EUROPEAN
COMMISSION

Brussels, 10.10.2019
SWD(2019) 375 final

COMMISSION STAFF WORKING DOCUMENT

Evaluation of the Union legislation on blood, tissues and cells

{SWD(2019) 376 final}

Table of Contents

List of abbreviations

ATMP	Advanced therapy medicinal products
BTC	Blood, tissues and cells
CoRE SoHO	Consortium of BTC representative societies
DLI	Donor Leukocytes for Infusion
EBA	European Blood Alliance
EBMT	The European Group for Blood and Marrow Transplantation
ECDC	The European Centre for Disease Prevention and Control
EHA	The European Hematology Association
EHC	The European Haemophilia Consortium
EPA	The European Plasma Alliance
ESHRE	The European Society for Human Reproduction and Embryology
FIODS	The International Federation of Blood Donor Organisations
FMT	Faecal Microbiota Transplants
GMP	Good manufacturing practices
GPG	Good Practice Guidelines
HIV	Human Immunodeficiency Virus
IHN	The International Haemovigilance Network
IPFA	The International Plasma Fractionation Association
IPOPI/PLUS	The International Patient Organisation for Primary Immunodeficiencies
ITE	Importing tissue establishments
IVF	In Vitro Fertilisation
MAR	Medically assisted reproduction
MSM	Men having sex with men
NAT	Nucleic Acid Test
OHSS	Ovarian Hyper stimulation Syndrome
PDMP	Plasma derived medicinal products
PMF	Plasma master file
PPTA	The Plasma Protein Therapeutics Association
PRF	Platelet Rich Fibrin
PRP	Platelet rich plasma
RAB	Rapid alert platform for human blood and blood components
RATC	Rapid alert platform for human tissues and cells
SAE	Serious adverse event
SAR	Serious adverse reaction
SARE	Serious adverse reactions and events
SoHO	Substances of Human Origin
TFEU	The Treaty on the Functioning of the European Union
VOC	Volatile organic compounds
VUD	Voluntary and unpaid donation
WMDA	World Marrow Donor Association
WNV	West Nile Virus

Glossary

Term	Definition
Advanced Therapy Medicinal Products	An advanced therapy medicinal product[1] means any of the following medicinal products for human use: • a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC, • a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC, • a tissue engineered product as defined as containing or consisting of engineered cells or tissues, and presenting properties for or being used or administered to human beings with a view to regenerating, repairing or replacing a human tissue.
Allogeneic use	Cells or tissues removed from one person and applied to another[2].
Antibodies	Antibodies are immunoglobulins (Ig). They are large proteins that are found in blood or other body fluids. Antibodies are part of the immune system that identify and neutralise foreign objects, such as bacteria and viruses.
Anticoagulant	An additive that stops or slows blood clotting.
Assisted Reproductive Technology-ART	All treatments or procedures that include the in vitro handling of human oocytes and sperm or embryos for the purpose of establishing a pregnancy. This includes, but is not limited to, IVF and transcervical embryo transfer, gamete intra-Fallopian transfer, zygote intra-Fallopian transfer, tubal embryo transfer, gamete and embryo cryopreservation, oocyte and embryo donation and gestational surrogacy. ART does not include assisted insemination (artificial insemination) using sperm from either a woman's partner or sperm donor.
Autologous (transfusion, donation or use)	Blood[3]: Autologous transfusion shall mean transfusion in which the donor and the recipient are the same person and in which pre-deposited blood and blood components are used.

[1] Regulation (EC) No 1394/2007 amending Directive 2001/83/EC and Regulation (EC) No 726/2004.
[2] Directive 2004/23/EC.
[3] Directive 2002/98/EC.

	Tissues and cells[4]: Autologous use means cells or tissues removed from and applied in the same person.
Basocellular Epithelioma	A common type of skin cancer.
Blood Establishments	Blood establishment shall mean any structure or body that is responsible for any aspect of the collection and testing of human blood or blood components, whatever their intended purpose, and their processing, storage, and distribution when intended for transfusion. This does not include hospital blood banks[5].
Bone marrow	See haematopoietic stem cells
Cytapheresis	A procedure for collecting particular cells from a donor or patient.
Faecal microbiota transplant – FMT	Fecal microbiota transplantation or FMT is the transfer of fecal material containing bacteria and natural antibacterial from a healthy individual into a diseased recipient.
Gametes	Sperm (spermatozoa) and eggs (oocytes).
Good Manufacturing Practice	Good manufacturing practice shall mean the part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use[6].
Haematopoietic stem cells	Cells in the bone marrow that produce new blood cells. Haematopoietic stem cells are found in bone marrow and in blood collected from the umbilical cord after the birth of a baby. They can also be collected from a donor's blood stream if the donor is treated with particular hormones that cause the cells to move out of the bone marrow into the blood.
Haemoglobin	A protein found in the red blood cells that is responsible for carrying oxygen around the body. Haemoglobin picks up the oxygen in the lungs, and then releases it in the muscles and other tissues where it is needed. Haemoglobin also contains iron which is critical for it to work properly.
Haemovigilance	The set of surveillance procedures covering the entire blood transfusion chain, from the donation and processing of blood and its components, through to their provision and

[4] Directive 2004/23/EC.
[5] See: Directive 2002/98/EC.
[6] Commission Directive 91/356/EEC.

	transfusion to patients, and including their follow-up.
Immunodeficiency	A state in which the immune system's ability to fight infectious disease and cancer is compromised or entirely absent.
Immunoglobulin	Glycoproteins that are part of the immune system.
Imputability	The likelihood that a serious adverse reaction in a recipient can be attributed to the tissue or cells applied or that a serious adverse reaction in a living donor can be attributed to the donation process[7].
In vitro fertilisation (IVF)	An assisted reproductive technology (ART) procedure that involves extracorporeal fertilisation.
Lymphocytes	White blood cells.
Medically assisted reproduction (MAR)	Reproduction brought about through ovulation induction, controlled ovarian stimulation, ovulation triggering, ART procedures, and intrauterine, intracervical, and intravaginal insemination with semen of donor.
Nucleic acid amplification technique	A testing method to detect the presence of a targeted area of a defined nucleic acid (e.g. viral genome) using amplification techniques such as polymerase chain reaction or transcription mediated amplification.
Partner Donations	The donation of reproductive cells between a man and a woman who declare that they have an intimate physical relationship[8].
Plasma Derived Medicinal Products	Medicinal products based on blood constituents which are prepared industrially by public or private establishments, such medicinal products including, in particular, albumin, coagulating factors and immunoglobulins of human origin[9].
Platelet	Platelets, also called thrombocytes, are a component of blood whose function (along with the coagulation factors) is to react to bleeding from blood vessel injury by clumping, thereby initiating a blood clot.
Platelet Rich Fibrin (PRF)	A fibrin meshwork, in which platelet cytokines, growth factors, and cells are entrapped and discharged after a period and can serve as a resorbable film.
Platelet Rich Plasma	Plasma in which the donor's platelets have been

[7] See: Commission Directive 2005/61/EC implementing Directive 2002/98/EC.
[8] Commission Directive 2006/17/EC.
[9] Directive 2001/83/EC.

(PRP)	concentrated.
Reproductive cells	Sperm, eggs and embryos.
Same Surgical Procedure	Processing of human substances (blood, tissues or cells) from a patient during surgery, within the surgical area.
Serious Adverse Event	Blood[10]: Any untoward occurrence associated with the collection, testing, processing, storage and distribution, of blood and blood components that might lead to death or life-threatening, disabling or incapacitating conditions for patients or which results in, or prolongs, hospitalisation or morbidity. Tissues and cells[11]: Any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or lifethreatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity.
Serious Adverse Reaction	Blood[12]: An unintended response in donor or in patient associated with the collection or transfusion of blood or blood component that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalisation or morbidity. Tissues and cells[13]: An unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity.
Tissue Establishment	Tissue establishment means a tissue bank or a unit of a hospital or another body where activities of processing, preservation, storage or distribution of human tissues and cells are undertaken. It may also be responsible for procurement or testing of tissues and cells[14].
Transmissible diseases	Comprises all clinically evident illnesses (i.e. characteristic medical signs and/or symptoms of disease) resulting from

[10] Directive 2002/98/EC.
[11] Directive 2004/23/EC.
[12] Directive 2002/98/EC.
[13] Directive 2004/23/EC.
[14] Directive 2004/23/EC.

the infection, presence and growth of microorganisms in an individual or the transmission of genetic conditions to the offspring. In the context of transplantation, malignancies and autoimmune diseases may also be transmitted from donor to recipient.

1. INTRODUCTION

In the European Union (EU), millions of blood donations are collected every year by 1,400 blood establishments, enabling the transfusion of millions of blood components[15,16]. Plasma, a blood component, is also used for the manufacture of plasma derived medicinal products (PDMP). Tissues and cells[17] are handled by over 4,000 tissue establishments[18] and can also be the starting materials for the manufacture of medicinal products and medical devices. Several of these substances are exchanged between Member States.

Blood, tissues and cells (BTC) all come from the same source - donations from human beings - either during life or after death. They are processed, tested and stored in blood and tissue establishments before being supplied to hospitals and clinics. In most cases, no alternative treatments exist to save or enhance human lives. However, these substances can also cause adverse reactions in patients, including the transmission of disease.

To ensure high levels of public health protection for all stages of the process, the Blood Directive (2002/98/EC) and the Tissues and Cells Directive (2004/23/EC) were adopted in 2002 and 2004, respectively, laying down common (minimum) quality and safety standards at Union level and aiming to facilitate increased exchange of these substances between Member States. In this report, these two Directives are referred to jointly as 'the basic Acts'. Implementing legislation was also adopted to provide technical requirements for both fields[19]. Since their adoption, some of the implementing Directives have been amended (see Annex IV).

There has been significant scientific and technological development in the sector and new risks of transmitting diseases, such as Zika, dengue fever and hepatitis E, have emerged since the legislation was adopted, more than 15 years ago. The field has also undergone organisational changes, including an increasing role of commercial players in a traditionally non-profit sector with a high level of public sector involvement. No evaluation of the basic Acts has taken place since their adoption. The European Commission has published several implementation reports for each sub-sector, each

[15] Red blood cells, platelets and plasma are components of a blood donation, and each can be transfused to patients.
[16] DG SANTE website, introduction to the Commission's work on blood.
[17] Including corneas, bone, skin and heart valves for tissue replacement surgery, stem cells from bone marrow and cord blood for transplantation and reproductive cells for medically assisted reproduction.
[18] DG SANTE website, introduction to the Commission's work on tissues and cells.
[19] **Blood**: Commission Directive **2004/33/EC** as regards technical requirements for blood and blood components, Directive **2011/38/EU** and Directive **2014/110/EU**; Commission **Directive 2005/61/EC** as regards traceability requirements and notification of serious adverse reactions and events; Commission Directive **2005/62/EC** as regards Community standards and specifications relating to a quality system for blood establishments; **Tissues and cells**: Commission Directive **2006/17/EC** as regards technical requirements for donation, procurement and testing; Commission Directive **2006/86/EC** as regards traceability requirements, notification of serious adverse reactions and events and technical requirements for coding, processing, preservation, storage and distribution; Commission Directive (EU) **2015/566** regarding the procedures for verifying the equivalent standards of quality and safety of imported tissues and cells; Commission Decision **2010/453/**EU on conditions of inspections; Commission Decision **2015/4460** on agreements with tissue and cell coding organisations.

based on information provided by Member States. The most recent reports, published in April 2016[20,21] highlighted a number of gaps and shortcomings.

1.1 Purpose of the Evaluation

The purpose of this evaluation is to provide a comprehensive assessment of the Union legislation on BTC - the basic Acts and their implementing Directives, examining their functioning across the EU. The European Commission's evaluation criteria[22], i.e. effectiveness, efficiency, relevance, coherence and EU-added value, are assessed. In particular, the evaluation assesses the extent to which the BTC legislation met its original objectives and whether it remains fit for purpose.

1.2 Scope of the Evaluation

This evaluation covers the two basic Acts, Directives 2002/98/EC on blood and 2004/23/EC on tissues and cells, as well as their implementing Directives[5] in all EU Member States from the date of their entry into force until the end of April 2019. For those Member States that joined the Union after the entry into force of the Directives, the evaluation covers the period from their date of accession.

There are many commonalities between the two basic Acts. They have the same legal basis[23], similar generic oversight requirements and they aim to mitigate very similar risks to safety and quality for all stages from donation to distribution for clinical use in a patient (see Figure 1). Many professionals and authorities work across the two sub-sectors. For these reasons, one evaluation was conducted to cover both legal frameworks.

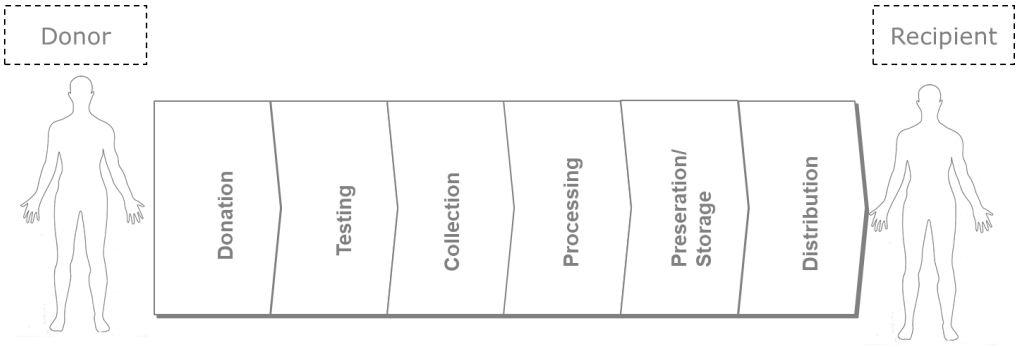


FIGURE 1: THE STEPS FROM BTC DONATION TO CLINICAL APPLICATION

[20] Report from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on the Implementation of Directive 2002/98/EC and implementing directives, setting standards of quality and safety for human blood and blood components - COM(2016) 224 final.
[21] Report from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on the Implementation of Directive 2004/23/EC and implementing directives, setting standards of quality and safety for human tissues and cells - COM(2016) 223 final.
[22] European Commission Better Regulation guidelines.
[23] Article 168 (4) (a) of the Treaty on the Functioning of the European Union (TFEU).

The Human Organs Directive, adopted in 2010 (2010/53/EU), was excluded from the scope of this evaluation, given that significant shortcomings had not been highlighted, as they had for BTC, and the quality and safety provisions are significantly different and less detailed[24].

The regulations governing medicinal products, including advanced therapy medicinal products (ATMPs) adopted in 2007[25], and governing medical devices, adopted only in 2017[26], are also excluded from the scope. However, the evaluation does cover the coherence of the BTC legislation with these frameworks.

In the light of the significant and increasing international exchanges of some BTC with third countries, the evaluation also considers coherence and similarities/differences with relevant regulatory frameworks for BTC outside the EU. In particular, the equivalence of safety and quality of BTC imported into the EU, mostly from the United States of America (USA), is addressed.

The BTC sector is one where many ethical issues arise, ranging from debates surrounding the use of technology for the creation of life to consent for donation after death. EU legal competence to regulate this field is limited, by the Treaty on the Functioning of the European Union (TFEU)[27], to safety and quality. Decisions and policies on the many ethical aspects remain at a Member State level, except where they have an impact on safety and quality. Where Member States choose to allow particular practices, such as testing or genetic manipulation of embryos, the safety and quality of those activities are regulated by these Directives and are included in the scope of this evaluation. Legal competence for issues related to the organisation of healthcare services (including BTC services) also remains at the Member State level.

[24] Human organs are transported directly from site of donation and procurement to site for transplantation. They do not pass through dedicated establishments for processing, storage and/or distribution.
[25] Regulation 1394/2007.
[26] Regulation (EU) 2017/745.
[27] Article 168 (4) (a) TFEU stipulates that the Union shall adopt measures setting high standards of quality and safety of organs and substances of human origin, blood and blood derivatives; these measures shall not prevent any Member State from maintaining or introducing more stringent protective measures.

2. BACKGROUND TO THE INTERVENTION

2.1 Concerns leading to the intervention

Three key concerns prompted the adoption of the blood, tissues and cells policy intervention.

The first was the spread of infectious diseases by blood transfusion and treatment with plasma-derived medicinal products, and the equivalent risks it posed for tissues and cells. The second was the lack of equivalency and coherence of standards for BTC across Member States. The third was the insufficiency of BTC supply, particularly blood and plasma for the manufacturing of medicinal products, through voluntary and unpaid donation (VUD).

Concern 1 - Widespread concerns due to disease transmission to patients

The primary driver for taking action in the 80's and 90's, was the infection of tens of thousands of patients across the EU with HIV, and later with hepatitis C, by the transfusion of blood components and by treatment with plasma-derived medicinal products. At least 20,000 transmissions of HIV by blood transfusion were recorded in just seven Member States (Figure 2); the total number for the EU is likely to have been significantly higher.

These events, with a high impact politically and socially, were widely reported in the media and resulted in court cases and government inquiries in a number of Member States. In the UK, Germany, Ireland and France, the cases were particularly public and issues regarding compensation are still the subject of a legal inquiry in the UK today[28] (see also Annexes II and III where more detail is provided).

[28] The UK legal inquiry on infected blood can be followed online.

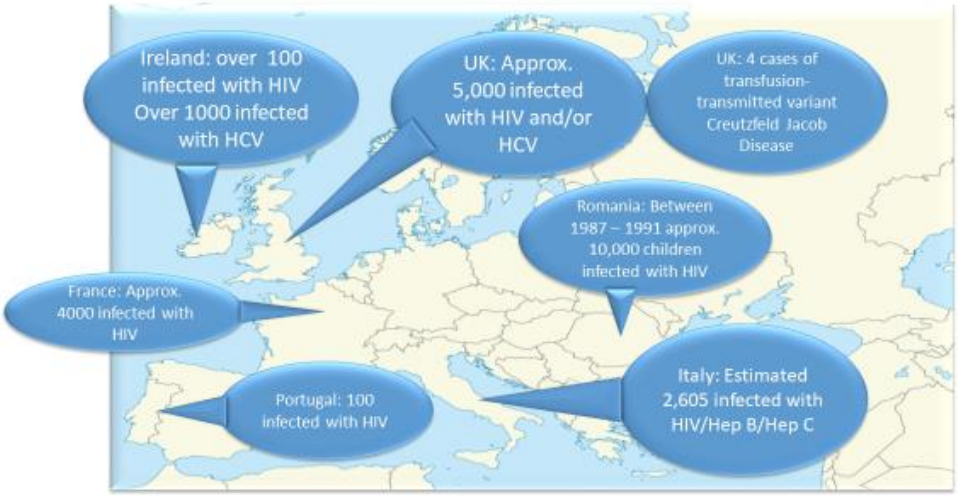


FIGURE 2: EXAMPLES IN THE HISTORY OF CONTAMINATED BLOOD AND BLOOD DERIVATIVES IN EUROPE PRIOR TO THE ADOPTION OF THE EU BLOOD DIRECTIVE

While infectious transmissions on a scale comparable to blood did not occur for tissues and cells, the equivalent risks to patients were indeed very real. A number of scientifically documented sentinel events highlighted that HIV, hepatitis C or Creutzfeldt Jacob disease transmissions by transplanted tissues and cells had occurred inside or outside EU and in the latter case continue to emerge due to long incubation times[29,30,31].

In the light of these disease transmission concerns, the Treaty of Amsterdam agreed in 1997[32] gives the Union the legal competence to set minimum quality and safety standards for substances of human origin, while allowing Member States to take more stringent measures.

The BTC intervention defined the EU safety and quality requirements for all stages of the chain from donor to recipient (Objective 1- Safety and quality requirements) and aimed to ensure effective regulatory oversight of the sectors (Objective 2- Oversight).

To achieve safety and quality of BTC (Objective 1), the following were put in place:

[29] Simonds RJ et al. (1992) Transmission of Human Immunodeficiency Virus Type 1 from a seronegative organ and tissue donor, NEJM 326 (11): 726-732.
[30] Conrad EU et al.(2005) Transmission of the hepatitis C virus by tissue transplantation J Bone Joint Surg 77(2): 214-224.
[31] Over forty transmissions of Creutzfeldt Jacob disease by transplantation of highly processed dura mater (a tissue that lines the skull) were detected from tissue processed in Germany and mostly exported to Japan. The long incubation period for this prion disease means that new cases continued to be detected decades later in Japan, with the total number of infected recipients reaching over 90 according to an update published by the US Centres for Disease Control in 2008. CDC (2008) Update: Creutzfeldt Jacob disease associated with cadaveric dura mater grafts: Japan 1978 – 2008 MMWR 57(43): 1181.
[32] (the now) Article 168 (4) TFEU: *'By way of derogation from Article 2(5) and Article 6(a) and in accordance with Article 4(2)(k) the European Parliament and the Council, acting in accordance with the ordinary legislative procedure and after consulting the Economic and Social Committee and the Committee of the Regions, shall contribute to the achievement of the objectives referred to in this Article through adopting in order to meet common safety concerns:*
a) measures setting high standards of quality and safety of organs and substances of human origin, blood and blood derivatives; these measures shall not prevent any Member State from maintaining or introducing more stringent protective measures;'.

(i) a set of legally binding quality and safety requirements to address all activities from donation to distribution, including screening, testing and handling requirements;

(ii) a set of legally binding requirements for blood and tissue establishments addressing personnel, facilities, quality management etc. and

(iii) processes for the adaptation of the requirements in line with scientific, technological and epidemiological changes.

To achieve an effective regulatory oversight of the sectors (Objective 2) the basic Acts included:

(i) the establishment/nomination of Competent Authorities responsible for oversight at Member State level;

(ii) establishment of a Competent Authority network at EU level;

(iii) set-up of inspection and authorisation systems and

(iv) set-up of vigilance systems (adverse reaction and event reporting and rapid alerts).

The national competent authorities in Member States are required to authorise blood and tissue establishments, to inspect them at a 2-yearly frequency, to report annually to the European Commission on serious adverse reactions (where a patient has been harmed), to report in a similar way on serious adverse events (where an incident posed a risk of harm to a donor or a patient), and to communicate with each other when more than one Member State may be involved. For tissues and cells, the authorities must also ensure the equivalence of imports from third countries in terms of quality and safety to those provided under EU legislation through the authorisation of 'Importing Tissue Establishments'. Finally, Member States are obliged to put penalties in place for non-compliance and to ensure appropriate data protection.

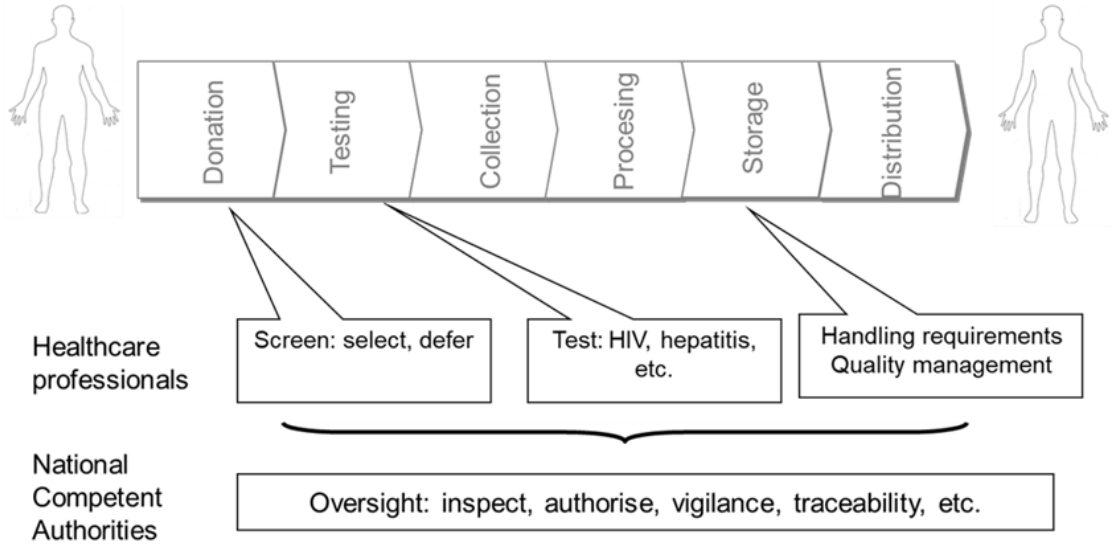


FIGURE 3: OBJECTIVES 1 AND 2 TO ACHIEVE SAFETY AND QUALITY FROM DONOR TO RECIPIENT AND AND EFFECTIVE OVERSIGHT

To mitigate risk and prevent unsafe activities, the European Commission is required to hold regular meetings with the competent authorities of the Member States to support the network and facilitate the collection and publication of data and the operation of shared platforms for information exchange (rapid alerts).

The implementation of the safety and quality and regulatory oversight objectives, and associated actions, were expected to lead to: (a) increased safety and quality in the chain from donor to recipient; (b) blood and tissue establishments operating in compliance with the defined standards; (c) provisions updated promptly in line with technological developments and new risks; (d) unsafe activities ceased or prevented; (e) vigilance data feeding quality improvement and increased visibility of risks and (f) risks mitigated through EU-wide communication and action.

Concern 2 - Lack of equivalency and coherence of standards across EU Member States

Surveys of blood service organisation and practices across the EU provided evidence of a wide variation in the standards of safety and quality being applied (see Annexe III). Movement of plasma and of tissue and cells between Member States was seen as an urgent problem to tackle because of the high frequency and volumes and concerns regarding a lack of standardisation and organisational structures, respectively [33]. Furthermore, Member States applied different rules for the different classification of substances under national frameworks.

To address these concerns, the intervention aimed to achieve a degree of harmonisation of safety and quality that facilitates inter-MS exchanges (Objective 3- harmonisation) but also to stablish a high level of legal certainty at Union level (Objective 4- legal certainty).

The implementation across the EU of the actions for safety and quality requirements, and for oversight (Objectives 1 and 2), also allow to achieve harmonisation of safety and quality (Objective 3). Agreed technical requirements and oversight also facilitate the inter-Member States exchanges, as long as the common minimum standards and the common oversight obligations are met. These measures aimed to result in increased mutual trust and confidence between MS, facilitating exchanges.

Legal certainty (Objective 4) was addressed by the scope and definitions provisions of the basic Acts[34] and through effective communication between authorities for different sectors within Member States. These aimed to ensure clarity across regulatory borderlines where BTC are used to manufacture medicines or medical devices or where the supply of critical devices impacts on the safety or supply of BTC.

[33] European Group of Ethics Opinion on Ethical Aspects of Human Tissue Banking.
[34] Articles 2 and 3 in both Acts.

Concern 3 - Insufficient supply of blood through VUD

Infectious transmissions from donations made by paid plasma donors in the United States and imported to the EU (mainly to the UK) were reported in the public domain. These imports, prompted by insufficiency of the local supply, were associated with significantly higher risks of contamination with hepatitis and HIV[35,36].

This concern led to a call for ensuring community sufficiency through Voluntary and Unpaid Donations (VUD), a strategy that aimed at avoiding the inclusion of potentially higher risk donors, motivated by payment, in the donor pool[37].

Therefore, to achieve EU sufficiency through the encouragement of VUD and a strong public sector was a priority (Objective 5 - sufficiency).

This was to be achieved by ensuring through legal provisions[38] that Member States encourage VUD, satisfy patient needs through EU VUD wherever possible and maintain a high level of safety.

The outcomes expected were good public willingness and awareness to donate voluntarily, with common understanding of compensation and incentive concepts and a decreased dependence on third country donations where higher risks might be accepted.

The above highlighted concerns were addressed by the EU legislation for BTC, which was adopted with two basic Acts, Directive 2002/98/EC[39] for blood and Directive 2004/23/EC[40] for tissues and cells. Figure 4 provides a summary of the concerns, objectives, actions and intended outcomes of the intervention (the intervention logic). The key reports and policy documents that highlighted the concerns, with their key findings, are described in Annex III. Annex IV provides a full description of the legal basis for the legislation and the provisions it includes.

[35] Eastlund T. (1998) Monetary blood donation incentives and the risk of transfusion-transmitted infection. Transfusion; 38: 874-82.
[36] Van der Poel CL, Seifried E, Schaasberg WP. (2002) Paying for blood donations: still a risk? Vox Sang. 83: 285-293.
[37] Although donors were tested for infectious HIV and hepatitis, individuals in the early stages of infection have not yet produced antibodies to the virus (they are in the so-called 'infectious window-period') so their infectious status can be missed by the anti-body tests used.
[38] Article 20 in 2002/98/EC and Article 12 in 2004/23/EC.
[39] 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. (OJ L 33, 8.2.2003, p.30).
[40] 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 (OJ L 102, 7.4.2004, p. 48).

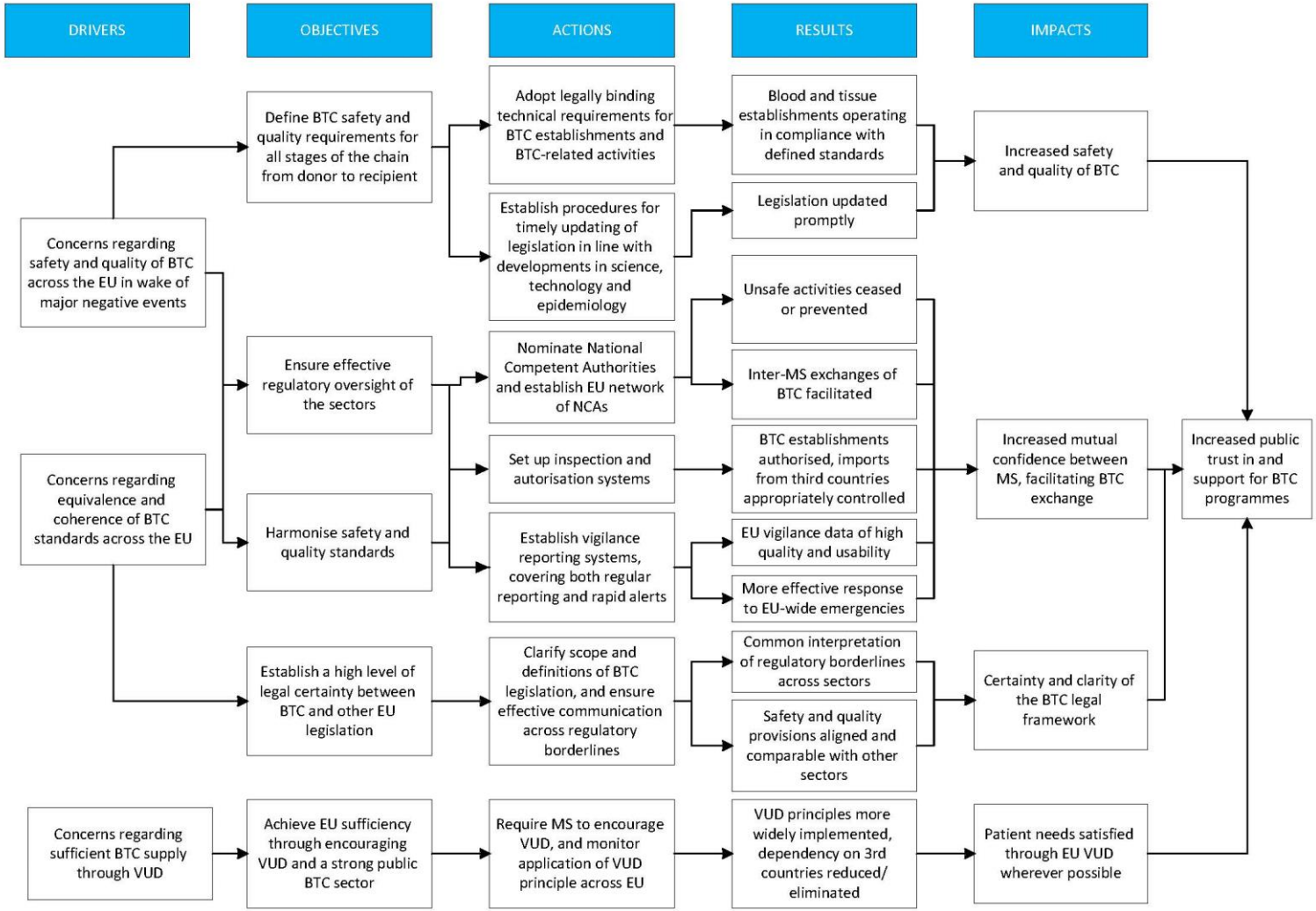


FIGURE 4: A SUMMARY OF THE CONCERNS, OBJECTIVES, ACTIONS AND INTENDED OUTCOMES OF THE INTERVENTION.

2.2 Baseline and points of comparison

The baseline used for the evaluation was the situation in fifteen Member States in the period prior to the adoption of the basic Acts, which was complemented with information from the 13 new Member States that joined the EU from 2004 onwards. There was no Impact Assessment carried, out prior to the adoption of the legislation, that describes the baseline. As many Member States did not have national reporting systems in place[41], precise baseline data are limited.

2.2.1 Blood

As early as 1994, the European Commission had raised concerns regarding blood safety and sufficiency, noting that the donor selection process differed across the Community. At that time, Directive 89/381/EEC required that testing of blood and plasma, when used as starting materials for blood derived medicinal products, had to comply with the recommendations of the Council of Europe, the WHO and the European Pharmacopoeia. However, as this Directive did not apply to whole blood, to plasma or to blood cells of human origin for transfusion, divergent testing requirements existed within the Community for blood donations for transfusion and plasma donations for manufacture of plasma derived medicinal products.

Licencing and accreditation of blood collection establishments differed widely across the Member States. Many had no licencing requirements for the collection of blood or plasma; no standard requirements for collection centres across the country; no routine and/or unannounced inspections by national authorities nor peer inspections to ensure that appropriate donor selection procedures were followed.

In 2001, voluntary non-remunerated blood donors were found only in five EU Member States out of 13. In others, incentives, family replacement[42] and remuneration were mechanisms used to encourage blood donation[43]. Haemovigilance was required by law in only 11 countries, and, consequently, infectious transmissions during this time were likely to have been underestimated.

The first Implementation Report[44] for Directive 2002/98/EC was published in 2006 and indicated that seven Member States had organised inspections and control measures in blood establishments in order to ensure compliance with the Directive's requirements,

[41] The situation varied depending on the type of substance but a recent survey of tissue and cell authorities indicated that over a third of Member States did not have authorities in place for transplanted tissues and cells, and over half for medically assisted reproduction, that could have gathered such reports. The survey was reported at a meeting of tissue and cell competent authorities in May 2019.

[42] The practice of asking family members to replace donations transfused to their relative by donating blood themselves. This practice raised concerns from a safety perspective, as donors are not self-selected and, therefore, might not reveal risk factors.

[43] Mascaretti et al. 2004 Comparative analysis of national regulations concerning blood safety across Europe. Transfusion Medicine, 14,105–111.

[44] First report on the application of the Blood Directive from the European Commission, 19 June 2006.

confirming that this oversight had not been in place previously. Only nine reported that donor selection procedures and donation deferral criteria were in place in blood establishments for all donors of blood and blood components.

See Annex V, Part A, for a full description of the baseline for blood.

2.2.2 Tissues and Cells

Prior to the adoption of the directive there were shortcomings and differences in the existing national rules, particularly in relation to donor selection and to the circulation of tissues between countries, which were highlighted in 1998 by the European Group on Ethics in Science and New Technologies[45] as well as by experts in the areas of organs, tissues and cells in 2000[46].

Health ministers from 11 EU Member States met in 2002 and supported a proposed directive on the therapeutic use of human cells and tissues for transplantation. At that time, only Spain, France, Belgium, and Denmark had specific legislation for tissue and cell banks. Most EU countries had regulations only for transplantation of solid organs[47].

Earlier publications from the UK had already raised concerns about the safety standards of bone banking[48,49]. In addition, there was an increasing degree of uncontrolled tissue movement between Member States and with third countries[50].

Prior to the adoption of the basic Act on tissues and cells, or to accession of countries to the EU, safety and quality rules and oversight were widely lacking[51]. By 2007, 11 Member States had not yet put inspection systems in pace and others had not yet inspected all tissue establishments or put vigilance reporting procedures in place[52].

See Annex V, Part B, for a full description of the baseline for tissues and cells.

