, see Annex 11.
[131] For further details, see External Study for the BTC Impact Assessment, ICF, Annex 14.

These case studies highlight that some products do not fall under the current provisions of the EU BTC legislation, despite being of human origin. This has led to divergent regulation across Member States.

Use of these products is also growing, with potential for further manipulation, in some cases, which is likely to lead to further borderlines with pharmaceutical framework in the future.

2) Therapies involving bedside processing (Platelet rich plasma, Autologous adipocyte cells):

There is evidence of some shift from BTC being processed in traditional settings towards a 'bedside' process, which has created new challenges in terms of ensuring appropriate safety and quality by inspection and oversight. The interpretation of 'same surgical procedure processes' (currently excluded from the scope [132] also currently varies across medical settings, creating diverging practices and standards. The referenced case studies highlight a need to address these issues, but a key challenge is understanding how regulation applies to the settings outside hospitals in which bedside therapies are often applied (e.g. cosmetic or sport therapy settings).

3) Products previously regulated under the BTC framework (Cultured keratinocytes, Chondrocytes, Cultured limbal cells):

As set out in the relevant case studies, changes in the classification of these substances, and associated implications for how equivalent authorised medicinal products can be provided, suggests reduced access to previously freely available BTC – due mainly to a lack of authorised commercial products or availability of such products at prices that are not generally affordable.

The case studies highlight changes in classification for these BTC led to divergent regulatory practices across the EU, including in the use of the ATMP hospital exemption provision.

4) Interplay with the medical devices' legislation (Demineralised bone matrix (DBM), Decellularised dermis, Decellularised heart valves):

The introduction of the EU Medical Device Regulation 2017/745 raised questions as to whether tissues from which cells have been removed (or rendered non-viable) should be regulated as medical devices (MD). Despite efforts by the Commission to clarify this issue, some regulatory confusion remains, including with the supply/registration of equivalent products from non-EU suppliers, suggesting a need for greater coordination between the BTC and MD sectors.

5) Need for coordination with the ATMP sector (Isolated hepatocytes, Pancreatic islets, Banked leukocytes, Human allogenic amniotic membrane, Minimally manipulated MA-Omental Film, Autologous bone marrow cell aspirate, Modulated immune cells):

The classification of a product as an ATMP rests on disputed distinctions (e.g. 'enzymatic digestion' as a 'substantial manipulation') which can create a lack of harmonisation in how substances or products (even those which are similar to each other) are eventually regulated.

6) Emerging field with no clear regulatory pathway (Extracellular vesicles (EVs)):

[132] Directive 2004/23/EC, Article 2 (a).

Discussions on how to classify EVs have increased in line with the growth in interest in this area [133], with a significant degree of regulatory uncertainty.

Summary tables of findings (including views on the impact of proposed measures in the BTC revision) are added at the end of this annex.

The key, recurrent message of the case studies is the sub-optimal coordination and mutual understanding between authorities responsible for different legal frameworks (BTC, pharma, ATMP, medical devices), and the negative impact this has on safety, quality, cost, access and innovation. The full potential of innovation is therefore not reached for EU citizens.

10.2.4 Borderline Workshop 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, 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. 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

[133] This is evidenced by the establishment of a Regulatory Affairs Task Force by the International Society for Extracellular Vesicles

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.

10.2.5 Summary of Borderline Case Studies conducted by the External Study supporting the BTC Impact Assessment (ICF)

For further details, see Annex 11. **Regulatory issue**	**Description**	**Safety and quality**	**Costs and affordability**	**Patient access**	**Innovation, research and development**	**Conclusion**
Currently unregulated therapies Donated human breast milk (DHBM) Faecal microbiota transplants (FMT)	These case studies highlight that some products do not fall under the current provisions of the BTC legislation, despite being considered substances of human origin. This has led to divergent regulation across Member States. Use of these products is also growing, with potential for	M1A will introduce standard safety and quality requirements for donor selection and testing; quality measures; storage, labelling, packaging and distribution; and traceability and vigilance. Enhanced donor protection (M2A) can help protect from commercial exploitation of donors and enforce application of VUD). Sharing information on national authorisation decisions (M4B) could help to improve exchanges on donor history, information on samples and procedures etc. Establishment of an advisory committee (M4A)	Costs can be expected for actors in these fields following the implementation of M1A and further measures to strengthen preparation process authorisation (M4B) – but stakeholders perceived costs to be justified by the benefits (e.g. enhanced safety and quality standards, regulation of the commercialisation of products such as HBM and FMT.	Under M1A, the introduction of standardised rules concerning donation and treatment could lead to more equitable access. It would also enhance harmonisation across the EU to guarantee wide availability of these therapies.	Incorporating unregulated therapies into EU law (M1A may encourage increased investment into these fields. Measures relating to the creation of advisory bodies (M4A) and standardised processes for preparation (M4B) could increase transparency, which in turn supports innovation by making it clear when something becomes a starting material for a medicinal product.	Proposed changes to bring these therapies into the scope of the BTC legislation will set a precedent for other human-derived microbiota to be regulated under the BTC framework (though stakeholders felt that all microbiome samples should be considered individually).

