Description of the policy options proposed for the revision of the EU legislation on blood, tissues and cells

This document provides descriptions of the options proposed under each of the five Objectives of the revision. A set of summary tables provide an overview of the proposals. Annexes provide more detail on each of the measures within the options .

Annex 6

Problem 1: Patients are not fully protected from avoidable risks

There are three options which all aim to increase patient protection from avoidable risks, by keeping technical rules for safety and quality up to date. The options share many of the same components but differ in where the rules (which blood and tissue establishments need to follow when preparing their risk assessments) are defined.

The scope of European law on BTC is extended to new cover additional types of BTC. Quality and safety principles are built into the new law. Blood and tissue establishments have to conduct risk assessments. Depending on the option, they must either follow rules written into EU law (Option 1-3), guidance provided by EU expert bodies (Option 1-2), or have freedom to use available guidance from a much wider range of sources (Option 1.3). Under all Options, the Commission will build an IT platform to share safety/quality information. Under Option 1-2 and 1-3, Member States are required to publish more stringent national rules in an accessible format.

Option component ("measure")		Option 1.1	Option 1.2	Option 1.3
M1.1	Principles for safety and quality principles in EU law	✓	✓	✓
M1.2	EU law is changed so that all SOHO/BTC for which the EU has legal competence are covered by EU safety and quality rules (bringing breast milk, faecal microbial transplants, etc. under EU law)	✓	✓	✓
M1.3	Member States are required to publish more stringent BTC rules in an accessible format		✓	✓
M1.4	The European Commission builds an IT platform that provides information on quality and safety requirements	✓	✓	✓
M1.5	National competent authority inspectors have to evaluate blood and tissue establishments' risk assessments to ensure that they have been conducted effectively and that the rules set adequately manage the identified risks	✓		
M1.6	Blood and tissue establishments are required to assess the risks associated with their procedures, and to set technical rules for safety and quality, compliant with the principles defined in EU law. They must base the rules on risk assessment and scientific evidence, and update whenever the need arises. They can follow inter/national guidance or standards from other bodies in setting their rules.	✓		
M1.7	Blood and tissue establishments are required to take into account ECDC/EDQM rules on quality & safety requirements. EDQM/ECDC update their guidance as required		✓	

M1.8	Blood and tissue establishments are required to take into account of quality and safety requirements that are defined in EU law. There is a mechanism to provide regular updates in response to changing risks and technologies (using Comitology rules).			✓

See Annex 1 for more detail on Objective 1 options.

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

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

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

See Annex 2 for more detail on the Objective 2 option.

Problem 3: Avoidable risks for BTC donors and for children born from donated eggs, sperm or embryos				
There are three options under Objective 3, all intended to reduce the avoidable risks for BTC donors and for children born from donated eggs, sperm or embryos. The intended outcome is they are protected from the risks that are specific to those groups, including exposure to hormonal treatment for egg and stem cell donation and the risks of genetic disease transmission to children born from assisted reproduction.				
Option component ("measure")		**Option 3.1**	**Option 3.2**	**Option 3.3**
M3.1	EU law incorporates high level principles to protect BTC donors, including reporting measures (SARE/monitoring outcome)	✓	✓	✓
M3.2	EU law incorporates high level principles to protect offspring born from donated gametes/embryos, including reporting measures (SARE/monitoring outcome).	✓	✓	✓
M3.3	EU law incorporates new definitions (e.g. to include genetic disease transmission by medically assisted reproduction using donor gametes or embryos as an 'adverse reaction')	✓	✓	✓
M3.4	The European Commission will develop the relevant component of an IT platform for quality and safety requirements	✓	✓	✓
M3.5	EU law requires establishments to define detailed quality & safety requirements to protect donors and protect children born from donated gametes or embryos	✓		
M3.6	EU law requires expert bodies to define detailed quality & safety requirements for donors and offspring of medically assisted reproduction, and requires establishments to 'take into account' the rules issued by the expert bodies.		✓	
M3.7	EU law incorporates quality and safety requirements for donors and offspring of medically assisted reproduction, and a mechanism to update these as needed			✓

See Annex 3 for more detail on Objective 3 options.