2.2.3 Situation in Member States that joined after 2004

In three of the Member States that joined the EU after 2004 (Romania, Bulgaria, Croatia), assessments during the accession process generally demonstrated limited or

[45] European Group on Ethics in Science and New Technologies (European Commission). Ethical aspects of human tissue banking.
[46] At a meeting organised by the Portuguese Presidency of the EU, together with the European Commission described in Sauer F et al. The Regulation of blood and tissues in the European Union. Pharmaceutical Policy and Law (2005) 6: 47-58.
[47] Xavier Bosch. Health ministers support pan-European transplantation standards, The Lancet Vol. 359, ISSUE 9306, P591, 16 February 2002.
[48] Michaud RJ, Drabu KJ. Bone allograft banking in the United Kingdom. J Bone Joint Surg Br 1994;76:350.
[49] Fehily D & Warwick RW. Safe tissue grafts: Should achieve same standards as for blood transfusion BMJ 1997; 314:1141.
[50] Sauer F, Delaney F and Fernandez-Zinke E. The regulation of blood and tissues in the European Union. Pharmaceuticals Policy and Law 6 (2005) 47-58.
[51] Results of a Commission Survey presented to the tissue and cell competent authorities meeting in May 2019.
[52] Summary Table of Responses from Competent Authorities: Questionnaire on the transposition and implementation of the European Tissues and Cells regulatory framework, 06 February 2007.

absent oversight functions for BTC, such as an established competent authority, inspections and authorisation activities. Vigilance programmes were not in place and many had to upgrade facilities, equipment and quality management in their tissue and cell services to meet the technical requirements for donation, testing, processing, preservation, storage and distribution. At least three Member States (Romania, Bulgaria and Lithuania), also had to change their donor base from paid or replacement donation[53] to VUD[54,55].

Annex V provides more information on the situation prior to the adoption of the BTC legislation.

[53] The term replacement donation refers to systems where there is a request/obligation on the family of a patient needing transfusion to donate blood in order to replace the blood used from the bank. This system is not considered compatible with VUD and is considered to put too much pressure on donors and to risk untruthful donor risk information.
[54] WHO Europe (2007) Blood Services in South Eastern Europe – Current Status and Challenges.
[55] Skarbalienė A Bikulčienė J (2016) Motivation and retention of voluntary, non-remunerated blood donors. Lithuanian case. Health Policy and management 2016, 1(9).

3. STATE OF PLAY

3.1 The BTC Sector

Blood, tissues and cells are collected, processed, stored, tested and supplied for human application by 1,400 blood establishments[56] and over 4,000 tissue establishments[57]. The blood sub-sector is broadly divided into blood or blood components for transfusion and plasma for the manufacture of medicinal products. Tissue establishments are broadly divided in three categories (see Figure 5).

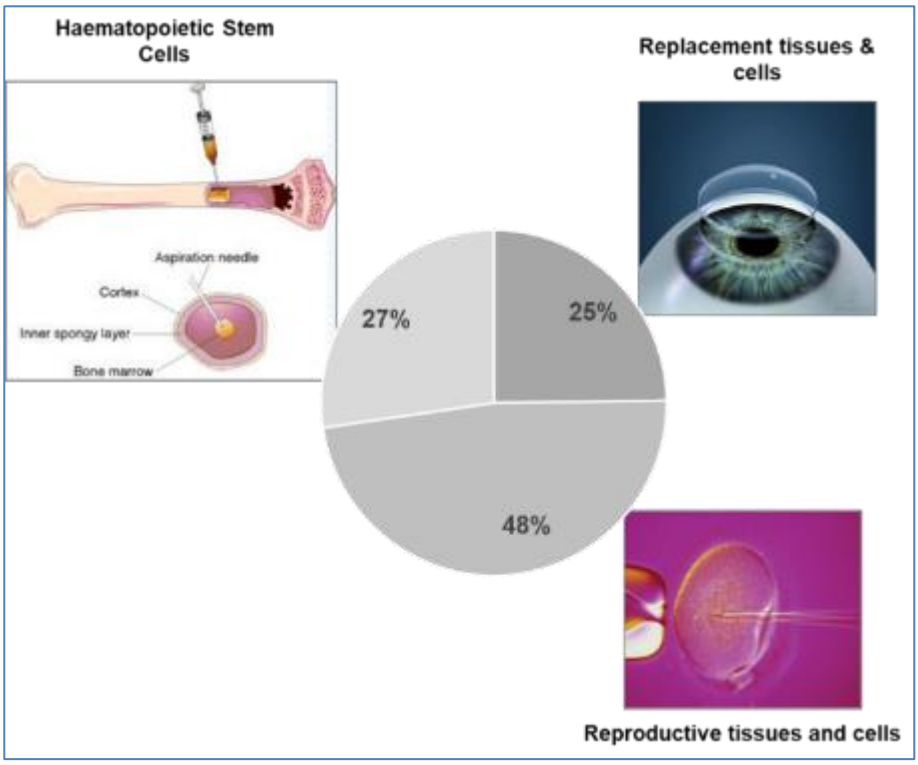


FIGURE 5: THE THREE CATEGORIES OF TISSUE AND CELLS ESTABLISHMENTS

Figure 6 provides aggregated data for the BTC provided by BTC establishments in the EU. Most blood establishments are national, regional or hospital based and are managed by the public health sector or by non-profit organisations such as the Red Cross, while the private sector plays an important role in the collection of plasma for the manufacture of plasma derived medicinal products. Tissue establishments include banks of corneas, bone, skin, heart valves, bone marrow and cord blood for transplantation, as well as sperm banks and clinics for medically assisted reproduction (MAR). Tissue

[56] Implementation report published in 2016.
[57] See Tissue Establishment Compendium hosted by the European Commission.

establishments providing tissues and cells for transplantation are mostly public or non-profit organisations while sperm banks and MAR clinics are both public and private. Tissues and cells can also be used as starting materials for medicinal product manufacture.

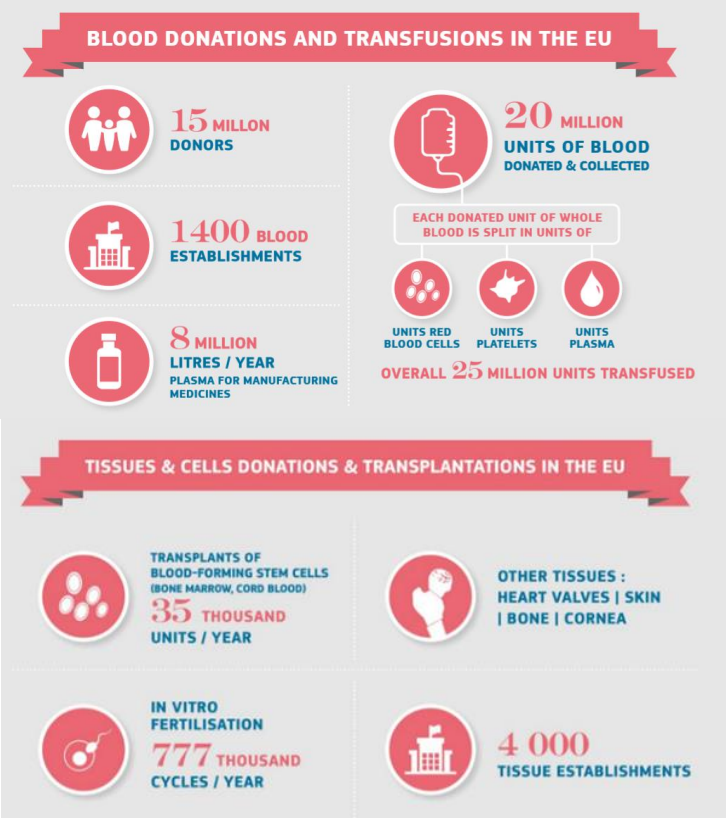


FIGURE 6: THE SCALE OF BTC ACTIVITY IN THE EU (DATA FROM 2018 OR MOST RECENT YEAR REPORTED)

Whole blood and blood components, such as platelets and red blood cells, have a limited shelf life and are rarely exchanged between Member States, with the exception of emergency or humanitarian situations. Plasma and plasma derived medicinal products have a longer shelf life and, as plants manufacturing plasma derived medicinal products exist only in twelve Member States, both plasma (the starting material) and the end products are frequently exchanged across borders, within the EU and with third countries. The EU is significantly reliant on importation of plasma from the United States to meet the needs of patients in the EU for plasma derived medicinal products. The level of inter-Member State exchange and global movement in general, varies depending on the type of substance of human origin.

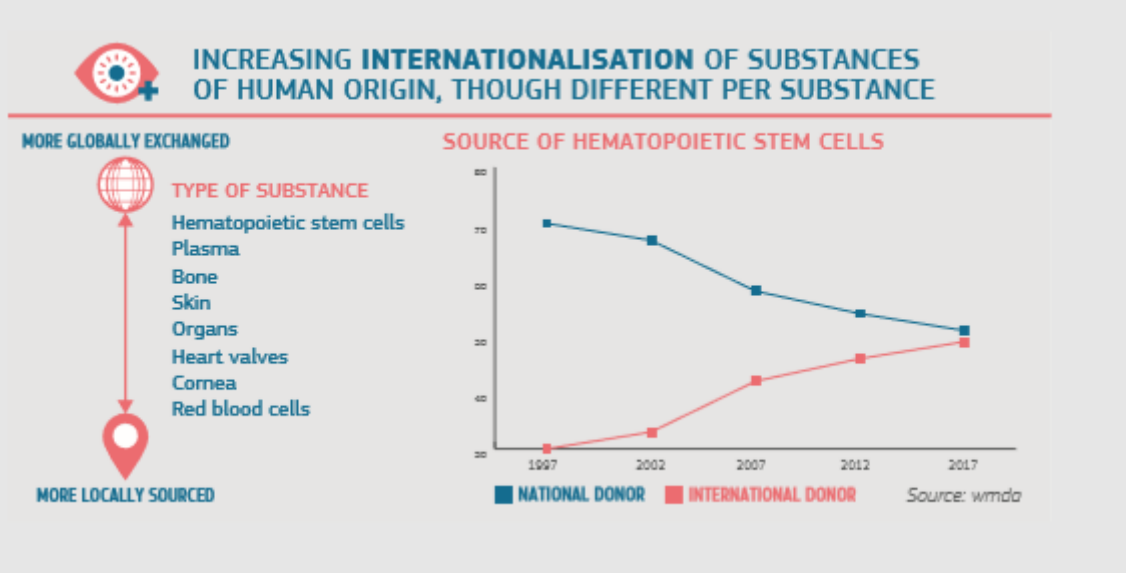


FIGURE 7: LEVELS OF INTERNATIONAL EXCHANGE VARY PER SUBSTANCES OF HUMAN ORIGIN

For tissues and cells, specifically, reports indicate significant volumes of human tissues and cells being exchanged internationally (see Figure 7), with haematopoietic stem cells (the stem cells in the bone marrow that make new blood cells) being the most exchanged substance. It is difficult, however, to draw firm conclusions regarding the volume of imports and exports of human tissues and cells due to the lack of mandatory reporting of such information at national level and the absence of a harmonised framework for data collection in the Member States. In addition, some Member States that do gather data on a national level, and share it on a voluntary basis, do not distinguish between distribution within the EU and import/export from/to third countries. It is clear, however, that large quantities of bone and skin are imported from the United States, mostly from commercial tissue banks, and that increasing numbers of bone marrow donations and other haematopoietic stem cells circulate globally to facilitate high level donor to recipient matching, a challenging requirement for successful transplantation in this sub-sector.

There is significant innovation in the sector, both in the way that BTC are processed in establishments and the way they are used in patients. These innovative approaches are commonly developed in the broad context of health service planning and they generally improve patient access to new treatments.

3.2 Transposition and updating of BTC legislation

Most Member States transposed the basic Acts (2002/98/EC and 2004/23/EC) within the defined deadlines in a complete and satisfactory manner. Between 2004 and 2006, implementing Directives were adopted for both basic Acts (2004/33/EC, 2005/61/EC, 2005/62/EC for blood and 2006/17/EC and 2006/86/EC for tissues and cells). By 2008, 25 of the 27 Member States reported having transposed the basic Act on blood and all

three implementing Directives[58]. By 2009, 26 Member States had completely transposed Directive 2004/23/EC, 2006/17/EC and 2006/86/EC.

As of February 2019, all current tissue and cell legislation, including more recent implementing Directives[59] and Decisions[60], has been transposed satisfactorily, with one exception[61]. For blood, all legislation has been satisfactorily transposed[62].

The powers given to the Commission to adapt technical requirements to scientific and technical progress were used in a small number of specific cases[63]. In general, however, the speed of technical development and of changing risks in the sectors proved challenging and many changes are not reflected in the current provisions (see Section 5.1).

There have been some formal complaints to the Commission and a small number of court cases linked to the legislation. The issues arising have mostly related to blood and blood components. In particular, cases concerned restrictions applied at national level on the purchase or import of plasma or plasma derived medicinal products. These restrictions on imports were linked to the source of the plasma, with Member States that aim to achieve sufficiency through VUD differentiating between plasma from unpaid donors and plasma from donors compensated financially[64].

The classification of certain substances as blood components or medicinal products has also been the subject of legal discussions, largely resulting from different interpretations of the scope of the basic act on blood and blood components (see Section 5.4).

Implementing Directive 2004/33/EC requires permanent deferral of prospective donors whose sexual behaviour puts them at 'high risk' of acquiring severe infectious diseases that can be transmitted by blood. The interpretation of 'high risk' led most Member States to apply permanent exclusion of prospective male blood donors who have sex with men (MSM). This led to complaints and one national court case that was referred to the Court of Justice of the EU[65]. The Court ruled that permanent deferral was not a

[58] Responses to Commission survey on the implementation of the blood legislation.
[59] Blood: Directive 2016/1214 amending Directive 2005/62/EC on good practice guidelines; Tissues and Cells: Directive 2015/566 on tissue and cell import, Directive 2015/4460 amending Directive 2016/86/EC on the Single European Code.
[60] Decision 2010/453/EU on conditions of inspections.
[61] One failure to transpose an amendment to Directive 2006/17/EC (Directive 2012/39/EU) that has been referred to the European Court of Justice (ECJ).
[62] Apart from the most recent amendment, Directive (EU) 2016/1214 amending Directive 2005/62/EC, where 27 Member States have notified transposition and the verification of completeness is ongoing.
[63] Blood: Directive 2011/38/EU amending Directive 004/33/EU regarding platelet pH values; Directive 2009/135/EC amending Directive 2004/33/EC to allow donor eligibility derogations for the Influenza epidemic; Directive 2004/110/EU amending 2004/33/EC to allow testing for West Nile Virus. Tissues and cells: Directive 2012/39/EU amending Directive 2006/17/EC to update HTLV and ART partner donor testing provisions.
[64] Some Member States consider financial compensation as payment and, therefore, as inconsistent with the principle of VUD described in Article 20 of the basic Act and aim to achieve national sufficiency through unpaid donation only. Efforts to restrict national use of derived medicinal products to those manufactured from unpaid donors have been challenged by industry that claims this approach contravenes the free market rules in place for medicinal products.
[65] C-528/13, Geoffrey Léger v. Ministre des Affaires sociales, de la Santé et des Droits des Femmes et Établissement français du sang.

proportionate measure. Many Member States have since amended their national rules to accept MSM donors after one year, or less, since the last exposure to risk.

A full list of court cases, with brief descriptions, is at Annex VI.

The European Parliament also raised questions, mostly concerning the same issues as those arising for blood in court cases. It also addressed issues such as plasma supply, VUD and access to BTC treatments. A full list of Parliamentary Questions of relevance to the BTC legislation is provided at Annex VII.

3.3 Oversight functions at Member State level

All Member States have designated one or more competent authorities to carry out the oversight obligations of the BTC legislation[66.] The types of organisation designated for this role vary significantly (see Section 5.2.1.2). The competent authorities inspect and accredit, designate, authorise or license the blood and tissue establishments. For tissues and cells, this authorisation is complemented by provisions for authorisation of the processes applied to the donations at the tissue establishment. For blood, on the other hand, it includes verification of compliance with defined quality criteria for each blood component prepared (Figure 8).

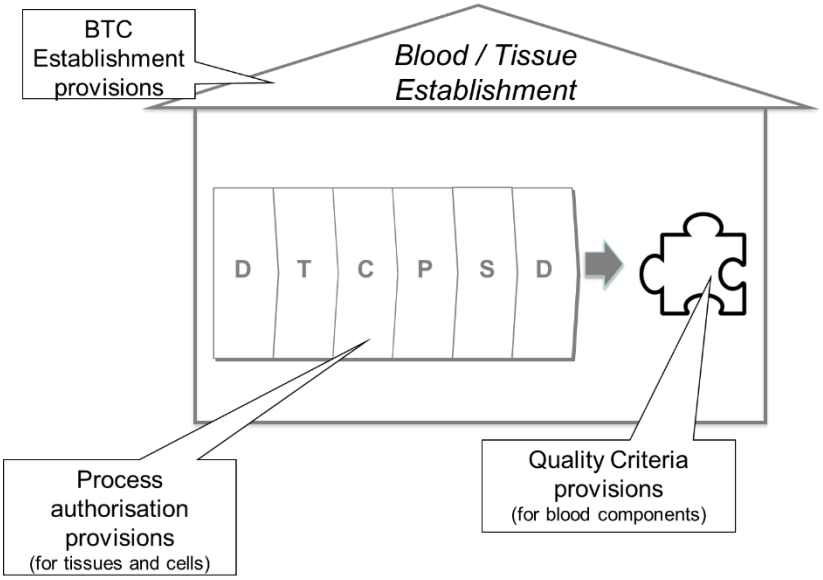


FIGURE 8: AUTHORISATION OF ESTABLISHMENTS AND PROCESSES.

3.4 Monitoring Arrangements

[66] Study supporting the BTC evaluation, ICF, page 64.

Implementation reports have been compiled by the Commission over the years, based on questionnaires completed by Member State competent authorities. The most recent reports were published in April 2016[67,68]. The gaps and shortcomings identified have been explored in the evaluation and are described in Section 5 of this report.

Vigilance and surveillance programmes are one of the cornerstones of the safety and quality framework, allowing the identification and detection of risks and the application of corrective and preventive measures. Since 2008, in line with obligations defined in the blood legislation[69], the EU Member States and Iceland, Liechtenstein and Norway have submitted to the Commission annual vigilance reports. The reports notify serious adverse reactions (SAR) which occur in recipients of blood and blood components and serious adverse events (SAE) which occur in the chain from donation to clinical application, posing a risk of harm. An equivalent provision is included in the tissue and cell legislation[70]. The Commission, in turn, must send to the competent authorities of the Member States a summary of the reports received. Definitions for SAR and SAE are provided in the legislation. The Commission has been working with the BTC competent authorities over several years to standardise data collection procedures and to improve both accuracy and comparability of the information submitted. The Commission provides the Member States with a template, and guidance for its completion, and the summary reports are published annually[71]. Serious adverse reaction (SAR) reports (per number of recipients) have stayed relatively stable and low since the adoption of the Directives (0.03 - 0.05 SAR per recipient for blood and 0.04 - 0.01 for tissues and cells). It is reported that legislative provisions for vigilance and traceability have helped to prevent harm to recipients[72].

The BTC legislation obliges Member States to report to the Commission on a regular basis on measures taken to encourage VUD and the Commission must inform the European Parliament and the Council of any necessary further measure it intends to take at EU level[73]. The Commission has fulfilled this obligation via a questionnaire survey of Member States on the implementation of the principle of VUD for blood and blood

[67] Report from the Commission on the implementation of the Directives 2002/98/EC, 2004/33/EC, 2005/61/EC and 2005/62/EC, 21 April 2016 (Blood);
Report from the Commission on the implementation of Directives 2004/23/EC, 2006/17/EC and 2006/86/EC (tissues and cells), 21 April 2016.
[68] Report from the Commission on the implementation of the Directives 2002/98/EC, 2004/33/EC, 2005/61/EC and 2005/62/EC, 21. April 2016 (Blood).
[69] Article 8 of Directive 2005/61/EC provides that Member States shall submit to the Commission an annual report, by 30 June of the following year, on the notification of serious adverse reactions and events (SARE) received by the competent authority using the formats in Part D of Annex II and C of Annex III.
[70] Article 7 and Annexes III, IV and V of Directive 2006/86/EC.
[71] The most recent published reports: Summary of the SARE Report for blood for 2017 and Summary of the SARE Report for tissues and cells for 2017.
[72] ICF study, pages 72-73.
[73] Article 20 of Directive 2002/98/EC and Article 12 of 2004/23/EC.

components and for tissues and cells. The most recent surveys were conducted in 2014 and published in 2016[74].

The principle of VUD for blood and blood components is recognised in all Member States, albeit interpreted differently across the EU. It is common practice to provide refreshments to donors (27 countries) and to give them small tokens such as pin badges, pens, towels, t-shirts and mugs (24 countries). In around half of the Member States, donors have their travel costs reimbursed and get time off work in the public and private sector. In some Member States, donors receive a fixed payment that is not directly related to actual costs incurred[75]; this is most common in those countries where large quantities of plasma is collected by private sector companies.

For tissues and cells, the legislative provision also requires encouragement of VUD but is slightly different to that for blood, allowing 'compensation', including for inconvenience. Although the principle of VUD is mandatory in the large majority of the Member States, its practical application varies across the EU. Many Member States allow payment of sperm and egg donors at national level, considering it as compensation.

3.5 Support for implementation

A number of activities and initiatives have supported the implementation of the BTC legislation since its adoption. The Expert Group of competent authorities responsible for substances of human origin (CASoHO E01718**)** meets with the Commission in three configurations, blood, tissues and cells and organs, once to twice a year each. The meetings provide a useful forum for increasing standardisation and for joint working[76]. The EU Public Health Programme has supported the implementation of the BTC legislation through Joint Actions, Projects and Service Contracts. The outputs have focused on those areas where legislation has been more challenging to implement or is most open to interpretation[77].

Expert support is also provided by the European Centre for Disease Prevention and Control (ECDC), which was established in 2005 (after the adoption of the two basic BTC Acts), which has access to the BTC Rapid Alert platforms[78], and by the Council of Europe, in particular through a series of Public Health Programme funded Grant Agreements with defined areas of collaborative work[79]. Although not referenced in BTC legislation (with the exception of the Council of Europe's Good Practice Guidelines

[74] Commission Staff Working Document on the implementation of the principle of voluntary and unpaid donation for human blood and blood components and Commission Staff Working Document on the implementation of the principle of voluntary and unpaid donation for human tissues and cells.
[75] Notably Germany, Austria, Hungary and the Czech Republic.
[76] A full list of interpretation issues raised in the group and their outcome is summarised at Annex VIII.
[77] A full list of Public Health Programme actions in the BTC field is shown at Annex IX.
[78] A full list of ECDC working in this field since 2012 is provided at Annex X.
[79] Annex XI summarises the work of the Council of Europe in this field and lists the areas of formal collaboration between DG Sante and the Council of Europe.

(GPG)[80] for Blood Establishments that are specifically referenced), the advice and guidance of both bodies is widely used by BTC professionals and authorities.

4. EVALUATION METHOD

4.1 Conducting the Evaluation

4.1.1 Evaluation Roadmap

A Roadmap was published on 17 January 2017 for a four-week period and the feedback received from 16 stakeholders was published[81] and taken into account in the conduct of the evaluation.

4.1.2 Stakeholder Consultation

Stakeholder consultation was one of the key sources of evidence that was used to support this evaluation. The level of stakeholder engagement in these activities was high and all the stakeholders mapped in the Roadmap were reached, either through the public events or by targeted activities (see Annex XII).

A Public Consultation was launched on 29 May 2017 and ran until 14 September 2017. Submissions were received from 158 organisations and 43 citizens. A summary of the outcome, together with the individual submissions, was published[82]. A Stakeholder Event was held on 20 September 2017 in Brussels. The event attracted a high level of interest, with over 200 stakeholders attending. A summary of the issues raised was provided in a published report[83].

Targeted Consultation was organised to fill any gaps in terms of stakeholders consulted and to explore certain emerging issues in more depth.

- Bilateral Meetings with key stakeholders allowed focused/specific input through direct interaction. Meetings with relevant EU agencies and with third country BTC Regulators were also held. Summary minutes were published on the DG SANTE website.
- Multi-lateral topic-specific meetings with selected stakeholders, including donor and patients associations, industry and professionals working in the sector[84]

[80] Good Practice Guidelines in the Guide to the Preparation, Use and Quality Assurance of Blood Components 19th Edition.
[81] DG SANTE website.
[82] Summary of Responses to the Public Consultation for the Evaluation of the Blood, Tissues and Cells Legislation by the European Commission 2018.
[83] Summary of the Blood, Tissues and Cells Stakeholder Event 20 September 2017.
[84] https://ec.europa.eu/health/blood_tissues_organs/consultations/call_adhocstakeholdermeeting_en.

together with Member State authorities, were held when more in-depth analysis of key emerging issues was required. These meetings, and the stakeholders involved, are listed in Annex XII. Summary minutes were published on the DG SANTE website.

A Synopsis report of Stakeholder Consultation activities and results is provided at Annex XII. Numerous stakeholders were also engaged in the activities carried out as part of the external study described below.

4.1.3 External Study

An external study[85] was commissioned to support this evaluation. This study was largely desk-based, with a review of over 300 documents, including reports provided by the Commission, relevant published literature and documents developed by other bodies (professional associations, international organisations etc.). The contractor also organised focus groups to address specific topics (including on medically assisted reproduction and on coherence with other legal frameworks), interviews with experts and targeted surveys to enhance their evidence gathering and analysis. The outcomes of the consultation activities organised by the European Commission were also provided as material for use in the study.

4.2 Limitations and robustness of the evaluation findings

Much of the evidence for the answers provided in this evaluation is considered robust. There is a rich literature, as evidenced by the bibliography in the external study supporting the evaluation, and stakeholders, from all sub-sectors, were motivated to share detailed information and opinions. Many of the issues raised are well documented, either in Commission monitoring reports, in professional publications or in technical meetings with stakeholders, organised in the context of the evaluation. The same gaps and shortcomings raised could be verified from multiple sources.

There were three important limitations to the evidence gathering exercise. Firstly, data available on the situation in Member States prior to the adoption of the legislation, with quantified indicators that could be compared to the current situation was limited. This made measuring the impact of the legislation in a quantitative manner more challenging. This was exacerbated by the heterogeneous situation across the EU at the time of adoption in terms of measures already in place and administrative capacity for oversight.

A second important limitation was related to quantifying the costs incurred by the BTC legislation for the assessment of efficiency. The majority of stakeholders impacted by the legislation are working in public sector hospitals, clinics and centres often carrying out

[85] Conducted by ICF Consulting and published together with this report.

many other functions apart from BTC activities. In this setting, typically, costs are poorly quantified and are often not allocated specifically to the activities affected by this legislation. Indeed, economic studies conducted for DG-SANTE in both main sub-sectors were greatly limited by the low cost-awareness of these organisations and the scarcity of robust cost data related to BTC-specific aspects of healthcare[86]. This factor was also identified as a constraint by the contractor conducting the external study[87]. Where BTC service provider costs are available, they relate to the full costs e.g. collection, testing and processing of blood, without separating those elements that were required by the EU legislation. Significant cost increments were incurred over the years since the adoption of the EU legislation because measures were introduced when new technologies, such as microbial inactivation processes, became available and were implemented despite not being mandated by the EU legislation. The implementation of these measures made service provision more expensive but the degree to which these costs were related to EU legislation is often limited. Additionally, many regulatory costs are the result or more stringent requirements introduced at a national level, such as more stringent donor testing requirements, that are not separately identified by stakeholders.

A third limitation related to the limited reliable data available on donation rates, clinical demand, sufficiency of supply and the extent of cross-border and third country exchanges, particularly for tissues and cells. Some data from vigilance reporting denominators was used, together with data gathered in an external study but the completeness and coherence of the data is not fully reliable and this made it difficult to assess the impact of some differences between Member States and confirm the degree of Union sufficiency for some BTC.

Given these limitations, it was challenging to assess the overall regulatory impact and the extent to which costs were proportionate to benefits. For the baseline situation, documents published to support the Commission proposal were used for blood and, for tissues and cells, a short retrospective survey of Member State competent authorities was carried out. For efficiency, a qualitative approach was adopted. Specific concerns on cost-effectiveness, as raised by stakeholders in the Public Consultation and by BTC authorities, were listed. The efficiency analysis focused on those topics, where there was a clear message that the benefits achieved by the provisions did not justify the costs accrued.

[86] Creative Ceutical Report, revised by the Commission to include stakeholders' comments;
Economic landscapes of human tissues and cells for clinical application in the EU- Final Report Rathenau.
[87] Study supporting the BTC evaluation, ICF, page 98.

5. ANALYSIS AND ANSWERS TO THE EVALUATION QUESTIONS

This Section provides answers to the questions defined in the Roadmap for this evaluation[88] under the European Commission's standard five evaluation assessment criteria.

5.1 Relevance

The legislation is not up-to-date with scientific, technological, epidemiological and societal developments and is not flexible enough to adapt provisions to such changes as they emerge.

The relevance assessment criterion was addressed by evaluation question 1, which was sub-divided in 3 sub-questions.

5.1.1 Evaluation question 1a): To what extent is the legislation sufficiently adapted to, adaptable to, and up-to-date with scientific, technical and epidemiological developments / innovation?

SUMMARY ANSWER: Significant scientific and technological developments have taken place since the legislation was adopted and many new epidemiological risks have emerged. Despite some minor amendments to update provisions in line with changing risks, legislation has not addressed most of the changes. As a result, some potential safety and quality measures are not appropriately updated in the legislation and, due to more stringent measures adopted by Member States to address this, the legislation is no longer consistently applied. The consequence is an insufficient achievement of the outcome planned for objective 1 (safety and quality) or of the outcome of objective 3 (harmonisation).

5.1.1.1 The legislation has not kept pace with science and technology

The most significant scientific and technological developments from the point of view of the BTC legislation fall under four main areas[89]:

[88] Evaluation of Union legislation on blood, tissues and cells-Evaluation and Fitness Check (FC) Roadmap by the EC.
[89] Additional, less significant, topics where developments have rendered the BTC legislation outdated, are addressed in the Study supporting the BTC evaluation, ICF, Table 8, page 30.

- **New ways of testing for viruses that can be passed from donors to recipients (transmissible viruses):** Testing for transmissible viruses by more sensitive technologies is now widely available and brings increased safety[90]. The BTC legislation names specific infectious agents and the precise methodologies to be used for testing[91], which may no longer guarantee adequate protection. Many Member States have therefore introduced more stringent testing requirements at national level[92], which may act as a barrier to exchange between them.

- **Significant developments in testing for genetic diseases:** Extensive genetic screening of gamete (sperm and egg) donors is now feasible, using panels of more than 100 genes, and genetic testing of embryos prior to implantation is also possible. Current legislation includes a generic provision for screening for genetic conditions known to occur particularly frequently in the donor's native population, but no specific genetic testing strategies are defined for the gamete donor population[93]. Thus, although genetic disease transmission is the primary risk for medically assisted reproduction (MAR)[94], and the consequences of a serious transmission can have an impact on multiple children[95], there are divergent levels of safety across EU Member States with regards to donor screening[96].

- **Much innovation in BTC processing methodologies:** This is true both for blood, where many new blood components have been introduced into routine use, and for tissues and cells. Pathogen reduction during blood processing, for example, is now required by national legislation for some components in some Member States[97]. For tissues and cells, each sub-sector has introduced innovative processing and preservations methods. The blood Directive functions through a precise quality specification for each individual blood component[98], which no longer ensure the safety and quality of components that are not included in the

[90] W. K. Roth, M. P. Busch, A. Schuller et al. (2011) International Survey on NAT testing of blood donations: expanding implementation and yield from 1999 to 2009. Vox Sang 102(1).
[91] Directive 2002/98/EC Annex IV and Directive 2006/17/EC Article 4 and Annexes II and III.
[92] See also the "Mapping of More Stringent Tissues and Cells Donor Testing Requirements - Mapping Exercise 2015" and the "Mapping of More Stringent Blood Donor Testing Requirements - Mapping Exercise 2015" which showed that the level of viral safety achieved across the EU is no longer standardised.
[93] Directive 2006/17/EC Annex III 3.6.
[94] Of the rapid alerts communicated between Member States in 2017, 15 of the total 18 alerts concerned genetic conditions detected in a gamete donor or in a child born from donated gametes.
[95] Danish Sperm Donor passed neurofibromatosis to five children BMJ 2012; 345:e6570.
[96] For recent scientific studies recommending up-to-date testing approaches, see Harper JC et al. Recent developments in genetics and medically assisted reproduction: from research to clinical applications. Eur J Hum Genet (2018) 26:12–33; Henneman L et al. Responsible implementation of expanded carrier screening Eur J Hum Genet (2016) 24(6):e1-e12; Edwards JG et al. Expanded carrier screening in reproductive medicine—points to consider. Obstet Gynecol. 2015; 125:653–62. See also Study supporting the BTC evaluation, ICF, page 49.
[97] Pathogen reduction is a new technology that reduces the risk of viral and bacterial transmission by blood components; See: Minutes of a meeting between the European Commission, Member State blood authorities and stakeholders.
[98] Directive 2004/33/EC Annex V: Quality and safety requirements for blood and blood components (as referred to in Article 6).

original set of specifications[99]. The tissues and cells directive is more flexible, by focusing on the authorisation of preparation processes at national level[100], but provisions are generic and lacking in requirements for the demonstration of positive outcomes for patients[101].

- **Novel clinical practices create new categories of patients and donors not covered by existing legislation:** Thus, for example, the storage of reproductive tissue or gametes for later use by the same patient[102] does not fall easily into the categories of "partner" or "non-partner" donation[103], and is thus not adequately regulated under the current safety provisions of the Tissues and Cells Directive[104]. A number of other developments in clinical application of substances of human origin have emerged and are seen as inadequately regulated (see Section 5.1.3 on legislative gaps below).

5.1.1.2 The legislation has not kept pace with changing epidemiology of diseases transmissible by BTC

Increased human travel, migration and global warming have contributed to substantial changes in the risks of transmission of emerging infections by BTC in the EU, along with other environmental and social factors. The infectious risks are addressed by testing or donor deferral rules in the legislation. Since the BTC legislation was adopted, the sector has faced risks from both viruses and parasites that were not present, or were present at much lower levels, in the early 2000s[105]. Chikungunya, Ebola, Zika and hepatitis E[106], among others, have emerged as threats at different time points. Provisions in the current blood legislation are quite specific and aimed at mitigating the risks that were current at the time it was adopted. For example, tattooing posed a significant risk of infection with viruses in the past but is now usually regulated and linked to very low risks of viral infection.

[99] There are 18 component specifications in Directive 2004/33/EC Annex II but 38 equivalent blood component monographs in the regularly updated Council of Europe Guide to the preparation, use and quality assurance of blood components 19th Edition.
[100] Directive 2006/86/EC Annex II.
[101] Ad-Hoc Meeting between Stakeholders and representatives members of the Competent Authorities on Substances of Human Origin Expert Group (CASoHO E01718), 22 February 2017.
[102] Oktay K (2017) Fertility Preservation in cancer patients. Oncology Times 39(4):1-8; Lallemant C Vassard D Nyboe Andersen A et al. (2016) Medical and social egg freezing: internet-based survey of knowledge and attitudes among women in Denmark and the UK Acta Obstet Gynecol Scand 95(12):1402-1410; Andersen CY and Kristensen SG (2015) Novel use of the ovarian follicular pool to postpone menopause and delay osteoporosis Reproductive Biomedicine 31, 128-131.
[103] The term 'partner donation' in the tissue and cell legislation is defined in Directive 2006/17/EC as 'the donation of reproductive cells between a man and a woman who declare that they have an intimate physical relationship'. Non-partner donation refers a donation by a person outside such a relationship.
[104] Reference to supporting passages in external study.
[105] In 2011, nine diseases transmitted by arthropods, were identified as posing an urgent communicable disease threat to the safety of BTC in the EU, most of which were not addressed in the detailed provisions of the Directive 2004/33/EC. Report of an ECDC Expert Meeting.
[106] ECDC has reported a 10-fold increase in hepatitis E infection from 2005 to 2015. One death from transfusion transmitted hepatitis E was reported in the European Commission's annual Blood SARE report 2016.

The example of **West Nile virus (WNV):** WNV has been in the EU since the early 2000's, the distribution and number of cases reported has increased steadily as shown on maps published by ECDC (see Figure 9). By 2014, validated WNV testing was available and Directive 2004/33/EC was amended[107] to allow testing and avoid serious blood shortages in those Mediterranean countries most affected.