For further details, see Annex 11. **Regulatory issue**	**Description**	**Safety and quality**	**Costs and affordability**	**Patient access**	**Innovation, research and development**	**Conclusion**
	further manipulation which may lead to future borderlines.	could facilitate harmonisation of standards that ensure higher quality and safety. Related measures (M4A) would support clarification in the case of manufacturing scale up or manipulation.			M4A (an advisory mechanism) would introduce efficiency and financial certainty for developers.	
Therapies involving bedside processing Platelet rich plasma Serum eye drops Autologous adipocyte cells	There is a shift from products being produced in a traditional settings towards a 'bedside' process, which has created new challenges in terms of appropriate quality, inspection and oversight. The	Removing the same surgical procedure exemption (M1A) was supported by stakeholders as a way to provide regulatory clarity and improve safety. Alongside this, implementing risk assessments on novel processes (M4B), and requiring clinical evaluation of high risk novel products (M4B) may also positively	M1A may increase the portfolio of work for CAs (by bringing more therapies into the scope of their legislation) with associated cost and resourcing implications. Likewise, measures to strengthen preparation processes (M4B) will increase costs as each	M1A may not increase access but would help to ensure *appropriate* access once these therapies were under the BTC legislation. Measures to strengthen preparation process	M1A could support innovation and investment. If a correct balance were struck, the proposed measures would not discourage innovation as long as the burden of implementing them is managed (e.g. with registration, reporting and clinical trial requirements).	The referenced case studies highlight a need to address these issues, but a key challenge is understanding how regulation applies to the 'non-traditional' settings in which bedside therapies are

For further details, see Annex 11. **Regulatory issue**	**Description**	**Safety and quality**	**Costs and affordability**	**Patient access**	**Innovation, research and development**	**Conclusion**
	interpretation of 'same surgical procedure' also currently varies across medical settings, creating diverging practices and standards.	impact on quality and safety, e.g. in the tracing of adverse reactions/events, as long as a proportionate approach is taken with patient safety in mind. M4A would be beneficial if therapies involving bedside processing use/combine with medical devices. However, stakeholders felt that advice should build on existing guidance (e.g. PRP is already included in the EDQM Tissues and Cells Guide).	establishment will have to evaluate products in their own setting (though authorisation data between and within Member States (M4B) would be beneficial to increase efficiencies).	authorisations (M4B) could enhance transparency (especially if mandatory) in turn helping to improve patient access as a result of more products being deemed safe for use and efficient.	Expert consultation in the establishment of the advisory mechanisms (M4B) could also support greater innovation in bedside manufacturing processes by improving trust between the BTC, MD and pharmacy sectors.	often applied (e.g. cosmetic or sport therapy settings).
Products previously regulated under the BTC framework	As set out in the relevant case studies, changes in the classification of	Stakeholders believed that the package of measures proposed under Objective 4 could help to bring products closer to the quality and	Costs should be proportional to the number of patients (and clinical indications) a product	These case studies highlight that patient access is intrinsically linked to	When regulatory pathways and frameworks change, investors can become sceptical about	The current regulation of these therapies as ATMP has clearly had an

For further details, see Annex 11. **Regulatory issue**	**Description**	**Safety and quality**	**Costs and affordability**	**Patient access**	**Innovation, research and development**	**Conclusion**
Cultured keratinocytes Chondrocytes Cultured limbal cells	these products, and associated implications for how products can be produced, has been perceived to limit access to previously freely available products – due mainly to a lack of (affordable) commercial products. The case studies highlight that it has also led to divergent regulatory practices across the EU, including in the use of the	safety standards of the ATMP Regulation, thereby increasing trust between adjacent sectors. Stakeholders also felt that the measures to collaborate at the EU level to clarify the regulatory status of treatments (M4B) could enable classifications to be made earlier in the development of products, therefore ensuring that all developers are working to the same standards.	or treatment can be used for. Any measures brought in under the BTC legislation which significantly increase resource and capacity requirements (e.g. M4B) may disproportionally affect public sector hospitals, preventing them from working in these fields. At the same time, affordability could increase with a more streamlined regulatory framework, which prevents different rules in different markets.	regulation. Measures to strengthen preparation process authorisation (M4B) and the ability for more coordinated decisions on classifications (M4A) could support greater patient access even when products are later commercialised.	investing. A clearly defined pathway is a key factor in making investment decisions (achieved through M4A). Currently, although many products reach early clinical studies, few obtain marketing authorisation due to limited resources and a high workload, and there are many challenges for public developers to accept the standards and requirements for ATMPs. A coordination mechanism (M4A) might help to support	impact on innovation and access, and there are questions of whether instead of singularly applying the ATMP framework, these therapies could be better regulated under the BTC framework.

For further details, see Annex 11. **Regulatory issue**	**Description**	**Safety and quality**	**Costs and affordability**	**Patient access**	**Innovation, research and development**	**Conclusion**
	ATMP hospital exemption provision.				improved public-private relationships earlier in the process.	
Interplay with the medical devices' legislation Demineralised bone matrix (DBM) Decellularised dermis Decellularised heart valves	The introduction of the EU Medical Device Regulation 2017/745 raised questions of whether tissues from which cells have been removed (or rendered non-viable) should be regulated as a medical device (MD). Despite clarification in this area, some regulatory	As reported in the case studies, in general, stakeholders did not feel quality and safety standards have been hindered by existing regulatory practices. At the same time, stakeholders felt the introduction of a proportionate and uncomplicated risk-based authorisation process (M4B) could encourage harmonisation of quality and safety standards, to the benefit of those already working to higher standards. Additionally, proposed	The addition of more measures could increase costs due to more requirements for data generation (e.g. the additional obligation regarding documentation or collection and reporting of data to the competent authorities under M4B). This can impact on the capacity and resource of actors in this field (and disproportionally the public sector).	Stakeholders believed that the proposed measures being considered (under Objective 4) would not significantly impact patient access to decellularised heart valves and dermis and DBM. Rather, they felt patient access was currently linked to factors such as the supply and	As set out in the case studies, there is a perceived risk of overregulation in this area which may lead to developers stopping their activities due to higher costs and administrative burdens. At the same time, M4A may provide earlier clarity on the regulatory pathway to ensure an upfront understanding among developers of the different stages and	These case studies provide an 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 M4A) would support this.

