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

Abstract and Executive Summary

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

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Abstract

This study, commissioned by the European Commission's European Health and Digital Executive Agency (HaDEA) and its Directorate-General for Health and Food Safety (DG SANTE), provides evidence to support the assessment of impacts of proposed reforms to the EU's legislation on blood, tissues and cells (BTC). An evaluation of the BTC legislation, published by the European Commission in 2019, concluded that it was substantially effective but that there were five main areas with gaps and shortcomings to address. The Commission has been working on the development of options to address these issues.

In this study evidence was collected from existing sources and new research undertaken to inform the identification and exploration of impacts. Activities undertaken included desk research, eleven participatory workshops which reached over 700 sector stakeholders, interview and other research for 15 case studies exploring the issues and challenges seen at the borderlines between BTC and other regulatory frameworks, targeted online consultations (surveys focusing on impacts and costs of the proposed options were distributed to BTC National Competent Authorities and BTC establishments and other stakeholder), and follow-up interviews with stakeholders.

The evidence was brought together and used to assess the impacts of the options proposed by the European Commission, as compared to the baseline. The analysis suggests that the proposed "joint regulation" model (whereby establishments are obligated to follow guidelines specified by EU expert bodies) provides a useful combination of regulatory agility and consistency across the EU. Additionally, the package of measures being considered by the European Commission is expected to make a positive contribution to resolving borderline issues at the interface with other legal frameworks, increasing regulatory harmonisation, tackling barriers to innovation, improving resilience to supply shortages and providing a consistent level of protection for patients, donors and children born as a result of medically assisted reproduction. Securing these benefits will entail some additional costs for the sector and for regulators.

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Executive Summary

ES1. Introduction and study purpose

This is the final report of the study by ICF S.A. that informs the European Commission's impact assessment of the revision to Directive 2002/98/EC and Directive 2004/23/EC and their implementing acts: the EU's legislation on blood, tissues and cells (BTC). The objective of this study is to provide evidence to support an assessment of the impacts of proposed reforms to the BTC legislation. The proposed reforms are intended to address the following five principal problems identified during an evaluation of the BTC legislation in 2019:

- Patients are not fully protected from avoidable risks as quality and safety requirements set out in the legislation are outdated;
- Divergent approaches to oversight cause unequal levels of quality and safety and barriers to the exchange of BTC across the EU;
- BTC donors and children born from donated eggs, sperm or embryos are exposed to avoidable risks;
- BTC legislation lags behind innovation and there are difficulties in defining the borderlines for BTC processed in new ways with other regulatory frameworks; and
- EU is vulnerable to interruptions in supply of some BTC, and there is a high dependence on plasma imports.

The COVID-19 pandemic also highlighted further shortcomings of the legislation, e.g. the lack of a provision for monitoring of the supply situation, lack of suitable and proportionate framework for the quick assessment of novel therapies (i.e., COVID Convalescent Plasma (CCP)).

The Commission has developed **three alternative policy options**, each of which provides an approach to addressing the target problems. Each of the options have several component measures. The options are differentiated by the approach they take to the setting of rules on standards for quality and safety, and preparedness measures:

- Option 1 is based on the principle of decentralised regulation. In various areas it gives autonomy to Blood Establishments and Tissues Establishments to establish their own standards/rules by making reference to diverse sources of guidance;
- Option 2 is based on the principle of joint regulation. Establishments are obligated to follow guidelines specified by EU expert bodies such as the EDQM and ECDC;
- Option 3 is based on the principle of centralised regulation, with all rules codified in EU law.

Detailed descriptions of the options, along with common measures designed to address the other problems identified in the evaluation, are provided in the study report. This study has compared the impacts expected under each of these options with a baseline scenario in which EU legislation on blood, tissues and cells (BTC) is not reformed.

ES2. Methodology

The study methodology, which was aligned to the Better Regulation Guidelines, involved:

- **Desk research**: More than 270 documents and data sources (reports, scientific literature, position papers, meeting minutes and the outputs of Commission consultations) were reviewed.