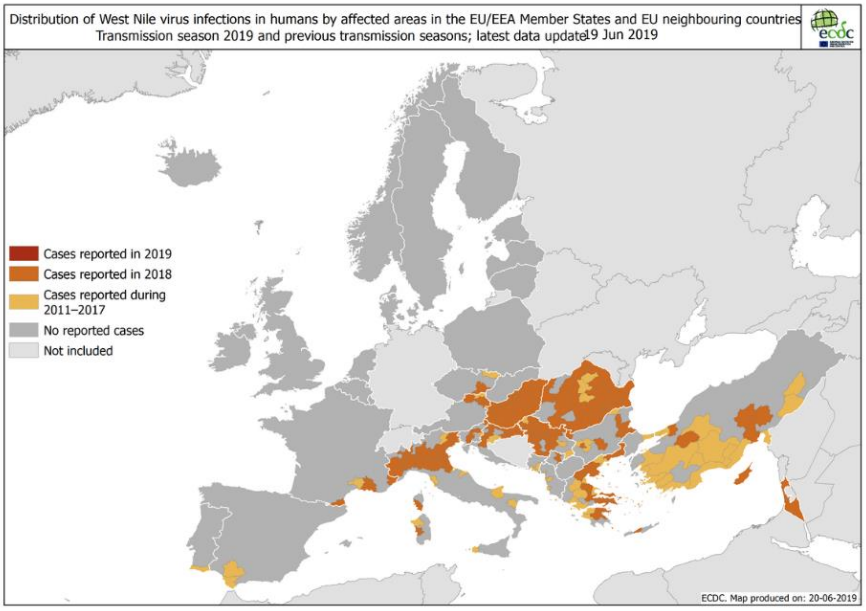


FIGURE 9: INCREASING WEST NILE VIRUS THREAT FROM 2011 TO 2019

The amended provision called for the safest option by requiring individual donor sample testing for WNV. Subsequently, it was concluded that the additional cost of applying the revised provision was not robustly justified by the science and could be replaced with testing in small pools of samples, with significantly lower cost implications (the added cost of individual sample testing versus mini-pool testing was estimated at circa 2 million Euros if applied to affected EU Member States), that would be equally effective[108]. The European Blood Alliance (EBA) now requests a further update to the Directive.

Other examples include tattooing, endoscopic examination and acupuncture that represented a significant risk of infectious disease transmission in the early 2000s but have become safer and better controlled. The provisions are no longer considered by many experts to reflect real risks and to cause, now, unnecessary donation losses[109]. The EBA, expert committees of the Council of Europe and the main EU-level professional associations all call for provisions with a more dynamic, risk-based approach to defining best practice for donor selection[110].

[107] Directive 2014/110/EC.
[108] Meeting of blood stakeholders, Member State Competent Authorities and DG SANTE in 2016.
[109] Blood, tissue and cell donor selection criteria report: 2017 from The Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO), UK.
[110] European Blood Alliance- EBA fact sheet on Blood Donor Selection..

5.1.1.3 Challenge of responding effectively to frequently changing disease transmission risks

There are two approaches to responding to these changing risks.

- **Regular updates of detailed legislative provisions**: Both basic Acts empower the Commission to lay down technical requirements and adapt them to scientific and technical progress, through the adoption of autonomous acts and following consultation of committees of Member State representatives[111]. The basic Acts also provide for the use of an urgency procedure for amending measures relating to donor eligibility and testing. These empowerments have been used by the Commission to develop the technical Directives[112], to make changes to these technical provisions[113] and to address an urgency[114]. However, considering the level of detail in the legislation and the frequency of these changes, often month by month, it has been challenging to keep the legislation up to date.
- **Authoritative risk-based guidance:** ECDC addresses the risk of transmission of communicable disease by substances of human origin, as they emerge, in a timely manner, with recommendations on testing and donor deferral (see Annex X and published risk assessments[115]). However, reflecting the fact that ECDC did not exist at the time the basic BTC Acts were adopted, there is no obligation in the current legislation to take ECDC recommendations into account.

On this topic, there is a general call across professionals working in BTC establishments, as well as the authorities that regulate them, for less detail in legislation, with clear references to authoritative and regularly updated guidance to be taken into account when setting rules for donor acceptance and testing.

5.1.2 Evaluation question 1b) To what extent is the legislation adapted to other changes in the sector such as commercialisation, internationalisation or other societal changes?

SUMMARY ANSWER: There have been important societal changes since the legislation was adopted, with an increased level of commercialisation and international exchange. The legislation was adopted at a time when the services it regulates were largely organised from within local public health services and commercial interests were limited. As a consequence, the clinical effectiveness and donor protection provisions no longer address the risks associated with these activities in a comprehensive manner, both for donors and for recipients (objective 1, safety and quality), or the sufficiency of supply (objective 5).

[111] Referred to as the 'Comitology' procedure – see Articles 28 and 29 in both basic Acts.
[112] Directives 2004/33/EC, 2005/61/EC, 2005/62/EC, 2006/17/EC, 2006/86/EC, (EU) 2015/566.
[113] Directives 2011/38/EU, 2012/39/EU, 2014/110/EU, (EU) 2015/565, (EU) 2016/1214.
[114] In response to a risk of blood shortages due to the Influenza A (H1N1) pandemic Directive 2009/135/EC.
[115] See regularly updated Zika Virus Rapid Risk Assessment and other ECDC risk assessments.

5.1.2.1 Provisions in BTC legislation do not address risks associated with increased commercialisation adequately

Article 12 of the basic Act for tissues and cells requires Member States to endeavour to ensure that the procurement of tissues and cells is carried out on a non-profit basis. It also requires Member States to provide guidelines restricting or prohibiting advertising the need for or availability of human tissues and cells with a view to offering or seeking financial gain or comparative advantage. The Act also includes a recital that calls for Member States to encourage a strong public and non-profit involvement in the sector[116].

The BTC Directives do not, however, prohibit the participation, per se, of the private sector in the processes from donation to supply for clinical use. Although the commercial sector already played a significant role in plasma collection and in the running of in vitro fertilisation (IVF) clinics and sperm banks at the time that the legislation was adopted, there has been a marked increase in commercial activity since then in many areas that were previously predominantly, or entirely, run by the public sector. Annex XIV includes examples of commercial BTC activities that have appeared, or significantly increased, in all BTC sub-sectors since the legislation was adopted.

Under the TFEU, Member States are responsible for issues relating to the organisation of health services. The issue of commercialisation is addressed, in this evaluation, only in terms of any impact it might have on a sufficient supply of BTC at the required levels of safety and quality. The impact of the increasing commercialisation described here touches on three key safety, quality and sufficiency issues:

- **Unsubstantiated claims for clinical effectiveness**: As the legislation has limited provisions for demonstrating clinical effectiveness, commercial companies can promote their products as 'superior' to the existing options for a particular clinical application or as effective for a range of conditions, without a legal obligation to justify such claims with robust clinical evidence. This could open the door to increased safety risks with no corresponding benefit[117].
- **Increasing commercial demand for donors**: In the context of the limited provisions in the legislation to protect and monitor donor health (see sub-Section 5.2.1.2), potential needs of commercial companies for increasing numbers of donors could present risks to donor health that will not be adequately mitigated by regulatory action. This risk is more important for donations that are more invasive and imply greater risk to the donor, such as egg donation[118].
- **Potential threats to the achievement of EU sufficiency of BTC**: The sustainability of supply might be threatened where the success of a commercial

[116] Directive 2004/23/EC Recital 18.
[117] This applies notably to the field of stem cells where claims for effectiveness are often unsubstantiated. See: Marks P Witten C and Califf (2017) R. Clarifying Stem-Cell Therapy's Benefits and Risks N Engl J Med 376; 11.
[118] Pearson H (2006) Health effects of egg donation may take decades to emerge Nature 442: 607–608.

company causes the public sector to withdraw, and results in a high dependence on one or a small number of commercial suppliers[119] that may choose to supply only the most profitable BTC[120]. The blood supply might also be threatened when potential blood donors are attracted away from blood donation by compensation given for plasma donation in the commercial sector[121]. In addition, there is a risk that commercial entities might allocate and supply the final processed donation to limited EU Member States or to third countries, where potential profits are highest, putting EU sufficiency at risk, even in circumstances where EU donation rates are high.

Summarising the impact of increased commercialisation, it can be said that the aspirations of the Directives in relation to the establishment of BTC services as public health activities organised on the basis of patient need are reflected in limited provisions that were not designed for the level of commercialisation now seen.

5.1.2.2. BTC legislation does not fully facilitate the internationalisation needed for the supply of certain BTC

It is notable that around half of all bone marrow transplants[122] performed in the EU are donated by donors in another Member State or a third country, provided via a global network of national and regional registries of potential donors. These registries are accredited by the World Marrow Donors Association (WMDA)[123] that matches donors to recipients and supports the movement of these cells around the world, while monitoring traceability and vigilance. This activity has grown rapidly over the years since the EU legislation was adopted as shown in Figure 10.

[119] Mannis MJ, Sugar J (2018) Is This the Future of Eye Banking? Cornea (editorial) Cornea 37(7): 811-812.
[120] Fact Sheet published by the European Blood Alliance.
[121] Fact Sheet published by the European Blood Alliance.
[122] Bone marrow or other sources of blood forming stem cells known as haematopoietic stem cells (HPC).
[123] https://www.wmda.info.

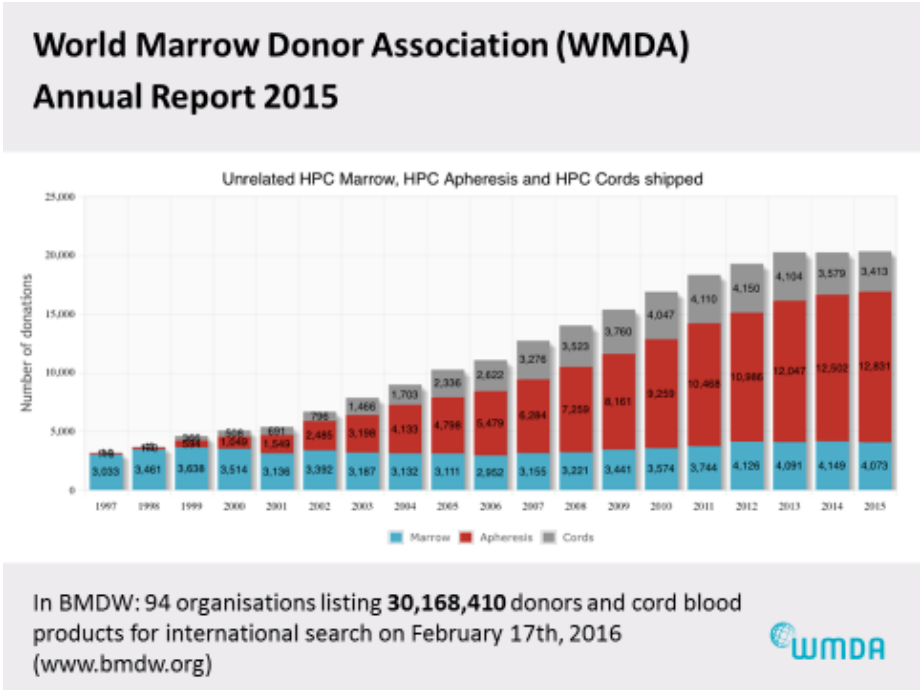


FIGURE 10: INCREASING GLOBAL DONATION OF HAEMATOPOIETIC STEM CELLS (HPC) FROM BONE MARROW (HPC MARROW), PERIPHERAL BLOOD STEM CELLS (HPC APHERESIS) AND CORD BLOOD (HPC CORDS)[124] FOR TRANSPLANTATION GLOBAL DISTRIBUTION.

This international distribution is needed for these cells that require a high level of donor to patient matching. Significant efforts by professional associations developing accreditation programmes have contributed to improving harmonisation of the safety and quality of donations supplied via these registries [125]. The World Marrow Donors Association (WMDA) has indicated that the current provisions leave a gap with regards to the role of national and international registries. They also point to the need for a global approach to vigilance in their field where rare events would not emerge without the collation of global data[126]. This is hampered to some extent, by EU vigilance definitions that are not standardised with definitions internationally.

The increasing demand for plasma derived medicinal products also currently relies on effective international exchange. This is addressed in Section 5.2.6.1.

5.1.2.3 Other Societal changes impact on the relevance of the BTC legislation

There have been other significant changes in society that have rendered specific provisions no longer suitable for achieving the objectives of the intervention. These include aging of the population, increasing demands for medically assisted reproduction

[124] Data presented at a meeting of Stakeholders with Competent Authorities for tissues and cells and DG SANTE in February 2017.
[125] For more, see: Website European Society for Blood and Marrow Transplantation- JACIE Standards.
[126] Punzel M. et al. Detection of hepatitis b virus DNA in the blood of a stem cell donor after granulocyte colony-stimulating factor treatment, Hepatology. 2016 Nov; 64(5):1803-1805. doi: 10.1002/hep.28667. Epub 2016 Jul 9.

(MAR) including across borders, the use of the internet for ordering of BTC and the use of BTC for cosmetic surgery (e.g. breast or penis augmentation). The implications of these developments for the relevance of the legislation are discussed in the external study that is published in parallel with this report[127].

Two issues that have caused particular concern are highlighted here.

- **Culturally unacceptable terminology**: Different technical provisions for many aspects of the chain from donation to clinical application vary between the 'partner donation' and the 'non-partner donation' scenarios in the context of MAR [128] . While the scientific basis of the different rules is accepted as rational, the term 'partners' as defined in the current legislation ('the donation of reproductive cells between a man and a woman who declare that they have an intimate physical relationship') [129] is questioned. It does not reflect the use of the term to also describe couples of the same gender in today's society.
- **Permanent exclusion from blood donation of men having sex with men**: Blood legislation that requires the permanent deferral from donation of persons whose sexual behaviour puts them at high risk of acquiring severe infectious diseases that can be transmitted by blood[130]. Although ECDC has confirmed that sex between men is the main mode of HIV transmission in the EU[131], the risks of HIV and hepatitis C transmission by donations from men having sex with men (MSM) are significantly reduced by the more sensitive tests available today. Thus, the interpretation that MSM implies a '*high risk of acquiring severe infectious diseases*', and therefore requires permanent deferral from blood donation[132], is no longer widely accepted as justified[133] and is seen by many as discrimination. Many Member States now implement the provision by a less stringent deferral for a limited period of time since the last exposure to risk[134]. Application of the provision in its strictest interpretation has led to a national court case being referred to the Court of Justice of the EU, to a number of complaints from citizens and to 16 questions from the European Parliament (see Annex VII). The variability across the EU, creates particular difficulties for the supply of plasma to medicinal product manufacturing companies working internationally[135].

[127] Study supporting the BTC evaluation, ICF, page 36-39.
[128] Notably, annexes 1 to 4 in Directive 2006/17/EC.
[129] Directive 2006/17/EC.
[130] Directive 2004/33/EC Annex III 2.1.
[131] Special report: HIV and men who have sex with men, by ECDC.
[132] Annex III of Directive 2004/33/EC.
[133] Sturrock BRH and Mucklow S (2018) What is the evidence for the change in the blood donation deferral period for high-risk groups and does it go far enough? Clin Med (Lond). 2018 Aug; 18(4): 304–307.
[134] Minutes of the blood CA meeting of November 2015.
[135] Summary Minutes of the Meeting of the CA for blood 10/11 October 2018.

5.1.3 Evaluation question 1c) Are there any gaps in terms of substances of human origin or activities that are not regulated by the Directives?

Summary Answer*:* Important technical, clinical and societal changes have taken place that have left gaps in terms of the regulation of some substances of human origin, that could effectively be covered by the BTC legislation. In the Online Public Consultation, around half of the respondents stated that they were aware of substances of human origin or activities that fall in regulatory gaps. The main consequence is that the substances are regulated in different ways across Member States, compromising the achievement of harmonisation, or they are not regulated, with the consequence that none of the other objectives is achieved for these substances.

5.1.3.1 New substances of human origin fall under the mandate of the Treaty on the Functioning of the European Union (TFEU) but outside the BTC scope

At the time the BTC legislation was adopted, the defined scope in the two basic Acts covered most of the human substances that were being used therapeutically and for which the TFEU gave competence to the EU to regulate safety and quality, apart from organs which were addressed in a third basic Act in 2010. A number of therapies have emerged, and are now in routine use, that fall outside the scope of the BTC legislation although they are substances of human origin and they imply similar risks to those regulated by it. Three examples are described here.

- **Blood components used for purposes other than transfusion**: These are excluded from the scope of the blood legislation[136]. Serum eye drops are used in ophthalmology and platelet rich plasma (PRP), platelet rich fibrin (PRF), and others are routinely prepared in hospitals and used in a range of surgery types.[137] Apart from CE marking, when the preparation involves the use of devices, there is no current EU regulation of these therapies that ensures safety and quality.
- **Faecal Microbiota Transplantation (FMT)**[138] is a rapidly growing therapy that aims to repopulate the gut microflora in patients with *Clostridium difficile* infection, following bone marrow transplantation or for other indications. In a meeting with the Member State competent authorities, the view was shared that FMT does not meet the definition of tissues or cells in Directive 2004/23, but does fall within the Treaty mandate of substances of human origin[139]. A recent Commission survey of the EU tissue and cell authorities indicated that 13

[136] Directive 2002/98/EC Article 2.
[137] PRP treatments, prepared with medical device kits, are currently valued at $100 million globally for the medical device industry, with Europe accounting for 25%. This value is expected to rise to almost 300 million by 2025 according to market research data provided by Medtech Europe.
[138] FMT is a rapidly growing therapy that aims to repopulate the gut microflora in patients with Clostridium difficile infection, following bone marrow transplantation or for other indications.
[139] Minutes NCA meeting Tissues and Cells, December 2014.

Member States do not regulate FMT, 5 regulate as a medicinal product (non-ATMP), 2 regulate under tissue and cell legislation and 1 regulates under Food legislation[140]. This issue is also addressed in the external study[141].

- **Donated human breast milk** has nutritional properties, it is also used to enhance immunity in preterm infants where the mother cannot breastfeed. In this case, also, a view was shared in the network of competent authorities that the substance falls under the Treaty legal mandate for substances of human origin but not within the definitions of tissues and cells in the current legislation[142]. Some Member States apply the tissue and cell legislation, others the food legislation and, in some cases, breast milk banking services are provided by blood banks in the EU and abroad[143,144]. At least 11 Member States currently do not regulate the activity while in others it is regulated under food, tissue and cell, or other frameworks[145].

These substances carry risks, including disease transmission[146,147,148], that could be mitigated by application of the rules in the BTC legislation. There is consensus among the Member State competent authorities that they should be regulated by provisions equivalent to those existing for BTC [149]. In some cases, requests for clarification have been made to the Commission (see Annex VIII). These cases have also been raised in other fora, including the Online Public Consultation and by the European Medicines Agency[150] as well as in the scientific literature[151,152,153]. There is general consensus that EU regulation is needed so that recipients of these treatments are protected in the same way as BTC recipients. It is notable that the Guide to the Safety and Quality of Tissues and Cells, published by the EDQM (Council of Europe) now includes guidance[154] for most of these autologous substances[155]. The consequence of the current situation is widely differing regulatory approaches in Member States, and no regulation in some, compromising the achievement of increased harmonisation.

[140] Tissues and Cells competent authority meeting minutes May 2019 with survey results.
[141] Study supporting the BTC evaluation, ICF, page 55.
[142] Minutes of competent authority meeting Tissues and Cells, December 2014.
[143] For more, see: Héma-Québe Website- Public Mothers' Milk Bank.
[144] For more, see: Banc de Sang Website- Banco de Leche Materna.
[145] Tissues and Cells competent authority meeting minutes May 2019.
[146] U.S. Food& Drug Administration. Information Pertaining to Additional Safety Protections Regarding Use of Fecal Microbiota for Transplantation..
[147] Keim SA, Hogan JS, McNamara KA et al. (2013) Microbial contamination of human milk purchased via the Internet. Pediatrics 132(5):e1227-35.
[148] GL Buser, S Mató, AY Zhang et al. (2017) Late-Onset Infant Group B Streptococcus Infection Associated with Maternal Consumption of Capsules Containing Dehydrated Placenta — Oregon, 2016 MMWR 66(25): 677-678.
[149] Minutes of tissues and cells competent authority meeting May 2019.
[150] Summary minutes of the meeting between EC and EMA Sept 2018.
[151] MB Smith, C Kelly and EJ Alm (20 February 2014) How to regulate faecal transplants. For medical use, human stool should be considered a tissue, not a drug Nature, 506: 290-291.
[152] J Chisholm, B Vontigerstrom, P Bedford et al. (2017) Workshop to address gaps in regulation of minimally manipulated autologous cell therapies for homologous use in Canada *Cytotherapy* 19: 1400–1411.
[153] M Ratner (2014) Fecal transplantation poses dilemma for FDA. Nature 32(5):401-402.
[154] This guidance is not binding in the EU or in Council of Europe Member States.
[155] Guide to the quality and safety of organs for transplantation, EDQM.

5.1.3.2 The exclusion of tissues and cells taken from patients and returned to them during the 'Same Surgical Procedure' leaves some processed substances unregulated.

The basic Act for tissues and cells specifically excludes tissues and cells procured and returned to the patient during the 'same surgical procedure'[156]. At the time the legislation was adopted, this exclusion aimed to avoid intervening in the practice of clinicians that remove, for example, a piece of bone or a blood vessel from one part of the body of a patient and use it to reconstruct another part of the body. The impact of this exclusion, however, has been to leave a number of processes now carried out in hospitals and clinics unregulated at EU level. An example is the separation of adipose cells from adipose tissue by centrifugation, with return to the patient for reconstruction of tissue defects, or for cosmetic purposes.

5.2 Effectiveness

This criterion was addressed by six evaluation questions. Questions 2 to 6 relate to the achievement of safety and quality, with a level of harmonisation that facilitates inter-Member State exchanges (Objectives 1, 2 and 3), while question 7 relates to the achievement of sufficient supplies to meet patient needs (Objective 5). The achievement of legal certainty (objective 4) is addressed in the coherence Section (5.4).

The evidence points to significant improvements in safety and quality of BTC and improved human health protection. However, shortcomings in relation to ensuring the safety of some citizen groups were identified, particularly BTC donors, and provisions for sufficiency and oversight are not adequately robust.

5.2.1 QUESTION 2: To what extent has the legislation increased the quality and safety of blood and tissues and cells and achieved a high level of human health protection?

SUMMARY ANSWER: In general, the legislation has achieved important improvements in the safety and quality of BTC across the EU, with oversight established in all Member States. There has been no major secondary spread of disease by BTC since its adoption, despite a number of new emerging infectious risks during this period, and there is evidence of overall trust in the sector.

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

However, the oversight provisions are broad and generic, with the result that there have been widely varying approaches to the set-up of regulatory oversight across Member States. Thus, some competent authorities are fully independent of the sector they regulate and have developed specialised expertise, while others risk conflict of interest or have limited technical expertise.

Additionally, EU level vigilance monitoring does not provide comparable data from Member States due to provisions that are not adequately clear and are, therefore, implemented differently. Shortcomings are identified in the provisions for health protection of some citizens, particularly BTC donors. Finally, provisions for authorisation of processing facilities and processing methods are not sufficient to ensure a high level of BTC quality and a demonstrably beneficial outcome in patients.

As a consequence, the legislation cannot fully ensure achievement of objective 1 (safety and quality), 2 (effective oversight) and objective 3 (a degree of harmonisation).

5.2.1.1 Significant improvements in Safety and Quality of BTC

In the Online Public Consultation, the great majority of stakeholders from all categories of respondent, including blood and tissue establishments, authorities and industry, considered the impact of the legislation to have been positive, increasing safety and quality to some extent, or to a great extent (see Annex XII). A Special Eurobarometer published in 2015 with responses from 27,868 EU citizens indicated a high level of confidence of EU citizens in the safety of the systems that supply BTC; 81% would accept being treated with one or more human substance[157]. The improvements are linked particularly to the following consequences of the legislation.

- **Safety and quality rules and oversight are in place.** Thus, blood and tissue establishments that organise donation, procurement, testing, processing, storage and distribution of BTC across the EU must comply with legally binding rules. Member States have nominated competent authorities that verify this compliance through a series of oversight functions including inspection, authorisation and vigilance.
- **Disease transmissions from donors to recipients are at a very low level.** Despite the emergence and re-emergence of many infectious agents since the adoption of the BTC legislation, the level of transmission by these secondary routes has been kept to an extremely low or negligible number of isolated cases[158,159].

[157] An earlier Eurobarometer specifically addressing blood donation and transfusion (2009, survey of 26,788 citizens) indicated that 57% of respondents considered that blood transfusions were safer that 10 years earlier.
[158] Annual EU Vigilance reports for BTC indicate that the risk of transmitting viral infection by transfusion in the EU is now less than 0.000001.

- **Quality Management is well established in blood and tissue establishments**. Risks to BTC recipients, other than disease transmission from donors, include contamination with bacteria or fungi during donation, processing or storage, cross-contamination from other donations, poor quality in relation to the clinically required characteristics or loss of traceability and mix-ups. These risks are reduced through the application of legally required quality management[160]. The facilities in which blood and tissue establishments operate across the EU have generally improved significantly[161] and the quality management rules have been strengthened over time[162]. Member States report high levels of compliance with the quality and safety rules, as verified through inspection and authorisation[163].
- **Rapid Alerts communicated between Member State authorities mitigate risk.** To facilitate Member States in effectively communicating rapidly with each other to mitigate risk associated with BTC distributed across borders, the Commission hosts rapid alert platforms. They are used routinely to communicate epidemiological risks and quality defects and allow Member States to modify donor selection or testing practices, conduct recalls or follow up patients as appropriate[164]. There were 21 alerts launched on blood and 18 on tissues and cells during 2017.

5.2.1.2 Provisions are not specific enough to ensure common and robust implementation of oversight

The two basic Acts include provisions for the establishment of oversight as the key tool for verifying safety and quality[165]. Although the establishment of oversight is seen as a major achievement of the legislation, a number of shortcomings have emerged that may limit its effectiveness.

[159] No virus transmissions by transplanted tissues and cells were recorded in the most recent EU SARE report for tissues and cells.
[160] For blood, Chapter IV of 2002/98/EC and implementing Directive 2005/62/EC as amended by (EU) 2016/1214 and for tissues and cells, Chapter IV of Directive 2004/23/EC and implementing Directive 2006/86/EC.
[161] This is confirmed by professionals that contribute to the updating of EDQM (Council of Europe) safety and quality guides. For tissues and cells, they consider that the application of clean room standards, even higher than those defined in the EU directives are necessary and are routinely provided across the EU for some substances. Such standards are now reflected in those guides.
[162] With the most recent initiative being the adoption of Good Practice Guidelines (GPG) developed jointly by the Commission and EDQM (Council of Europe) for Blood Establishments and referenced in a recent amendment to an implementing Directive (EU) 2016/1214. Those guidelines are broadly based on the EU Guidelines for Good Manufacturing Practice for the manufacture of medicinal products. An equivalent GPG, with a similar focus is currently under development at EDQM for tissue establishments, indicating a similar trend in that sector.
[163] Commission Implementation Report 2016 and Tissues and Cells Implementation Report 2016.
[164] Rapid Alert system for human Tissues and Cells (RATC) and for human Blood and Blood Components (RAB)-Summary of 2017 activities.
[165] Article 4 paragraph 1 in both Directive 2002/98/EC and Directive2004/23/EC.

- **Independence and technical expertise of competent authorities not fully ensured**: In contrast to other regulatory frameworks[166], the BTC Directives do not specify generic oversight principles to be followed by competent authorities[167]. Widely varying approaches to the set-up of BTC authorities, with the functions being carried out by medicinal product authorities in some Member States, BTC specialist authorities in others and national or regional health administrations in still others are in place. Consequently, enforcement powers, levels of independence from the sector and from government, as well as technical competencies vary significantly.
- **Inspections are conducted differently across the EU**: Both basic Acts include provisions for the inspection of establishments working in this sector[168]. Inspections of blood and tissue establishments are carried out in variable ways across the EU[169, 170]. Some are conducted by generalist inspectors, with backgrounds in quality management and inspection of other health product related sectors such as pharmaceuticals. Others are conducted by specialists from the BTC sector with high-level technical knowledge in the specific sub-sector they are inspecting. Still others are conducted by general health inspectors that are working on a local or regional basis, inspecting a wide range of health facilities from operating rooms to hospital canteens. A Decision adopted by the Commission on the conditions of inspection for tissues and cells[171], and a number of Public Health Programme actions on this topic (see Annex IX), have brought a degree of improvement and harmonisation, with some common guidance and training. However, significant differences between national inspection systems persist. The variability may impact on inter-Member State confidence in oversight, particularly in the absence of any provision for verification of equivalence in inspection approaches across the EU. The experiences of EU level inspection system auditing in the food and medicinal product sectors are examples where this challenge has been overcome in other areas of EU oversight[172].

[166] Article 126 (b) of Directive 2001/83/EC on medicinal products specifies requirements for independence and lack of conflict of interest for competent authority personnel. Articles 35 (2) and 38 of Medical Device Regulation 2017/745 provide for similar principles of independence and transparency of authorities Article 37 of Food Regulation 178/2002, also defines an independence principle for Member State authorities.
[167] This issue is addressed in the external study supporting the BTC evaluation, ICF, page 78.
[168] Directive 2002/98/EC Article 8 and Directive 2004/23/EC Article 7.
[169] This has been documented in Commission Implementation Reports.
[170] Survey conducted in a Health Programme project. Fehily D, Delvecchio C, Di Ciaccio P et al. (2007): "The Eustite project: working towards harmonised implementation of European regulation of tissues and cells". Organs, Tissues and Cells 2007; 10(1): 31-36.
[171] Commission Decision 2010/453/EU.
[172] In those frameworks, there are various mechanisms for verifying their effectiveness, such as EU level auditing of inspectorate systems. Examples are Article 79 of Regulation 536/2014 (in force but not applicable yet) that provides for the Commission to conduct controls in order to verify whether Member States correctly supervise compliance with provisions for clinical trials. Similarly, Articles 45(1) and (2) of the Food Regulation 882/2004 provide for Commission verification of Member State control systems.

- **Divergent approaches to preparation process authorisation**: Almost every type of BTC is subjected to a manipulation process in the blood or tissue establishment, before being supplied to clinicians for use. In this case, also, there is wide variability in the procedures for application and approval of preparation processes and variable quality criteria applied across the EU, sometimes leading to a lack of mutual acceptance of authorisations between Member States[173]. Many authorities review detailed dossiers and require clinical outcome data as part of their authorisation of preparation processes, while others apply a minimal approach. Stakeholders and authorities agree that process authorisation needs to be strengthened and should, in many circumstances, include requirements for review of clinical outcome data[174,175,176,177,178.] A general consensus on this topic has emerged for both blood and tissues and cells with a common view that the gap in the current legislation makes the achievement of objective 1 (quality and safety) particularly challenging from the point of view of 'quality'.
- **Variable approaches to reporting of serious adverse events and reactions**: The legislation obliges authorities to ensure that serious adverse reactions and events are notified to them. They submit summaries of the notified cases to the Commission each year (see legal provisions described in Annex IV). The EU wide annual vigilance reporting obligation has brought a much-valued aggregation of data and information, supporting policy development at national and EU level. However, the provisions are generic, leaving room for variable interpretations. The challenges include agreeing on the level of seriousness of adverse events and reactions that should trigger reporting. For example, 62% of the serious adverse events reported for blood in the EU in 2016 were reported by just two Member States. Standardising the reporting of denominator data, to allow meaningful comparisons between Member States and across the EU over time, has also been challenging. For skin grafts, for example, some report by number of packets while others report by area of skin in centimetres squared. In addition, the provisions do not address all areas of risk to citizens, with limited or unclear reporting requirements for adverse reactions in donors[179] and in offspring of medically assisted reproduction (MAR). These latter issues are further

[173] This was highlighted in a survey conducted as part of the Joint Action VISTART on vigilance and inspection in BTC establishments and confirmed in a subsequent survey by the Joint Action GAPP on BTC preparation process authorisation.
[174] In the field of MAR, for example, key stakeholders stated: 'The ultimate measure of quality in [Assisted Reproduction Technology} ART should be considered as 'live births per treatment initiated'.
[175] Clinical outcome is also monitored in the medium-to-long term for many other tissues and cells (see Annex XV).
[176] Many professionals conduct patient studies that come close to, or comply fully with, requirements for clinical trials on medicinal products.
[177] The main consortium of BTC representative societies (CoRE SoHO) has stated that it considers that clinical outcome monitoring should be regulated, in particular for novel and more complex processing methods.
[178] BTC authorities are working together in a Health Programme Joint Action to explore how to improve practices in preparation process authorisation, including by reviewing clinical outcome data.
[179] Inconsistent voluntary reporting by Member States. Although 23 Member States voluntarily reported donor reactions in the 2017 exercise for blood, 50% of the reactions were reported by one Member State.

described under 5.2.1.2 below. These shortcomings limit the potential for learning from adverse incidents.

Vigilance is enhanced by provisions for Member States to rapidly inform each other of incidents implying risks for patients in more than one Member State. This communication is facilitated by a Rapid Alert platform hosted by the Commission. This platform is used routinely to communicate epidemiological risks and quality defects and allow Member States to modify donor selection or testing practices, conduct recalls or follow up patients as appropriate, to minimise the impact of unexpected risks[180].

The platform is much appreciated by the Member States although there continues to be debate regarding what should be the criteria for triggering an alert and how much information should be shared outside the authority network. These issues have been raised at meetings of competent authorities and a Public Health Programme Joint Action that explored current vigilance programmes for BTC[181].

Alerts related to BTC are often of relevance to other regulated sectors. For example, defects in medical devices can have significant impacts on the safety and quality of BTC as donor blood samples are tested with CE marked *in vitro* diagnostic kits and BTC are processed and/or stored in certified medical devices. In addition, BTC can be used for the manufacture of medicinal products and medical devices (see Section 5.4 on Coherence). Alerts in the communicable disease field can be of key importance to the selection and testing of donors of BTC. In this context, lacking provisions for ensuring effective communication with alert systems in different but related sectors are seen as a shortcoming.

Effective responses when there is an adverse outcome depend on robust traceability of BTC[182,183]. Collaborating coding standards organisations have highlighted that the current provisions lack a requirement for regular testing of the traceability systems in place, to verify that all distributed BTC can be traced to the patients in whom they were used[184].

5.2.1.3 Provisions do not adequately protect all affected citizens

The evaluation has identified some provisions that are limited or absent in terms of protecting the safety of all those citizens affected by the chain from donation to clinical use (see Figure 11).

[180] Rapid Alert system for human Tissues and Cells (RATC) and for human Blood and Blood Components (RAB)- Summary of 2017 activities.
[181] See: Website VISTART.
[182] The tissue and cell legislation includes specific provisions for coding, in recognition of the degree to which these substances are exchanged across Member States.
[183] Directive 2004/23/EC, Article 25 and Directive 2015/566.
[184] Minutes of meeting between DG SANTE and representatives of the coding standards organisations ICCBBA and Eurocode 3 October 2018.

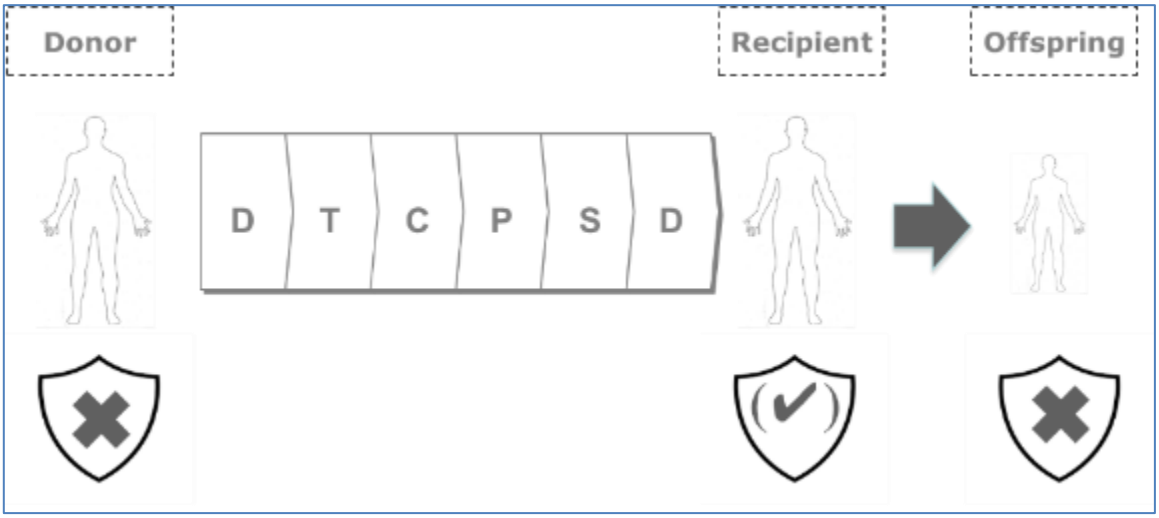


FIGURE 11: INADEQUATE PROTECTION OF ALL AFFECTED CITIZENS IN THE BTC CHAIN

Firstly, provisions to protect BTC donors from risks associated with donation are not seen as adequate. In the aftermath of the infectious disease transmission crises that preceded the adoption of the BTC legislation, it is not surprising that the legal provisions in the Directives focused very much on safety for recipients, and therefore on the safety of the BTC themselves. Donating BTC might also, however, put donors at risk, particularly when their health is already compromised in some way or when the donation requires some form of (hormonal) treatment, as in egg donation and peripheral blood stem cell donation[185], or an invasive procedure, as in egg donation and bone marrow donation[186]. Even without hormonal treatment or an invasive procedure, high frequency donation of blood or plasma might cause a donor to have diminished reserves of Haemoglobin and/or other proteins. Iron depletion is particularly important in young blood donors, pre-menopausal female blood donors, frequent blood donors and those blood donors whose haemoglobin levels are close to the minimum for eligibility. In spite of these risks, the current legislation includes only limited donor protection provisions, many of which are not sufficiently specific or are no longer adequate.