For further details, see Annex 11. **Regulatory issue**	**Description**	**Safety and quality**	**Costs and affordability**	**Patient access**	**Innovation, research and development**	**Conclusion**
	confusion remains, including with the supply/registration of equivalent products from non-EU suppliers, suggesting a need for greater coordination between the BTC and MD sectors.	mechanisms for providing classification advice (M4A) and improving coordination (M4A) could improve classification and oversight processes (thereby ensuring appropriate vigilance practices, and clarifying whether something requires a CE mark or not).	However, the magnitude of impact is dependent on what standards that establishments are already working to.	availability of the relevant organs; and the type of health and reimbursement system in place.	costs involved in product development.	
Need for coordination with the ATMP sector Isolated hepatocytes Pancreatic islets Banked	The classification of a product as an ATMP rests on disputed distinctions (e.g. 'enzymatic digestion' and 'substantial manipulation')	Greater coordination would reduce the variability of approaches taken across MS, particularly for unproven therapies as monitoring/enforcement at a national level in this area is generally low. It will also resolve the "black hole"	There may be short-term costs to make applications to advisory committees (M4A), but the process of joint decision-making would ensure efficiencies in the	Stakeholders felt measures to strengthen preparation processes (M4B) and then share this data (M4B) encourage standardisation	Strengthening preparation process authorisation (M4B) and the proposed mechanisms (M4A) could help to increase confidence and trust between adjacent sectors, with	M4A can potentially improve coordination/communication between sectors and EU and national bodies, and increase the

For further details, see Annex 11. **Regulatory issue**	**Description**	**Safety and quality**	**Costs and affordability**	**Patient access**	**Innovation, research and development**	**Conclusion**
leukocytes Human allogenic amniotic membrane Minimally manipulated MA-Omental Film Autologous bone marrow cell aspirate Modulated immune cells	which can create a lack of harmonisation in how products (even those which are similar to each other) are eventually regulated.	when products fail to meet an ATMP classification. Some stakeholders felt the impact of M4A would be greater if decisions were binding. Increased oversight of novel preparation processes (M4B) would help ensure adequate standards are in place for all starting materials regardless of how they are eventually used and regulated. Safety and quality could be enhanced further through the implementation of measures under Options 2 or 3 as there would be fewer divergent interpretations.	longer-term (by ensuring the correct regulatory pathway is followed from the outset). Stakeholders stressed that smaller, less-resourced public sector organisations should have access to the same level of advice and expertise as commercial developers. Stakeholders stressed that requirements under M4.6 and M4.7 also need to be calibrated to the number of patients that data can be collected from.	and harmonisation, therefore improving access through cross-border exchange and acceleration in countries where there is currently limited treatment available. Patient representation (e.g. in committees established under M4A) could help to ensure the perspective of the patient is considered in	implications for further research and development (e.g. more joint working between public and private actors). Additionally, they could contribute to homogenous classifications and clarify what regulatory pathway should be followed and support shared learning opportunities. However, some stakeholders felt the revised BTC legislation had to be agile and flexible to adapt to innovative	knowledge and expertise available to developers, if aligned well to existing CAT classification processes.

For further details, see Annex 11. **Regulatory issue**	**Description**	**Safety and quality**	**Costs and affordability**	**Patient access**	**Innovation, research and development**	**Conclusion**
				classification decisions.	therapies and fields.	
Emerging field with no clear regulatory pathway Extracellular vesicles (EVs)	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.	The case study on EVs shows that, as with many novel BTC-derived products for which there is no clear regulatory pathway, there may be a high degree of variation in the quality and safety standards followed by different developers and across different countries. Consulted stakeholders therefore felt measures proposed to strengthen the preparation process authorisation for novel products (M4B) are appropriate for regulating very novel products. Additionally, greater	The cost and affordability of novel products is tied to the regulatory pathway. In general, the tighter the regulatory requirements (e.g. risk assessments for novel products under M4B), the higher the costs and time to innovate. But in an emerging field like EVs, where there is considerable innovation, high regulatory costs may be inevitable, even for small changes in processes.	Implementation of a strengthened preparation process (M4B) as well as greater coordination between adjacent sectors (M4A) may play a role in reducing patient access to unregulated novel products still in the early phase of development.	With novel products like EVs, the regulatory framework needs to be applied in a way to facilitate innovation. On this basis, stakeholders preferred a pragmatic and flexible approach to assessing risk. Having more coordination among regulatory bodies at the EU level (M4A) and standardising risk assessment models at the national level (M4B) may facilitate this, but taking a more	The developing field of EV-based research highlights that 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)

For further details, see Annex 11. **Regulatory issue**	**Description**	**Safety and quality**	**Costs and affordability**	**Patient access**	**Innovation, research and development**	**Conclusion**
		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).			pragmatic approach is also contingent on several other factors, including the expertise and training of inspectors (to ensure they support rather than hinder continuous improvements).	about how and where material is obtained and the way it can be used (e.g. EVs can be a therapy in itself, or used as a vector, or enhancer for therapies).