Problem 4: BTC legislation lags behind innovation				
The three options under Objective 4 intend to tackle the problem that the scale and pace of innovation in the BTC sector is reduced by various features of the existing regulatory framework, including insufficient provision for authorisation of novel BTC, insufficient provisions for proof of clinical value of BTC and unclear borderlines between the BTC framework and those for medicinal products, medical devices, etc.. There is no forum that can classify BTC-based therapies and technologies at the interface of other EU legal frameworks. The aim is to facilitate innovation of safe (based on clinical data) BTC therapies (so removing barriers to innovations). Most of the Objective 4 measures appear in all options. The options differ in what rules the establishments are required to use when conducting their risk assessments.				
Option component ("measure")		**Option 4.1**	**Option 4.2**	**Option 4.3**
M4.1	The "same surgical procedure" exclusion for point of care preparations is refined/removed.	✓	✓	✓
M4.2	An EU level advisory mechanism is established to recommend/advise MS on when/what BTC requirements should be applied in part or in full	✓	✓	✓
M4.3	A mechanism is introduced to prompt regulators of 'adjacent' legal frameworks (SOHO/Pharma/Medical Devices) to better coordinate their rules, especially in respect of substances that are regulated under more than one legal framework.	✓	✓	✓
M4.4	An EU level advisory mechanism will advise where other frameworks (in particular medical devices and medicinal products) might be applied for particular novel BTC. Implementation might involve exchange/mutual consultation with advisory bodies for MP (EMA innovation task force, EMA CAT) and MD frameworks (Borderlines and Classification Working Party).	✓	✓	✓
M4.5	EU law sets principles for authorisation procedure (good practice for authorisation procedures including validation of facilities, equipment and processing and clinical data requirement according to level of risk and novelty) to demonstrate safety and efficacy in patients.	✓	✓	✓
M4.6	EU law requires that, for major changes in the steps of collection, processing and use of BTC, competent authorities have to grant prior authorisation based on data demonstrating safety and benefit for patients that justifies any risks associated with treatment with BTC prepared in innovative ways.	✓	✓	✓
M4.7	EU law sets rules for implementing a clinical trial for BTC (if high level of risks)	✓	✓	✓
M4.8	The European Commission will develop an exchange (IT) platform for competent authorities to exchange info regarding (novel) process authorisations (the platform would be used for (voluntary) acceptance of authorisations among MS). This includes clinical evidence collected by clinicians with the support of learned societies.	✓	✓	✓
M4.9	EU law requires establishments to conduct risk assessments on novel processes. These are evaluated by the competent authority inspectors.	✓	✓	✓

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

See Annex 4 for more detail on Objective 4 options.

Problem 5: EU vulnerable to interruptions in some BTC supply

These options are involved to reduce the risk of shortages due to insufficient or unreliable BTC supply by establishing system to monitor donations and supply and to support pre-emptive and/or corrective action in case of disruptive epidemiological outbreaks, or similar events. There are eight measures, most are common to all options.

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

See Annex 5 for more detail on Objective 5 options and Annex 6) for the definitions of 'critical BTC'.

Annex 1 Problem 1: Patients are not fully protected from avoidable risks

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

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

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

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

M1-3 EU law amended to require MS to publish more stringent rules in an accessible format

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

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

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

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

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

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

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

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

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

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

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

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

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

This measure effects change by obligating blood and tissue establishments to 'take into account' [i.e. to operate in accordance with] and thus, where required, modify their working practices in ways that help to assure consistently high levels of protection for patients.

Alongside the legislative element which imposes that obligation, this measure includes administrative action by the Commission to prompt (and where necessary fund) the relevant EU expert bodies to prepare and issue rules that the blood and tissue establishments will then refer to. The rule-setting activity could be on a rolling basis; periodic or on Commission request.