In both BTC basic Acts reporting donor reactions is mandated, as part of vigilance, only when the safety or quality of the donated substance itself has been compromised; this is very rare. The great majority of donor reactions are, therefore, not reportable according to the legislation, even in cases of donor death. Reporting of these cases at national level varies considerably across Member States, as evidenced in the voluntary reporting currently conducted in the EU exercises on serious adverse reactions and events (SARE)[187]. In the most recent SARE reports[188], 7,658 reactions in blood donors were

[185] A commonly used alternative to bone marrow donation involves treating donors with a hormone called Granulocyte Colony Stimulating Factor (G-CSF) that releases granulocytes and stem cells from the bone marrow into the blood stream allowing them to be collected from the blood stream by apheresis in a manner similar to the collection of plasma or platelets. Donors of eggs are stimulated with Follicle Stimulating Hormones over a 10 day period to cause many follicles to produce eggs and allow the collection of multiple eggs at one time.
[186] Bone marrow donation involves the use of needles to withdraw liquid marrow from both sides of the back of the pelvic bone and egg donation involves collection by a transvaginal surgical aspiration procedure.
[187] The annual collation of Serious Adverse Reactions and Events at EU level for blood and for tissues and cells.

reported by 23 countries but 50% of these were reported by a single Member State. Similarly, 700 reactions in tissue and cell donors (including partner and non-partner gamete donors) were reported voluntarily by 19 countries, while 9 countries did not report any. These data indicate that voluntary reporting is not fully effective, despite the important frequency of donor reactions.

Protection prior to and following donation is, thus, a concern across the sectors, among both professionals and authorities. At a meeting with key blood stakeholders[189] and blood competent authorities, the topic of donor protection was explored in depth and robust evidence was presented to confirm that this issue is of high priority and that current provisions are not adequate[190]. An equivalent meeting of the key professional organisations in the tissue and cell sub-sector with authorities in that field identified the same concern, in particular for egg donation[191] and for donation of blood stem cells from bone marrow or blood[192]. In 2010, a Directive on organ donation and transplantation was adopted[193]. This Directive includes provisions for the protection of living organ donors, for their follow-up post-donation and for the reporting of adverse reactions in donors, regardless of the impact on the quality or safety of the donated organ. These provisions, adopted on the same legal basis as the BTC Directives, reflect an objective of achieving safety for donors as well as recipients and a high level of human health protection. The major concerns for protecting recipients from disease transmission risk following the HIV and hepatitis C crises of the 1980s and 1990s are now counter-balanced by a concern for the protection of donors.

Children born from sperm, egg or embryo donation were identified as a second group of citizens that is inadequately protected by the current provisions. The provisions for reporting transmissions of genetic conditions in offspring via vigilance programmes are unclear. The definition of 'serious adverse reaction' refers to outcomes in 'recipients', not clearly taking into account the offspring resulting from MAR using donated sperm or eggs. While at least one large sperm bank supplying across the EU argues that serious genetic conditions inherited by children from a sperm donor do not meet the definition of

[188] Summary of the 2017 SARE Report on Blood and Summary of the 2017 SARE Report on Tissues and Cell.

[189] All EU level organisation representing blood establishments, plasma collectors and plasma fractionators were present.

[190] Minutes of the Ad-Hoc Meeting between Stakeholders and representatives members of the Competent Authorities on Substances of Human Origin Expert Group (CASoHO E01718) 22 February 2017.

[191] To protect non-partner gamete donors, the European Society for Human Reproduction and Embryology (ESHRE) proposed consideration of the following actions: to limit the number of oocyte donations per donor; to define strict rules on economical compensation (cross-border differences); to require reporting of complications of egg retrieval, including Ovarian Hyper-stimulation Syndrome (OHSS, a medical condition that can occur in women following hormonal stimulation of egg growth) in non-partner donations, at an EU level and to improve traceability in cross-border MAR, eliminating the possibility of direct distribution of gametes to patients.
The equivalent European Society in the field of haematopoietic stem cells (The European Society for Blood and Marrow Transplantation, EBMT) stressed that their donors undergo a medical procedure with no benefit to themselves and noted in particular that children are increasingly donating for siblings and should be robustly protected from risks of donation. They consider that all incidental findings should trigger proper care and counselling. See Minutes of the Ad-Hoc Meeting between Stakeholders and representatives members of the Competent Authorities on Substances of Human Origin Expert Group (CASoHO E01718) 22 February 2017.

[192] Ad-Hoc Meeting between Stakeholders and representatives members of the Competent Authorities on Substances of Human Origin Expert Group, February 2017 .

[193] Directive 2010/53/EU.

a serious adverse reaction in the legislation and should not be communicated in the EU rapid alert platform[194], this view is not supported by the major professional association for MAR[195,196] or by the competent authorities[197,198]. In addition, the professional association also considers that the absence of mandatory requirements for monitoring the health of children born through MAR is an important gap in the legislation[199].

The protection of recipients is strong but provisions are too rigid. Apart from the outdated provisions to prevent disease transmission from donors, described in the Relevance Section (5.1), some technical provisions for the facilities in which BTC are processed are also unclear and give rise to different standards applied in Member States to prevent contamination or cross-contamination during processing. This is a particular issue for tissues and cells[200]. For almost all tissues and cells, there is exposure to the processing environment during processing. For this reason, the legislation includes provisions for the air quality of processing areas, making reference to Annex 1 of the Good Manufacturing Practice (GMP)[201] standards for processing of sterile medicinal products, but with less demanding air quality specifications, reflecting the specificities of this sector[202]. These provisions have resulted in improvement of the quality in tissue and cell processing facilities across the EU, to a common minimum standard, but they are also seen as problematic. By setting fixed minimum requirements, they are now seen to allow the processing of some tissues and cells in environments that might not be clean enough when the risks associated with the particular process and the particular mode of clinical application are significant. In contrast, they are considered to be too stringent for situations where microbial contamination does not represent a significant risk to recipients. The latter situation is addressed under Efficiency (see Section 5.3) as the costs of providing processing rooms that are classified according to GMP are significant.

5.2.2 QUESTION 3: Has the legislation led to any unintended effects (positive or negative)?

SUMMARY ANSWER: Unintended effects have been relatively minor and included increased bureaucracy and administrative costs at both the authority and the professional level, as well as some challenges for smaller blood and tissue

[194] Annex to Submission to the Online Public Consultation by Cryos International, Denmark.
[195] Summary of the Blood, Tissues and Cells Stakeholder Event 20 September 2017.
[196] Meeting between the Commission and the European Society for Human Reproduction and Embryology 3 May 2018.
[197] Meeting of Tissue and Cells competent authorities 20-21 June 2018, item 9.2.2.
[198] The results of a 'neighbour check' survey by Denmark were reported in the meeting of Tissues and Cells competent authories 13-14 May 2019, item 5.3.4.
[199] Meeting with stakeholders and competent authorities on 22 February 2017, item 5.
[200] Blood is processed in closed blood bag systems that protect the substance from the risks of contamination from the environment or cross-contamination from other donations and, therefore, provisions for facilities where blood and blood components are less critical.
[201] EudraLex Volume 4 of "The rules governing medicinal products in the European Union".
[202] Specifically, Directive 2006/86/EC includes a provision (Annex II) that tissues and cells must be processed in an area equivalent to a grade A with a background of at least grade D, as a minimum. A number of exceptions are noted where a lower standard can apply.

establishments and some shortages of particular BTC in a very few specific cases in particular Member States.

Negative side effects of the BTC legislation are elaborated under the Efficiency Section (5.3) and relate to the burden of reporting requirements, the need for some smaller establishments to consolidate and the loss of donations and supply in some very limited situations. The many positive effects of the legislation are seen to have been intended.

5.2.3 QUESTION 4: What, if any, have been the barriers preventing effective implementation of the legislation?

SUMMARY ANSWER: Some broad, or missing, definitions in the BTC legislation have created barriers to effective implementation due to divergent interpretation at Member State level. Views vary in particular on the application of the principle of Voluntary Unpaid Donation. This has limited the achievement of harmonised standards and hence of inter-Member State exchange. In addition, both authorities and establishments are hampered by limited resources to support implementation.

5.2.3.1 Variable interpretations of certain key definitions

A number of shortcomings of the current legislation relate to different interpretations of definitions but are addressed under other criteria in this report. For example, the terms 'inspection' (see Efficiency Section - 5.3), 'Serious Adverse Reaction' (see question 2, above), the term 'blood establishment' and 'partner' have all been subject to differing interpretations, with practical consequences for the way the rules are applied and the sector is regulated[203].

5.2.3.2 The principle of Voluntary unpaid donation is applied in different ways

One of the key concepts in the legislation is that of 'voluntary unpaid donation' (VUD). VUD is not defined specifically in either of the basic Acts. Directive 2004/23/EC on tissues and cells, however, provides more detail than the blood basic Act, including that compensation to make good expenses and inconveniences related to the donation may be acceptable[204].

Member States have taken different approaches to interpreting what VUD means. The differences in purchasing power between Member States may contribute to the context whereby a measure is considered a "compensation" in one country and is viewed as an

[203] A number of other definitions, e.g. 'storage', 'distribution', 'transport', 'tissue', 'cells' and 'medical practitioner', have led to discussions at the meetings of competent authorities due to differing interpretations, which are further described in Annex VIII and in the Study supporting the BTC evaluation, ICF, page 88.
[204] Directive 2004/23/EC Article 12, paragraph 1.

"incentive" in another. To fulfil their legal obligations[205], Member States report every three years to the Commission on the measures taken with regard to VUD[206,207]. These reports indicate that all Member States consider that they comply with the principle, even though some pay fixed or variable amounts to egg and plasma donors and others offer as much as a day of paid leave from work for blood donation. Some consider the payment of egg donors to be reasonable compensation[208] while others see it as trafficking[209].

The issue arises mostly in the areas of plasma and egg donation, two of the substances that are moved frequently between Member States or are the subject of cross-border treatment. The consequences have been important, with some Member States putting up barriers to the movement of BTC, notably plasma collected by the private sector, where they consider that it has not been collected in compliance with the VUD principle. In addition, some Member States do not permit private plasma collectors to run donation programmes for this reason, limiting the volumes of plasma collected and contributing to the reliance on the US for this substance. Restrictive practices, related to VUD, have led to complaints and court cases (see Annex VI) and questions in the European Parliament[210].

On 11 September 2012, the European Parliament published a Resolution[211] calling for a more stringent approach to the implementation of the VUD principle for tissues and cells, raising particular concerns particularly on egg donation and calling for donor protection measures[212].

Work carried out at the Council of Europe[213] and by the Nuffield Council of Bioethics in the UK[214] is moving forward current thinking on how to approach and apply the concept of VUD and proposing definitions that they consider easier to apply consistently.

[205] Directive 2004/23/EC Article 12, paragraph 1 and 2002/98/EC Article 20, paragraph 2.
[206] The Commission must inform the Parliament and the Council of any necessary further measures it intends to take. The Commission fulfils this obligation by publishing the results of a VUD survey of Member States and providing it to the Parliament and the Council.
[207] Commission Staff Working Document on the implementation of the principle of voluntary and unpaid donation for human blood and blood components and Commission Staff Working Document on the implementation of the principle of voluntary and unpaid donation for human tissues and cells.
[208] V. Pavone "50% of European egg donation happens in Spain. Why?"- International Medical Travel Journal .
[209] B.Jones "Human egg-trafficking scam uncovered in Romania"-BioNews .
[210] Of the 79 Questions tabled in the European Parliament (since the BTC legislation was adopted - see Annex VII), 12 have pointed to concerns regarding the interpretation of the VUD principle.
[211] European Parliament resolution of 11 September 2012 on voluntary and unpaid donation of tissues and cells (2011/2193(INI)).
[212] The resolution addressed implementation of the current rules but also called for a revision of main Act on tissues and cells and of the Regulation on Advanced Therapy Medicinal Products, to bring them in line with the organ Directive adopted in 2010 as regards provisions on VUD.
[213] Guide for the implementation of the Principle of Prohibition of Financial Gain with respect to the human body and its parts, as such, from living or deceased donors.
[214] "Human Bodies: Donation for Medicine and Research".

5.2.3.3 Limited resources hamper good and consistent implementation

Both authorities and establishments report that limited resources have presented barriers to the implementation of the legislation. This issue is addressed under Efficiency (see Section 5.3).

5.2.4 QUESTION 5: Are the rules on oversight sufficient to address the increased internationalisation?

> **SUMMARY ANSWER:** Some aspects of increasing internationalisation are considered not to be adequately addressed by the legislation. Activity data reporting requirements are not sufficient to allow for a clear picture regarding the volumes of tissues and cells imported to the EU, exported from the EU or exchanged between Member States. Provisions are lacking to regulate direct online distribution, for mutual recognition agreements with third countries and for addressing the role of donor registries in ensuring safety and quality of cells that are distributed internationally. This impacts negatively on the achievement of oversight (objective 2), but also on the achievement of community sufficiency (objective 5).

The BTC legislation aimed to facilitate exchanges between Member States by establishing equivalent levels of quality and safety across the EU. BTC imported from outside the EU should be demonstrated to be of equivalent safety and quality. This is specifically regulated for tissues and cells[215] . Despite these provisions, some gaps and inadequacies have been identified, which are relevant in the context of increased internationalisation[216] and commercialisation (see Section 5.1.2.1 and 5.1.2.2).

5.2.4.1 No clear picture of international exchange of BTC due to limited monitoring provisions

There are limited provisions for data reporting, which means that, while certain general trends are evident, it is challenging to have a precise and clear EU picture of volumes of imports or exports for all BTC, particularly for tissues. Neither do most authorities have a clear overview of the level of dependence on third countries, on the level of community sufficiency, or on the numbers of donors moving between Member States or entering the EU to donate.

There is a consensus that certain data reporting should be mandated at EU level[217]. This would allow authorities to monitor import and export and assess whether international activities are threatening EU supply or creating high dependency on other continents. In

[215] Directive 2015/566 includes provisions for the authorisation of individual tissue establishments to carry out the imports, including the assessment of equivalence.
[216] See the external Study supporting the BTC evaluation, ICF, pages 50-52.
[217] A meeting of EU professional experts and authorities, convened by the Council of Europe and DG SANTE in 2017 and reported on at the Meeting of Tissue and Cell competent authorities on June 21-22 2018, item 7.

addition, it would ensure transparency to citizens and provide comparable denominators to better interpret vigilance reports.

Such monitoring provisions would also allow authorities to assess the development of online distribution of tissues and cells (particularly sperm and bone for dental applications) which has raised safety and quality concerns, particularly linked to traceability and vigilance[218].

5.2.4.2 Barriers to international exchange may hamper access to BTC

While high levels of export from, or import to, the EU might imply risks to the achievement of EU sufficiency, international exchange is essential in some cases. This applies, for example, to ensuring that patients have access to BTC that are not (or not sufficiently) available in the EU, such as plasma and certain types of tissues, and to facilitating high level genetic matching between donors and recipients for bone marrow and other types of haematopoietic stem cells (HPC) transplants.

For tissues and cells, the import Directive [219] places the obligation on tissue establishments, specifically and individually authorised as Importing Tissue Establishments, to verify equivalent safety and quality for imported tissues and cells. This differs from other sectors, where EU level agreements with third countries facilitate and simplify the international exchange of products such as medicinal products and medical devices. International stakeholders, particularly tissue establishments, report significant challenges when trying to export to the EU[220].

Regarding exchange within the EU, the possibility for Member States to add more stringent requirements to the minimum requirements foreseen in the EU BTC legislation, although clearly permitted by the Treaty, is also reported as a barrier. This is further elaborated under the Section on EU added value (5.5).

5.2.5 QUESTION 6: What, if any, are the challenges to maintaining compliance with the legislation?

SUMMARY ANSWER: The challenges raised in response to question 4, above, are equally relevant to this question along with all of the rapidly changing factors that are outlined under the Relevance and the Coherence criteria. The most important of these are the limited resources at authorities and establishments, the rapidly changing technological and epidemiological landscape and the borderlines with other regulatory frameworks.

[218] Notably the direct ordering and distribution of bone to clinicians (see Annex VIII, part 2, item 9) and of sperm to individuals has raised concerns among the tissue and cell authorities and, for sperm, has led to changes in Danish national law (see Annex VIII, part 2, item 30).
[219] Directive 2015/566.
[220] Summary of the Blood, Tissues and Cells Stakeholder Event 20 September 2017.

5.2.6 QUESTION 7: To what extent, if any, has the legislation impacted on patient access to blood, tissues and cells?

SUMMARY ANSWER: In general, while sufficiency is defined by demand and supply, legal provisions for achieving the sufficiency objective are limited. The supply of blood and blood components for transfusion is generally sufficient and demand for red blood cells is decreasing. Some BTC-specific negative impacts on supply have resulted from technical provisions in the legislation that are no longer considered to be scientifically justified. The most important sufficiency challenges, however, relate to the EU reliance on imports for plasma for the manufacture of plasma derived medicinal products and for some tissues, and to a lack of provisions for ensuring sufficiency in emergency situations.

The supply situation in the EU is different for different types of BTC:

- The supply of blood and blood components for transfusion generally meets demand in the EU although shortages can be associated with seasonal factors, usually affecting particular Member States, or regions of Member States, such as the loss of donations due to an increased risk of West Nile Virus infection in summer in some Mediterranean countries. In general, the demand for red blood cells is decreasing due to changing clinical practice, particularly the implementation of an approach known as Patient Blood Management than can significantly reduce the exposure of patients to the risks of transfusion[221,222,223].
- There is a significant shortage of plasma for the manufacture of plasma derived medicinal products that is increasing with increasing demand, with a consequent reliance on import from the United States (see more detail below).
- There appears to be a high level of importation of some tissues for transplantation (see more detail below).
- Bone marrow, and other types of haematopoietic stem cells, are exchanged internationally to achieve the necessary high level of donor to recipient matching and shortages tend to be associated with the need for matching for certain ethnic groups.
- In the field of medically assisted reproduction, access to donated eggs and sperm can be limited by national rules that are beyond the competence of the EU in this field.

[221] M Mueller, H Van Remoortel, P Meybohm et al. Patient Blood Management Recommendations from the 2018 Frankfurt Consensus Conference JAMA.2019;321(10):983-997.
[222] Building national programmes of Patient Blood Management (PBM) in the EU- A Guide for Health Authorities, by the EC March 2017.
[223] Supporting Patient Blood Management (PBM) in the EU- A Practical Implementation Guide for Hospital, by the EC March 2017.

5.2.6.1 Shortages due to limited provisions for ensuring sufficiency

Although sufficiency of supply was a key objective, provisions to ensure it are very limited, focusing only on the need to encourage VUD and recitals on achieving community sufficiency through VUD. This Section describes the two important areas where indications are that the EU has not achieved sufficiency and is reliant on imports to meet patient needs. The lack of EU-level mandatory provisions for monitoring supply, demand, import/export and inter-Member State exchanges, makes it challenging to understand the extent to which these flows are the result of marketing activities by the commercial sector (see Section 5.1.2.1) or genuine shortages of BTC for essential procedures.

This issue could be seen in comparison to other regions (e.g. the US and Japan) where legal provisions support the achievement of sufficiency. Examples include obligations for monitoring supply to facilitate taking pre-emptive action, requirements to report to an authority when donations fall below a certain level or blocking of export when local patient needs have not been met.

The first important case of **insufficient supply** concerns **plasma** where the EU is highly dependent on imports from the US. Plasma is the starting material for the manufacture of a range of medicinal products[224]. While in the EU, the number of private plasma collection centres[225] increased from 37 in 2005 to 103 in 2016[226], this is far from sufficient to keep up with increasing demand for manufacturing of plasma derived medicines. According to the non-profit plasma manufacturing association, the International Plasma Fractionators Association (IPFA), 8 million additional plasma collections would need to be organised in the EU in order to supply all EU patients with the plasma derived medicines needed. The private sector plasma manufacturing association, PPTA (Plasma Protein Therapeutics Association), in a detailed response to the Online Public Consultation, highlights that EU supplies only meet around 60% of the overall demand for plasma for the manufacture of medicinal products in Europe, with the difference being primarily imported from the US[227]. The US is the main global source for plasma, supplying the EU and – to a lesser extent – other areas. Data from PPTA shows that the global volume of plasma collected for the manufacture of medicinal products increased by 269% between 1990 and 2014[228], and with an average annual growth rate of

[224] Plasma derived medicines are proteins, such as immunoglobulins and clotting factors that are derived (essentially filtered or purified) from the liquid plasma. Around 70% of patients with primary immunodeficiencies (PID) need lifelong treatment with immunoglobulins (Ig) and have no alternative treatment available. Patients with haemophilia and similar disorders also rely on a robust supply of clotting factors.

[225] Plasma for medicinal product manufacture can be separated from donated whole blood or collected directly from the donor using a machine that separates the blood cells and returns them to the donor (the process is known as apheresis). The majority of apheresis donation in the EU is organised by the private sector in Germany, Austria, Hungary and the Czech Republic but the public sector blood services and the Red Cross are also running and developing their plasmapheresis programmes. According to ICF ref (European Commission, 2018d) there is a significant variability of supply across the EU.

[226] Meeting of the Competent Authorities on blood and blood components 22-23 June 2017.

[227] PPTA submission to the Online Public Consultation, Annex II.

[228] Plasma Protein Therapeutics Association-Vision paper.

over 9%, the sector is expected to more than double between 2015 and 2023[229]. Data provided in an article by The Economist[230] shows that in 2014, the US transferred 15.9 million litres to Europe, 0.083 to Canada, 0.055 to Latin America, 0.074 to Asia-Pacific and 0.001 to the Middle East and Africa.

All stakeholders (public, private, blood and plasma collectors and plasma derived medicinal product manufacturers) recognise this dependency and point to an important risk to the continuity of the supply if there were a supply interruption from the US[231]. The situation is underlined by stakeholders, in the context of the steadily increasing global demand for these products, particularly immunoglobulins. The US FDA has recently raised concerns regarding increased demand and shortages of immunoglobulins in the US[232] that might exacerbate the impact of the EU dependence on that region. The issue has also raised concerns in the European Parliament, where the ENVI Committee is discussing a Union Act proposed by a group of cross-party MEPs[233] that calls on the Commission to revise the blood legislation in order to address plasma sufficiency**.**

PPTA considers that co-existence between the public sector, with voluntary unpaid non-compensated donations, and the private sector, with voluntary unpaid but compensated donations would facilitate efforts to increase plasma collection across the EU[234]. The European Blood Alliance, in its position paper on the subject[235], calls for increasing the efficiency of apheresis plasma collection in blood establishments and for reducing the wastage of plasma separated from whole blood, while maintaining a principle of non-payment.

The Council of Europe, with the support of the European Commission, organised a dedicated symposium early 2019[236] that resulted in a set of recommendations for action by blood services, national authorities, companies and international institutions to address the situation. Key recommendations of relevance to the EU legal framework relate to the need for stronger donor protection and vigilance measures, in order to allow for a safe increase in collection of plasma within the EU. Other points pertaining to blood legislation relate to monitoring of supply trends (such as in the US and Japan), the free market of plasma and plasma derived medicinal products (import, export, local supplies) and improving the interaction between the blood and pharmaceutical frameworks.

The second area where there appears to be significant import from the USA is less robustly documented and concerns the **import of tissues for transplant**, particularly

[229] Allied Market Research (2018).
[230] The Economist (2018). Bans on paying for human blood distort a vital global market.
[231] Ad-Hoc Meeting between Stakeholders and representatives members of the Competent Authorities on Substances of Human Origin Expert Group (CASoHO E01718), 22 June 2017.
[232] U.S. FDA Website - Information on Immune Globulin (Human) Product Shortage.
[233] Any Member of the European Parliament may table a proposal requesting the Commission to propose a Union act (a new act or the amendment of an existing act) on the basis of the right of initiative granted to Parliament under Article 225 TFEU.
[234] Meeting between the European Commission and PPTA on 19 June 2018.
[235] European Blood Alliance fact sheet on European self-sufficiency for blood components and plasma for fractionation.
[236] EDQM Website.

bone for dental and orthopaedic procedures but also skin and ocular tissue. An external study on the economic landscape of tissues and cells in the EU points to high quantities of surplus musculoskeletal tissues, some corneal grafts and specific sizes of heart valves, being exported to Europe[237]. This study also indicated that this level of importation might impact the viability of smaller and more local tissue establishments. Data from the Eurocet database, and quoted in that study, indicates that almost 25% of distributed musculoskeletal tissue distributed in the EU in 2012 was imported[238]. Eurocet data published for 2017 indicates that this proportion fell to 11% of distributed musculoskeletal tissue[239], but the data should be seen as indicative as not all Member States send data to this platform and some send incomplete data. This importation is also referred to in a report of US tissue banking activity[240] based on a survey of USA tissue banks in 2015, where the UK and Germany are listed as countries importing tissues from a high percentage of US banks.

5.2.6.2 Negative impact on supply due to some specific technical provisions

In general, technical provisions in the legislation did not cause shortages. However, there are a small number of reports of reduced access in specific situations.

- **Cornea collection rates** and available supply were reported as negatively impacted in some Member States[241] due to a provision that blood samples for donor testing be taken from deceased donors within 24 hours of death[242]. Many have pointed to an absence of scientific evidence to support this provision and to publications that indicate that blood samples taken later are adequate for reliable donor testing[243,244].
- The plasma industry considers that there is considerable **plasma wastage**, particularly plasma separated from whole blood. This results from:
    - some eligibility criteria for whole blood donation that are unjustified for the donation of plasma for the manufacture of medicinal products[245];

[237] Study of the economic landscape for tissues and cells, commissioned by the European Commission and published in 2015, page 12.
[238] Study of the economic landscape for tissues and cells, commissioned by the European Commission and published in 2015, Table 17, p77. The table quotes data from the Eurocet database showing that of 222,925 musculoskeletal grafts distributed in the EU in 2012, 53,879 were imported, mainly through the UK and Germany.
[239] Eurocet Website.
[240] *USA Department of Health and Human Services* The 2012 and 2015 National Tissue Recovery through Utilisation Survey Report, p78-79.
[241] Summary Minutes of the meeting between the Committee (Executive Board) of the European Eye Bank Association and DG SANTE B4, 26 January 2018.
[242] Annex II paragraph 2.4 Directive 2006/17/EC.
[243] Edler E, Wulff B, Schroeder A-S et al. (2011) A prospective time-course study on serological testing for human immunodeficiency virus, hepatitis B virus and hepatitis C virus with blood samples taken up to 48 h after death. Journal of Medical Microbiology: 60, 920–926.
[244] Meyera T, Polywkaa S, Wulff B (2012) Virus NAT for HIV, HBV, and HCV in Post-Mortal Blood Specimens over 48 h after Death of Infected Patients – First Results. Transfus Med Hemother 2012; 39:376–380.
[245] The issue of applying more liberal donor eligibility criteria for plasma only donors has also been raised by the private sector representatives of the industry.

- the need to apply the pharmaceutical standard of good manufacturing practice (GMP) immediately after collection of whole blood if the plasma is to be used for the manufacture of plasma derived medicinal products (the blood legislation applies only as far as collection and testing is concerned[246]) even though the plasma is stored in a closed system;
- Differing interpretations of VUD and deferral of prospective male donors who have sex with other men (MSM) requirements (see Annex VIII) lead to some plasma not being used for the manufacture of medicinal products.

5.2.6.3 Provisions are not foreseen to ensure supply in emergency situations

National or regional shortages due to mosquito-borne disease outbreaks in Southern Member States [247], where it was necessary to defer donors in line with the EU legislation[248], and interruptions to the supply of critical medical devices (in particular, *in vitro* diagnostics[249]) have caused concern in recent years[250]. There are no specific legal provisions to support inter-Member State exchanges or to other local supply sustainability during crises. On one occasion, (H1N1 epidemic in 2009) the empowerment provided for in Article 29 of Directive 2002/98/EC (urgency procedure) was used to introduce a rapid amendment[251] to allow for temporary derogations from EU donor eligibility requirements to mitigate the risk of blood shortage. Emergency planning to ensure sustainability of the blood supply has emerged as a key priority for authorities[252] and for stakeholders in the blood[253] field.

5.3 Efficiency

Assessing cost effectiveness has been particularly challenging in this evaluation, given that no specific cost impact analysis was carried out in the early 2000s and data, even on current costs, are very difficult to define precisely. In this largely public sector, costs are often not analysed by specific activity and are merged with other healthcare provision

[246] Article 2, paragraph 1 of Directive 2002/98/EC.
[247] As early as 2012, the spread of West Nile Virus was causing concern for Greece, Italy, Romania and France who began work on preparedness planning to protect the blood supply from the impact of the outbreak.
[248] Directive 2004/33/EC.
[249] A recent withdrawal of Syphilis testing kits due a defect caused significant supply problems in some Member States.
[250] For example the minutes of a meeting of competent authorities for blood and blood components on 22-23 June 2017 noted a communication from the European Blood Alliance indicating supply difficulties for many EU blood establishments following withdrawal of a defective text kit for syphilis and Romania and Bulgaria reported a blood supply crisis caused by a recall of a test kit for hepatitis C.
[251] Directive 2009/135/EC.
[252] Meeting of Competent Authorities for blood 27-28 February 2018.
[253] Ad-Hoc Meeting between Stakeholders and representatives of members of the Competent Authorities on Substances of Human Origin Expert Group (CASoHO E01718), 10 October 2018.

costs. These challenges were also identified by the external contractor and are described in the published study[254].

> Generally, there is a general consensus among stakeholder groups that costs were justified by benefits for patients[255]. There are a few exceptions related to particular technical provisions and the rules regarding frequency of inspection.

5.3.1 Evaluation question 8: How cost-effective has the application of the quality and safety requirements in the legislation been for operators. Have the benefits outweighed the costs?

SUMMARY ANSWER: There is a consensus among operators that the benefits for patients of implementing the legislation have outweighed the costs for operators. However, some specific exceptions to this emerged, for certain technical provisions and certain sub-sectors.

In the course of the online public consultation for this evaluation, evidence of unjustified costs did not emerge as a major challenge to the implementation of the legislation[256]. The professionals and authorities responding to the Online Public Consultation pointed to some specific costs as unjustified, or partially justified. Similar findings are reported in the independent study published together with this report[257]. This Section addresses those specific provisions where costs incurred were considered to be unjustified.

5.3.1.1 The costs of implementing some blood donor eligibility criteria are not justified by improved safety

As described under Relevance (Section 5.1), some specific donor eligibility requirements[258] imply costs but no longer bring additional safety. For example, tattooing, endoscopic examination and acupuncture now carry less risk of disease transmission[259,260]. Age and haemoglobin donation limits are also questioned by experts in the sector[261,262]. The provisions result in unjustifiably lost donations and additional

[254] External Study for the BTC Evaluation, ICF, pages 98-99.
[255] The exceptions to this were one large sperm bank and a small number of national associations from one country that considered the legislation to be inapprropriate for medically assisted reproduction.
[256] See published Summary of Responses to the OPC, pages 13 – 15.
[257] External Study for the BTC Evaluation, ICF, page 100.
[258] Defined in Directive 2004/33/EC, Annex III and in Directive 2006/17/EC. Annexes I and III.
[259] UK Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO), Donor Selection Criteria report (2017).
[260] Borra et al (2016) (2016) Blood donor deferral: time for change? An evidence-based analysis. International Journal of Clinical Transfusion Medicine, 4: pp.55–66.
[261] Borra et al (2016) (2016) Blood donor deferral: time for change? An evidence-based analysis. International Journal of Clinical Transfusion Medicine, 4: pp.55–66.

resources dedicated to explaining to donors why their donation cannot be accepted and to recruiting replacement donors. It was not feasible to quantify these costs in the evaluation but published evidence suggests that, despite the many different reasons for donor exclusion (donor or patient safety, product quality, feasibility of the collection, etc.), no justifying scientific evidence was available for 60% of the top 30 reasons for deferral[263]. It is suggested that many measures used to increase safety in blood banking cost significantly more than the standard cost-effectiveness threshold of $50,000 per quality-adjusted life year (QALY) [264, 265]. Donor eligibility criteria were not subjected to cost/benefit assessment when introduced and some of them now imply cost inefficiencies.

5.3.1.2 Certain donor testing provisions bring unjustified costs

Most donor testing provisions are fully in line with, or are less stringent than, existing professional standards and their costs are not disputed. This is not the case, however, for certain situations and sub-sectors. The unjustified donor testing provisions that have been most evident during this evaluation concern the testing of sperm and egg donors and the testing provisions for West Nile Virus in blood donors. The issues are summarised in Table 1.

TABLE 1: DONOR TESTING INEFFICIENCIES IDENTIFIED IN THE PUBLIC CONSULTATION

Provision	In-efficiency
Blood samples must be obtained at the time of each non-partner gamete donation[266]	Non-partner gamete donors make multiple donations over weeks and the donations can be quarantined frozen before release for use. Repetitive testing for each donation is costly without benefit in terms of safety[267].
Donations from donors who visited an area with West Nile Virus should not be accepted unless an individual sample is tested for WNV by nucleic acid technology (NAT)[268]	Individual (ID-)NAT tests cost 7 Euro more per donation tested compared to applying an (MP-) NAT test in pooled plasma samples from multiple donations[269], while the MP NAT tests provide a comparable level of safety[270, 271].

[262] Stainsby D, Butler M. Recommendations for the Removal of the Upper Age Limit for Regular Whole Blood and Component Donors. Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee; 2008.
[263] Borra et al (2016) Blood donor deferral: time for change? An evidence-based analysis. International Journal of Clinical Transfusion Medicine, 4: pp.55–66.
[264] The quality-adjusted life year or quality-adjusted life-year (QALY) is a generic measure of disease burden used in economic evaluation to assess the value for money of medical interventions. A cost–effectiveness ratio, i.e. EUR spent/QALY gained, represents the magnitude of additional health gained per additional unit of resources spent of an intervention or policy option.
[265] Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness–the curious resilience of the $50,000-per-QALY threshold. N Engl J Med. 2014; 371(9):796–797.
[266] Point 4.2 of Annex III of Directive 2006/17/EC.
[267] As discussed in the NCA meeting tissues and cells of November 2017 and June 2018.
[268] Directive 2014/110/EU.
[269] A study by the European Blood Alliance demonstrated that the cost of this provision could reach an additional 2 million Euros if all at-risk donors are tested across the EU by individual sample testing rather than in pools of samples from six donors (MP-NAT). Analysis presented at meetings of blood competent authorities and stakeholders.

5.3.1.3 The costs of compliance with the processing facility requirements are not justified by increased levels of safety for some tissue and cell types

Air quality standards for the processing of tissues and cells should comply with certain standards referenced to GMP for medicinal products[272]. The application of the minimum requirement is considered overly stringent where the risks associated with contamination and cross-contamination during processing are extremely low to negligible[273],[274] due to both the length of time of exposure to the processing environment and the mode of application to the patients.

Providing a processing environment with a classified air quality is one of the most costly measures provided for in the legislation, sometimes reaching €1 million or higher to install, depending on the size and the cleanliness grade, and significant subsequent maintenance costs[275],[276]. The provisions are not cost efficient in those situations where the processing environment does not impact in a proportionate way on the safety of the tissues and cells provided for clinical application.

5.3.1.4 Traceability requirements for tissues and cells are cost-effective only for tissue establishments that were not already using an established coding standard.

The Single European Code (SEC) introduced in 2015 aims to ensure the traceability of tissues and cells intended for human application. The legislation brought increased transparency on the regulatory status of tissue establishments providing tissues and cells and a harmonised code to support traceability of tissues and cells across the EU. The external study indicates that for stakeholders that were already complying with an international coding standard, a significant portion of establishments, this provision brought costs associated with IT upgrades and labelling changes that did not bring additional benefits over the existing systems[277] leading to cost inefficiencies in the system.

On the other hand, it provided a cost-effective solution for those tissue establishments that did not already have a coding system in place. A survey conducted by the

[270] ECDC has confirmed that an equivalent level of safety can be achieved by testing at the beginning of a donation period and again at the end, with quarantine of the donations until final negative results are recorded. ECDC assessment requested and reported at 2 meetings of blood competent authorities in February 2017 and November 2017.
[271] The US FDA allows testing of pooled samples and recommends that blood services establish a threshold of West Nile virus activity at which they should switch to individual sample testing.
[272] EudraLex Volume 4 "Good Manufacturing Practice (GMP) guidelines".
[273] Mortimer D (2005) A critical assessment of the impact of the European Union Tissues and Cells Directive (2004) on laboratory practices in assisted reproduction. Reproductive BioMedicine Online Vol 11. No 2: 162–176.
[274] Summary Minutes of the Meeting between the European Society for Human Reproduction and Embryology (ESHRE) and DG SANTE B4 03 May 2018.
[275] Study by the Rathenau Instituut, 2015, Economic landscapes of human tissues and cells for clinical application in the EU.
[276] Study supporting the BTC evaluation, ICF page 103.
[277] Summary Minutes of the Meeting between representatives of ICCBBA and Eurocode and DG SANTE B4, 03 October 2018.