Table 10.1: Summary of the issues raised by the borderline case studies developed by the External Study for the BTC Impact Assessment. For further details, see Annex 11.

ANNEX 11: BORDERLINE CASE STUDIES

This annex contains the following individual borderline case studies, developed by the external study supporting the Impact Assessment.

- Human breast milk
- Faecal Microbiota Transplantation (FMT)
- Platelet-rich plasma
- Serum eye drops
- Autologous adipocyte cells
- Cultured Keratinocytes
- Chondrocytes
- Cultured limbal cells
- Demineralised bone
- Decellularised dermis
- Decellularised (human) heart valves
- Consolidated case study examining the ATMP classification process
- Extracellular vesicles

Each case study follows the same structure:

- Part A describes the current preparation and use of the 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.

11.1 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).

11.1A Definition of the borderline issue

11.1A1 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 necrotizing 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 USA, 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.

11.1A2 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 MS 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 MS 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 MS taking different regulatory approaches to the regulation of DHMB there are other important (technical) differences being practised across MS 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 pasteurization.

Expert stakeholders reported that inconsistent regulatory approaches and the lack of harmonisation has the potential to adversely impact the safety and quality of DHMB. 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

i Further information about the regulations and laws DHBM was regulated under was not available in the meeting minutes.

safety CAs and T&C 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 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 pasteurized 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 underutilized 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.

11.1B 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 2.1 (high level principles to protect BTC donors), Measure 2.7 (EU law incorporates quality and safety requirements for DHMB 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 authorization, 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.

11.1B1 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 MS 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.

11.1B2 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.

11.1B3 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 (USA) 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 standardized 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].

11.1B4 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.

11.1C 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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11.2 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.

11.2A Definition of the borderline issue

11.2A1 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 EUR 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].

11.2A2 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. More examples of classifications by Member State found in the literature are provided in Table 11.1 below.

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 unharmonized 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.

11.2B 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 2.7 (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), outlined below:

- 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 standardized mixtures of bacteria (or another yet undiscovered stool extract that could theoretically underlay 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 authorization).

An academic article which mapped some examples of different approaches to FMT regulation[35] indicated that the USA, Canada, and Australia are investigating or undertaking a Biological agent classification for FMT, with stringent regulation and restricted use. In the USA, 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.

11.2B1 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 emphasized 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].

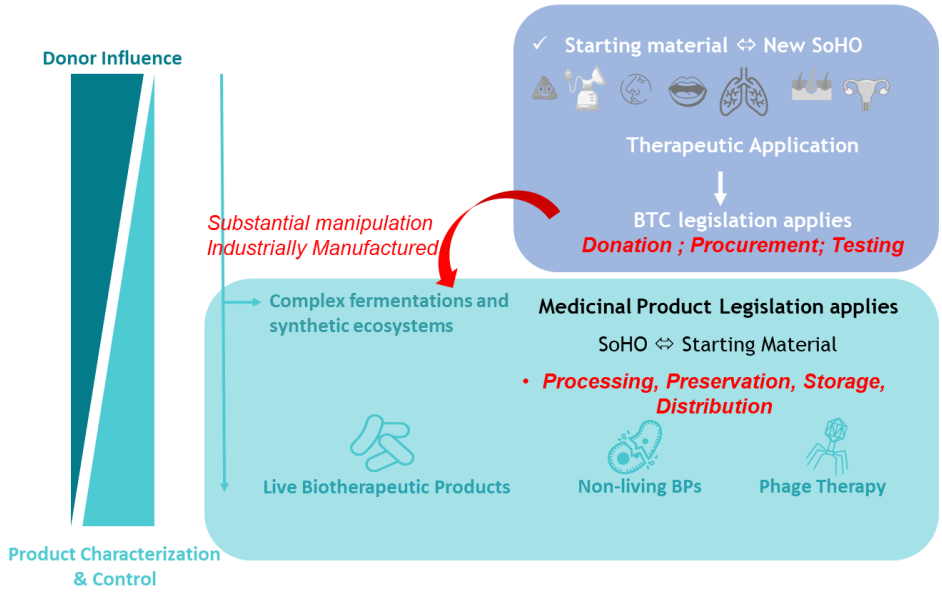
More specific measures and recommendations for the regulation of FMT are described below.

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 USA 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 any 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 expert provided the graphic in Figure 15 below to illustrate the regulatory split:

Proposed regulation of FMT from a consulted expert



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.

11.2B2 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.

11.2B3 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 centralization and standardization, 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.

11.2B4 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 USA 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 USA. 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.

11.2C 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.

Table 11.1: Example FMT classifications by Member State

Member State	Classification
Netherlands	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].
Italy	
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	Non-biologic Medicinal product (a drug), with variable regulation according to jurisdiction[71,72]
Germany	
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 authorizing 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 hospitalized patients with rCDI 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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11.3 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.