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

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

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

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

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

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

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

- The authority (and inspectorate) shall be fully independent of the BTC sector
- The authority (and inspectorate) shall have operational independence and be free to take decisions on application of the prevailing BTC law free of outside interference or influence
- The authority shall maintain robust procedures to manage the risk of conflicts of interest
- The authority shall have mechanisms to ensure transparency in its decisions on regulatory matters
- There will be effective national coordination among competent authorities within the same country
- The authority shall ensure that its staff have the skills and qualifications required for them to competency discharge their assigned functions
- The authority's inspectors shall be provided with powers under national law sufficient for their decisions on matters relating to regulation of BEs and TEs to be enforceable.

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

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

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

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

This measure is expected to have indirect impacts on establishments. Depending on the strategic response by the NCAs (i.e. whether NCAs reallocate the same resource or just reduce the inspection effort allocated to low risk establishments), it may reduce the inspection burdens on low risk establishments and/or increase the administrative burden on high risk establishments. It provides scope for 'earned recognition', lowering inspection burdens for well-run establishments.

The risk-based approach to inspection may in turn lead to a reduction in actual risk to patients in higher risk establishments, and so ultimately to improve health and safety outcomes.

For activities with medium and low safety and quality impact, a desk based approach with (i) a registration with reporting obligations and Preparation Process Authorisation (e.g. same surgical procedure with processing), or (ii) only a registration with reporting obligations (e.g. donor registries) will be set in the

legislation, with common criteria in legislation for CA to decide which level to apply. The NCA will still have the option to inspect the “activity”.

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

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

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

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

M2.5 EU law is amended to implement a legal framework for Joint Member State inspections of blood and tissue establishments

Under this measure EU law provides for joint Member State inspections of blood and tissue establishments. As with alternative measures it is intended to have direct effects on the quality and consistency of systems, and indirect effects on the Member States’ confidence in the systems of other countries. The joint inspections can also help with pooling expertise of inspectors in certain techniques. Such changes are expected to help support the exchange of BTC within Europe.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Annex 4 Problem 4: BTC legislation lags behind innovation

M4.1 Point of care preparations: The "same surgical procedure" exclusion currently provided in the T&C Directive for point of care preparations is refined/removed.

This measure will remove the exception that is currently applied to point of care (PoC) preparations used in the same surgical procedure. The purpose of this is to remove any ambiguity about the legal treatment of such point of care preparations and subject them to the same safety standards as other BTC practices. This should increase the consistency of approach. The enhanced safety will help to reduce risks to patients and help facilitate innovation. This will require adding proportionate requirements to ensure safety and quality for such PoC preparations, and proportionate requirements for oversight.

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

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

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

It is understood that the recommendations provided by the committee would be advisory in nature rather than having legal force. The effect would come through the clarification embodied in its advice. Competent authorities are assumed to change

their regulatory approach to align to recommendations from the committee. Innovators (in establishments or elsewhere) would benefit from the clarifications - ambiguity about how their innovative therapy/technology will be regulated will be addressed. The barriers to innovation that stem from lack of clarity about how the legislation would is to be applied in particular circumstances would be lowered, leading to more innovation in the sector and a larger number of BTC applications that provide benefit to patients becoming available.

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

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

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

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

M4.4 A new EU level advisory mechanism will advise where other frameworks (in particular medical devices and medicinal products) might be applied for particular novel BTC.

This measure will address the borderline problems by establish an advisory mechanism to provide advice on matters of interpretation relating to issues at the interface of the EU's BTC legislative framework and other adjacent legislative frameworks (e.g. pharmaceuticals, medical devices). A potential implementation model is for the committee defined at M4.2 to be given a mandate to engage with parallel committees (from other legislative framework) to resolve borderline issues.

It is understood that the recommendations provided by the committee would be advisory in nature rather than having legal force. The effect would come through the clarification embodied in its advice. Competent authorities are assumed to change their regulatory approach to align to recommendations from the committee. establishments would then modify their practices based on changes to NCA approach. The barriers to innovation that stem from lack of clarity about how the legislation would is to be applied in particular circumstances would be lowered, leading to more innovation in the sector and a larger number of BTC applications that provide benefit to patients becoming available.