Commission in 2011-2012[278], before the adoption of the EU coding legislation, revealed that most Member States had a unique code for each donation being assigned predominantly by the tissue establishments and not, therefore, providing uniqueness nationally or in the EU.

5.3.2 Evaluation Question 9: Are there particular administrative or other burdens for specific groups of operators, including downstream users of blood, tissues and cells as starting materials for medicinal products?

SUMMARY ANSWER: For most operators, the administrative burdens were not highlighted as unjustified by the benefits. However, limited burdens were identified for some stakeholders, particularly downstream manufacturers of products made from blood, tissues or cells.

5.3.2.1 Some donor eligibility provisions are not justified for manufacturing of plasma-derived medicinal products

Manufacturers of PDMPs report facing burdens associated with donor eligibility provisions that are not justified for plasma donated for this purpose because of the subsequent manufacturing steps applied, including microbial inactivation (see Section 5.2.6.2).[279] The cost of donor tests that do not add safety when the plasma is used for medicinal product manufacture implies an unjustified burden for these stakeholders.

5.3.2.2 Costs of complying with BTC import eligibility provisions are challenged by ATMP developers as inefficient

Directive 2015/566 on verifying equivalent standards of quality and safety of imported tissues and cells (i.e. from outside the EU) requires Member States to authorise certain tissue establishments as 'importing tissue establishments' (ITEs). These establishments must then verify equivalent quality and safety of the tissue and cells to be imported. For imported tissues or cells that are destined for manufacture of Advanced Therapy Medicinal Products (ATMP), the ITE must verify the equivalence of the donation, procurement and testing steps.

This is seen as a burden by EU ATMP manufacturers that must find an authorised ITE, which is willing to be contracted by them, to carry out this verification. Alternatively, they must apply for authorisation themselves as an ITE under the tissues and cells

[278] Annex 1: Individual country responses to the survey on the implementation of the EU Tissues and Cells Directives conducted in 2012 and based on 2011 information.

[279] An illustrative example provided was the requirement for Human T cell lymphotropic virus (HTLV I and II) testing, which International Plasma Fractionators Association (IPFA, public sector) stated can be transmitted by blood transfusion but all risk is removed during the process of plasma derived medicinal product manufacture. See summary minutes of the Meeting between International Plasma Fractionators Association (IPFA) and DG SANTE B4, 17 April 2018.

legislative framework, an additional regulatory burden. Both of these options are seen as unjustified by the benefits. The burden is exacerbated by divergent donor testing and eligibility requirements in many Member States caused to the implementation of more stringent national provisions (see Section 5.1). This issue was raised by ATMP stakeholders in the Stakeholder Event[280], in the Public Consultation[281] and in the External Study.[282]

Medicinal product authorities have also raised concerns regarding the burden associated with the need to apply the donation, procurement and testing provisions of the tissue and cell legislation for autologous ATMP treatments[283].

5.3.3 Evaluation Question 10: To what extent has the legislation resulted in cost implications for hospitals/patients using/receiving blood, tissues and cells?

> **SUMMARY ANSWER**: It was not possible to disentangle costs for BTC from overall costs of hospital treatments using BTC. However, stakeholders did not raise concerns related to additional costs for hospitals for receiving BTC that are in compliance with EU legislation.

Challenging to estimate additional costs for hospitals. The mechanisms for funding BTC supply in the EU are regulated at national level and vary considerably between Member States[284]. Where hospitals are charged, the prices have increased over time but it has not been possible to separate the increased costs caused by the legislation and those that were the result of other factors such as increasing costs of materials, testing etc. Neither during meetings and events with stakeholders in the course of the evaluation, nor in the Online Public Consultation were costs to hospitals/patients, incurred by the EU legislation, raised as being prohibitive or unjustified. This is likely to be because costs for BTC are usually integrated in costs for procedures such as surgery or transplantation and represent a small portion of the overall intervention cost.

[280] Report of the BTC Stakeholder Event, 20 September 2017.
[281] 18 of 112 responding organisations considered that the legislation, introduces significant or major inefficiencies or unjustified burdens when ensuring the safety and quality of medicinal products manufactured from BTC.
[282] Key stakeholders, such as the Alliance for Regenerative Medicine and the International Society for Cell Therapies, raised this concern. Study supporting the BTC evaluation, ICF, page 119.
[283] Minutes of a Joint meeting between Tissue and Cell competent authorities, medicinal product authorities and members of the Committee for Advanced Therapies.
[284] They range from supply to hospitals/clinics free of charge by establishments that are centrally funded, to cost recovery by public sector organisations (with fees set nationally or by the establishments themselves), or supply by private sector companies (with prices set independently).

Limited evidence of unjustified costs for patients. In these sectors, it is rare for patients to pay specifically for the BTC that are used in their treatment, unless they are being treated privately and in that case, the cost of the BTC is usually incorporated in the overall treatment cost. The issue of costs for patients has not emerged in the evaluation apart from in the particular case of couples having medically assisted reproduction treatment with the use of their own sperm or eggs where the cost burden for patients was resolved by an amendment[285].

5.3.4 Evaluation Question 11: To which extent does the oversight required by regulatory bodies pose a burden to public authorities (has the burden been proportionate to achieving the original oversight objectives of the legislation?)?

SUMMARY ANSWER: In general, significant costs were associated with putting the required oversight functions in place, particularly in those Member States that did not have them before the legislation was adopted or before they joined the EU. However, the burden on authorities is largely justified by the benefits, with the exception of the fixed rule on inspection frequency. The latter emerged as being over-burdensome without proportionate benefits.

5.3.4.1 Provision for a fixed 2-yearly inspection frequency is costly and does not verify compliance in the most efficient and effective way

Both basic Acts include provisions for the conduct of inspection and control measures at blood and tissue establishments at 2-yearly intervals[286]. In the absence of any definition for 'inspection' or 'control measure', most Member States interpret the provision as a requirement to visit each establishment and conduct an on-site inspection, although a Commission Decision published in 2010 provides for the conduct of a desk based inspection of tissue establishments in some circumstances[287]. Given that there are 5,400 BTC establishments in the EU and that inspections involve an average of 2 inspectors for 2-3 days, with additional days allocated to review of documentation prior to inspection and reporting writing following inspection, the investment in this activity is very considerable. In general, it brings a much valued assurance of compliance with the legislative provisions and opportunities for improvement where shortcomings are observed.

[285] Testing costs are often borne by the patients themselves and were significant when the patients had to be tested at each gamete collection. Directive 2006/17/EC was amended in 2012 Directive 2012/39/EU to make the provision less stringent, allowing testing to be performed up to 3 months before the first collection of gametes and to remain valid for up to 24 months. It is estimated that more than 160 million Euros a year was saved. See Hughes, C., Grundy, K., Emerson, G., and Mocanu, E. (2011). Viral screening at the time of each donation in ART patients: is it justified? Human Reproduction, 26(11): pp.3169–3172.
[286] Directive 2002/98/EC Article 8, paragraph 2 and Directive 2004/23/EC Article 7, paragraph 3.
[287] Commission Decision 2010/453/EU.

However, the fixed 2-yearly frequency has arisen as an important inefficiency in the oversight system. It is noted that some establishments are very small with limited activities, for example mobile blood collection sites[288], while others are large and complex. Some perform very well while others have more frequent non-compliances and adverse incidents. Inspectorates, already resource limited, must return to inspect small and/or well performing establishments that imply low risk for donors or patients, rather than investing their time and resources in visiting establishments with identified risk, or high impact on patients, more frequently or in other activities. There is general consensus among BTC authorities that a fixed 2-yearly frequency is not cost efficient[289,290]. The European Medicines Agency has issued a guidance document on the use of a Risk Based Approach[291] to inspection scheduling. Inspections in other regulated sectors, such as medicinal products and medical devices, and in the BTC sector in the US, are usually scheduled on the basis of risk assessment.

5.4 Coherence

The coherence of the BTC legislation was addressed by evaluation question 12, with 4 sub-parts focusing on different aspects of coherence. This evaluation looked at the coherence of the BTC legislation with other Union-level regulatory frameworks such as medical devices and medicinal products, but did not evaluate those other frameworks.

There are some technical inconsistencies between the different Directives in the field of substances of human origin. More importantly, the degree of interdependence between the BTC legislation and other EU regulatory frameworks is sometimes challenging and, in some cases, the application of the BTC safety and quality requirements when BTC are used as starting material for products regulated under other frameworks may be a shortcoming.

While most BTC based products and substances fall clearly into one or other regulatory framework (BTC, medicinal products, medical devices), there are a small number of cases at the borderlines where classification is more challenging. This is illustrated by some uncertainty and differences between Member States in the classification and regulatory frameworks applied for the same substances. In addition, the criteria and mechanisms for defining

[288] See Annex VIII Part 1 Number 4.
[289] Summary Minutes of the Meeting of the Competent Authorities on Blood and Blood Components 11/12 November 2015.
[290] Although it has been difficult to precisely establish the cost implications of this rule, it is estimated that the cost across the EU for BTC inspections runs to many millions of euros every year. Study supporting the BTC evaluation, ICF, Annex 6, page 217.
[291] Published on EMA's secure platform for Medicinal Product Authorities.

whether the full scope of the BTC legislation is applicable are sometimes a subject of discussion.

5.4.1 Evaluation question 12a) To what extent is the legislation on blood and tissues and cells consistent and coherent within its own provisions?

SUMMARY ANSWER: There is broad internal consistency although some testing and process authorisation requirements differ without a justifiable rationale. The concept of voluntary unpaid donation is described differently in the two Acts and traceability for tissues and cells is more stringently regulated than for blood. The latter is justified by the greater degree of exchanges of tissues and cells between Member States.

5.4.1.1 Different descriptions of the voluntary unpaid donation concept

Provisions on voluntary unpaid donation (VUD) are included in both the blood and tissue and cell basic Acts but with different descriptions.

- The tissue and cell Act specifies that 'donors may receive compensation, which is strictly limited to making good the expenses and inconveniences related to the donation', leaving to the Member States to define the conditions for compensation (Article 12). As a result, the compensation of oocyte donors with sums up to, and beyond, 1,000 Euros is common and sperm donors are compensated with much smaller amounts in most Member States[292].
- No such provision for compensation is included in the blood Act.

It is noted however that the degree of inconvenience and the time required for different types of donation differ considerably, some, such as oocyte or bone marrow donation requiring hormonal treatment and a significant intervention while others imply minimal discomfort (see Section 5.2).

5.4.1.2 Some technical differences in safety and quality provisions

A series of less significant technical differences between the blood and the tissue and cells Directives has emerged, such as donor testing for specific diseases (e.g., syphilis), traceability and import rules, authorisation of preparation processes, requirements for quality systems and reporting adverse reactions (see Annex XVI, Table 1). The latter is largely justified by the greater degree of inter-Member State exchanges of tissues and cells.

[292] For example, the Human Fertilisation and Embryology Authority (HFEA-UK) defines expense limits of 35£ for sperm donors and 750£ for egg donors, per donation.

Apart from raising doubts regarding the need for the provision in one legislation if it is not needed in the other where the risks should be similar, these differences may also have an impact in a small number of cases where it was unclear whether a substance falls under the blood or the tissue and cell framework. The most important of these related to Donor Lymphocyte Infusions (DLI)[293], used to increase success of bone marrow transplants for blood cancer patients. Justifiable arguments can be made for applying either the blood or tissues and cells legislation. This can lead to Member State questions on whether the appropriate safety and quality requirements are applied for DLI that are exchanged cross-borders following collection in another Member State.

5.4.2 Evaluation question 12b) To what extent is the legislation coherent and consistent with other relevant Union legislation?

SUMMARY ANSWER: Some provisions, such as those for VUSD and donor protection, are stronger in the organ legislation compared to the BTC legislation. Issues related to the borderlines with medicinal products and medical devices were highlighted. A lack of regulatory clarity may result in disincentives for BTC establishments to invest and innovate.

5.4.2.1 Some incoherence with Legislation on Organs

The Directive on organ donation requires Member States to 'ensure' (rather than to 'encourage') the **principle of Voluntary Unpaid Donation**. Financial incentives or benefit for the donor are to be avoided. However, as in the tissue and cell legislation, but unlike the blood legislation, compensation of living organ donors is permitted for expenses and loss of income (Article 13). This more binding requirement is in line with the EU Charter of Fundamental Rights[294], which entered into force in 2010 with the TFEU. Some public sector blood and tissue stakeholders are therefore calling that this more stringent application of the principle of VUD is also introduced in the BTC framework.

Considerably more stringent provisions are in place to **ensure living organ donor protection** compared to donors of BTC, including the need for registers of donors and donor follow-up at a national level. Finally, the provisions extend to the oversight (including authorisation) of clinical transplantation centres, a scope that is significantly broader than that in place for BTC. Concerns on the absence of such provisions in the BTC framework for donor protection and for clinical follow-up are brought forward under the Effectiveness Section (see Section 5.2).

[293] Although the cells are separated from blood, they are usually collected from bone marrow (or peripheral blood stem cell) donors and applied to patients as a support to a transplant of those cells, which are regulated under the basic act for tissues and cells (see Annex VIII, Part 1, item 3 and 21 and Part 2, item 1).
[294] Article 3 of the Charter calls for "the prohibition on making the human body and its parts as such a source of financial gain".

In this context, there have been only a small number of **borderline cases**. Most notable, was the case of hand or face transplantation. From an anatomical point of view, these involve the transplant of a number of combined tissues in a single complex structure. Following extensive discussions with both networks of organs authorities and of tissue/cell authorities, the Member State authorities agree that the donation and transplantation process that must be followed, without the need for a tissue establishment, makes the organ legislation more appropriate than the tissue and cell legislation to regulate this activity (see Annex VIII, part 2, item 9).

There also are some **technical inconsistencies** between the BTC and organs legislation. In general, the regulatory provisions of the organ Directive[295] are less detailed than those in the BTC legislation. For example, there is no EU-wide reporting of adverse outcomes required and oversight and quality management provisions are not as detailed. These differences are partly justified by a context where organ donation and transplantation are temporally closely associated, without the possibilities for complex processing or storage and by the high benefit to risk ratio in this field.

There are recent calls for closer collaboration between organ and BTC competent authorities on some of these technical requirements, in particular for vigilance reporting[296].

5.4.2.2 Coherence with other Legislation in the field of Health – medicinal products

Legal provisions: There is a direct link between the BTC directives and the medicinal product legislation. According to Article 2(1) of the Blood Directive, it applies to collection and testing of human blood and blood components whatever their intended purpose and to their processing storage and distribution when intended for transfusion. This means that the entire path from donation to supply for clinical use is regulated by the Blood Directive if the final use is for transfusion. When plasma is used for manufacturing of medicinal products only the first steps, collection and testing, are regulated by the blood legislation while those steps from manufacturing onwards are regulated by the medicinal product legislation[297].

Similarly, for tissues and cells for human application, the first steps, procurement and testing, are regulated by the Tissue and Cell Directive (Article 2(1)), whatever the intended use. The subsequent steps are also regulated by the Tissue and Cell Directive as long as the tissues and cells are not used for the manufacture of products that are covered by other Directives. This means that tissues and cells used for manufacturing of medicinal products are regulated by the medicinal product legislation for the steps from manufacturing and onwards. In this case, tissue and cell based medicinal products that have been substantially manipulated or are not intended to be used for the same essential

[295] Directive 2010/53/EU on standards of quality and safety of human organs intended for transplantation.
[296] In their June 2018 meeting, organs Competent Authorities reiterated an interest in having an expert network within the existing SoHO Vigilance expert sub-group to focus on organ vigilance.
[297] Directive 2001/83/EC.

function in the recipient are regulated by the Advanced Therapy Medicinal Product (ATMP) legislation since 2007[298].

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. While most BTC based substances/products fall clearly into either the medicinal or BTC legal framework, the evaluation suggests that in some cases it is challenging to decide on classification and determine which legislation applies. This Section describes some of the challenges this has created for different stakeholder groups including BTC establishments, stakeholder associations and national competent authorities[299,300].

Extent of problem: While most of the BTC and BTC based products fall clearly within one legal framework or the other, the evaluation has shown that on some occasions the same substances have been subject to divergent classifications in different Member States[301,302], as illustrated in a 2019 survey of EU Member States tissue and cell authorities[303]. This has led to the application of different legal regimes for the same substance in different Member States.

One example of divergent classification pointed out by EATCB[304], the main representation of EU replacement tissue banks, is a skin cell based suspension used for treating wounds, injuries and skin diseases, for which 9 Member States classify the activity as BTC and 7 Member States as medicinal product (ATMP or hospital exemption)[305]. Other examples of divergent classifications identified in a survey from April 2019 relate to substances like liver cells, fat cells or platelet rich plasma, serum eye drops or amniotic membrane (for more details, see Annex XVI).[306]

The challenges created by such divergent classifications were raised several times in the course of the BTC evaluation (Online Public Consultation[307], Commission Stakeholder event[308], ad hoc meetings with stakeholders[309]) by various stakeholders including BTC public authorities, practitioners and manufacturers from both BTC and medicinal sectors.

---

[298] Regulation (EC) 1394/2007.
[299] External Study supporting the BTC evaluation, ICF, p. 121-122 (study to be published together with the SWD).
[300] Commission Summary of Responses to the Public Consultation for the Evaluation of the Blood, Tissues and Cells Legislation, p. 17-18.
[301] Forgo N and HildebrandtM (2013) Joint conference on the impact of the EU legislation on therapeutic advance. Cytotherapy 15: 1444-1448.
[302] Pearce KM, Hildebrandt M, Greinix H et al. (2014) Regulation of advanced therapy medicinal products in Europe and the role of academia.
[303] See Annex XVI to this SWD.
[304] Presentation to the meeting of the network of National Competent Authorities on Tissues and Cells.
[305] See Annex XVI to this report.
[306] It should be noted that CAT make their recommendations on classification on the basis of individual product manufacturing processes and not on categories of products.
[307] 20 organisations responding to the Commission Public Consultation for the Evaluation of the Blood, Tissues and Cells Legislation considered that there were substantial inconsistencies with medicinal products legislation. These included large EU level professional associations, national level BTC professional associations, BTC and medicinal product competent authorities, BTC establishments and Council of Europe (EDQM), (Commission Summary of Responses to the Public Consultation for the Evaluation of the Blood, Tissues and Cells Legislation, p. 16-18).
[308] Summary of the Blood, Tissues and Cells Stakeholder Event organised by the European Commission Services (DG SANTE) on 20 September 2017 in the context of the BTC evaluation, p. 9.

The Council of Europe (EDQM) refers to inconsistencies and ambiguities in the scope and regulatory borderlines that lead to confusion and hamper oversight and patient access[310]. The Common Representation for Substances of Human Origin (CoReSoHO), the main sector organisation that represents blood and non-reproductive tissue establishments, identified the need for a clear definition of criteria for the classification of tissues and cells, in order to avoid that the same product is considered a tissue/cellular therapy in one Member State, and a medicinal product (ATMP) in another[311]. Public authorities from three large Member States mentioned inconsistencies, gaps and double status of products in their contributions to the public consultation[312]. Furthermore, the challenges were highlighted by the External Study conducted to support the Evaluation[313].

Consequences: While it is difficult to quantify precisely the impact of specific classification decisions in borderline cases and divergent classifications across Member States, the problem is closely linked with the very different requirements under the two legal frameworks, reflecting proportionately the different risks associated with BTC versus manufactured product.

Organisations representing tissue establishments have indicated that they hesitate to enter into the development of new processes when it is not clear what legal requirements apply and, thus, what level and type of investments might be needed. This could affect innovation in the BTC field[314,315,316,317]. This is exacerbated when these establishments have invested already to perform activities which have traditionally been carried out by BTC establishments and have been regulated under the BTC legislation for many years, and that since the introduction of the ATMP Regulation (in 2007) have been reclassified as Medicinal Products in some Member States[318,319].

In addition, the Danish Ministry of Industry considered that the challenge related to classification uncertainty could create administrative burden or additional investment (resource and time) for innovative health companies, and ultimately may result in costs and delays to patients' accessing new innovative therapies[320]. The concerns on patient

[309] DG SANTE and stakeholder meetings in 2017-2018. See for instance (i) the meeting with Consortium of SoHO societies; (ii) the meeting with the European Eye Banking Association .
[310] Submission to the OPC by Council of Europe/EDQM with file title CoE-EDQM.pdf and its annex.
[311] Submission to the OPC by the Common Representation for Substances of Human Origin (CoReSoHO).
[312] Submission to the OPC by the Federal Ministry of Health (DE), as well as by two public authorities not consenting to publish their submissions.
[313] Study supporting the BTC evaluation, ICF, page 121 and following.
[314] DG SANTE meeting with Consortium of SoHO societies of 14 March 2017 (European Blood Alliance, European Society for Blood and Marrow transplantation, European Association of Tissue Banks and European Association of Eye Banks).
[315] Summary of the Blood, Tissues and Cells Stakeholder Event organised by the European Commission Services (DG SANTE) on 20 September 2017 in the context of the BTC evaluation, p. 8ff.
[316] Response by the European Society of Blood and Marrow Transplantation (EBMT) to the IMI consultation on Advanced Therapies Concept Paper, 2016.
[317] Economic landscapes of human tissues and cells for clinical application in the EU (2015) Rathenau, p 225-226.
[318] Submission to the OPC by the Common Representation for Substances of Human Origin (CoReSoHO).
[319] Economic landscapes of human tissues and cells for clinical application in the EU (2015) Rathenau, p 27-8.
[320] Proposals for simplification of EU-Legislation Prepared jointly by the Danish Minister for Business, Industry and Financial Affairs and the Danish Business Forum for Better regulation March 2019, p. 4.

access are supported by national competent authorities for BTC [321] and are also highlighted by professionals[322,323,324,325,326].

Moreover, where it happens that Member States classify the same product in divergent ways, this could create challenges to inter-MS exchanges. Although many of the substances/products at the current borderline are autologous, and cross-border exchange is not frequent at this stage, this is likely to change as innovation in both the BTC and the ATMP field is expected to move forward[327]. The situation can also create challenges for import from third countries that wish to supply to multiple Member States.

Causes of the problem: When establishing the applicability of acts other than the BTC directives, divergent classification may occur due to different national interpretation of certain key definitions and requirements:

- Some stakeholders, including the Ministry of Health of Germany and the Etablissement Francais de Sang, as well as the external study supporting this evaluation, mentioned the lack of clarity on the term 'prepared industrially or manufactured by a method involving an industrial process'[328,329], which is a determining factor for whether a product, fall within the scope of the medicinal products legislation[330]. This lack of clarity is problematic because of the direct link between the two legal frameworks as explained above.
- Also the term 'substantial manipulation', relevant to determine whether the ATMP Regulation[331] is applicable or not, has been subject to variable interpretation, as seen in the examples listed in Annex XVI. For example, processing such as enzymatic isolation of cells have been considered substantial in some Member States and non-substantial in others
- Moreover, the term 'used for the same essential function' has sometimes proved difficult to interpret [332, 333, 334, 335] and can result in identical

[321] Summary reports of the Tissue and Cell Competent Authority meeting of 13-14 May 2019.
[322] Meeting with the Common Representation of SoHO Associations, 14th of March 2017.
[323] Meeting with the International Society for Cell Therapy (ISCT) 14 June 2018.
[324] Meeting with the Executive Board of the European Eye Bank Association.
[325] Pirnay JP, Vanderkelen A, De Vos D et al. (2013) Business oriented EU human cell and tissue product legislation will adversely impact Member States' health care systems.
[326] Dimitropoulos et al. (2016), Burn Patient care lost in good manufacturing practice. Annals of Burns and Fire Disaster, XXIX, 2, p111.
[327] Economic landscapes of human tissues and cells for clinical application in the EU (2015) Rathenau, p219 ff.
[328] Submission to the OPC by the Federal Ministry of Health (DE) and the Etablissement Francais de Sang (FR).
[329] ICF report supporting this evaluation, p 120-121.
[330] Art 2 of 2001/83/EC.
[331] The ATMP Regulation 1394/2007 includes a non-exhaustive list of 'non-substantial' manipulations, which are governed by BTC rules, see Annex 1 of the Regulation. For non-listed, including new processes, a case-by-case decision needs to be taken whether they are to be considered substantial or not.
[332] Chabannon C, Caudnay-Rigot O, Faucher C et al. (2016) Accreditation and regulations in cell therapy. ISBT Science Series 11(1): 271-276.
[333] Izeta A, Herrera C, Mata R et al. (2012) Cell-based product classification procedure: What can be done differently to improve decisions on borderline products? Cytotherapy 18:809-815.
[334] Cuende N, Herrera C and Keating A (2013) When the best is the enemy of the good: the case of bone-marrow mononuclear cells to treat ischemic syndromes. Haematologica 98(3): 323-324.
[335] ICF report supporting this evaluation, p 121-122.

substances prepared through similar processes to be subject to different safety and quality requirements[336].

Mechanisms to support Member States to apply the criteria and definitions in a common way exist, but are seen by some stakeholders as lacking coherence[337].

One response to this issue comes from the mandate entrusted to EMA by the ATMP Regulation to produce non-binding 'scientific recommendations' in relation to classification issues regarding medicinal products based on the advice of the Committee on Advanced Therapies established under the ATMP regulation. However, the Committee functions by responding to queries concerning specific medicinal products submitted by the substance/product developer[338], and only assists in determining whether a specific medicinal product falls, on scientific grounds, within the definition of an ATMP, and *not* with providing indications of what the product is if it is not an ATMP. The Committee's recommendations to applicants are issued on the basis of the criteria illustrated in a Reflection Paper[339] issued in 2015 and their summaries are published.

Tissue and Cell authorities discuss borderline issues on occasions in their regular meetings (Competent Authorities on Substances of Human Origin Expert Group, CASoHO E01718), but have no legal mandate to make formal recommendations to Member States in view of ensuring a uniform interpretation of the complex legislative framework.

The potential benefits of a cross-sector multi-disciplinary forum covering all innovative health frameworks, including ATMP, for reaching common recommendations on classification across this borderline has been highlighted in a REFIT Platform proposal by Denmark in 2019[340] and by BTC competent authorities[341].

5.4.2.3 Coherence with other Legislation in the field of Health – medical devices

As described above, the scope of the tissue and cell legislation covers all the steps from donation to supply for clinical application for human tissues intended for human application unless they are used to manufacture products that are covered by other legislation, in which case the tissue and cell legislation covers only donation, procurement and testing.

[336] Submission to the OPC by the European Directorate of Quality of Medicines/Council of Europe (EDQM/CoE) and the International Society for Cell Transplants (ISCT).
[337] The submissions received in the Commission public consultation for the Evaluation of the Blood, Tissues and Cells Legislation from stakeholders and citizens cf. the submission from the International Society for Cell Therapy (ISCT), European Eye Bank Association (EEBA), Common Representation for Substances of Human Origin (CoReSoHO), EDQM/Council of Europe.
[338] Art 17.1 of Regulation (EC) N° 1394/2007.
[339] Reflection paper on classification of ATMP (2015).
[340] Proposals for simplification of EU-Legislation Prepared jointly by the Danish Minister for Business, Industry and Financial Affairs and the Danish Business Forum for Better regulation March 2019, p. 4.
[341] Summary reports of the Tissue and Cell Competent Authority meeting of 13-14 May 2019.

The 2017 Medical Device Regulation[342] explicitly excludes tissues and cells, from its scope except for:

- Products manufactured utilising derivatives[343] of non-viable[344] tissues or cells of human origin.
- Products that combine a medical device with non-viable tissues or cells or their derivatives. Any device which, when placed on the market or put into service, incorporates, as an integral part, non-viable tissues or cells of human origin or their derivatives that have an action ancillary to that of the device shall be assessed and authorised in accordance with the Medical Device regulation. In that case, only the provisions for donation, procurement and testing laid down in Directive 2004/23/EC shall apply. However, if the action of those tissues or cells or their derivatives is principal and not ancillary to that of the device, and the product is not governed by the Medical Device Regulation, the product falls also for its processing, storage and distribution under the rules for tissues and cells. For the safety and performance of the device part the relevant general safety and performance requirements set out in the Medical Device Regulation shall apply[345].

Despite the further clarity brought by the Medical Device Regulation, a 2019 survey amongst tissue and cell competent authorities indicated divergence in Member State classification. While most countries regulate demineralised bone, decellularised heart valves and decellularised skin as tissues and cells, demineralised bone was reported in one country to be regulated as medical device (see Annex XVI, Table 3).The question concerning whether tissues that do not contain living cells should now to be subject to the new medical device regulatory framework has been raised[346]. Tissue and Cell competent authorities consider them to be appropriately regulated under the tissues and cells legislation, without major concerns on safety and quality.

Given that many tissue products currently supplied under the tissue and cell legislative framework are non-viable, and that it is not the intention of the Medical Device Regulation to cover tissues and cells which fall within the scope of Directive 2004/23/EC, a clear and consistent understanding of the borderline between the two sets of legislation concerning non-viable tissues and cells and their derivatives is important for all involved.

In recent years, a wide range of **new bedside equipment** allows BTC collection and processing at the patient's side. These processes fall outside the current BTC legislative

[342] Regulation (EU) 2017/745.
[343] In Article 2 (17) of Regulation (EU) 2017/745 'Derivative' is defined as meaning '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'.
[344] In this context non-viable means not living.
[345] Annex I of Regulation (EU) 2017/745.
[346] This topic is under discussion in the Borderline & Classification subgroup of the Medical Devices Co-ordination Group.

scope. They include equipment for the collection and reinfusion of blood during surgery to devices for the preparation of platelet rich plasma or stem cells from adipose tissue. In the course of the evaluation, both authorities and professionals have raised the need for BTC regulatory oversight of these processes due to the specificity of that legislation for ensuring safety and quality of processed tissues and cells. While the equipment itself is normally subject to the Medical Device Regulation, there is no regulation to ensure safety and quality of BTC produced with this equipment. Solutions would need to be found in cases where tissues or cells are processed at the bedside in a manner that might require an authorisation from a tissue and cell authority, without impact on the surgical procedure itself. This is not possible under the current legislation due to the exclusion of autologous tissue and cell processes carried out in the 'same surgical procedure'[347].

The materials and equipment used in the process from donation to supply of BTC, including donor testing, are almost all certified medical devices. The **critical importance of medical devices** at almost every step in the collection, testing, processing, storage and distribution has been highlighted when there have been **interruptions to the supply** of a particular device due to a defect[348]. This has happened in recent years in relation to haemoglobin testing devices used on donors, in vitro diagnostic test kits for infectious disease testing of donor blood samples and culture media used to culture embryos in assisted reproduction centres (see also Section 5.2.6.3). Such sudden interruptions have for example required the French national blood service to switch test-kits overnight, with the help of the UK national service, in order to allow for continued supply of safe blood. Ensuring sustainability of supply, particularly for blood and blood components, has emerged as a priority that is not adequately addressed in the current BTC legislation, particularly in circumstances of epidemiological or other crises. Discussions have taken place on this topic, with competent authorities, with EDQM (Council of Europe) and with the medical device industry. They indicate that any initiative to ensure the sustainability of the BTC supply chain must include effective cross-sector planning, monitoring and vigilance actions related to the critical medical device supply[349]. It needs to be noted that the Medical Device framework itself does not address criticality or shortages of devices.

5.4.2.4 Coherence with other Legislation in the field of Health – communicable diseases

In 2004, the EU adopted a Regulation on communicable diseases[350], establishing the European Centre for Disease Prevention and Control (ECDC). A subsequent EU Decision[351] provides for a network for the epidemiological surveillance of communicable

[347] Article 2, paragraph 2(a) 2004/23/EC.
[348] See example in the study supporting the BTC evaluation, ICF, page 124.
[349] Summary Minutes of the Ad-Hoc Meeting between Stakeholders and representatives of members of the Competent Authorities on Substances of Human Origin Expert Group (CASoHO E01718) 10 October 2018.
[350] Regulation (EC) No 851/2004.
[351] Decision 1082/2013/EU on serious cross-border threats to health.

diseases, operated by ECDC, and for the "Early Warning and Response System" (EWRS) [352] that ensures rapid inter-Member State communication of emerging communicable disease threats. In the Online Public Consultation for this evaluation, a proportion of respondents (21% for blood and 27% for tissues and cells) indicated their view that there are minor or significant inconsistencies with that legislation, reflecting a view that the surveillance requirements are not adequately reflected in the BTC legislation.

5.4.2.5 Coherence with other EU Legislation

The Charter of Fundamental Rights of the European Union was adopted in 2007[353] and includes a provision that the human body as such shall not be a source of financial gain, as well as one prohibiting eugenic practices, in particular those aimed at the selection of persons. A proportion of respondents to the Online Public Consultation (35% for blood and 27% for tissues and cells) considered that there are minor or significant inconsistencies between the Charter and the BTC legislation, reflecting a view that these issues are not adequately addressed for BTC.

5.4.3 Evaluation question 12c) Are the requirements of the Directives suitable when blood, tissues and cells are used as starting materials for the manufacture of medicinal products/medical devices?

> **SUMMARY ANSWER:** The requirements are generally adequate although some donor eligibility provisions are inappropriate and the need to import tissues and cells via authorised tissue establishments emerged as an unjustified burden for ATMP developers.

As described in 5.4.2.2 and 5.4.2.3, BTC can be the starting material for other categories of health products, including plasma-derived medicinal products, advanced therapy medicinal products (ATMP) and medical devices. See Figure 12.

[352] See also: Commission Implementing Decision (EU) 2017/253.
[353] Charter of Fundamental Rights of the European Union.

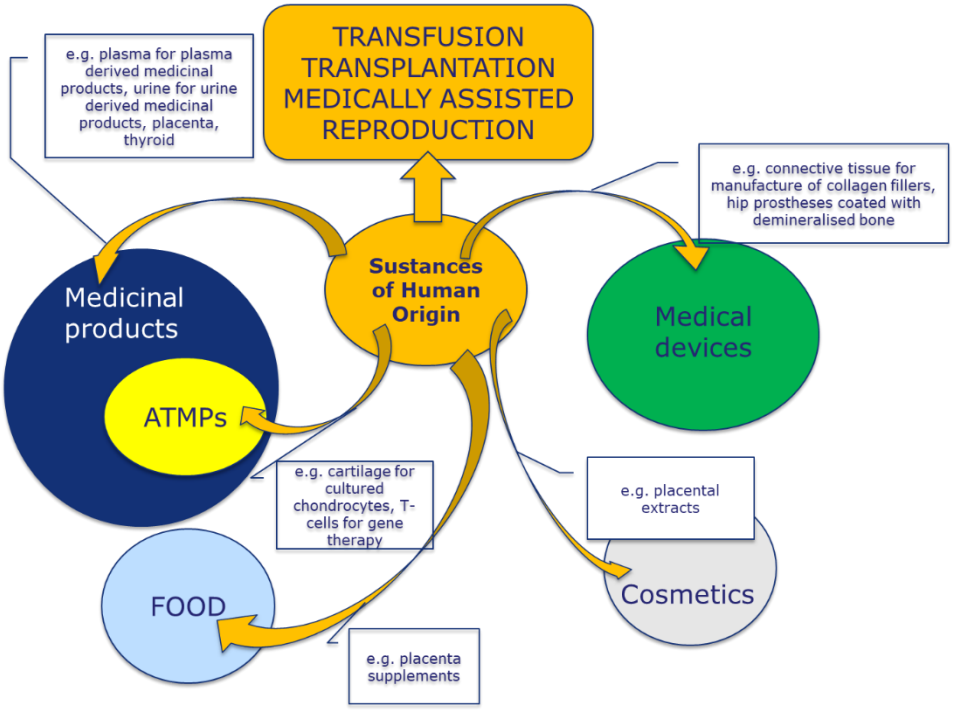


FIGURE 12: BTC AS STARTING MATERIALS FOR MANUFACTURED PRODUCTS REGULATED UNDER OTHER LEGISLATIVE FRAMEWORKS[354]

This situation sometimes raises the question whether the provisions for collection/donation/procurement and testing of BTC are adequate when the BTC are subsequently used for manufacturing under these other legal frameworks. This aspect of coherence was raised in the evaluation in relation to both plasma-derived medicinal products and to ATMPs.

As explained in the Efficiency Section (see Section 5.3), for plasma-derived medicinal products, donated plasma is subjected to a process that includes many microbial inactivation steps and that completely removes any cells. In this context, many of the donor eligibility and testing provisions are seen as unjustifiably stringent due to the significantly lower risk in the final product[355].