- **Workshops**: Eleven participatory online stakeholder workshops were organised, with attendance from over 700 stakeholders from a range of organisations. The workshops addressed a variety of topics relevant to the reforms including authorising novel BTC; regulating point-of-care BTC processing; strengthening oversight; strengthening donor protection; key definitions; ethical principles; and borderlines with other regulated frameworks.
- **Targeted online consultations:** Surveys were administered over a four-week period to (i) BTC national competent authorities (NCAs) and (ii) other stakeholders. Each contained a cost inquiry and a questionnaire about potential impacts of the options. Follow-up interviews and e-mail exchanges with key stakeholders were conducted to obtain more detailed feedback on specific measures and data gaps.
- **Borderline case studies:** 15 case studies were prepared to provide further evidence on borderline issues. Data collection for each case study involved a desk review and consultation with experts. In total, 44 stakeholders across 25 organisations were consulted through this process.

The outputs of the various research tasks were brought together in the synthesis stage. The study team then estimated costs of the options and analysed the benefits of the options for safety and quality, security of supply, access, innovation, etc. A series of criteria were specified to capture the variety of impacts of the options, relative to the baseline. The Commission used these for the impact assessment, guided by a multi-criteria assessment tool – SOCRATES – developed by the Joint Research Centre.

The study benefitted from technical inputs and advice from three independent experts who formed a Steering Committee which worked with the core project team.

ES3. Findings

ES3.1. Health impacts

Impact on patient treated with BTC:

The study found that measures targeting quality and safety for patients would potentially benefit millions of people a year through greater agility of the regulatory system to respond to avoidable risks; increase in consistency of regulatory practice across the EU; ability to mobilise relevant scientific and technical knowledge in the BTC sectors for the updates of guidance, and increased availability of timely information for risk management on serious adverse events for patients.

The performance of the three alternative policy options against these target impacts varies quite considerably based on the existing operational practices of BTC establishments. Generally:

- Option 1 is generally no better than the current situation, and could possibly lead to less consistency of practice across Member States.
- Option 2 is generally expected to have the biggest positive impact by allowing for more agile, consistent updating of guidance (via expert bodies such as the European Centre of Disease and Control and the European Directorate of Quality Medicines) that reflects current scientific and technical knowledge. Importantly, it will also facilitate the rapid development of advice in emergency situations such as the recent Covid-19 pandemic.
- In contrast, Option 3 is expected to be more cumbersome than Option 2 due to the lengthy process required for comitology, but nonetheless provides a robust solution to facilitate protection of patients across the EU.

Impact on donors and offspring

The measures targeting quality and safety for donors and offspring could provide enhanced protection for large numbers of people every year. All options are expected to improve the availability of information needed for risk management, via common measures proposed for reporting on serious adverse reactions or outcomes. Options 2 and 3 are expected to offer enhanced and consistent protection. Option 2 was judged by stakeholders to be an effective way to bring scientific and technical expertise to support management of high-risk events or adverse outcomes, and to be more agile in updating rules in line with the latest evidence.

Impact on oversight:

All three policy options include the same package of measures intended to strengthen oversight of the BTC sector so that rules are implemented more uniformly, inter-Member State confidence is improved and regulatory barriers to cross-border exchange of BTC lowered. Thus, the impacts (as compared to the baseline scenario) are expected to be the same for all options.

Some measures directly address NCAs, others require the European Commission to implement measures that will indirectly strengthen oversight capability (such as audits of national control systems, and a shared IT platform that will support dissemination of information to and among competent authorities).

Within each MS, it is hoped the measures will help to strengthen oversight practices and ultimately lead to better patient / donor / child outcomes. This will then (indirectly) support collective impacts to be realised at EU level (e.g. enhanced mutual trust, a greater exchange of BTC among Member States, faster uptake of new BTC applications recognised by other Member States, improvements in the quality of inspections performed, etc.).