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

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

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

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

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

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

This legal measure works together with M4.5 and M4-6. It will define when a clinical trial is required to assess the safety of a novel BTC application. Rather than set a new set of requirements for clinical trials it will refer to existing rules on clinical trials.

By providing clarity on when proof of safety/efficacy need to be demonstrated in a clinical trial this measure will provide increased consistency of regulatory practice and safety across the EU (clinical trials are already applied in some Member States). It will also help to provide greater clarity for innovators on the circumstances in which a trial is required.

M4.8 EU will develop an exchange (IT) platform for NCAs to exchange info regarding (novel) process authorisations (the platform would be used for (voluntary) acceptance of authorisations among MS). This includes clinical evidence collected by clinicians with the support of learned societies.

This is a non-legal measure. A shared IT platform, funded and supported by the Commission, will facilitate efficient sharing of information among Member States about their authorisations of novel BTC applications. The theory is that Member States will be more likely (and/or quicker) to authorise a novel BTC application if they see, via the platform, that the same application has been authorised by another Member State and would have access/reference to the data used for the authorisation. Despite its voluntary basis, this measure would lead to an alignment in the way Member States organise such authorisations. To have the desired effect competent authorities will need to register their own authorisations on the platform. The platform would also give access to, as well as support the collection and analysis of clinical evidence collected by clinicians with the support of learned societies.

M4.9 EU law is modified to obligate establishments to conduct risk assessments on novel processes. These risk assessments will be evaluated by the competent authority inspectors to ensure that they have been conducted effectively and the preparation process authorisation was adequate.

This measure is intended to strengthen the quality and consistency of the risk assessments applied to novel BTCs. It will require establishments to acquire the competence to carry out the risk assessment (or retain a third party to conduct the assessment on their behalf). The precise details of the risk assessment procedure are defined in an accompanying measure – M4.10, M4.11 or M4.12, depending on the option.

The quality assurance mechanism introduced via the obligation placed on competent authority inspectors will extend the scope of work for competent authorities. Depending on the option (Option 4.1, 4.2 or 4.3), the inspectors will need to assess the risk assessments' conformity with a diversity of guidance and standards (M4.10), guidance issued by an EU expert group (M4.11) or the requirements specified in EU law (M4.12).

M4.10 EU law is modified to obligate establishments to design the risk assessments on novel processes and decide on the nature and extent of laboratory and/clinical studies needed to demonstrate safety and quality. The establishments could follow national or international guidance or standards from other bodies in conducting their risk assessments.

This measure places an obligation on establishments to develop risk assessment protocols for novel processes. It gives them the freedom to use a variety of sources of guidance and standards in doing so. This measure works in concert with M4-9. When combined with M4.1-M4.9 it defines Option 4-1. It is an alternative to M4.11 and M4.12.

M4.11 EU law is modified to require establishments to conduct risk assessments on novel processes in compliance with technical guidance on the conduct of RA and studies (from expert bodies) referred to in EU legislation

This measure places an obligation on establishments to conduct risk assessment protocols for novel processes in accordance with guidance prepared by nominated EU expert bodies. This measure works in concert with M4-9. When combined with M4.1-M4.9 it defines Option 4-2. It is an alternative to M4.10 and M4.12. To give effect to this measure it is also necessary for the Commission to task relevant expert body/bodies with the development and maintenance of the technical guidance, and for this guidance to be made available for use.

M4.12 EU law is modified to require establishments to conduct risk assessments on novel processes in compliance with technical rules (on the conduct of risk assessment and studies needed) that are set in EU legislation.

This measure places an obligation on establishments to conduct risk assessment protocols for novel processes in accordance with rules specified in EU law. This measure works in concert with M4-9. When combined with M4.1-M4.9 it defines Option 4-3. It is an alternative to M4.10 and M4.11. Updates to the rules would require modification of EU law.

Annex 5 Problem 5: EU vulnerable to interruptions in some BTC supply

M5.1 EU law is amended to impose mandatory monitoring obligations on blood and tissue establishments for critical BTC

This measure requires BE/TE to monitor supply and demand situation, for defined critical BTC (see Annex 6). The scope of this monitoring obligation is derived from EDQM recommendations. The measure does not in itself have an impact beyond imposing an obligation to collect/store relevant data. Its effect on 'the supply problem' comes when used in combination with other M5 measures.