11.3A: Definition of the borderline issue

11.3A1 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 USD 500–USD 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 polymerized 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 USA[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 USD 540.31 m 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 USD 476.1 m in 2020 and suggested it would expand at a compound annual growth rate of 12.0% from 2021 to 2028[13].

11.3A2 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 USA, the FDA has cleared PRP to be used for various orthopaedic indications[21], and PRP is often brought 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 USA, whereby the professional providing PRP is liable rather than the manufacturers of the device[23].

11.3A3 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".

11.3A4 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.

11.3B 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: M4.2-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 (change in scope of the blood legislation) and M1.9 concerning the same surgical procedure exclusion under Objective 1.

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).

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.

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).

11.3B1 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 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.

11.3B2 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.

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 MS 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 blood establishments (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.

11.3B3 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 blood establishments 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.

11.3B4 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.

11.3C 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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11.4 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.

11.4A: Definition of the borderline issue

11.4A1 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 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 EUR 1 b (USD 1.2 b)[13] and current market estimates (Global Data)[14] suggest the dry eye market will reach USD 11.1 b 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 eye drops, 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].

11.4A2 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

i US, France, Germany, Italy, Spain, the United Kingdom, Japan, China and India

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.

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

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.

experience of single blood centres according to national or regional blood establishments[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].

In a separate paper, one of interviewed stakeholders from the UK writes that "the 'unlicensed' status of serum eye drops 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.

11.4B 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), Measures 1.6-1.8 (regarding the definition of rules on safety and quality), and Measure 1.9 on the same surgical procedure exclusion; the six related measures promoting oversight under Objective 3; and several measures under Objective 4 (M4.2-M4.4 concerning strengthened clarification processes and M4.5-M4.6 concerning strengthened authorisation processes).

11.4B1 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 2 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).

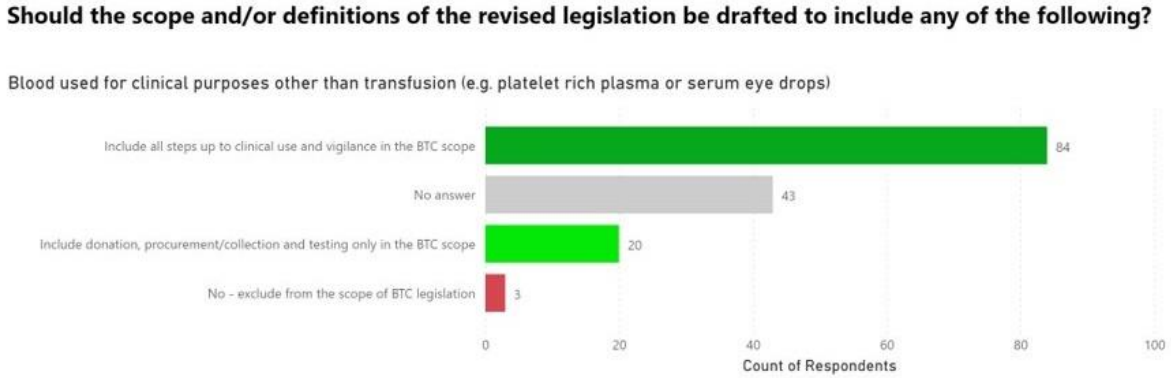

Figure 11.2: Responses to a question in the targeted consultation

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 3).

11.4B2 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).

11.4B3 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.

11.4B4 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 drops[28]. 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.

11.4C 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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11.5 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.

11.5A Definition of the borderline issue

11.5A1 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 USA, 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 an 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 (CAT) has made a recommendation can be found in the table at the

end of this case study (A9.2.1).

11.5A2 Current regulatory status of autologous adipocyte cells

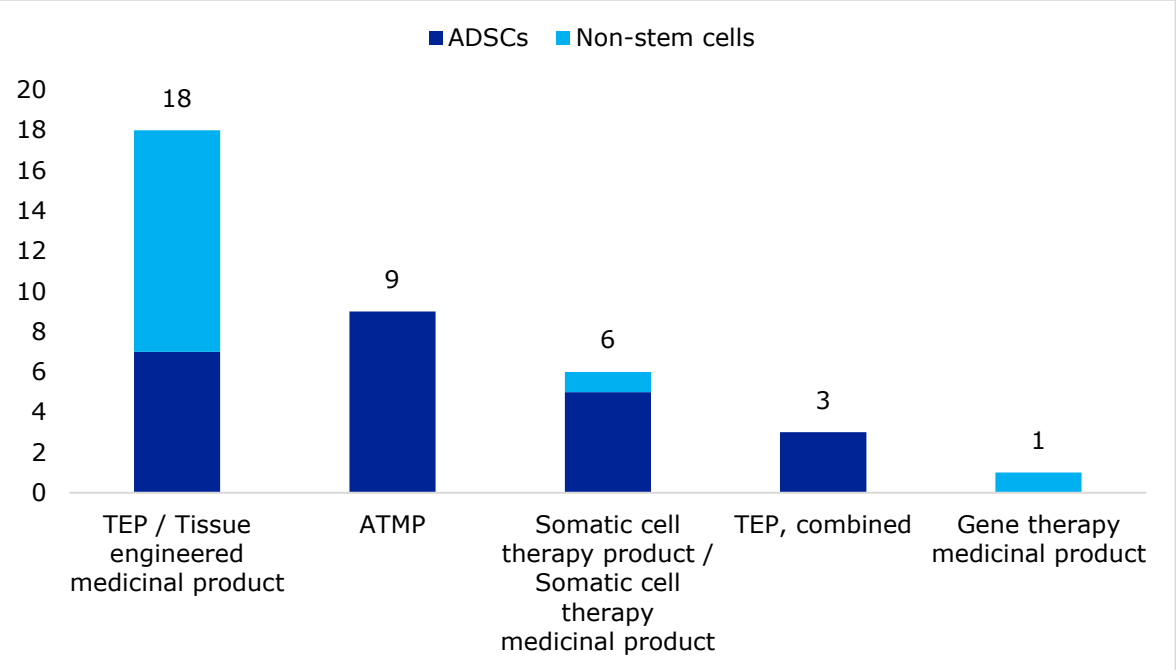
When autologous adipocyte cells are procured, processed and re-transplanted in the same surgical procedure, they currently fall outside the EU regulatory framework. However, if they are procured, processed and stored they fall within the framework.