Impact on supply resilience:

The measures are expected to improve overall supply risk management in the BTC sector; the availability of information to predict and manage shortages/risks of interruption including emerging infectious health threats; and preparedness to implement effective and timely management of shortages/risks of interruption including emerging infectious health threats. It is less clear that the measures will address structural supply issues, such as the EU's reliance on US plasma supplies.

Insofar as most measures are common to all Options, and many establishments are already likely to have some form of contingency planning arrangements, the expected variance in performance of Options is less than in some other areas of this analysis. The main difference between Options is the approach proposed to specification of the rules to be followed by establishments in developing contingency plans and guidance for sufficiency data reporting:

- Option 1 extends the existing model (whereby establishments prepare contingency plans to requirements set by competent authorities, customers and other external bodies).
- Option 2 has the benefit of a consistent approach and timeliness of update of guidance set by EU authorities in relation to preparedness and contingency plans.
- Option 3 is expected to provide consistency but lack agility, although this consideration is less relevant for the problem of shortages compared to other problem areas, as rules in this area are expected to change less often.

ES3.2. Economic impacts

Innovation and research:

Several measures are common to all options. As a result, all options are expected to:

- Have a positive impact on the development of more consistent evidence demonstrating quality, safety and efficacy of BTC with similar risk/benefit profiles, which would be closer to requirements in adjacent legal frameworks. In particular, under all options, measures have the potential to enhance interaction with other advisory bodies (e.g., the Committee for Advanced Therapies and Borderline and Classification subgroup which sits with the Medical Device Coordination Group).
- Partially resolve issues that impede R&D in the BTC sector (including by public sector innovators), by fostering public-private partnerships; enhancing transparency of research (circulation of data, research results or researchers). The availability of clinical outcome data relating to novel BTC applications/preparations via an IT platform (to be developed by the EU Commission, as proposed in the measures) is expected to enhance transparency, mutual trust and confidence in the BTC sector.
- Support Member States to share data on national preparation process authorisations – therefore enhancing the consistency and efficiency of authorisation processes as a whole across the EU. However, the magnitude of impact will be highly dependent on the information developers want to share, particularly due to confidentiality clauses for proprietary data.
- Improve accessibility to novel BTC therapies.

Costs to regulators and establishments:

The table below illustrates the main impacts of the proposed reforms on enforcement and adjustment costs (specified as a range) for EU institutions, NCAs and establishments over ten years (costs expressed in EUR thousand).

Organisation	Indicator	Option 1	Option 2	Option 3	Comment
European Commission	Annual enforcement costs	1,499-1,721	7,294-7,516	8,591-8,813	The main costs related to the funding of advisory and classification coordination mechanisms, the development and maintenance of an IT platform, funding the development and updated of guidance (Option 2) or rules in EU legislation (Option 3) and costs relating to strengthening and harmonisation of oversight procedures.
	One-off adjustment costs	6,071	6,071	6,071	
National competent authorities	Annual enforcement costs	19,732-21,587	18,728-20,590	18,728-20,590	Main costs will be adjustment costs to transition to new operating models. Some authorities (~7%) may incur costs due to the extension of the legislation to currently unregulated BTC therapies. At least 14 Member State (and an estimated 20 in total) already use risk-based inspections; most of the incremental costs are expected to fall on those NCAs that do not currently have this. There is the scope for savings if the maximum duration allowed between inspections is extended