M5.2 EU law is amended to require mandatory reporting and notification of sufficiency data for certain critical BTC in case of shortage/drop in supply (rapid notifications)

This measure imposes an obligation on establishments to notify competent authorities about shortages/supply issues in certain circumstances, for a sub-set of critical BTC (i.e. a more restricted set of BTC than the scope of M5.1) . The establishments will take the initiative to report when a shortage becomes apparent.

M5.3 EU law is amended to require mandatory measures for emergency supply responses

This measure will impose an obligation on establishments to develop and adopt contingency plans that show how they will handle supply shortages. The

requirement for contingency plans will apply to a sub-set of critical BTC only (the same scope of BTC as M5.2).

M5.4 The Commission will develop the relevant component of an IT platform for exchange of information on supply and activity

This is a non-legal measure. A shared IT platform, funded and supported by the Commission, will facilitate efficient sharing of information among establishments / Member States and expert bodies on activities and supply. It will ensure timely access to data for coordinated action for crisis management. This measure will apply to all options.

M5.5 EU law is amended to strengthen MS ability to intervene to control and adjust supply, as necessary, under their national competence, and allow evidence-based support action at EU level.

This measure, codified in EU law, will give Member States additional power to manage supply within their competence and powers to the EU to act.

This is a strategic risk management measure that has an 'enabling' function. The precise conditions under which such powers would be available are not currently defined. The focus of this measure is on 'critical BTC' as defined in M5.1 above.

M5.6 EU law is amended to require establishments to develop monitoring and notification systems and contingency plans. These will be reviewed for adequacy by the authority during inspection.

This measure introduces a 'decentralised' model of supply risk management. It would apply to critical BTC only, as defined in M5.1. It would give effect to M5.2 and M5.3.

Individual establishments monitor their own situation. Data must be supplied to the competent authority only if there is a request from the authority. The measure does not oblige the competent authority to share those data with the European Commission.

Under this measure no standard or guidance is provided for the contingency plans that individual establishments are obligated to prepare under M5.3. The quality of those contingency plans must be assessed by the relevant competent authority (extending the scope of work of the NCAs). The NCAs will need to develop their own approach to dealing with the variability of the contingency plans.

This measure is used in combination with M5.1 to M5.5, and as an alternative to M5.7 and M5.8. As such, it defines Option 5-1.

M5.7 EU law is amended with references to guidance from expert bodies for rules on sufficiency data reporting (inc. monitoring and notifications) and on emergency preparedness/contingency.

This measure sets up a continuous, EU-wide system for collection and monitoring of sufficiency data for critical BTC. This would cover reporting of donations, distribution, import, export and use by BTC establishments to national authorities and to the Commission. The rules on data reporting are specified by EU expert

bodies. In this measure the contingency plans that establishments will produce are expected to conform to guidance prepared and maintained by a designed EU expert body.

This measure would require establishments to continually collect and submit the prescribed data in the required format at the required frequency. The proposed IT system, and other aspects of this system, are being examined in a study procured by the Commission. NCAs will oversee compliance.

This measure is used in combination with M5.1 to M5.5, and as an alternative to M5.6 and M5.8. As such, it defines Option 5-2.

M5.8 EU law is amended to include rules on sufficiency data reporting (incl monitoring and notifications) and on emergency preparedness

This measure is identical to M5.7 except that the rules on data reporting and emergency preparedness are defined in EU law rather than by EU expert bodies.

This measure is used in combination with M5.1 to M5.5, and as an alternative to M5.6 and M5.7. As such, it defines Option 5-3.