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 CAT is presented in Figure 14; the most common classification recommendation was Tissue-Engineered Product (TEP), 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 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.

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.

ATMP recommendations on autologous adipocyte cells made by CAT[iii]



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 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.

iii A generic 'ATMP' classification is provided where 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).

iv The German Tissue Act defines all tissues and cell preparations as pharmaceutical drugs governed by the German Drug Act

11.5A3 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: substantial manipulation and non-homologous use. During an interview with representatives from CAT, it was agreed that the definitions of substantial and homologous use have led to many questions from stakeholders 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. 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.

v This process was at the time used for reconstructive surgery, for example breast reconstruction.

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 USA as in the EU. A presentation at a EMA ATMP Workshop in 2014[20] stated that the USA 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 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 Legislation on Blood, Tissues and Cells by a representative of a public authority in an EU Member State suggested there may be potential impacts on patient 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

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."

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 USA 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.

11.5B 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 (M4.2-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) as well as M1.9 concerning the "same surgical procedure" exclusion.

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).

11.5B1 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.

11.5B2 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 (M4.6), 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.

11.5B3 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 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.

11.5B4 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 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.

11.5C 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.

Table 11.2: CAT recommendations on autologous adipocyte cells

Public description of active substance or product description	Indication (public) or therapeutic area	Outcome of classification	Date of CAT recommend-ation
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 medici nal 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 (ALS)	Somatic cell therapy product	27/10/2015

Public description of active substance or product description	Indication (public) or therapeutic area	Outcome of classification	Date of CAT recommend-ation
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	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
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 ofautoimmune drug resistant epilepsy	Somatic cell therapy medicinal product	06/06/2017
Cultured autologous adipose derived regenerative mesenchymal stem cells	Intended for the treatment ofautoimmune 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 ofautoimmune 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 medici nal product	16/06/2017
Autologous adipose tissue-	Intended for chronic	Somatic cell	19/07/2017

Public description of active substance or product description	Indication (public) or therapeutic area	Outcome of classification	Date of CAT recommend-ation
derived mesenchymal stem cells	wounds healing (venous leg ulcers, post-traumatic wounds)	therapy medicinal product	
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 (using a proprietary system from manufacturer 1)	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
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	Repair of cartilage lesions	ATMP	30/06/2020
	Diabetic foot syndrome	ATMP	09/10/2020

Public description of active substance or product description	Indication (public) or therapeutic area	Outcome of classification	Date of CAT recommend-ation
tissue			
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	TEP, 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	TEP	25/09/019
Adipose-derived ex-vivo expanded mesenchymal stem cells	Treatment of diabetic foot ulcers	TEP	25/09/019
Human autologous adipose tissue - derived mesenchymal stem/stromal cells	Bone and cartilage defects including osteoarthritis	TEP	25/09/019

Source: European Medicines Agency. (2021) Scientific recommendations on classification of advanced therapy medicinal products.

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11.6 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).

11.6A: Definition of the borderline issue

11.6A1 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 (EC) No. 1394/2007 on Advanced Therapy Medicinal Products (ATMP), the Committee for Advanced Therapies (CAT) recommended that cultured keratinocytes be reclassified as ATMP in 2010.

11.6A2 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. 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 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 MS: nine EU MS regulate keratinocytes separated from skin by enzymatic digestion, without culture, as T&C; seven regulate it as an ATMP, two decide on a case-by-cases basis, and three do not regulate[8].

One stakeholder engaged for this study suggests that – despite clarifications from CAT on the scope/definition of substantial manipulation – there are still some challenges regarding interpretation. 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 (ECTD 2004) 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 EUR 5.3 m 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

i After having documented the efficacy at a not-for-profit production cost.

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 EUR 6.74 /cm^2 with full grafts ranging from EUR 24 000 (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]. 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 EUR 2 000 for treatment, but this jumped to EUR 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 (EC) 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 tissue establishments, 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 the therapy to the hospitals[17]. According to Pirnay (2012), this put the preparation of these tissue and cell products outside the capability of many tissue

establishments, 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 MS (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.

11.6B 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 (M4.2-M4.4 concerning strengthened clarification processes, M4.5-M4.6 concerning strengthened authorisation processes and M4.7 concerning clinical data) as well as Measure 1.9 (same surgical procedure exclusion).