Organisation	Indicator	Option 1	Option 2	Option 3	Comment
	One-off adjustment costs	2,406-3,199	2,788-3,708	2,597-3,453	(e.g., for low-risk establishments). Option 1, in which NCAs evaluate establishments' own risk assessments, will create more complexity (and thus cost) for regulators. Procedures for the evaluation of novel BTC processes or substances are potentially resource-intensive for NCAs, particularly where evidence from clinical studies needs to be assessed. The extent of this activity among NCAs will vary by the volume of 'innovation activity' and scale of the BTC sector in the country. EU support will be important to facilitate this. An increase in joint inspections (currently estimated at 10 per year) may also reduce costs (not yet quantifiable).
Establishments	Annual enforcement costs	71,268-84,091	63,570-84,091	68,393-84,091	Relatively few establishments will have to comply with an entirely new set of rules. Organisations brought under the scope of the BTC legislation for the first time (~7%) will incur additional costs in registration, authorisation, inspection and compliance. Based on the underlying assumptions of this study, proposals for harmonising the approach to authorisation of novel BTC applications which will lead to the greatest additional costs. There may be some additional costs relating principally to contingency planning and data reporting, however, most establishments already have in place similar measures. The functionality of the reporting system and reporting thresholds/conditions will affect the ongoing costs to establishments.
	One-off adjustment costs	170,298-248,382	124,372-190,254	124,372-190,254	

Sustainability of health budgets:

Costs of **increased oversight** are expected to affect NCAs and regulated establishments, but generally to the benefit of increased standardisation across the EU. A potential risk is that competent authorities subject to new requirements are not able to mobilise the financial resources required to fund the transition to the new operating model. EU support will be important to facilitate this.

Measures proposed to enhance the **efficacy of authorisation processes** of novel applications of BTC will help to harmonise risk management approaches across the EU. The proposal to use an IT platform to share information should also help to improve the overall efficiency of authorisation activity (e.g. by avoiding duplication of evidence generation and administrative effort for both applicants and authorities). There may also be possible savings from joint work and information exchange already carried out by Member States. Overall, efficiencies might be slightly lower under Option 1 due to the variability in procedures used (e.g. for risk-assessments).

There is potential for the proposed measures to impact the **sustainability of health budgets** in different ways, but the difference that the reforms would make is not feasible to determine given the scale and complexity of the systems and contexts.

Competitiveness, trade and investment:

The measures to support innovation in BTC are expected to have a positive impact on EU competitiveness in this sector. The consensus stakeholder view on Options 2 and 3 is that

they will increase the level of harmonisation within the EU for BTC, both through rule-setting and through new mechanisms that advise on borderline issues and matters of interpretation related to the BTC legislative framework.

No material difference between options in trade impacts is expected, including dependency on imports of plasma.

ES3.3. Wider impacts

Small but positive impacts on **fundamental rights** are expected from all options as a result of enhanced protection to children born from donated sperm, eggs or embryos, changes to the protection and therefore rights of all donors and patients, and enhanced data protection measures.

Sufficient data on the distribution of entities by size are not available to assess specific impacts on the **operation and conduct of small-medium size enterprises**. Stakeholder consultations did surface some concerns that the additional costs associated with the reforms would be more difficult for smaller establishments to absorb and that there would be some further consolidation of the sector. Some of these effects will be internalised within public healthcare systems.

Research and consultations did not yield any information suggesting that the options would result in **impacts to natural resource use or environmental impacts**, either within the public health system or at a wider system level. The options are also not expected to lead to **digital impacts** such as the development of healthcare technologies or other technologies that will contribute to the EU's digital economy. The primary innovation impact foreseen is in BTC treatments and products.

ES4. Conclusions

Overall, the balance of evidence appears to favour the delivery model provided by Option 2. It offers a combination of agility and pan-EU consistency that is not presented by the alternative governance models provided by Option 1 or 3. If Options 2 and 3 are seen as equally likely to enhance quality and safety standards, and improve supply risk management, then the greater agility of the Option 2 approach suggests the potential for greater efficiency and effectiveness. Whilst all of the options are expected to increase coherence, Option 2 would better guarantee a future-proof approach. A key condition is the process used for determination and update of the rules produced by expert bodies under Option 2 which would need to provide for appropriate engagement, consultation and consideration of the costs and benefits.

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