For ATMPs, in contrast, the donor selection and testing provisions in the current legislation might not be stringent enough, as it is rarely possible to sterilise those products and they might, in the future, be supplied to high numbers of recipients from a single donor. In addition, ATMP developers have pointed to challenges when importing tissues and cells into the EU as starting materials. In this situation, the tissue and cell legislation requires import via an authorised importing tissue establishment[356]. This prevents the ATMP developer from importing directly to their facility (See Section 5.3.2.2).

[354] Human tissues and cells are specifically excluded as ingredients in the manufacture of cosmetics in the EU. However, products are advertised online that are based on extracts from BTC.
[355] See Annex VIII Part 1, number 11 and 13.
[356] Submission of the Alliance of Regenerative Medicine to the OPC.

For medical devices tissue and cell authorities should be consulted during the authorisation of medical devices containing tissues or cells or their derivatives. These do not extend to vigilance and traceability activities following the clinical application of the device. There are no provisions in the BTC legislation to ensure appropriate communication across the regulatory borderlines for ensuring vigilance, traceability or efficacy/performance of devices manufactured with human tissues and cells as a starting material. It is noted that in some Member States[357], this issue is solved because the medical device, medicinal product and BTC authorities can ensure appropriate communication and collaboration, in several cases by being all within one organization.

5.4.4 Evaluation question 12d): To what extent is the legislation coherent with other relevant international / third country approaches to the regulation of the quality and safety of blood and tissues and cells?

> **SUMMARY ANSWER:** There is general consistency between the EU BTC requirements and those of the US as the key country with whom BTC are exchanged. However, some BTC are classified differently in different jurisdictions, making international exchange more difficult. In contrast to the EU, recommendations on classification, in other jurisdictions, involves discussions in cross-sectoral committees. In addition, BTC vigilance requirements are more comprehensive in the EU than in other jurisdictions.

In the course of the evaluation, the Commission held discussions with a number of key international regulators and stakeholders to explore differences in legislative provisions and regulatory approaches in this field. The most important of these is the FDA/CBER in the United States[358], because of the large quantities of plasma and tissues that are exported from there to the EU. While there are many commonalities between the legal provisions and regulatory approaches of the other jurisdictions that were explored, there were some differences of interest identified.

The Commission collaborates with the European Directorate for Quality Management (EDQM) of the Council of Europe that publishes regularly updated guidance on quality and safety of blood, tissues and cells[359]. The guidance is widely accepted in the EU and the other Council of Europe Member States as representing best practice in this sector. EDQM commits to ensure that their guidance does not contradict the provisions of the EU BTC legislation. In just one case, good practice guidelines (GPG) for blood establishments, a Directive was amended to require that Member States take the EDQM guidance into account[360]. In general however, as described in Section 5.1, while the

[357] In NL and UK, these authorities have common fora to discuss topics of common interest. In some countries, like FI or IE, the authorities for BTC, medical devices and medicinal product are within one organisation.
[358] Meeting between the Commission and FDA/CBER to discuss the EU BTC evaluation.
[359] EDQM Guide for tissues and cells; EDQM Guide for blood.
[360] Commission Directive (EU) 2016/1214 of 25 July 2016 amending Directive 2005/62/EC as regards quality system standards and specifications for blood establishments.

EDQM guidance has been regularly updated to reflect important developments in the area, the EU legislation has remained more static and in some cases even outdated, resulting in some degree of incoherence internationally.

5.4.4.1 Some diverging areas of BTC regulation between the US and the EU

The FDA is the sole regulatory entity with the authority for regulating blood and blood components, cell, tissue and tissue-based products (HCT/Ps) in the U.S. FDA does not classify HCT/Ps. Developers make their determination on classification and FDA provides recommendations or binding decisions if asked. HCT/Ps are regulated only by the Public Health Service Act, with traditional, minimally processed substances falling under the lighter rules in Section 361 (comparable with the EU TC framework). The legal basis for this regulation is limited to the prevention of communicable disease transmission, a scope that is narrower than the legal basis for regulation in the EU. More than minimally manipulated substances fall under the more stringent rules of Section 351 as well as those of 361[361] (comparable with the EU ATMP framework).

Further criteria cause certain HCT/Ps, including some that are combined with handling agents or other synthetic substances, to be classified as medical devices. The US classifies some BTC differently from the EU[362].

Tissue and cell stakeholders find the differences in classification to be a burden that makes export to the EU more difficult[363, 364]. This is in particular relevant for demineralized bone supplied by US companies and for bone marrow, and other types of haematopoietic stem cells, which are often exchanged globally.

FDA discusses classification of tissue and cell based products across the different sectors in a Tissue Reference Group and publishes common recommendations on classification that provide clarity and certainty to stakeholders in the U.S.

The regulatory authorities in Korea, Japan and Australia have an approach similar to the U.S. This contrasts with the EU where, as described above, each sector has its own advisory body, with the exception of the BTC sector.

[361] Although the extent of manipulation is the key criterion, other criteria also apply. To fall under 361 alone, they need to (1) be minimally manipulated, (2) be intended for homologous use only (based on the manufacturers objective intent), (3) not be combined with another article and (4) not have a systemic/ metabolic effect or be dependent on the activity of a living cell, unless for autologous or reproductive use. See 21 CFR 1271.10(a).

[362] Such as unrelated haematopoietic stem cell transplants, encapsulated pancreatic islet cells and demineralised bone combined with handling agents.

[363] Summary of the Blood, Tissues and Cells Stakeholder Event 20th September 2017.

[364] Summary Minutes of the Meeting between American Association of Tissue Banks (AATB) and the European Commission (DG SANTE B4) 9 March 2018.

5.4.4.2 Use of different types of guidance allow FDA to keep technical specifications up to date

As noted under the Relevance criterion, it is challenging for authorities to keep the many specific technical requirements in the BTC legislation up-to-date and in line with changing technologies and risks.

To address this same challenge, FDA uses different types of guidance:

- FDA regularly publishes 'guidance for industry' to recommend measures for achieving compliance with binding legislation and regulations; such guidance itself is not legally binding but is widely followed. A key advantage of issuing guidance is that its development takes less time, on average 6-12 months (compared to at least 12 months for a change to regulations), and therefore allows for more flexible updating of technical specifications.
- When needed, FDA/CBER can also rapidly issue guidance for immediate implementation, with the submission of public comments permitted any time after issuance of the guidance. In 2016, for example, the risks posed by Zika virus (ZIKV) were addressed mostly through guidance for immediate implementation.
- It is also notable that documents developed by professional associations (e.g. guidance from the American Association of Blood Banks are formally recognised by FDA as an acceptable approach to meet FDA requirements. This collaboration has worked well for standards developed by the association on a donor history questionnaire and a Circular of Information required by legislation to be issue to hospitals together with blood components for transfusion.

5.5 EU Added Value

This assessment criterion is addressed by two evaluation questions addressing overall added value at the EU level and the impact of more stringent requirements at national level.

In general, the Directives improved the quality and safety of BTC in a manner that would not have happened, or would have happened more slowly, without EU legislation. However, more stringent national requirements, although permitted by the Treaty, limit the EU added value, particularly in terms of exchanges between Member States.

5.5.1 Evaluation Question 13: To what extent has the legislative framework at EU level added value to the regulation of blood and tissues and cells across the EU-28 in a manner that could not have been achieved by measures taken at national or global level?

SUMMARY ANSWER: The Directives improved safety and quality across the EU, through defining minimum safety and quality requirements and putting oversight in place. This achievement would have taken considerably longer, would have developed in divergent ways bringing inconsistent levels of safety and quality and might not have happened in some Member States, without EU legislation.

5.5.1.1 Safety and quality rules and BTC oversight were introduced in many Member States

The situation regarding safety and quality rules, as well as oversight, varied considerably across the EU prior to the adoption of the legislation. A number of the economically stronger Member States had robust rules and oversight in place, particularly those that had needed to respond to transfusion-transmitted epidemics of HIV and hepatitis (see Section 2.1). Many others, however, and all of those that joined the EU after the adoption of the legislation, had few, or no, safety and quality rules and little oversight in place and relied on the professionals to follow international safety and quality standards. Annex V, describes the baseline situation, referring to a number of key source documents. A recent retrospective survey of tissue and cell authorities demonstrated that, prior to the adoption of the 2004/23/EC, or to their accession to the EU, 7 Member States did not have binding rules for safety and quality of replacement tissues and 8 did not have equivalent rules for haematopoietic stem cells or for MAR. Similarly, 12 had no regulatory oversight for MAR, while 7 and 8 had no oversight for replacement tissues and haematopoietic stem cells, respectively[365].

The early implementation reports[366] and discussions in Public Health Programme funded actions carried out after the adoption of the legislation, pointed to intense activity across the EU in the establishment of new inspection and vigilance systems. Professionals saw, and still see, the initiative as one that increased, or standardised, quality and safety[367,368,369,370]. It appears that many, or even most, blood and tissue establishments had to improve their facilities and their quality management systems.

[365] Minutes of tissue and cell competent authority meeting May 2019.
[366] First report on the application of the Blood Directive June 2006;
Summary Table of Responses from Competent Authorities: Questionnaire on the transposition and implementation of the European Tissues and Cells regulatory framework February 2007.
[367] European Blood Alliance (20 Book 1 Safety by Regulation (2013).
[368] Burgermeister J (2004) Doctors hail new EU directive on tissues and cells. BMJ 328:10.
[369] Governing the Human Body: Examing EU Regulatory Developments in Relation to Substances of Human Origin (2005) Journal of Social Welfare and Family Law, 27:3-4.
[370] Hartshorne G (2005) Challenges of the EU 'tissues and cells' directive. Reproductive Biomedicine Online 18 August 2005.

5.5.1.2 Significant added value of EU-wide vigilance, traceability and networking

Significant added value is seen from the increased networking and collaboration between Member States, resulting from the implementation of the EU provisions, in a number of areas.

- The **regular meetings** of authorities (Expert Group CASoHO E01718) have facilitated discussion, and helped to find solutions, for many issues, as demonstrated in Annex VIII[371].
- The provisions for reporting serious adverse reactions and events on an annual basis to the Commission has brought the added value of an **aggregated view of safety**, allowing a more accurate estimation of risk.
- The **Single European Code** for tissues and cells has improved traceability of tissues and cells as they circulate in the EU, with public transparency on the authorisation status of tissue establishments[372].
- The legislation has provided an impetus for significant levels of EU financial support for implementation through the Public Health Programme. Apart from the practical outputs of the actions: inspection guidance, training for professionals and inspectors, common vigilance tools, IT platforms etc., these projects and Joint Actions have brought positive outcomes in terms of building and sharing strong expertise across the EU. See Annex IX.

The organisations responding to the Online Public Consultation confirmed these positive findings[373].

5.5.2 Question 14. To what extent do stricter national measures pose an obstacle to exchange of supplies between Member States?

SUMMARY ANSWER: More stringent national requirements, permitted by the Treaty, emerged as a factor posing barriers to effective sharing of BTC within the EU and with third countries. These are put in place, to a significant extent due to outdated technical provisions and important developments in the sector.

[371] The expert group of competent authorities has established BTC expert sub-groups focusing on Vigilance practices (Vigilance Expert Subgroup), Inspection practices (Inspections Expert Subgroup) and traceability/coding practices (Coding Expert Sub-group – for tissues and cells only).
[372] See the EU compendium of authorised tissue establishments.
[373] See the summary results of the Public Consultation.

5.5.2.1 More stringent national requirements pose barriers to inter-Member State exchanges of BTC

The Treaty[374] gives competence to the EU for the adoption of safety and quality standards but allows Member States to put in place more stringent requirements to protect their citizens. Many Member States have chosen that option, in particular to address important developments in the sector and the difficulties of updating the EU provisions quickly, as well as to reflect geographical differences in transmissible disease risk. This was particularly highlighted in a mapping exercise, conducted by the Commission services in 2015, on more stringent donor testing measures required or recommended for BTC donors in Member States. The mapping exercise was published for blood[375] and for tissues and cells[376] and indicates that the level of viral safety achieved across the EU is no longer standardised. This has been highlighted as limiting EU added value by professionals in the field[377,378] by third country organisations that export to the EU[379] and by researchers wishing to use BTC in multi-country clinical trials[380] . In the Public Consultation, 30% of responding organisations indicated that more stringent national requirements pose significant obstacles to inter Member State exchanges.

[374] Article 168 (4)(a) TFEU.
[375] "Mapping of More Stringent Blood Donor Testing Requirements - Mapping Exercise 2015".
[376] "Mapping of More Stringent Tissues and Cells Donor Testing Requirements - Mapping Exercise 2015".
[377] Summary Minutes of the Meeting between the International Society for Cell Therapy and DG SANTE B4 14 June 2018.
[378] Summary Minutes of the Meeting between the Board of the European Association of Tissue Banks and DG SANTE B4 18 September 2018.
[379] Summary Minutes of the Meeting between American Association of Tissue Banks (AATB) and the European Commission (DG SANTE B4) 09 March 2018.
[380] Internal Commission discussions with the Directorate General for Research.

6. CONCLUSIONS

This evaluation evaluated the BTC legislation, adopted in 2002 for blood and 2004 for tissues and cells, according to the 5 criteria of effectiveness, relevance, efficiency, coherence and EU-added value. It builds on a Public Consultation, an external study, literature review, expert interviews and scientific documents, as well as a wide range of meetings with key stakeholders and National Competent Authorities. The two main limitations for this exercise were low data availability on the situation in Member States prior to the adoption of the legislation, and difficulties to quantify costs incurred by the BTC legislation.

i) The legislation effectively increased the level of safety and quality of BTC across the EU

Common minimum safety and quality requirements were mandated in all Member States and oversight was established to ensure inspection, authorisation and vigilance, bringing significant changes compared to the situation prior to the adoption of the BTC legislation. Despite a number of new disease outbreaks since the early 2000s, transmissions of infections by BTC have been maintained at low to negligible levels. This has restored public trust in the BTC sector and its oversight, which had been negatively impacted by large-scale transmission of infectious diseases such as HIV and hepatitis by BTC in the 80's and 90's.

These safety and quality objectives remain relevant. However, there have been significant developments since the legislation was adopted. Some contributed to improvements in safety and benefits for patients, but others brought new risks. This partly puts the future relevance and effectiveness of the legal frameworks into question. What follows are areas where the evaluation found the legislation to have shortcomings or gaps.

ii) The current rules are no longer up to date with the dynamic BTC sectors

Many of the detailed and prescriptive safety and quality requirements are no longer adequate to address fully the challenges associated with rapid technological, scientific and epidemiological developments.

For example, many requirements for BTC donor testing in the current legislation are out of date following the development of more sensitive tests for HIV and hepatitis. The current required tests provided for in the BTC legislation no longer reflect current best practice. In addition, the current donor eligibility rules no longer address many of the important risks for ensuring safety. For example, current donor acceptance requirements do not fully take into account (re-)emerging diseases (such as Zika, hepatitis E, malaria

or West-Nile Virus). Similarly, current criteria for the quality verification of the BTC applied to patients are either lacking or are reported not to reflect current clinical uses and processing methods. Some Member States have added new, more stringent safety measures, which can sometimes reduce the relevance of those already provided for in the BTC legislation or render them unnecessary. While this is possible under the Treaty, it has resulted in divergence and unequal protection of patients across the EU.

In addition, some new therapies, such as faecal microbiota transplants (FMT) and donated breast milk, have developed since the BTC legislation was adopted and are not covered by the definitions and scope of the current BTC legislation. This has resulted in divergent classifications and regulatory approaches, in different Member States, to ensure safety and quality for these treatments.

In line with these findings, many of the EU requirements no longer reflect best practice and guidance issued by authoritative expert bodies in the field, including the Council of Europe or the European Centre for Disease Prevention and Control (ECDC).

The approach in the current legislation is that requirements should be updated in line with technical and scientific progress through the comitology procedure. However, it has proven resource intensive and challenging due to the very rapid and multiple changes in the field in combination with the current rather specific technical requirements. The efficiency assessment shows that the application of many outdated donor selection provisions now imply costs that are not proportionate to the benefits in terms of safety for recipients.

iii) Key oversight principles are not sufficiently robust

One of the main findings of the effectiveness assessment is that several oversight requirements in the BTC legislation are not adequately specified to ensure robust oversight of the BTC sectors. These shortcomings relate to a lack of generic principles that would ensure independence of the competent authorities, from BTC establishments and a lack of provisions for verification of effective implementation of oversight functions in Member States. The shortcomings are common across the BTC sub-sectors.

The shortcomings concern the oversight provisions relating to vigilance, inspections and authorisations. Requirements that emerge as being overly general, leaving room for different interpretations and variable implementation across the EU, resulting in unequal levels of protection for EU donors and patients. For example, inspection and authorisation are carried out differently, and reporting of adverse incidents and alerts is inconsistent, across Member States, limiting the possibilities for aggregation of data and evaluation of risk. Provisions for fixed frequency inspection are also seen as cost inefficient. The lack of common requirements for reporting data on numbers of donations, clinical applications and international exchanges limit the potential for data aggregation for policymaking and sufficiency monitoring. In addition to compromising

the effectiveness of legislative framework, these shortcomings reduce its potential EU added value.

The limited specifications for oversight are particularly relevant in the context of an increased number of commercial actors to be authorised and a high degree of innovation to be authorised, as shown in the assessment of relevance.

iv) Some citizen groups, such as donors and offspring are not adequately protected

Another finding of the effectiveness assessment is that, while the current provisions focus on the safety of transfusion, transplantation and medically assisted reproduction recipients, there are limited provisions to protect the health of other specific groups of citizens, notably BTC donors or offspring of medically assisted reproduction treatments.

There are insufficient measures in place to protect BTC donors, since it is not required to report serious adverse reactions that affect donors unless the quality or safety of the donated substance has been affected, even in cases of donor death. Although many Member States do report donor reactions to the EU level on a voluntary basis, this is not consistently done. Protecting donors is considered key to maintaining high levels of safety and quality of the donated BTC, as well as high levels of public confidence in the system. Donor protection and public confidence are critical to ensure sustained levels of donation, in particular where there is an increase in demand and therefore also in expectations to donate.

Children born from sperm, egg or embryo donation were highlighted, by the medically assisted reproduction sector, to be inadequately protected by the current provisions on safety and quality, compromising overall effectiveness. While there are requirements to protect women from diseases possibly transmitted through donated gametes or embryos, there are no requirements to follow-up on children born from these donations and very limited requirements for testing gamete donors for genetic conditions. This sub-sector is growing rapidly so the shortcomings highlighted are more relevant today than they were in the past.

v) The legislation does not keep pace with innovation

This evaluation has revealed a high level of innovation in the BTC sector over the past 15 years. The evidence suggests that this is likely to continue or increase. New ways to collect, prepare, store and apply BTC to patients can bring significant health benefits, usually in a cost-effective manner that achieves wide patient access. But these developments also need to be enframed by adequate legislation. Increasing commercialisation of some innovations, sometimes with unsubstantiated claims for clinical benefits, can exacerbate the challenge.

The effectiveness assessment pointed to a gap in provisions for authorisation of novel BTC processing methods, including patient follow-up, monitoring of clinical outcome and demonstration of clinical effectiveness, which are now too limited to ensure high quality and effective use of BTC. For example, blood components can be prepared in new ways, without clinical studies to demonstrate equivalent or improved functioning of the component in the recipient. Professionals and some authorities have put more stringent authorisation measures in place, resulting in divergent levels of safety and effectiveness for patients across Member States.

Facilitating innovation also requires legal clarity and good interplay with other legislative frameworks, particularly those regulating medicinal products and medical devices. The coherence assessment has shown that, while most BTC and BTC-based products fall clearly into one or other regulatory framework, there are sometimes difficulties in defining some of the borderlines, particularly for the more novel BTC described in the relevance assessment. Some criteria are interpreted differently and the EU level support mechanisms for classification lack a cross-sectoral forum for classification discussions and advice. This causes some uncertainty for producers and users on the applicable regulatory frameworks in different Member States. Organisations representing blood and tissue establishments reported that this uncertainty can create disincentives to embark on potentially costly innovation.

The coherence assessment also pointed to an increasing number of innovations where medical devices are used at the bedside or in the operating theatre to prepare BTC from a patient for immediate application to the same patient, following a processing step. While the exclusion, from the current legislation, of tissues and cells that are collected and used within the 'same surgical procedure' is important for unprocessed BTC, it limits the effective oversight of some promising autologous BTC therapies where processing is carried out near to the patient.

Many blood and tissue establishments also pointed to insufficient collaboration between authorities responsible for different legal frameworks when BTC become starting materials for medicinal products or medical devices. This concerns the need to define appropriate donor eligibility criteria where BTC are to be used for the manufacture of batches of manufactured products. Effective cross-sectoral communication for vigilance reporting in these circumstances is also seen as important for the facilitation of innovative developments based on BTC as starting materials.

vi) Requirements are insufficient to support sufficiency and a sustainable supply for all BTC

The effectiveness assessment also underlined that the current legislation is limited in provisions that help achieve sufficiency, although one of the objectives for adopting the legislation was indeed to ensure sufficiency and continuity of supply. The relevance assessment shows a rise in commercialisation and internationalisation of some BTC, in particular plasma used to manufacture medicinal products. While the number of private

plasma collection centres in the EU has increased in recent years, this is far from sufficient to keep up with increasing demand for plasma derived medicines. This has led to high dependency on import of plasma from the US.

Crises that might threaten the donation and supply of BTC, such as epidemiological outbreaks, have highlighted the even greater importance of ensuring sufficiency as part of contingency planning for emergencies. The current legislation does not address this topic and there are divergent approaches across Member States. While some Member States have preparedness plans to manage a supply interruption, others do not. This makes intra-Member State collaboration more complex in cases of need, and limits the potential EU added value.

Were possible areas for simplification identified?

This evaluation identified the following areas for possible simplification: the oversight for the blood, tissue and cell sector, the approach to updating of technical requirements, the classification of novel therapies that might also involve other legal frameworks, the reporting requirements for professionals and authorities and inspection frequency.

Will the issues identified resolve or deteriorate over time?

Many of the gaps and shortcomings identified in this process and described in this report have been evident for some years and both professionals and authorities have initiated voluntary collaborative actions to address them, with support from the EU Public Health Programme and collaboration with expert bodies such as ECDC and the Council of Europe.

Trends identified in this evaluation may increasingly challenge access to safe blood, tissue and cell therapies, of high quality, for EU citizens.

Annex I: Procedural information

1. Lead DG/ Planning

The Directorate General for Health and Food Safety (DG SANTE – Unit B4) is the lead DG for this evaluation. (PLAN/2016/154).

2. Organisation and timing

The initiative is a mixed ex-post Evaluation. An Interservice Steering Group (ISSG) was established in October 2016 and met regularly to provide input at key stages of the process. The following services were represented in the ISSG:

- SG (Secretariat-General);
- LS (Legal Service);
- GROW (Internal Market, Industry, Entrepreneurship and SMEs);
- RTD (Research and Innovation);
- JUST (Justice and Home Affairs).

The Roadmap was published on 7 January 2017 and was followed by an Online Public Consultation, which ran from 29 May until 14 September 2017. From the second half of 2017 until the second half of 2018 independent supporting study was undertaken by an external contractor.

3. Exceptions to the better regulation guidelines

None

4. Evidence, sources and quality

This evaluation report is supported by the following sources of evidence:

- Study supporting the evaluation of the EU legislation on Blood and Tissues and Cells (SANTE/2017/B4/010)
- Submissions to the Online Public Consultation and the summary report of these;
- Inputs during the September 2017 Stakeholder Event and the summary report of this event;
- Meetings with key stakeholders and the minutes of these meetings;
- Meetings of the BTC national competent authorities and the minutes of these meetings.

Additional sources and literature used are referenced in the annex to the study listed above.

Annex II: Transmissions of infections to EU patients by blood transfusion, treatment with plasma derived medicinal products and tissues and cells in the 1980 and 1990s.

This Annex provides details on the transmissions and sentinel events that occurred across Europe and raised concerns regarding the safety of BTC.

Blood and plasma derived medicinal products

1. United Kingdom:

Transmission of HIV and Hepatitis to Haemophilia Patients:

In the 1970s and 1980s over 4,500 people with haemophilia and other bleeding disorders were multiply-infected with HIV, Hepatitis B and C and a range of other blood-borne viruses. Over 3,000 people have since died and of the 1,243 people known to be infected with HIV less than 250 are still alive[381].

Factor concentrates, such as Factor VIII for treatment of haemophilia A were, in the 1970's, a revolutionary new treatment allowing patients for the first time to be treated prophylactically, to reduce the likelihood of bleeds and the resulting joint damage. These new treatments, however, were produced using a process, which involved pooling human blood plasma from up to 40,000 donors and concentrating it to extract the required factor. Blood products were known to transfer viruses such as Hepatitis and this risk was vastly increased when they were pooled using the new techniques. This risk was further exacerbated when supplies of UK produced factor concentrates were not sufficient to cope with NHS demand, and products were increasingly imported from the United States. In the US, high-risk paid donors were used, as well as using blood collected in prisons increasing the risk of contamination with blood-borne viruses

An independent inquiry under Lord Archer reported in 2009 and made strong recommendations but as an independent inquiry it was unable to insist on testimonies from key individuals and organisations. In 2008, the Scottish Government set up a public inquiry under Lord Penrose; no culpability was assigned. In 2018, the Langstaff Inquiry was commissioned by the Government and began taking evidence from victims. Its work is currently ongoing[382,383].

Transmission of vCJD:

Variant Creutzfeldt–Jakob disease (vCJD) is a fatal neurological disease, caused by the same agent (abnormal variant of prion protein) as bovine spongioform encephalopathy (BSE or 'mad cow disease') in cattle and caused by eating beef from affected animals. It

[381] Putting an end to the sequelae of contaminated blood transfusions. The Lancet Haematology. Volume 5, Issue 6, PE232, June 2018. , June 01, 2018Pe232, June 01, 2018.
[382] https://www.bbc.com/news/health-45591584.
[383] https://haemophilia.org.uk.

was first identified in the UK in 1996. By the end of 2012 there had been 174 cases in the UK, peaking in 2000.

Four cases of transfusion-transmitted vCJD infection have been identified to date, from three apparently healthy donors who later developed vCJD. All occurred with non-leucodepleted red cells donated before 1999. Three of the four recipients died of vCJD a few years after the implicated transfusion. The fourth recipient died of unrelated causes but had abnormal prion protein in the spleen at post-mortem examination (significance uncertain). There are still many uncertainties around the pathogenesis and epidemiology of vCJD and no practical screening test for blood donors has yet been developed. The vCJD risk-reduction measures introduced in the UK include importation of plasma for fractionated blood products (1998), leucodepletion of all blood components (1999), importation (and viral inactivation) of fresh frozen plasma for all patients born on or after 1 January 1996 (when dietary transmission of vCJD is assumed to have ceased) (2002), exclusion of blood donors who have received a blood transfusion in the UK since 1980 (2004) and importation of solvent detergent plasma for adult patients undergoing plasma exchange for thrombotic thrombocytopenic purpura (2006).

Countries outside the UK, including the USA, Canada, New Zealand, Australia, Hong Kong and several European countries including Germany, Switzerland, Austria and Eire have taken the precautionary step of excluding blood donors who have spent more than a defined period living in the UK between 1980 and 1996 in order to avoid the risk of vCJD entering the blood transfusion chain.

2. Ireland

Hepatitis C Infection of Women who received Anti-D Immunoglobulin

Anti-D immunoglobulin, a product made from donated blood, was given to new mothers whose own blood type was Rhesus Negative but who gave birth to Rhesus Positive babies. It was administered to safeguard the health of future babies the woman might have as some of the Rhesus Positive could have passed through the placenta into her bloodstream and she would have developed antibodies to it. Those antibodies, left in her system, could seriously damage or kill the foetus in a future pregnancy.

In the 1960s, around 40 babies a year died in this way so the development of the anti-D treatment was considered a welcome breakthrough and its use became normal practice in maternity hospitals in the 1970s.

In 1994 the Blood Transfusion Service Board (BTSB) became aware of the contamination of two batches of Anti-D from two separate donors, one in 1977 and the other in 1992. It was thought that Anti-D from these batches had been administered to over 1000 women. The Finlay Tribunal of Inquiry was set up in 1996 and concluded the contamination of the anti-D batches could have been prevented. The Hepatitis-C

Compensation Tribunal, set up on a transitional basis in 1995, was formally established in 1997 as a result of the findings[384].

On foot of the tribunal report, a criminal investigation began into the BTSB. Three senior employees were arrested in 2003 and two were charged with causing grievous bodily harm to Anti-D recipients, but one died before his case could come to court and the other, who instigated lengthy legal challenges to her arrest, finally had all charges against her withdrawn in 2009 due to the death of witnesses.

The Hepatitis-C Compensation Tribunal paid out around €310m in 1,539 awards to women, their spouses, and children in its first seven years. In total it has paid out almost €1bn in awards and legal costs associated with more than 4,500 claims. There are still around 800 claims to be dealt with and further transmission could yet be confirmed[385].

Infection of Haemophiliac Patients with HIV and Hepatitis C from Blood Products:

In May 2000, the Lindsay Tribunal of Inquiry was established to investigate the infection of an estimated 252 haemophiliacs with HIV and/or hepatitis C from contaminated blood products. At the time the tribunal began its work, seventy-eight haemophiliacs had died from illnesses related to their infection. It emerged that 104 individuals had been infected with HIV prior to 1985. These patients had received contaminated Factor IX (produced nationally by the Blood Transfusion Service) and commercial (non-heat treated) batches of Factor VIII. Factor IX product was prepared from donations prepared before the introduction of routine HIV antibody testing. The commercial product (Factor VIII) was purchased from the USA and was prepared from paid blood donors in the USA where there was a much higher risk of HIV/AIDs at the time. In addition, these products were not heat treated, a process which was known at the time to inactivate such viruses. The Inquiry was critical of the decision making process undertaken by Clinicians and Senior Scientific Staff at the BTSB in relation to the production, purchasing and continued use of these products despite the emerging knowledge of HIV/Aids infection in the Haemophiliac Community in the 1980s. A Compensation Court was also established as a result of the findings of this Inquiry and it is estimated that over €1bn has been awarded to date as a result of state failings regarding the safety of blood and blood products[386],[387].

3. Romania

HIV Infection of Children from 'unscreened and untested' blood microinfusions

In 1989, a dramatic epidemic of nosocomial HIV infection was discovered predominantly among orphans and hospitalized children in Romania, infected through transfusions of unscreened blood (micro infusions of unscreened and untested blood administered to counteract malnourishment and anaemia) and injections with improperly

[384] The Finlay Report.
[385] https://www.irishexaminer.com/viewpoints/analysis/anti-d-scandal-was-a-bloody-disgrace-259488.html.
[386] Report of the Tribunal of Inquiry into the Infection with HIV and Hepatitis C of Persons with Haemophilia and Related Matters..
[387] https://www.irishtimes.com/news/health/victim-of-contaminated-blood-products-was-awarded-2-96m-1.3251084.

sterilized equipment. 94% of initial cases identified were in children under the age of 1[388].

A combination of factors, from failure of screening blood to lack of communication about the risks to physicians and citizens – caused HIV to spread rapidly among children, resulting in an unprecedented epidemic. By the year 2000, 60% of Europe's pediatric HIV/AIDS cases were registered in Romania, mostly in infants living in public institutions. In mid-2002, 12,559 cases of HIV were registered in Romania (9936 in children), of which 2699 were already deceased. From 2002 onwards, with the assistance of the WHO, a number of government programmes were established to help tackle this epidemic by preventing the spread of further infection and also by providing appropriate treatment to those children already infected.

4. France

HIV Infection by blood transfusion and treatment with plasma derived medicinal products.

In total, it is estimated that approximately 4000 individuals in France may have been infected with HIV during a period of time between the late 1970s and early 1980s. Of these, some 1,250 haemophiliacs are believed to have been infected. Of these, 400 have died.

Errors identified included the collection of blood in prisons and in public places frequented by drug addicts; the neglect of a memorandum on how to prevent contamination by blood transfusion, for more than a year and delays in the decision to treat blood by heating. It was inferred that the French Government did not introduce routine screening for HIV in a timely manner and delayed the commercial availability of a blood test used in the United States in favour one being developed in France.

As a result of these events, a former Prime Minister, a former Social Affairs Minister, and a former Secretary of State for Health were brought before the Court of Justice, a special tribunal created in 1993 in France to judge members of the government for crimes or misdeeds allegedly committed during the performance of their duties[389]. They were required to answer to charges of involuntary homicide and involuntarily compromising the well-being of others. The Prime Minister and Social Affairs Minister were acquitted but the former Health Minister was convicted for his role in the contamination. In addition, in 1993, the former Head of the National Blood Bank was sentenced to four years in prison, and the Head of the Blood Transfusion Research Bureau was jailed for two years. Two others were given suspended sentences[390.]

Tissues and Cells

[388] Dente K, Hess J. Pediatric AIDS in Romania--a country faces its epidemic and serves as a model of success. MedGenMed. 2006; 8(2):11. Published 2006 Apr 6.
[388] Popovici F. et al. Acquired Immunodeficiency in Romania. The Lancet. Volume 338, ISSUE 8768, P645-649, September 14, 1991.
[389] Ex-Ministers to face trial in French Blood Scandal BMJ. 1998 Aug 1; 317(7154): 302.
[390] Scandal Over Tainted Blood Widens in France.

While tissue and cell transplantation has not been associated with the large scale transmission of infectious diseases that has occurred in the transfusion of blood components and the administration of blood derived medicinal products, viral, bacterial, and fungal infections have been transmitted via transplantation of tissue allografts such as bone, skin, cornea, and heart valves, and cells such as islets, hematopoietic stem cells, and semen[391]. Single donors may provide allografts for >100 organ and tissue recipients; each allograft carries some, largely unquantifiable, risk of disease transmission which highlights the need for tight quality and safety criteria such as appropriate donor screening and testing[392]The following are a number of key case studies reported in literature and in the media concerning the transmission of infectious diseases as a result of tissue and cell transplantation.

Case Study 1: HIV Transmission by Bone in Germany[393].

In 1997 it was reported that a leading transplantation centre in Germany was ordered to pay compensation to a 58 year old man who developed AIDS after receiving a bone graft from a donor who was a drug misuser. In January 1985 the man, who had a clavicle fracture, received a transplanted lyophilised bone chip from a donor who was a drug misuser, and who had died from drug overdosage. The donor was not tested for HIV. At the time there were only around 150 cases of AIDS in Germany. At least two more patients, out of 12 who received bone transplants from the same donor, later died from AIDS. The Superior Court of Hanover decided there was no doubt that the plaintiff had been infected with HIV via the bone graft. Although the judges conceded that in 1985 it was not known that viral diseases could be transmitted by lyophilised bone grafts, the court insisted that the donor's drug addiction should have been a warning signal to doctors.

Case Study 2: Transmission of HIV-1 from a sero-negative Organ and Tissue Donor in the USA[394].

In 1991, a woman whose only risk factor for HIV-1 infection was the receipt of a bone allograft in December 1985 was identified by the health department in her state as being infected. Subsequent investigation revealed that the donor was a 22-year-old HIV-1—seronegative man who died after being shot in the head in October 1985, that 4 solid organs and 54 other tissues had been distributed from the donor, and that a total of seven of the recipients (4 solid organ recipients and 3 fresh frozen bone recipients) were infected with HIV-1.

Case Study 3: Transmission of hepatitis C virus to several organ and tissue recipients from an antibody-negative donor in the USA[395].

[391] Eastlund T. 1995. Infectious disease transmission through cell, tissue, and organ transplantation: reducing the risk through donor selection. Cell Transplant Sep-Oct;4(5):455-77.
[392] Fishman JA, Greenwald MA, Grossi PA. 2012. Transmission of infection with human allografts: essential considerations in donor screening. Clin Dis Infect Sep; 55(5):720-7.
[393] Karcher HL. HIV transmitted by bone graft. BMJ. 1997; 314(7090):1300.
[394] Simonds RJ et al. 1992 Transmission of Human Immunodeficiency Virus Type 1 from a Seronegative Organ and Tissue Donor. N Engl J Med 1992; 326:726-732.

In 2002, hepatitis C virus (HCV) transmission through tissue transplantation had been rarely reported, however it was possible that a donor with undetected viremia may infect several recipients. In June 2002, in the US, a patient developed acute symptomatic Hepatitis C shortly after transplantation of a patellar tendon with bone allograft. The donor had died in 2000 and his premortem serum had tested negative for anti-HCV (2nd Generation ELISA test). Ninety-one tissues or organs had been recovered from the donor. The donor was anti-HCV-negative but was HCV RNA-positive (genotype 1a). Forty persons received transplants from this donor during a 22 month period. Five persons were HCV-infected before transplantation or had a genotype other than 1a, and 5 persons had no post-transplantation serum specimens available. Of the remaining 30 recipients, HCV infection occurred in 8 recipients: 3 of 3 organ recipients, 1 of 2 saphenous vein recipients, 1 of 3 tendon recipients, and 3 of 3 tendon with bone recipients. These 8 recipients had viral isolates genetically related to those of the donor. No cases occurred in recipients of skin (n = 2), cornea (n = 1), or irradiated bone (n = 16).