11.6B1 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

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.

confidence in the safety and quality of other MS processes (and thereby increase cross-border trade).

The same stakeholder explained that, in regard to the 'same surgical procedure' (M1.9), 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/authorizing 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".*

11.6B2 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 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.

11.6B3 Patient access

According to one stakeholder the proposed reforms to the BTC legislation, particularly those relating to Objective 4 (M4.2-M4.12) and M1.9 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 T&C 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.

11.6B4 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 MS. 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.

11.6C 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.

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11.7 Chondrocytes

The stakeholders consulted for this case study were two clinicians highly experienced in performing chondrocyte procedures, working in Spain and the UK respectively.

11.7A: Definition of the borderline issue

11.7A1 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

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.

expected to be valued at USD 3,440.5 m in 2027 and is expected to exhibit a compound annual growth rate (CAGR) of 10.2 % during the forecast period (2020-2027)[7].

11.7A2 Current regulatory status of chondrocytes

Three indications of autologous chondrocytes have been recently classified by CAT as ATMPs specifically tissue engineered products (TEPs)[8]:

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 tisseel lyo (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):

11.7A2.1 MACI (matrix-applied characterized 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.

11.7A2.2 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 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].

11.7A2.3 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 cm^2. 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 GBP 10 000 in the UK[31], cheaper in Germany as it is domestically-manufactured (EUR 6 000 EUR) and higher still in the USA (USD 50 000).

11.7A3 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

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).

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 EUR 7000 to EUR 35,000-45,000 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).

11.7B 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).

11.7B1 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).

11.7B2 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.

11.7B3 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.

11.7B4 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.

11.7C Conclusions

In regard to autologous chondrocytes, as this product 'fits' the current definitions of an ATMP provided by 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 the 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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11.8 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.

11.8A Definition of the borderline issue

11.8A1 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

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.

An illustrative diagram of the eye can be found on Mednotes (http://mednotes.co.uk/clinical-anatomy/head-musculoskeletal/anatomy-of-the-eye/)

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 (EC) 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 (EC) 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'[i], limbal stem cells were classified by CAT as a somatic stem cell therapy as the cell culturing process meets the definition of 'substantial

i 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).

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 (CAT) recommended that a marketing authorisation should be granted to Holoclar®, a cultured limbal stem cell product, for the 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[ii] 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

ii 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

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[iii], 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 Advanced Therapy Medicinal Product (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 with the network of European clinics, which will be in direct contact with the production and control of the product"*[17].

11.8A2 Overview of the regulatory issue

Cultured limbal cells provide an example of a therapy that was developed by tissue establishments under the tissue and cells legislation, but is now considered (under the recommendation of 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 the therapy and demonstrated its efficacy prior to the ATMP authorisation.

iii 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

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 the 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[iv] than the 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 EUR 206 802 in failures in 10 years (follow-up) compared to EUR 220 943 – EUR 618 639 for simple limbal epithelial transplantations. Additionally, the total potential partial cost including surgery was estimated at EUR 300 709 for Holoclar by the authors compared to EUR 241 943 – EUR 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.

iv 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 (EUR 21 893), conjunctival limbal allograft tissue from living relatives (EUR 65 479), keratolimbal allograft (EUR 77 393), simple limbal epithelial transplantation (EUR 21 000), best supportive care (EUR 88 377) and Holoclar (€93,907).

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[v] (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.

11.8B 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 strengthened clarification processes, M4.5-M4.6 concerning strengthened authorisation processes).

11.8B1 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

v 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).

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 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.

11.8B2 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).

11.8B3 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.

11.8B4 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.

11.8C 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 CAT will help to ensure there is a clear regulatory pathway for developers.

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11.9 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).

11.9A: Definition of the borderline issue

11.9A1 Description of the borderline substance

Demineralised bone matrix (DBM) is a specialized 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]. Tissue establishments 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 such as chitosan and polymethylmethacrylate (evaluated in animals[7]), or gelatin (to provide a scaffold) and chitooligosaccharide (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 10 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 1 500 preparations of DBM, and in 2020 this number had shrunk to approximately 1 000.

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 USA, 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, tissue establishments 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.

11.9A2 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].

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 the 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 USA, 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].

11.9B: 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 M4.4-M4.5 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.

11.9B1 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

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.

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 (M4.1 or M4.2), 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 M4.1-4.3) 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 (M1.9). Experts from a non-profit tissues and cells institute reported that, in response to M1.9, surgeons and physicians facing higher regulatory efforts could stop their activities. The experts also reported that M4.7 (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.

11.9B2 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.

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 (M4.5-

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.

M4.7) 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".

11.9B3 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.

11.9B4 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.

11.9C 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.

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11.10 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.

11.10A: Definition of the borderline issue

11.10A1 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?

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[2]. 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[3]. 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'[4]. 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[5].

An illustrative explanation is provided by ACS Biomater (2016)[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

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.

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 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].

iii CE Mark certification verifies (self-certification using a Notified Body) that the device meets all regulatory requirements of the Medical Devices Directive

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.

11.10A2 Overview of the regulatory issue

Decellularised dermis is seen to be regulated in divergent ways across the MS[24], with most regulating as a tissue. A Commission survey of EU tissue and cell competent authorities indicates 13 regulate under the tissues and cells legislation, while seven have no current regulation or do not have the 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).