Annex 6 Definitions of 'critical BTC' used in Objective 5 options

Table A6.1 **Tissues:** Working definition of 'critical BTC' (tissues) adopted for the appraisal of Objective 5 measures on supply monitoring and reporting and contingency planning / emergency preparedness

		Requirement:	**Mandatory monitoring obligation**	**Notification when sudden supply risk; BE/TE contingency plans**
		Measure reference:	**M5.1**	**M5.2 , M5.3**
Ocular Tissue	Cornea, full thickness (high endothelial cell density)		Yes	Yes
Ocular Tissue	Cornea, full thickness (low endothelial cell density)		Yes	Yes
Ocular Tissue	Cornea for Endothelial Keratoplasty (precut/peeled in the Tissue Establishment)		Yes	Yes
Ocular Tissue	Sclera		Yes	No
Ocular Tissue	Other ocular		Yes	No
Placental Tissue	Amniotic membrane		Yes	No
Placental Tissue	Amniotic membrane eyedrops		Yes	No
Placental Tissue	Other placental		Yes	No
Cutaneous Tissue	Skin		Yes	Yes
Cutaneous Tissue	Acellular dermal matrix		Yes	No
Cutaneous Tissue	Keratinocytes/melanocytes		Yes	No
Cutaneous Tissue	Other cutaneous tissues		Yes	No
Cardiac Tissue	HV, aortic		Yes	Yes
Cardiac Tissue	HV, pulmonary		Yes	Yes
Cardiac Tissue	HV, aortic decellularised		Yes	Yes
Cardiac Tissue	HV, pulmonary decellularised		Yes	Yes
Cardiac Tissue	Non-valved patches and conduits		Yes	No
Cardiac Tissue	Pericardium		Yes	No
Cardiac Tissue	Other heart tissues		Yes	No
Vessels	Vessels, arteries		Yes	No

		Requirement:	**Mandatory monitoring obligation**	**Notification when sudden supply risk; BE/TE contingency plans**
		Measure reference:	**M5.1**	**M5.2 , M5.3**
Vessels	Vessels, veins		Yes	No
Muscoloskeletal Tissue	Whole or part of structural/supporting bone		Yes	No
Muscoloskeletal Tissue	Tendons (including with bony attachments)/ligaments/fascia		Yes	No
Muscoloskeletal Tissue	Osteochondral grafts		Yes	No
Muscoloskeletal Tissue	Bone filling material (excluding femoral heads)		Yes	No
Muscoloskeletal Tissue	Femoral heads		Yes	No
Muscoloskeletal Tissue	Demineralised bone matrix (including combined with a carrier)		Yes	No
Muscoloskeletal Tissue	Meniscus		Yes	No
Muscoloskeletal Tissue	Other musculoskeletal (e.g. ear ossicles, cranial bone, cartilage)		Yes	No
Neuronal Tissue	Nerves		Yes	No
Adipose Tissue	Adipose Tissue		Yes	No
Pancreatic Tissue	Pancreatic islets		Yes	Yes
Hepatic Tissue	Hepatocytes		Yes	No
Parathyroid Tissue	Parathyroid tissue		Yes	No
Haematopoietic Cells	HPC from bone marrow for transplantation		Yes	Yes
Haematopoietic Cells	HPC from peripheral blood for transplantation		Yes	Yes
Haematopoietic Cells	Peripheral blood mononuclear cells for transplant support (e.g. donor lymphocytes for infusion)		Yes	No
Haematopoietic Cells	Peripheral blood mononuclear cells for other purposes, excluding ATMP (e.g. production of CAR-T cells, NK cells)		Yes	No
Haematopoietic Cells	HPC from cord blood for transplantation		Yes	Yes
Haematopoietic Cells	Other cells (e.g. bone marrow for other purposes), excluding ATMP		Yes	No

Table A6.2 **Blood:** Working definition of 'critical BTC' (blood) adopted for the appraisal of Objective 5 measures on supply monitoring and reporting and contingency planning / emergency preparedness

	Requirement:	**Mandatory monitoring obligation**	**Notification when sudden supply risk; BE/TE contingency plans**
	Measure reference:	**M5.1**	**M5.2 , M5.3**
Whole blood		Yes	Yes
Red blood cells		Yes	Yes
Platelets		Yes	Yes
Fresh frozen plasma		Yes	No
Plasma for fractionation		Yes	Yes
Rare Red blood cells		Yes	No