Comment: In this instance as with the previous case, it was likely that both donors were in the 'window period' of infection before the development of detectable antibodies to HIV and HCV. Cases such as these demonstrate not only the possibility of the spread of infection to numerous recipients from a single donor but also of the need to ensure that appropriate testing protocols using the most up to date (but validated) test methods are implemented for both organ and tissue donors.

Case Study 4: Creutzfeldt-Jakob Disease associated with Dura Mater Graft processed in Germany and transplanted in Japan[396].

During 1975–2008, a total of 132 cases of dura mater graft-associated Creutzfeldt-Jakob disease (dCJD), a fatal neurodegenerative disease caused by replicating, transmissible prion proteins, had been identified in Japan and accounted for >60% of patients worldwide with dCJD. This relatively high number of cases was most likely related to the increased use in Japan of the primary vehicle of transmission, Lyodura brand cadaveric dura mater grafts produced before May 1987 (After May 1987, the manufacturer changed its production process to reduce the risk for prion transmission). It had been identified that the manufacturer had previously mixed dura from multiple donors during batch processing of single lots and sterilized the grafts with gamma irradiation, a procedure that does not inactivate prions. It was also reported that the company did not maintain records identifying donors, so they could not be traced. It is estimated that 20,000 persons received a Lyodura graft each year during 1983–1987 in Japan. During 2008–2017, an additional 22 dCJD patients, with onset from 1985 through 2016, were identified in Japan, resulting in 154 dCJD patients in Japan. No new dCJD patient whose surgery occurred after 1993 has been identified. However, the latency

[395] Tugwell BD et al. 2005. Transmission of Hepatitis C Virus to Several Organ and Tissue Recipients from an Antibody-Negative Donor. Ann Intern Med;143:648–654.
[396] Ae R, Hamaguchi T, Nakamura Y, et al. Update: Dura Mater Graft-Associated Creutzfeldt-Jakob Disease - Japan, 1975-2017. MMWR Morb Mortal Wkly Rep. 2018;67(9):274–278. Published 2018 Mar 9.

period is now known to be at least 30 years and because of the known potential for even longer latency periods for prion diseases, this outbreak is likely to continue.

Data from the WHO Notify Library of adverse occurrences with Medical Products of Human Origin

The Notify Library is a joint global initiative, co-sponsored by the World Health Organization (WHO) and the Italian National Transplant Centre (CNT) as its Collaborating Centre that supports the sharing of published vigilance information for teaching purposes and for greater public transparency on the use of MPHO. The library aims to be comprehensive, describing all types of reactions or events that might have teaching value and assist in the estimation of risk in relation to what is known as MPHO's (Medicinal Products of Human Origin) including blood for transfusion and tissues and cells for transplantation[397].

The Notify Library is a publically accessible database of adverse outcomes collected and analysed by dedicated editorial groups of international experts, regulators and clinicians. The database is not a vigilance reporting programme but a collection and review of information identified primarily by literature review (published articles in scientific journals and/or books) although case reports from regulatory or professional vigilance programmes (grey literature) are also considered for inclusion. For each adverse occurrence type, at least one reference source is cited and the project's collaborating international experts provide a structured analysis.

A review of the records relating to viral infection of recipients of human tissues and cells for transplantation in this database revealed the following number of references. Note: These numbers to not relate to number of recipients but to the number of records contained within the Notify Library (which is not exhaustive) and some records refer to multiple recipients.

Replacement Tissues:

	Musculoskeletal	Skin	Cardiovascular Tissue	Ocular	Nerve
HIV	6	1	-	-	-
Hep B	1	-	1	2	-
Hep C	3	-	2	-	-
HTLV	1	-	-	-	-
CMV	-	3	-	2	-
Rabies	-	-	2	2	-

[397] www.notifylibrary.org.

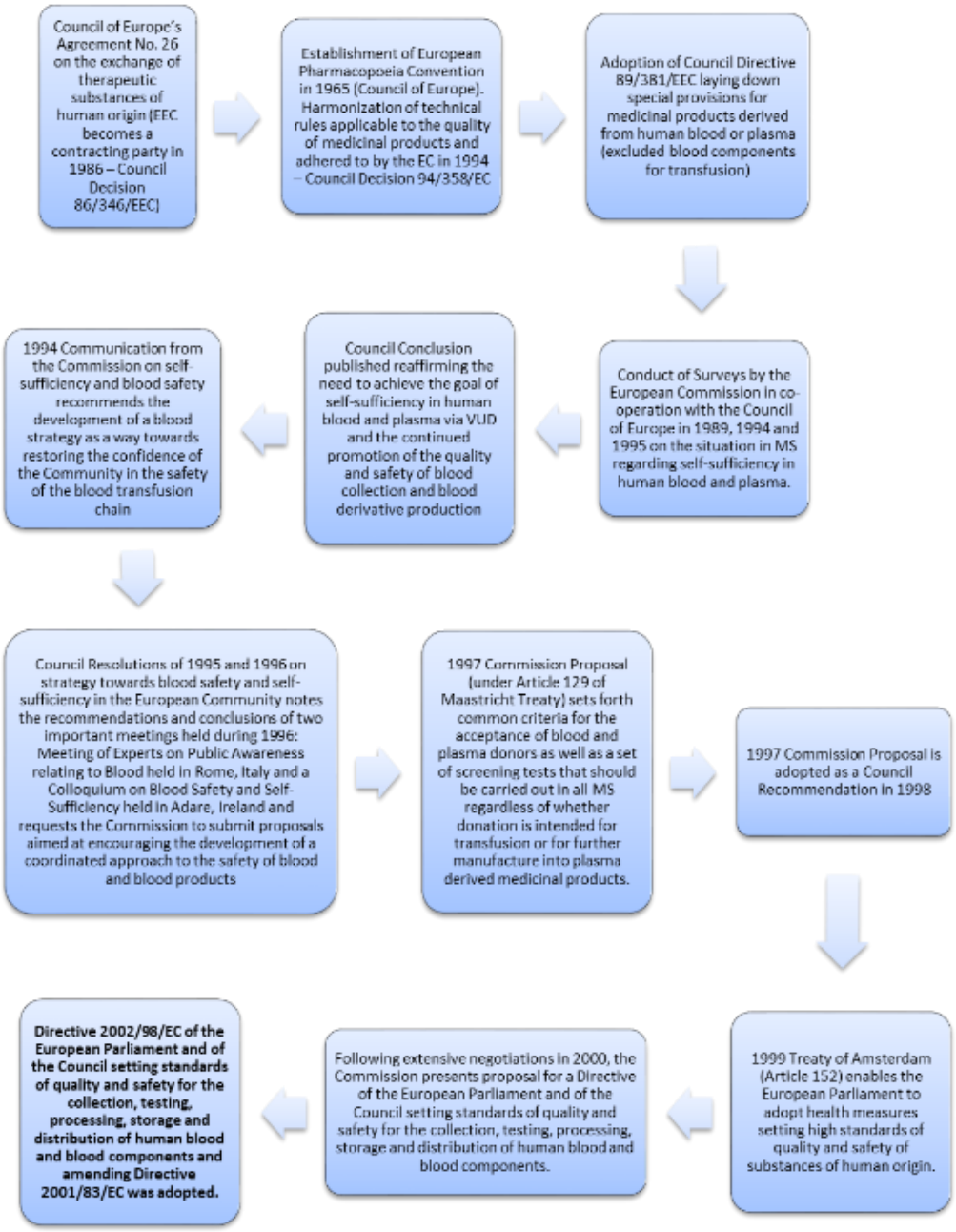
HSV	-	-	-	1	-
EBV	-	-	-	-	1

Cells:

	Haemopoietic Stem Cells	Pancreatic Islets	Reproductive Cells
HIV	1	-	2
Hep B	1	-	2
Hep C	-	-	-
HTLV	1	-	-
CMV	4	1	-
Parvovirus	3	-	-
Dengue	2	-	-
EBV	4	-	-

Annex III: The Background to the Regulation of Blood and Blood Components in Europe

The adoption of the basic Act on blood and blood components in 2002 was preceded during the previous decades by a series of initiatives and reports at European level. These are summarised in the figure below and described in the subsequent text.



In 1958, the Council of Europe's Agreement No. 26[1] on the exchange of therapeutic substances of human origin became the starting point for cross-border activities in this field. Its main purpose was to facilitate exchanges of human blood and its derivatives between Member States of the Council of Europe in cases of urgent need and under the expressed condition that no profit was made. In 1986, the European Community became a contracting party to this agreement as outlined in Council Decision 86/346/EEC[2].

Part 2 of the Council of Europe's Agreement No. 26 outlined special provisions (basic quality and safety criteria) for the collection and preparation of whole human blood, human red cell concentrate, dried human plasma and derivatives such as human albumin, human plasma protein fraction, human immunoglobulin, specific immunoglobulins, fibrinogen, coagulation factor VIII and coagulation factor IX.

A further significant step in this field was the establishment of the European Pharmacopoeia Convention, which was signed in 1964 under the aegis of the Council of Europe. It aimed to harmonise the official technical rules applicable to the quality of medicinal products and substances, including blood, and was adhered to by the European Community in June 1994 as outlined in Council Decision 94/358/EC[3].

The European Community had, in 1965, included human blood in the definition of medicinal products (Council Directive 65/65/EEC[4]). In the late 1970's and through the 1980's, the reports of blood contaminated with HIV were undermining the public's confidence in the blood supply and public health efforts were ongoing in trying to prevent the transmission by blood and other substances of human origin of infectious agents. This led to the adoption of Council Directive 89/381/EEC[5], which laid down special provisions for medicinal products derived from human blood or plasma. This Directive included the concept of Community self-sufficiency in human blood and plasma through the encouragement of voluntary, non-remunerated donations when intended to be used for the production of plasma derived medicinal products but still excluded in its scope blood, plasma and blood cells when used for transfusion.

In 1989, the Commission in cooperation with the Council of Europe undertook a survey[6] about the situation in the MS regarding self-sufficiency in human blood and plasma. This was followed by two additional surveys in 1994[7] and 1995[8]. The Commission's resulting report[9] to the Council on the state of Community self-sufficiency resulted in the Council adopting conclusions[10] in which the need to achieve the goal of Community self- sufficiency in human blood and plasma via voluntary unpaid donations through co-operation between Member States was reaffirmed and the continued promotion of the quality and safety of blood collection and blood-derivative production was inter alia agreed.

The Council's continuing concern about the quality, safety and efficacy of blood and blood products resulted in it requesting, at its meeting of 13 December 1993, the Commission to prepare a report related to the legal provisions and current practices in the Member States on the collection, control, and treatment of blood and the distribution and trade in blood and blood

products with a view to proposing common safety criteria. Immediately following this meeting, the Commission invited Member States to provide their legal regulations and administrative provisions in this area[11].

The 1994 Communication from the Commission on blood safety and self-sufficiency[11] was an important report, which drew upon the responses provided by the Member States in written submissions and during meetings of experts on self-sufficiency and blood safety convened by the Commission. It addressed issues raised by the Ministers for Health, and provided, as a background, a review of progress towards blood self-sufficiency in the Community as well as coverage of this area by existing Community rules and regulations. It specified the need for Community action in this area particularly in the context of the Council's Resolution concerning the field of public health and the Commission Communication on AIDS and certain other communicable diseases. It recommended the development of a blood strategy as a way towards restoring the confidence of Community citizens in the safety of the blood transfusion chain and fostering the goal of self-sufficiency.

Council Resolution of June 1995 on blood safety and self-sufficiency in the community[12] agreed on the need to define a strategy for reinforcing trust in the safety of the blood-transfusion chain and promoting self-sufficiency in the Community and outlined a number of potential activities for the Commission to continue collaboration on at Member State level. These activities included the development of policies and agreed procedures in the donor-selection process among blood-collection establishments, the implementation of efficient, validated and reliable screening tests, the development and use of quality-assessment criteria and good practices regarding the collection, processing and transfusion of blood and blood products and patient follow-up procedures, development of a haemovigilance system on the basis of existing networks for the collection of epidemiological data related to the blood-transfusion chain, encouragement of health professionals to make optimal use of blood and blood products, the establishment of basic criteria for inspection and training of inspectors, and the dissemination to the public of information on blood and blood products and on collection, processing and transfusion procedures, taking into account socio-cultural differences.

Council Resolution of November 1996 on a strategy towards blood safety and self-sufficiency in the European Community[13] took note of the conclusions and recommendations agreed at two important meetings held during 2006; the first a meeting of experts on public awareness relating to blood held in Rome in April and the second, a colloquium on blood safety and self-sufficiency held at Adare, Ireland, in September. In particular, it agreed that the conclusions and recommendations of the Adare colloquium provide for concrete steps in order to realise the strategy called for in previous resolutions towards promoting blood safety, in particular to reinforce trust and confidence in the safety of the blood-transfusion chain, and towards promoting self-sufficiency in the Community.

The Council requested that steps be taken to ensure that rapid progress is made in taking forward this work and accordingly invited the Member States to review their policies, procedures and

programmes aimed at ensuring the safety of the blood-transfusion chain and invited the Commission to submit proposals as a matter of urgency in support of the actions of the Member States, with a view to encouraging the development of a coordinated approach to the safety of blood and blood products.

In 1997, the Commission took at major step forward when it published its first proposal[14] under Article 129 (Paragraph 4a and 5) of the Maastricht Treaty setting forth common criteria for the acceptance of blood plasma donors as well as a set of screening tests that should be carried out in all Member States, whether the donation was intended for transfusion or for further manufacturing into plasma derived products. This proposal was subsequently adopted as a Council Recommendation[15] in 1998.

In 1999, Article 152 of the Amsterdam Treaty enabled the European Parliament and Council to adopt health measures setting high standards of quality and safety of substances of human origin without preventing Member States from introducing more stringent measures.

The Commission presented its proposal[16] for a Directive of the European Parliament and of the Council setting standards of quality and safety for the collection, testing, processing, storage, and distribution of human blood and blood components and amending Council Directive 89/381/EEC in May 2001 following extensive consultations with all stakeholders during 2000.

Following negotiations between with European Parliament, the Council and the Commission in 2002, Directive 2002/98/EC of the European Community and of the Council on setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC[17] was finally adopted and Member States were required to have transposed its provisions into their national law by the 8th February 2005.

Three further 'Implementing Directives' were adopted in 2004 and 2005. These had been delegated to the Commission via the 'comitology procedure'. The first implementing Commission Directive 2004/33/EC of 22nd March 2004 concerned certain technical requirements for blood and blood components[18]. The second implementing Commission Directive 2005/61/EC of 30th September 2005 contained traceability requirements and requirements for the notification of serious adverse reactions and events[19] and the subject of the third implementing Commission Directive 2005/62/EC of 30th September 2005 was Community standards and specifications relating to a quality system for blood establishments[20].

References for Annex III:

1. Council of Europe Agreement No. 26 on the Exchange of Therapeutic Substances of Human Origin.
2. Council Decision 86/346/EEC accepting, on behalf of the Community, the European Agreement on the Exchange of Therapeutic Substances of Human Origin.

3. Council Decision 94/358/EC accepting, on behalf of the European Community, the Convention on the elaboration of a European Pharmacopoeia.
4. Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products.
5. Council Directive 89/381/EEC laying down special provisions for medicinal products derived from human blood or plasma. OJ L181 of 28.06.1989, p44.
6. Van Aken, W.G. Collection and use of human blood and plasma in Europe. Council of Europe Press, 1993, p31.
7. Van Aken, W.G. The collection and use of human blood and plasma in the European Community in 1991. CEC/LUX/V/F/1/59/94. July 1994, p39.
8. Delaney, F.M. The collection and use of blood and plasma in the European Community in 1993. CEC/LUX/V/F/1/33/95. November 1995, p43.
9. Communication from the Commission to the Council, the European Parliament and the Economic and Social Committee on Blood Self-Sufficiency in the European Community. (COM93) 198 final. Brussels, 25 May 1993. P13.
10. Council conclusions of 13 December 1993 on self- sufficiency in blood in the European Community OJ C 15, 18.1.1994, p. 6–6.
11. Communication from the Commission on blood safety and self-sufficiency 21st December 1994 COM (94) 652 final.
12. Council Resolution of 2 June 1995 on blood safety and self-sufficiency in the Community Official Journal C 164 , 30/06/1995 P. 0001 – 0001.
13. Council Resolution of 12 November 1996 on a strategy towards blood safety and self-sufficiency in the European Community Official Journal C 374 , 11/12/1996 P. 0001 – 0001.
14. Commission Proposal for a Council Recommendation on the suitability of blood and plasma donors and the screening of donated blood in the European Community. COM (97) final of 17.11.1997.
15. Council Recommendation 98/463/EC, OJ L 203 of 21.07.1998, p14.
16. Proposal for a Directive of the European Parliament and of the Council setting standards of quality and safety for the collection, testing, processing, storage, and distribution of human blood and blood components and amending Council Directive 89/381/EEC (2001/C 154 E/14)
COM (2000) 816 final 2000/0323(COD).
17. 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.
18. 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.
19. 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.

20. 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.

Annex IV: The Legal Basis and the Legal Framework adopted

Primary Legislation

Healthcare governance within the EU is predominantly a competence of the individual Member States. Although the principle of subsidiarity embodies that when possible and reasonable, decision-making power stays with the Member States, the European Union does have a mandate and obligation in the policy domain of public health. This mandate is provided in EU primary legislation through Article 168 TFEU, as amended in 1999 by the Amsterdam treaty. This article specifically provided a legal basis for legislating in these sectors in its paragraph 4:

> *'By way of derogation from Article 2(5) and Article 6(a) and in accordance with Article 4(2)(k) the European Parliament and the Council, acting in accordance with the ordinary legislative procedure and after consulting the Economic and Social Committee and the Committee of the Regions, shall contribute to the achievement of the objectives referred to in this Article through adopting in order to meet common safety concerns:*
>
> *(a) measures setting high standards of quality and safety of organs and substances of human origin, blood and blood derivatives; these measures shall not prevent any Member State from maintaining or introducing more stringent protective measures;'*

Secondary legislation

The EU legislation for blood and tissues and cells was proposed, negotiated and adopted with two basic Acts, Directive 2002/98/EC[398] for blood and Directive 2004/23/EC[399] for tissues and cells. Each of these Directives defines a scope that covers a major portion of the substances of human origin that are used for application to patients.

Scope

Directive 2002/98/EC applies to the collection and testing of human blood and blood components, whatever their intended purpose, and to their processing, storage and distribution when intended for transfusion. This scope excludes the processing, storage

[398] 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 (OJ L 33, 8.2.2003, p.30).

[399] 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. (OJ L 102, 7.4.2004, p. 48).

and distribution of blood or blood components used for the manufacturing of medicinal products or medical devices or for application to humans in procedures other than transfusion (e.g. serum used as drops in the eye, platelet-rich plasma used in orthopaedic surgery). Blood stem cells (haematopoietic stem cells), even if collected from whole blood, are explicitly excluded. In general, the provisions apply to the activities of 'blood establishments', and their oversight, up to the point of distribution to hospital blood banks or to manufacturers of medicinal products or devices. However, some articles are listed as being applicable also to hospital blood banks that store and issue units of blood (components) to patients and may do some compatibility testing; inspection and authorisation obligations do not extend to hospital blood banks. There are provisions, however, that require traceability to the recipient and haemovigilance reporting after transfusion.

Directive 2004/23/EC applies to the donation, procurement and testing of human tissues and cells intended for human application or for manufacturing of products derived from human tissues and cells but covered by other directives. Where the tissues or cells are intended for human application, the Directive also applies to processing, preservation, storage and distribution. Recital (7) confirms that haematopoietic stem cells from any source, as well as foetal tissues or cells, gametes and embryonic stem cells are also within the scope. Recital (10) notes that the scope also covers human tissues or cells used in the manufacture of cosmetic products, noting however, that such use was prohibited by other current legislation. Human application covers procedures of transplantation and medically assisted reproduction. The scope is further clarified by the definition of human tissues and cells that, in effect, excludes other substances of human origin, such as breast milk or faecal microbiota.

The Directive specifically excludes blood and blood components as well as tissues and cells used as an autologous graft within the same surgical procedure. The latter intended to avoid the regulation of surgical procedures where a piece of tissue (e.g. bone or muscle) is moved from one part of the body to another (e.g., during reconstructive surgery). Organs or parts of organs to be used for the same function as the entire organ are also excluded. The use of tissues and cells for research that does not include clinical application, i.e. *in vitro* or animal research is excluded from the scope. In line with the blood Directive, the provisions cover the process from donation to distribution for clinical application, but not the steps carried out in the facility where the tissues or cells are applied to patients, although here too, traceability to the recipients and adverse outcome reporting after clinical application are required.

Key provisions

The two basic Acts provide the framework for the oversight of these sectors, defining obligations for competent authorities in Member States and for the European Commission. Member State competent authorities are required to inspect and authorise blood and tissue establishments and to organise programmes of vigilance reporting in relation to serious adverse reactions (where a donor or patient has been harmed) and serious adverse events (where an incident posed a risk of harm to a donor or a patient).

The authorities must ensure that imported BTC from third countries are equivalent in terms of quality and safety to those provided under EU legislation. They must submit annual summary reports of serious adverse reactions and events to the European Commission and must communicate with each other when adverse occurrences imply the need for corrective or preventive action in more than one Member State. There are also obligation on Member States to submit reports to the European Commission on the implementation of the legislation and of the measures taken to encourage VUD, at intervals defined in the Directives. Further generic provisions oblige the Member States to put penalties in place for non-compliance and to ensure appropriate data protection.

The European Commission has obligations under these basic Acts to submit the Member State reports on implementation to the Parliament, the Council, the Economic and Social Committee and the Committee of the Regions and to inform the European Parliament and the Council of any necessary further measure it intends to take at Community level in relation to VUD. The European Commission is also required to hold regular meetings with the competent authorities of the Member States.

Apart from these general oversight provisions, both of the basic Acts also include a number of technical requirements for ensuring quality and safety at the blood establishment and tissue establishment level. For example, the blood Directive includes annexes defining the information to be provided to prospective donors, the elements to be included in annual activity reports, the labelling requirements for blood components and the minimum infectious disease and blood group testing requirements for donors.

Tertiary legislation

Most of the technical requirements for blood and tissue establishments are described in implementing Directives. The basic Act on blood was complemented by three implementing Directives[400].

Commission Directive 2004/33/EC as regards technical requirements for blood and blood components includes detailed provisions on donor eligibility, storage and transport conditions and specifications for the quality control criteria to be applied for each type of blood component that was in use at the time. Some limited technical amendments have since been made to Directive 2004/33/EC[401].

Commission Directive 2005/61/EC as regards traceability requirements and notification of serious adverse reactions and events focuses on providing more detailed requirements for traceability, vigilance reporting and import from third countries.

[400] Directives 2004/33/EC as amended, 2005/61/EC, 2005/62/EC, 2006/17/EC as amended, 2006/86/EC as amended and Directive (EU) 2015/566.
[401] Directive 2009/135/EC, Directive 2011/38/EU, Directive 2014/110/EU.

Commission Directive 2005/62/EC as regards Community standards and specifications relating to a quality system for blood establishments focuses on the requirements for quality management and was amended by Directive 2016/1214[402] to oblige Member States to take into account the Good Practice Guidelines jointly developed by the Commission and the European Directorate for the Quality of Medicines and Healthcare of the Council of Europe and published by the Council of Europe[403] when providing the required good practice guidelines to their blood establishments.

The basic act on tissues and cells was also complemented by three implementing technical Directives.

Commission Directive 2006/17/EC as regards technical requirements for donation, procurement and testing focuses on donor eligibility and testing. Some limited technical amendments have since been made to this Directive[404].

Commission Directive 2006/86/EC as regards traceability requirements, notification of serious adverse reactions and events and technical requirements for coding, processing, preservation, storage and distribution provides the criteria for the authorisation of tissue establishments and tissue and cell preparation processes. This directive was amended to include provisions for the Single European Code, to be applied to tissues and cells[405].

A third Commission Directive, *(EU) 2015/566 regarding the procedures for verifying the equivalent standards of quality and safety of imported tissues and cells* was adopted more recently. A Commission Decision on conditions of inspections was also adopted[406], along with a Commission Decision on agreements with tissue and cell coding organisations[407].

[402] Directive (EU) 2016/1214.
[403] Good Practice Guidelines, included in the Guide to the preparation, use and quality assurance of blood components, Appendix to Recommendation No. R (95) 15 of the Committee of Minsters on the preparation, use and quality assurance of blood components adopted on 12 October 1995.
[404] Directive 2012/39/EU.
[405] Commission Directive 2016/565.
[406] Commission Decision 2010/453/EU.
[407] Commission Decision 2015/4460.

Annex V: Baseline

Part A - Blood and Blood components for transfusion

For this evaluation, a number of key documents have provided information on the baseline prior to the adoption of the BTC legislation. The key documents and the most significant points highlighted in them are summarised in this Annex

1. Key Document: Communication from the Commission on blood safety and self-sufficiency in the European Community 1994.
Background: At its meeting of 13 December 1993, the European Council requested the European Commission to prepare a report related to the legal provisions and current practices in the Member States on the collection, control, and treatment of blood and the distribution and trade in blood and blood products with a view to proposing common safety criteria. The Commission invited Member States to provide their legal regulations and administrative provisions in this area. While the results of these activities were not directly made available, the Communication from the Commission in 1994 draws upon the responses provided by the Member States in written submissions and during meetings of experts on self-sufficiency and blood safety convened by the Commission and provides an insight into the status of blood safety, quality and sufficiency at this time and makes note of the future activities required for improvement in this area.
Key Observations: • It was noted that regulations and practices related to donor recruitment and voluntary non-remunerated donations in the Member States varied widely from explicit legislation, to general health regulations but with no precise reference to remuneration, or no specific stipulations. A few Member States stated that in their legislation non-compliance with the principle of voluntary non-remunerated donations could result in legal action. • In the Member States at this time, donors were generally voluntary and under no pressure to donate. Some strictly prohibited directed donations by family or friends or where the donor and recipient know each other. In situations where blood shortages exist, however, friends and family members of patients in a few Member States may be asked to donate. In those that were not self-sufficient, physicians could make treatment conditional on the availability of blood, which sometimes put pressure on the patient as well as on his/her relatives to donate. • It was evident, at the time, that the interpretation of the concept of non-remuneration was not uniform throughout the Community. Incentives to encourage blood and plasma donations did take place including time off work beyond that actually required for the donation and flat rate "expense allowances" were allowed in many MS. • The donor selection process, also differed across the Community. Whether the donation was for whole

blood or plasmapheresis plasma, it was noted that variations existed in the frequency of the clinical examination, ranging from a medical examination at every donation to none routinely required; in the person who conducted the donor interview who varied from a physician to a trained staff member of the collection centre; and in the information programmes for both donors and the general public. The process, however, generally included the administration of a questionnaire, which again differed both within and across Member States.

- It was noted that it would be beneficial if an agreement was reached as regards the rules and practices for donor selection, including for first time and repeat donors as well as donors of whole blood, cellular components and plasma which could be applied across the Community.

- Directive 89/381/EEC required that testing of blood and plasma when used as starting materials for blood derived medicinal products shall comply with the recommendations of the Council of Europe, the WHO and the European Pharmacopoeia. However, as this Directive did not apply to whole blood, to plasma or to blood cells of human origin, divergences existed within the Community regarding the testing requirements for blood and plasma donations.

- It was noted that some Member States did not differentiate at the collection stage between blood for transfusion and blood that is destined or may be used for fractionation; others do. As a consequence, testing requirements that may be compulsory in one Member State for blood and plasma for fractionation may not be in another. Concern was raised that this was hindering the free movement of blood and blood products and are therefore an impediment to the goal of Community self-sufficiency.

- At this time, there were preliminary indications that the regulatory controls regarding licencing and accreditation of blood collection establishments differed widely across the Member States. Many had no licencing requirements for the collection of blood or plasma; no standard requirements for collection centres across the country; no routine and/or unannounced inspections by national authorities nor peer inspections, and differing time periods for licence renewals.

- In one Member State, the extraction of blood and blood components for transfusion as well as the extraction of plasma for fractionation constituted the manufacture of medicinal products, for which a licence was required. In others, this interpretation did not apply.

- It was noted that serious consideration needed to be given to harmonising the licensing and accreditation of blood collection, processing and distribution establishments across the Community that did not fall within the scope of Directive 89/381/EEC.

- While no specific comment was made on the status of haemovigilance practices in the MS at the time of this report, it can be assumed that these were not yet developed in the MS or in the very early stages of development. It was noted that the establishment of a Community-wide surveillance system on blood transmitted diseases and adverse reactions at both national and Community level could help to keep transfusion specialists informed, in a timely and orderly fashion, of new infectious agents in particular, their potential danger, and appropriate measures to be taken to avoid their transmission. It also noted that existing haemovigilance and pharmacovigilance systems, therefore, would need to be examined in order to assess their contribution to such a system.

- Finally, the document identified the main activities that could be undertaken in the development of a blood

strategy including:

- Development of scientifically sound policies and agreed procedures in the donor selection process among blood collection establishments within the Community in order to provide the necessary reassurances of the safety of blood products originating from whatever Community source;
- Implementation of efficient validated and reliable screening tests in the Community;
- Development of quality assessment criteria and good manufacturing practices regarding collection, testing, processing, and transfusion of blood and blood products and patient follow-up procedures;
- Development of a haemovigilance system for the collection of epidemiological data related to the blood transfusion chain;
- Development of educational programmes directed towards health professionals on the optimal use of blood and blood products;
- Support for the dissemination of information on blood and blood products and the collection, processing and transfusion procedures through promotional materials, films, campaigns etc.

2. Comparative analysis of national regulations concerning blood safety across Europe. Mascaretti et al. Transfusion Medicine, 2004, 14,105–111

In October 2001, representatives of 17 European countries (Albania, Bosnia–Herzegovina, Bulgaria, Croatia, Czech Republic, Federal Republic of Yugoslavia, Finland, France, Germany, Greece, Italy, Macedonia, Romania, Slovenia, Spain, Turkey and UK) met in Sarajevo at a course organised by the European School of Transfusion Medicine (ESTM) to discuss their countries' regulations concerning different aspects of the safety of blood transfusion.

This publication presented a preliminary analysis of the activities being undertaken in these countries to ensure the safety of their blood supply directly before the implementation of the European Blood Directive in February 2005.

The following key observations were noted:

- Most countries (13/17) had specific transfusion laws. However, it was noted that the majority of these laws were rather recent (only two published before 1990).
- 9/17 countries had hospital-based systems as opposed to national organisations and 9/17 had national systems while Spain had a 'mixed system' with a national programme in 11 of 17 regions. Of the seven EU states, only four had national programmes. Finland, the country with the lowest population density, was among the countries with a National Transfusion Service. Of the 9 countries with a hospital-based system, five (Croatia, Czech Republic, Italy, Macedonia and Slovenia) warranted a greater centralisation of transfusion organisations.
- Quality assurance was common among investigated countries (14/17) and in these was stipulated by law.
- Voluntary associations were responsible for donor promotion in the majority of countries (13/17).
- Exclusively, voluntary non-remunerated donors were found in 5/17 countries, whereas in the remaining

ones, incentives, family replacement and remuneration were mechanisms stimulating blood donation.

- In all 17 countries, regulations require that donor suitability be checked by, or under the responsibility of medical doctors; in most cases, these use selection criteria that are established by official regulations (15/17).
- In 16 countries of 17 (data for Turkey were not available), regulations require that blood and components were screened for anti-HIV1/2, anti-HCV, HBsAg and anti-treponemal antibodies. In a few nations, additional tests are required for all blood units donated (however, these were not specified).
- Regulations on good clinical use of blood and derivatives were present in most countries but applied only in some.
- Haemovigilance was required by law in 11 countries, but, there was some discrepancy between what was written and what was done in relation to haemovigilance procedures. It was noted that in 13/17 countries, transfusion centres were always notified in cases of adverse transfusion reactions.

3. Report from the Commission to the Council, the European Parliament, the European Economic and Social Committee and the Committee of the Regions – First Report on the application of the Blood Directive. Brussels, 19.6.2006 COM (2006) 313 final.

Article 26 of Directive 2002/98/EC requires Member States to submit to the European Commission, beginning on 31 December 2003 and every three years thereafter, reports on the activities that they have carried out in relation to the implementation of its provisions.

This first Commission report provided an overview of the situation in the 15 Member States that belonged to the European Union as of 31 December 2003.

The following key observations were noted in this report:

- As of December 2003, 14 Member States had designated a competent authority in accordance with the Directive. Four, however, had more than one – Germany, due to its federal system, had 29; Spain, with its autonomous communities, had 18; and Denmark and Sweden each had two.
- The competent authority in 11 of the Member States had designated, authorised, accredited or licensed blood establishments to carry out collection, testing, preparation, storage and distribution activities.
- The competent authority in 7 Member States had organised inspections and control measures in blood establishments in order to ensure compliance with the Directive's requirements. The timeliness of inspections and control measures, however, varied from every six months to every three years. Emergency inspections were carried out when necessary.
- Six Member States had empowered officials representing the competent authority to carry out inspections and control measures in blood establishments and facilities of third parties in their State that had been entrusted by the authorised blood establishment to carry out Evaluation and testing procedures.
- Six Member States indicated that their blood establishments were aware that serious adverse events and reactions had to be notified to the competent authority in accordance with the procedure and notification

format.

- Eight Member States already had procedures in place to enable blood or blood components associated with serious adverse events and reactions to be accurately, efficiently and verifiably withdrawn from distribution.
- Nine Member States confirmed that personnel directly involved in the collection, testing, processing, storage, and distribution of human blood and blood components is qualified for their tasks and has been provided with timely, relevant and regularly updated training.
- Eleven Member States had ensured that each blood establishment instituted and maintained a quality system based on the principles of good practice. Shortcomings, however, were acknowledged in some Member States.
- All Member States had taken measures to ensure that blood and blood components collected, tested, processed, stored, released and/or distributed on its territory were traceable from donor to recipient and vice versa. Eleven Member States indicated that blood establishments had implemented an identification system for each blood donation and each blood unit and its components.
- Nine Member States reported that Evaluation procedures and donation deferral criteria were in place in blood establishments for all donors of blood and blood components.
- Fourteen Member States indicated that provisions are in place for assessing the suitability of individuals to donate blood, including an examination of and an interview with the donor prior to any donation.
- Eleven Member States had taken measures to encourage voluntary and unpaid blood donations with a view to ensuring that blood and blood components are in so far as possible derived from them.
- Fourteen Member States reported that their blood establishments test each donation of blood and blood components in conformity with requirements listed in Annex IV of the Directive.
- Although the requirements for the quality and safety for blood and blood components were adopted through the Comitology procedure (article 29(f)) after the reporting date, seven Member States reported that their blood establishments had to ensure that the quality and safety requirements for blood and blood components met high standards.

4. Trends and Observations in the collection, testing and use of blood and blood components in Europe. EDQM Report 2001-2011[408]

In 2015, the EDQM published its cumulative report on the trends and Observations in the collection, testing and use of blood and blood components in Europe covering the decade from 2001 to 2011.

The basis for this analysis is formed by data provided annually since 2001 to the Council of Europe by its Member States and reported on the webpage provided, in individual annual reports, on the collection, testing and use of blood and blood products in Europe.

[408] EDQM Report on the Trends and Observations on the Collection, Testing and Use of Blood and Blood Components in Europe..

While the reporting of data is open to the 46 Member States of the Council of Europe, the majority of consistent data is provided by the EU MS and is therefore relevant as a data source to identify certain improvements that have been made in the decade which saw the introduction and implementation of the European Blood Directives.

The data presented in this report refers mainly to the usage of blood and blood components in the Member States and to the occurrence of infectious markers in donors and trends in the presentation of donors for donation, however, three key points were also noted which demonstrate improvements from the baseline in 2001 prior to the implementation of the European Blood Directives.

The following key observations were noted in this report:

- While there were no changes in the proportion of Member States which test all donations with the following serological tests: Anti-HIV 1+2 / HBsAg, Anti-HCV, Anti-HTLV and Syphilis. Only anti-HBc testing increased by 1.1 absolute percentage points per year (p=0.4 %). A substantial increase was observed, however, in the implementation of HIV- and HBV-NAT for testing (respectively 3.8 and 4.5 absolute percentage points per year) of all donations, leading to 56 % (HIV-NAT), 47 % (HBV-NAT) and 53 % (HCV-NAT) of Member States testing all donations in 2011.

- There was no indication of a consistent trend in the proportion of countries with a national or expert committee in place for blood transfusion (while this is not a legislative requirement, it is good practice and is recommended by the Council of Europe Guide to the Quality and Safety of Blood and Blood Components. Also no significant change was observed in the proportion of countries that had implemented labelling of at least 50 % of donations or have at least 50 % of donations covered by standards. However, the proportion of Member States which labelled component codes (allowing for more complete traceability of donations) significantly increased over the years, up to 100 % since 2009 (p=3 %).