11.10B: 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 (M4.1-M4.3 concerning strengthened clarification processes and the establishment of a coordination body across adjacent legal frameworks, M4.4-M4.5 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.

11.10B1 Safety and quality

One tissue bank representative explained that, although the measures to strengthen authorisation and preparation processes (M4.4-M4.5) 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 (M4.5), 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 (M4.2) 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".*

11.10B2 Costs and affordability

According to a representative from a tissue bank, many tissue establishments 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.

11.10B3 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.

11.10B4 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 (M4.3) 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 (M4.2) 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.

11.10C 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 M4.1-M4.3) would support this.

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11.11 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.

11.11A: 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).

11.11A1 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*

i A fibrous sac that encloses the heart and great vessels.

standard procedure for treatment with allograft valves might offer further improvements in allograft quality and [an] increase in durability"[8].

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].

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 Chișinau (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).

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].

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 tissue establishments currently decellularise heart valves in Europe.

11.11A2 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 the 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 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.

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;

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.

11.11B: 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 (M4.2 and M4.3 concerning strengthened clarification processes and the establishment of a coordination body across adjacent legal frameworks, M4.4-M4.5 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.

11.11B1 Safety and quality

One tissue bank representative explained that, although the measures to strengthen authorisation and preparation processes (M4.4-M4.5) 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 (M4.5), 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 (M4.2) 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".*

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According to a representative from a tissue bank, many tissue establishments 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.

11.11B3 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.

11.11B4 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 (M4.3) 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 (M4.2) 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.

11.11C 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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11.12 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).

11.12A Definition of the borderline issue

11.12A1 Description of the borderline substance/product/application

11.12A1.1 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 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 "heterogeneous 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].

11.12A1.2 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 CAT that this initial classification of January 2017 was revisited by 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 CAT is unable to publish commercial or propriety information.

11.12A1.3 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 4 500 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[170] 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 national competent authorities 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].

[170] The act of cooling or chilling a material and then reducing it into a small particle size.

11.12A1.4 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:

> 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, TEP, 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.

11.12A1.5 Modulated immune cells

Modulated[171] 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.

11.12A2 Overview of the regulatory issue

Representatives from CAT stated that ATMP classification procedure has been used widely, with over 500 classifications issued to date. The applicants include pharmaceutical

171 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.

companies, but also SMEs, academic developers and hospitals. The procedure is fast (60 days) and is free of charge. The scientific recommendations from CAT are not legally binding, but nevertheless perceived to be accepted by the national competent authorities; the CAT interviewees were not aware that Member States have ignored the classification outcome or have issued different classification for the same product[172].

In case of cell-based therapies, 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/CAT/600280/2010 rev.1). The same criteria are used in many parts of the world (e.g. USA, Canada, Japan) to determine the cell-based products that need a pre-authorisation approval (ATMPs).

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).

11.12B 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.

11.12C 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 national competent authorities. Classifications are **specific to the product and the indication**. Changes to manufacturing process and or different indications can result in a

[172] From time-to-time, the CAT will ask their members if there are any issues with classification decisions, and from this they know that, in general, central classifications from the CAT are routinely accepted. Member States will make their own classification decisions as well and it is this part which may create possibilities for deviations. However, the CAT have not explicitly heard about non-acceptance of ATMP decisions from the CAT.

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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11.13 Extracellular Vesicles

Two expert representatives from the International Society for Extracellular Vesicles were consulted for this case study.

11.13A: Definition of the borderline issue

11.13A1 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[cccxcix], 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[cd].

Microvesicles (MVs): Small vesicles that originate from plasma membrane, regarded as mediators of stem cell function, enabling and guiding their regenerative effects[cdi].

Apoptotic bodies: Small sealed sacs containing information and substances from dying cells[cdii].

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 the therapeutic value of MSCs in various diseases according to the www.ClinicalTrials.gov database[cdiii].

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[cdiv]. Recently, some researchers have also been exploring the potential EVs from MSCs and possibly other cell sources as treatments for COVID-19[cdv].

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 the 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.

11.13A2 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. According, representatives from the CAT, there is a lot of pre-clinical trial activity in the area, but you cannot 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'[cdvi], 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 (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[173]) produced a letter requesting to work with regulators to contribute their collective expertise to the

173 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.

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"*[cdvii]. 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.

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[174]. 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[175]) depending on the EV source and manufacturing processes may be meaningful for developing EV-based products[cdviii]. 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[cdix]. 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.

11.13B: 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 (M1.2 to expand the scope of the BTC legislation to cover all SoHO except organs) and several measures under Objective 4 (M4.1-M4.3

174 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.

175 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.

concerning strengthened clarification processes, M4.4-M4.5 concerning strengthened authorisation processes, M4.6 for requiring clinical evidence for innovations/new claims).

11.13B1 Safety and quality

Generally, stakeholders interviewed for this case study felt that the measures proposed to strengthen the preparation process authorisation for novel products (M4.4-M4.5, M4.6) 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 that proposed by GAPP and under consideration in M4.4-M4.5) 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 M4.4-M4.5, 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.

11.13B2 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.

11.13B3 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[cdx]. 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[cdxi].

11.13B4 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 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 (M4.1-M4.3) and standardising risk assessment models at the national level (M4.5) 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 the Failure Mode and Effects Analysis (FMEA) strategy 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.

11.13C 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. 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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