- There was an overall increase of 2.7 percentage points per year in the proportion of Member States, which have established a quality assurance system. Since 2008, all reporting Member States had either had established QS in place or planned to establish one.

5. Peer Review of Blood Services in Romania 26-28 July 2004 (Pre-Accession) Mission Report Reference 10255 (EC Reference)

In advance of the accession process of Romania to the European Union in 2005, a Peer Review mission was carried out by the European Commission accompanied by relevant experts between 26 and 28 July 2004 in order to assess the situation with regard to the country's blood services.

The aim of the mission was to consider the proposed Romanian legislation related to blood, to identify difficulties and weaknesses, and to propose, if appropriate, suitable and sustainable solutions in order to facilitate the transposition of Community legislation related to blood (Directive 2002/98/EC, Commission Directive 2004/33/EC) and the implementation of its requirements in the lead up to accession.

During this peer review mission, the review team highlighted a number of key issues to be addressed by the Romanian Government and existing Blood Service in order to meet the requirements of the European Blood Legislation.

- It was recommended that the State designate a Competent Authority, without operational functions related

to the blood services, as well as an independent body authorised to carry out inspections.

- It was noted that the modernisation of blood establishments and hospital blood banks in terms of facilities and equipment was of high priority.
- It was also noted that the establishment of both national and local programmes on donor recruitment and retention based on voluntary, non-remunerated blood donations, with a clearly identified and separate budget, was urgently required. The use of family and replacement donors at this time was noted.
- It was also recommended that procedures for the notification of adverse events and reactions needed to be introduced and implemented.
- There was a need for training programmes, particularly those related to Quality management, to be introduced – at national, regional and local levels - to upgrade staff awareness and knowledge in order to comply with the requirements of the Blood Legislation.

Part B- Tissues and cells

Key document 1
Communication from the Commission to the Council, the European Parliament, the European Economic and Social Committee and the Committee of the Regions on the application of Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. Brussels, 2010 COM(2009)708 final
Background 1
• Article 26 of Directive 2004/23/EC required Member States to submit to the European Commission, before 7 April 2009 and every three years thereafter, a report on the activities undertaken in relation to the provisions of the Directive, including an account of the measures taken in relation to inspection and control. • The Commission is required to transmit these reports to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions, and to provide them with a report on the implementation of the requirements of the Directive, in particular as regards inspections and monitoring. • This report was based on the replies to questionnaires on transposition and implementation that Member States sent to the Commission on a yearly basis and is particularly focussed on the year 2008. • This first Commission report provides an overview of the situation in the 27 Member States at the time.
Key observations 1
The following key observations were noted in this report: • All Member States indicated they had designated a competent authority in accordance with the requirements of the Directive. In 21 Member States, the designated competent authority was responsible for all types of tissues and cells. France, Greece, Portugal, Finland and the United Kingdom had a specific competent authority for reproductive tissues and cells. • Under Article 5, the competent authority or authorities must ensure that tissue and cell procurement complies with the stipulated requirements. The procurement organisations do

not have to be accredited/designated/authorised/licensed by the competent authority or authorities but the conditions of procurement need to be verified. These could be checked via an inspection of the procurement organisation or via an inspection of the tissue establishment receiving tissues and cells from a particular procurement organisation. In this respect, six Member States (Bulgaria, Germany, Denmark, France, Ireland and the United Kingdom) carried out 53 inspections of procurement organisations during 2008.

- An accreditation/designation/authorisation/licensing system of tissue establishments was in place in 23 Member States. The system was decentralised in five Member States where the process was channelled through federal states, regions or autonomous communities. Three Member States did not have an accreditation/designation/authorisation/licensing system in place at the end of 2008. Although the accreditation/designation/authorisation/licensing system was for the most part established in the Member States, around half of them indicated that they had yet to finalise the accreditation/designation/ authorisation/licensing of each individual tissue establishment in their territory.

- 14 Member States had specific systems for authorising tissue and cell preparation processes. In the other Member States, in the absence of specific authorisation systems, tissue and cell preparation processes were normally verified and authorised during a general inspection for the purpose of accreditation/designation/authorisation/licensing of a tissue establishment. In some Member States, a different institution, independent from the competent authority or authorities, is responsible for validating and authorising of the preparation process. This is the case in Romania, where the Medical College of Physicians is responsible for the approval of the preparation processes. Only three Member States conducted inspections solely for the purpose of authorising preparation processes in 2008.

- As of 31 December 2008, a total of 1 716 tissue establishments were accredited/designated/authorised/licensed: 42 skin establishments, 172 musculo-skeletal establishments, 63 ophthalmic establishments (cornea, sclera, etc.), 49 vascular establishments (heart valves, vessels, etc.), 193 haematopoietic stem cell establishments (other than cord blood), 91 cord blood banks, 769 reproductive tissue and cells establishments, 270 multi-tissue establishments and 67 other types of tissue and cells establishments (chondrocyte cells, genetically modified cells, keratinocyte cells, myeloblast cells, etc.).

- Comprehensive inspection systems were in place in 23 Member States. Only 15 Member States had conducted initial or regular inspections of tissue establishments in 2008. 4 Member States did not yet have inspection systems in place.

- 11 Member States had clearly identified tissue establishments explicitly authorised to import tissues and cells. 8 Member States had a register of tissue establishments in third countries from which imports were performed. Sixteen Member States reported that they imported tissues and cells from third countries during 2008. Slightly less than 50% of Member States importing tissues and cells use bilateral agreements to verify the equivalence of standards for quality and safety of the tissues and cells. International standards like EATB, AATB, JACIE, WMDA and NETCORD are also used, depending on the tissue and/or cell involved.

- In many cases data concerning volumes of imports were not available; Member States indicated that 1 122 units of haematopoietic stem cells (HSC), 2 281 units of musculo-skeletal tissue, 4 units of skin and 7 units of reproductive tissues and cells were imported during 2008.

- Only nine Member States had a register of tissue establishments authorised to export tissues and cells to third countries. 14 Member States exported tissues and cells during 2008. In many cases data concerning volumes of exports are not available, but Member States indicated that 269 units of HSC, 489 units of ophthalmic tissue, 6 225 units of musculo-skeletal tissue and 10 units of amniotic membrane were exported.

- 19 Member States had created an annual report on the activities of tissue establishments that made the reporting of the yearly activities by tissue establishment easier. 16 Member States received annual reports from their tissue establishments corresponding to 2008 activities. Only 12 Member States had made the tissue establishments' reports publicly available during 2008. 20 Member States indicated that they have a public register available (Belgium, Bulgaria, Czech Republic, Denmark, Germany, Estonia, Ireland, Spain, France, Italy, Cyprus, Lithuania, the Netherlands, Austria, Poland, Portugal, Slovenia, Romania, Finland and the United Kingdom).

- All Member States except for Greece and Latvia had a vigilance system in place to report, investigate, register and transmit information about serious adverse events and reactions, which may influence the quality and safety of tissues and cells. Criteria for the reporting of adverse events to the competent authority had been laid down by 22 Member States. Criteria for the reporting of adverse reactions to the competent authority had been laid down by 21 Member States. In accordance with Article 7(1) of Directive 2006/86/EC, Member States must submit to the Commission an annual report on the serious adverse reactions and events notified to the competent authority. The first annual report on this subject was submitted to the Commission by only 13 Member States.

- All the reporting Member States comply with the minimum testing requirements of Directive 2006/17/EC. Some Member States applied other tests in addition to those established as minimum requirements in the Directive, in particular NAT testing for HIV/HBV/HCV.

- Under Article 24(1), tissue establishments have to have a written agreement with a third party each time an external activity takes place which may influence the quality and safety of tissues and cells. 22 Member States indicated that tissue establishments in their territory had notified third-party agreements.

- By July 2009, 26 Member States had notified to the Commission their national transposition measures in relation to Directive 2004/23/EC. National transposition measures in relation to Directives 2006/17/EC and 2006/86/EC had been communicated to the Commission by 25 Member States. In July 2009, there were five infringement procedures open for failure to achieve full transposition of the Directives in two Member States.

  Comment: This report demonstrated that implementation of the legislative requirements was

progressing since the finalisation and publication of the Tissues and Cells Directive in 2004, however, there was still some variance in practices with a number of MS needing to undertake significant work to meet the legislative requirements.

Concerns regarding the development of specific systems for authorising the tissue and cell preparation process; finalisation of the accreditation/designation/authorisation/licensing process in respect of each individual establishment; the carrying out of inspections in all Member States; monitoring of imports/exports; fulfilment of the reporting requirements (tissue establishments' annual reports on activities, register of accredited/designated/authorised/licensed tissue establishments at the level of the Member States and at EU level) and preparation of annual reports on adverse events and reactions for the Commission.

Key document 2

Peer Review of Tissues and Cell Banking and Transplantation in Romania. Mission Report July 2004. Mission Reference: 10257. (EU Reference)

Background 2

- This Peer Review Mission was undertaken in order to perform and analysis of the tissue and cell retrieval, processing and grafting system in Romania. It was commissioned by DG SANCO and DG Enlargement/TAIEX of the European Commission and took place over 3 days in July 2004.

- The main focus of this mission was to determine whether adequate administrative rules, infrastructure and capacity were in place within the tissue and cells transplant system in order to ensure compliance with EU Directive 2004/23/EC.

Key Observations 2

- During this peer review mission, it was noted that traditional tissue banking services were poorly developed in Romania, though there was some banking and transplantation of corneas, skin, bone and tendons.

- The banks that existed were located in specialist hospital units and focused their activity on trying to supply tissue for the clinical departments in which they were based. There were no centralised services with multi-tissue retrieval or banking and there appeared to be no involvement of the blood services in the development of tissue banking. It was noted that gamete and haemopoietic progenitor cell services were better resourced and more developed.

- Tissue retrieval from deceased donors was organised almost exclusively from the very small number of brain dead (heart-beating) organ donors, despite the acknowledgement that a far greater source of potential donors would be non-heart-beating cadavers, and the absence of any legal barrier. Successful programmes for non-heart beating tissue donation existed in the past, notably for corneas, but were abandoned or stopped once the legal requirement for donor family consent was introduced.

- There has never been a large scale programme of public education regarding tissue

donation and Romanian colleagues described a reluctance among hospital staff to approach bereaved families for consent. They also made reference to logistical challenges, given that the majority orthodox Christian community prefers to bring the deceased home before burial, sometimes for a number of days. It was agreed that these barriers could be overcome with adequate public and professional support and education.

- Importation of tissue grafts must be authorised by the Ministry and was generally considered to be a prohibitively expensive option, with some exceptions such as heart valves.
- The delegation did not see reports or evidence of tissue exportation. At least two approaches had been made by US owned 'for profit' tissue banks, proposing that bone be retrieved from cadavers and sent to their facilities for processing. A proportion of the processed bone (20%) would have been returned as payment. Given the scarcity of cadaveric bone donors in Romania, these proposals could not be taken further.
- The delegation noted that the recently adopted European Directive on tissues and cells included a number of requirements that needed to be addressed in Romania, to ensure eventual compliance. These included:
    - Designation of a Competent Authority/ies;
    - Establishment of a system for inspection and accreditation, designation, licensing or authorisation of tissue establishments;
    - Establishment of a system for inspection and accreditation, designation, authorisation or licensing for all implied processes and activities;
    - Maintenance of a registry of accredited establishments and activities;
    - Assurance of traceability from donor to recipient;
    - Protection of donors (privacy, health, consent etc.);
    - Establishment of a system for the notification of serious adverse reactions or events following tissue or cell transplantation;
    - Establishment of a system to control Import / Export of tissues and cells;
    - Establish a comprehensive Quality System in all tissue establishments;
    - Notification of adverse or serious events following tissue or cell transplantation;
    - Assessment of whether imported tissues comply with equivalent safety and quality standards to those required by the directive
    - Ensuring availability of appropriate staff and facilities as detailed in the directive and its annexes.

Key document 3

Peer Review of Tissue and Cell Banking and Transplantation in Bulgaria. Mission Report July 2004.

Background 3
• This Peer Review Mission was undertaken in order to perform and analysis of the tissue and cell retrieval, processing and grafting system in Romania. It was commissioned by DG SANCO of the European Commission and took place over 3 days in July 2004. • The main focus of this mission was to determine whether adequate administrative rules, infrastructure and capacity were in place within the tissue and cells transplant system in order to ensure compliance with EU Directive 2004/23/EC.
Key Observations 3
• The delegation noted that the situation with regard to the programme for transplantation of tissues and cells in Bulgaria included key elements which would facilitate future improvement; the legal framework was well advanced, there existed a National Transplantation Agency, there were many competent practitioners ready and willing to improve the system and international co-operation was already developed and should facilitate further improvement in time. • The new Transplantation Act (Effective January 1st 2004) was quite comparable to the new EU Directive. However, it was not clear if technical specifications for authorisation and inspection activities had been clearly or adequately defined. • Furthermore, the inspection system proposed needed to be clarified; inspection guidelines and work in the education and training of inspections was required. • The public tissue banks visited during the mission required significant upgrade to facilities and equipment in order to meet the requirements of the new EU Directive. • Considerable work and education was required regarding the implementation of quality systems required to meet the specifications to be defined in the new EU Directive. • It was noted that the co-existence of private-for-profit and public tissue and cell banking activities contributes in upgrading the activity level of transplants of tissues and cells but could lead to some undesirable distortion and must be regularly re-evaluated and remain under the strict control of the national authorities and the representatives of national society. • The quality and safety of reproductive tissue and cells needed to be addressed in legislation, as it was not covered under the newly effective 'Transplant Act.

Annex VI: Cases sent by national courts to the European Court of Justice for a preliminary ruling on questions of Union law relating to the BTC sectors.

ECJ Cases

1. **C-421/09 – Humanplasma: Case about the implementation of rules on VUD to imports of blood for transfusion;**

Description of the case

This reference for a preliminary ruling concerns the interpretation of Articles 28 EC and 30 EC. The reference to the Court was made in proceedings between Humanplasma GmbH ('Humanplasma'), a company established under Austrian law, and the Republik Österreich (Republic of Austria) concerning the legislative prohibition on the importation of erythrocyte concentrates provided from blood donations, which were not entirely unpaid.

The case having been brought before it, the Landesgericht für Zivilrechtssachen Wien (Regional Civil Court, Vienna) decided to stay the proceedings and to refer the following question to the Court for a preliminary ruling:

'Does Article 28 EC (in conjunction with Article 30 EC) preclude the application of a national provision under which the importation of erythrocyte concentrates from Germany is permitted only where the blood was donated without any payment having been made (with not even expenses being covered), that being a condition which is also applicable to the obtaining of erythrocyte concentrates within Austria?'

Summary of the Judgment

Article 28 EC, read in conjunction with Article 30 EC, must be interpreted as precluding national legislation that provides that the importation of blood or blood components from another Member State is permitted only on the condition, which is also applicable to national products, that the donations of blood on which those products are based were made not only without any payment being made to the donors but also without any reimbursement of the costs incurred by them in connection with those donations.

Such legislation which has the aim, first, of ensuring that blood and blood components marketed in the Member State at issue satisfy the criteria of high quality and safety and, second, of attaining the objective enshrined in Article 20(1) of Directive 2002/98 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components, that is, encouraging voluntary and unpaid blood donations, addresses human health concerns such as those acknowledged in Article 30 EC.

Therefore, those objectives are, in principle, capable of justifying a restriction of the free movement of goods.

However, considered in isolation, the obligation that the blood donation should have been made without any of the costs incurred by the donor having been reimbursed is not necessary in order to ensure the quality and safety of the blood and the blood components. That conclusion is supported by the fact that neither Directive 2002/98 nor Recommendation No R (95) 14 of the Committee of Ministers to the Member States of the Council of Europe, to which that directive refers, requires donations to be completely unpaid but provide that small tokens, refreshments and reimbursements of travel costs connected with the donation are compatible with voluntary, non-remunerated donation, with the result that those elements cannot be considered as liable to compromise the quality and safety of those donations or the protection of human health.

Such legislation therefore goes beyond what is necessary to attain the objective pursued, that is, to ensure the quality and safety of the blood and of the blood components.

2. C-512/12 - Octapharma France: Case about the extent to which MS can apply more stringent requirements in line with Directive 2002/98/EC

Description of the case

This request for a preliminary ruling concerns the interpretation of Article 168 TFEU, of Article 2(2) of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, and of Article 4(2) of 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.

The request was made in proceedings between Octapharma France SAS (‘Octapharma’) and the Agence nationale de sécurité du médicament et des produits de santé (ANSM) (National Agency for Medicinal Product and Health Product Safety), and the Ministère des Affaires sociales et de la Santé (Ministry of Social Affairs and Health) concerning the Agency’s decision of 20 October 2010 setting out the list and fixing the characteristics of labile blood products (‘the decision of 20 October 2010’), on the ground that the Agency placed on that list plasma prepared by means of an industrial process such as, inter alia, fresh frozen plasma, leucocyte-reduced, virus-inactivated by solvent-detergent (‘plasma SD’).

Taking the view that the resolution of the dispute before it depends on the interpretation of European Union law, the Conseil d’État decided to stay the proceedings and to refer the following questions to the Court of Justice for a preliminary ruling:

(1) Is plasma from whole blood which is prepared by a method involving an industrial process and which is intended for transfusions capable of having the provisions of Directive [2001/83, as amended by Directive 2004/27] and those of [Directive 2002/98] applied to it simultaneously, as regards not only its collection and testing, but also its processing, storage and distribution; for that purpose may the rule laid down [in Article 2(2) of Directive 2001/83, as amended by Directive 2004/27] be interpreted as meaning that the Community legislation on medicinal products alone applies to a product which falls simultaneously within the scope of another piece of Community legislation only where that latter is less strict than the legislation on medicinal products?

(2) Must the provisions [of Article 4(2) of Directive 2002/98] be interpreted, where necessary in the light of Article 168 TFEU, as allowing the maintenance or introduction of national provisions which, because they submit plasma which is prepared by a method involving an industrial process to a stricter regime than that to which medicinal products are subject, provide justification for setting aside the application of all or part of the provisions of Directive [2001/83, as amended by Directive 2004/27], in particular those which make the marketing of medicinal products subject to the sole condition of the prior grant of a marketing authorisation and, in the affirmative, under what conditions and to what extent?'

Summary of the Judgment

1. Directive 2001/83 on the Community code relating to medicinal products for human use, as amended by Directive 2004/27, and Directive 2002/98 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 must be interpreted as meaning that plasma from whole blood which is prepared by a method involving an industrial process and which is intended for transfusions comes, in accordance with Article 109 of Directive 2001/83, within the scope of Directive 2002/98 with respect to its collection and testing, and within the scope of Directive 2001/83, as amended by Directive 2004/27, with respect to its processing, storage and distribution, on condition that it satisfies the definition of a medicinal product under Article 1(2) of the latter directive.

2. Article 4(2) of Directive 2002/98 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components, read in the light of Article 168 TFEU, must be interpreted as meaning that it allows the maintenance or introduction of national provisions which make plasma which is prepared by a method involving an industrial process subject to a more rigorous regime than that to which medicinal products are subject solely with respect to its collection and testing.

3. C-528/13 – Léger: Case about whether MS can permanently defer men having sex with men from donating blood on safety grounds

Description of the case

This request for a preliminary ruling concerns the interpretation of point 2.1 of Annex III to 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.

The request was made in proceedings between Mr Léger and the Ministre des Affaires sociales, de la Santé et des Droits des femme (Minister for Social Affairs, Health and Women's Rights) and the Établissement français du sang (French Blood Agency) concerning the refusal to accept Mr Léger's blood donation on the ground that he had had sexual relations with another man.

The Tribunal administrative de Strasbourg decided to stay the proceedings and to refer the following question to the Court for a preliminary ruling:

'In the light of Annex III to Directive [2004/33], does the fact that a man has sexual relations with another man constitute in itself sexual conduct placing him at a risk of acquiring severe infectious diseases that can be transmitted by blood and justifying a permanent deferral from blood donation for persons having engaged in that sexual behaviour, or is it merely capable of constituting, in the light of the circumstances of the individual case, sexual behaviour placing him at a risk of acquiring infectious diseases that may be transmitted by blood and justifying a temporary deferral from blood donation for a period determined after cessation of the risk behaviour?'

Summary of the Judgment

Point 2.1 of Annex III to Commission Directive 2004/33 implementing Directive 2002/98 as regards certain technical requirements for blood and blood components must be interpreted as meaning that the criterion for permanent deferral from blood donation in that provision relating to sexual behaviour covers the situation in which a Member State, having regard to the prevailing situation there, provides for a permanent contraindication to blood donation for men who have had sexual relations with other men where it is established, on the basis of current medical, scientific and epidemiological knowledge and data, that such sexual behaviour puts those persons at a high risk of acquiring severe infectious diseases and that, with due regard to the principle of proportionality, there are no effective techniques for detecting those infectious diseases or, in the absence of such techniques, any less onerous methods than such a counter indication for ensuring a high level of health protection of the recipients. It is for the referring court to determine whether, in the Member State concerned, those conditions are met.

In that connection, it is for the referring court to determine in particular whether the questionnaire and individual interview with a medical professional, provided for in Annex II B(2) to Directive 2004/33, are able to identify more precisely the type of behaviour presenting

a risk for the health of recipients, in order to impose a less onerous contraindication than a permanent contraindication for the entire group of men who have had sexual relations with a man.

4. C-296/15 – Medisanus: Case about whether a MS can envoke rules on VUD and national self-sufficiency as a restriction on the free movement of plasma derived medicinal products.

Description of the case

This request for a preliminary ruling concerns the interpretation of Article 2 and Article 23(2) and (8) of Directive 2004/18/EC of the European Parliament and of the Council of 31 March 2004 on the coordination of procedures for the award of public works contracts, public supply contracts and public service contracts, read in conjunction with Article 83 of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, with Article 4(2) of Directive 2002/98 and with Article 18 TFEU.

The request was made in proceedings between Medisanus d.o.o. and Splošna Bolnišnica Murska Sobota (Murska Sobota General Hospital, Slovenia) ('the hospital') concerning the legality of a clause in the tender specifications relating to a public procurement procedure launched by that hospital for the supply of medicinal products.

The Državna revizijska komisija za revizijo postopkov oddaje javnih naročil (State Public Procurement Tribunal) decided to stay the proceedings and to refer the following question to the Court for a preliminary ruling:

'Must Directive [2004/18], in particular Article 23(2), Article 23(8) and Article 2 thereof, read in conjunction with

– Directive [2001/83], in particular Article 83 thereof;

– Directive [2002/98], in particular Article 4(2) thereof; and

– the TFEU, in particular Article 18 thereof,

be interpreted as precluding a specification that industrially manufactured medicinal products must be obtained from "Slovenian plasma" (a requirement based on the domestic legislation ...)?'

Summary of the Judgment

Article 2 and Article 23(2) and (8) of Directive 2004/18/EC of the European Parliament and of the Council of 31 March 2004 on the coordination of procedures for the award of public works contracts, public supply contracts and public service contracts, and Article 34 TFEU

read in conjunction with Article 36 TFEU, must be interpreted as precluding a clause in the tender specifications for a public contract which, in accordance with the law of the Member State to which the contracting authority belongs, requires medicinal products derived from plasma, which are the subject matter of the public procurement at issue, to be obtained from plasma collected in that Member State.

Annex VII: Written Parliamentary Questions concerning the BTC legislation since 2002

To read the full question and answer go to this webpage and enter the parliamentary term, the question number and the year:

http://www.europarl.europa.eu/plenary/en/parliamentary-questions.html

SUBJECT	**Number of questions (N=77)**	**Number of specific subject related questions**
Blood	53	15 on MSM; 12 on sufficiency of supply; 9 on infection crises; 8 on VUD; 2 on free market and 7 others
Tissues & Cells	24	7 on cord blood banking; 3 on sufficiency of supply; 4 on VUD; 3 on transposition/implementation; 7 others

Number of questions	**Topic**	**Question number/year**
	BLOOD	
15	Deferral of Men having sex with Men (MSM) from blood donation: Gender discrimination or justifiable safety measure to protect recipients from infectious disease risks.	P-1842/2003 P-3639/2005 E-5739/2006 E-4492/2006 E-3671/2009 E-006484/2011 E-012319/2013 E-006727/2014 E-011959/2015 E-007504/2015 E-006958/2015 E-007052/2015 E-007026/2015 E-007293/2015 E-005284/2016
12	Sufficiency of the blood (and plasma) supply	E-0594/2005 E-5800/2007 E-5473/2010 E-012357/2011 E-012355/2011 E-010598/2011

		E-010557/2011 E-002285/2014 E-008923/2015 E-006689/2016 E-001017/2018 E-005795/2018
9	Infection/ transmission crises	E-2307/2005 E-1505/2005 E-4937/2006 E-4736/2006 E-9712/2010 E-000324/2011 E-002446/2013 E-008278/2014 E-003401/2016
8	Voluntary unpaid donations	P-2174/2006 P-4259/2007 P-2557/2007 E-4962/2008 P-2933/2008 P-2779/2010 E-005884/2011 P-005818/2011
2	Free market	E-2314/2003 E-4719/2007
1	Epilepsy as an exclusion criteria for donation	E-2796/2006
1	Separation between blood products and plasma	E-4201/2008
1	Blood testing using NAT	E-001921/2011
1	Assistance for individuals with disabilities in donation	P-001468/2013
1	Blood substitutes	E-005542/2014
1	Ebola risks	E-010202/2014
1	Age limit for donation	E-005013/2015
TISSUES AND CELLS		
7	Private Cord blood banking and the measures taken to harmonise sampling models, maximise clinical use and ensure traceability.	E-3677/2002 E-4710/2009 E-0037/2010 E-010212/2011 O-000032/2011 E-003479/2014 E-002705/2017
3	Sufficiency and supply	E-008172/2012 E-010175-12 P-004347/2014

4	Voluntary unpaid donations	E-1361/2005 P-1755/2007 P-1735/2007 E-1727/2008
1	Illegal trafficking between EU and USA	E-4095/06
1	On consultations concerning technical procurements for donation and testing of human tissues and cells.	E-3345/2006
1	Financing human embryonic stem cells for research and care	E-1384/2007
3	Transposition/ compliance assurance	H-0241/2009 E-010578/2010 E-000687/2011
1	Testing requirements	E-007210/2011
1	Preservation of tissues and cells	E-009595/2011
1	Concerning the classification of medical products (ATMPs) and the application of the hospital exemption.	E-013101-13
1	Alert systems	E-007415/2013

Annex VIII: Interpretation Questions arising in the National Competent Authority (NCA) Meetings with the Commission[409]

Part 1: Blood

No.	Meeting of Competent Authorities (blood)	Reference to relevant text of Directive(s):	Issue:	Outcome:
1.	September 2005	Point 2.4 of Annex V of Directive 2004/33/EC (Quality Control Parameters)	Quality Control Specification requires that the *protein content of fresh frozen plasma* should be not less than 50g/l. Makes quality control testing of FFP unnecessarily cumbersome and expensive without any measurable increase in safety and quality. Small expert meeting (May 2006) to come up with a recommendation that can be presented to the Regulatory Committee for an opinion and possible amendment of the Directive.	NCA meeting blood (Sept 2006) agreed with expert recommendation that 50g/l threshold for total protein content in fresh frozen plasma is not unnecessarily cumbersome.
2.	September 2005, September 2006 and September	Point 1.2 of Annex III of Directive	Required *Haemoglobin Levels* in Donors prior to Donation: threshold at 125g/l for women and 135g/l for men.	April 2010 NCA meeting concluded there was currently no conclusive evidence to justify a reduction in Hb

[409] On each occasion it was highlighted by the Commission that "working interpretations" developed by the Commission and/or the NCA's only represent the views of the Commission services and/or the NCAs; it is for the Court of Justice to decide on the correct interpretation of Union Law.

	2007	2004/33/EC (Haemoglobin Levels in donors prior to donation)	At September 2005 NCA Meeting blood, one NCA highlighted that this threshold had led to an exclusion of around 15% of female donors in that country. At September 2006 NCA meeting blood, suggestion to allow a capped leeway to lower the haemoglobin level, in order to decrease the exclusion rate of donors in some countries or regions due to their specific populations. Many NCA's confirmed that the haemoglobin levels as set in the directive lead to the exclusion of many potential donors, especially in young women, specific sub-populations or geographical areas. The principle of granting more flexibility to countries concerned by these high exclusion rates was broadly supported. The Commission committed to clarifying legal options available, and requested NCAs to send written comments and evidence.	levels from those already specified in the Directive. (It should be noted that a decision was taken to allow temporary reduction of the Hb thresholds during the influenza pandemic A (H1N1) in order to reduce the possibility of a shortage of blood and blood components, Directive 2009/135/EC.)
3.	September 2006	Directive 2002/98/EC Article 3 'Definitions'	Donor Leukocytes for Infusion (DLI) explicitly fall under the Blood Directive, while they are exclusively used in the frame of bone marrow transplants, which are regulated by the Tissue and Cell Directive. Multiple interpretations among Member States regarding the legal framework to apply to the DLIs. This may result in bone marrow transplant centres	NCA meeting T&C (Feb 2007), considered it recommendable that in view of the de facto use, Art. 2 of Directive 2002/98/EC would expressly exclude from its scope of application DLI used in the context of haematopoietic stem cells transplant and following the same requirements that these cells.

			having to be registered and inspected under both directives. The European Group for Blood and Marrow Transplantation (EBMT) regrets this situation and is calling for having the DLIs regulated only by the Tissue and Cell Directive. Several competent authorities confirmed that they face difficulties indeed in choosing which legal framework should be applied, leading to differing national practices.	
4.	September 2006	Directive 2002/98/EC Article 8 – Inspection and Control Measures	*Inspection frequency of Blood Establishments as they apply to Mobile Collection Centres*: EMEA and some Member States call for clarification of Article 8 of Directive 2002/98/EC on inspections of blood establishments require clarification with regards to the frequencies of inspections of mobile collection sites.	NCAs agreed that: *Mobile collection sites are operated and managed under the quality system of the reference blood establishment. The equipment used is supplied by the reference blood establishment, and its maintenance and calibration is performed by the reference blood establishment. Full information regarding mobile collection sites' operation and management, as well as their equipment, are reviewed during the inspection of the reference blood establishment. The inspections of mobile collection sites' premises are done as necessary.*

5.	Blood Regulatory Committee September 2009 and October 2009	Point 1.2 of Annex III to Directive 2004/33/EC & Point 2.2.1 of Annex III to Directive 2004/33/EC	Member States confronted with a serious risk of shortage or an actual shortage in the supply of blood and blood components directly due to the A(H1N1) Influenza pandemic, may, on a temporary basis allow the following derogations: (a) by way of derogation from point 1.2 of Annex III to Directive 2004/33/EC, reduce the minimum haemoglobin levels in donors blood to no less than 120 g/l for females and 130 g/l for males; and/or (b) by way of derogation from point 2.2.1 of Annex III to Directive 2004/33/EC, apply a deferral period of no less than 7 days after cessation of symptoms of a flu-like illness.	These derogations were legislated for in Directive 2009/135/EC published on the 3rd November 2009 and applicable until 30th June 2010.
6.	April 2010	Annex V of Directive 2004/33/EC Quality Control Parameters	*Maximum pH levels for platelets* at the end of shelf life Member States' survey supported the findings of the BEST Study which indicated that pH above 7.4 does not influence the in vivo recovery and efficiency of platelets, that the discard of non-compliant platelet concentrates can be problematic and that it was likely that there would be an increasing number of non-compliant units due to the evolution of collection methods and storage bags. It was concluded that it was not justified to maintain the upper pH limit for platelet concentrates as laid down in Annex V of Directive 2004/33/EC and that this would require amendment of the Directive	Draft Implementing Directive to amend Annex V of Directive 2004/33/EC was presented at this meeting and was voted in favour of at the Meeting in October 2010. (Note: At this meeting, the Competent Authorities called for a review of the technical requirements specified in Directive 2004/33/EC given recent scientific developments in the field) The Commission adopted the draft, which was subsequently published as COMMISSION IMPLEMENTING DIRECTIVE 2011/38/EU amending

			through the regulatory procedure.	Annex V to Directive 2004/33/EC with regards to maximum pH values for platelets concentrates at the end of the shelf life.
7.	April 2010	Annex III (Point 1.3) of Directive 2004/33/EC	*Protein Levels in Donor's Blood: to be checked at least annually*. One NCA considered it appropriate to monitor donor health when plasmapheresis donors donate regularly. However, this was considered disproportionate in some countries where donors are only allowed to donate plasma between 4 and 6 times per year. It was suggested that there should be a lower limit set, e.g. 6 donations per year above which an annual protein test is required.	The Commission noted the concern but stressed that this issue went beyond the interpretation of Directive 2004/33/EC and advised further discussion at the EDQM level.
8.	Joint Meeting of the Competent Authorities and Regulatory Committee on Blood and Blood Components October 2010	Annex V of Directive 2004/33/EC	Quality Control Standards for *Fresh Frozen Plasma* requires that *Factor VIIIc is measured* as a marker of statistical process control in Fresh Frozen Plasma. Acceptable results are an average (after freezing and thawing) of >70% of the freshly collected unit. One NCA queried if this was in fact the standard method of quality monitoring in all MS. A questionnaire was circulated to all CAs and EDQM was also requested to provide feedback on current guidance.	
9.	Joint Meeting of the Competent Authorities and Regulatory	Directive 2002/98/EC Article 2 - Scope	PRP (Platelet Rich Plasma) and whether it falls within scope of Directive 2002/98/EC: An initial query from MS was put forward at the Joint Competent Authority/Regulatory Committee	At the Meeting of the Competent Authorities on Blood and Blood Components in October 2012, it was indicated that this procedure could fall

	Committee on Blood and Blood Components October 2010 NCA meeting May 2011		Meeting in October 2010, as to whether autologous platelet rich plasma used for e.g. orthopaedic purposes is within the scope of the SoHO legislation. The EC committed to reverting on this topic. At the 2011 meeting, one CA again raised the matter of PRP (platelet-rich plasma) therapy, which is among other things used in orthopaedic or cosmetic therapies. This medical procedure includes the following steps: blood is collected on site and thereafter put into a small centrifuge to separate platelet-rich plasma, which is then re-injected into the patient, e.g. in the muscles/tendons. PRP therapy normally takes place in one procedure (thus there is no storage) in an operating theatre or medical office. One CA aimed to clarify whether this medical procedure falls under the scope for collection and testing under Directive 2002/98/EC, and in particular the wide reference provided in article 2 stating that *"this Directive shall apply to the collection and testing of human blood and blood components, whatever their intended purpose"'.* The feedback provided from eight National Competent Authorities at this meeting considered that as PRP is used for autologous purposes within a single procedure, safety and quality standards laid down in the legislation are not applicable. Other NCAs supported this view. It was noted that the centrifuge equipment falls under the safety and quality requirements of the Medical Devices	under the scope of the blood directive as it applies "to the collection and testing of human blood and blood components, whatever their intended use …" The NCA's however expressed that in practice it would be hard to make this relatively new procedure comply to the provisions of the 2002 blood legislation. It was indicated that this new practice could be considered in future legal changes.

			regulation.	
10.	Joint Meeting of the Competent Authorities and Regulatory Committee on Blood and Blood Components October 2010 Meeting of the Competent Authorities on Blood and Blood Components May 2011	Directive 2004/33/EC Annex 3 Point 2.1	Deferral Criteria for CJD and vCJD in Blood Donors Directive 2004/33/EC Annex 3 Point 2.1: At the NCAs meeting in October 2010, the European Medicines Agency indicated its intention to update the CHMP Position Statement on CJD and plasma derived and urine derived medicinal products. It was considering recommending certain exclusion criteria for blood donors to ensure the safety of plasma-derived and urine-derived medicinal products. Possible additional exclusion criteria included permanent deferral for: - donors who have spent a cumulative period of 1 year or more in the UK between the beginning of 1980 and the end of 1996, - recipients of blood transfusions in the UK, - recipients of transplants and - donors who have undergone neurosurgery. Directive 2004/33/EC Annex 3 Point 2.1 describes the legislative deferral criteria in blood donors for CJD and vCJD as follows: Persons who have a family history which places them at risk of developing a TSE, or persons who have received a corneal or dura mater graft, or who have been treated in the past with medicines made from human pituitary glands. It also states that for variant Creutzfeldt Jacob Disease, further precautionary measures may be recommended. The NCAs expressed serious concern at the	At the Meeting of the Competent Authorities on Blood and Blood Components in October 2012 and following on from previous discussion on this topic, the Commission services presented a draft paper for the preparation of a consensus list of neurosurgery procedures and transplants for which blood donors should be deferred, based on ICD nomenclature. MS' comments focused on the need to balance between (1) a too general deferral, e.g., deferring all patients after surgery on peripheral nerves, which would lead to too many unnecessary deferrals and missed donations and (2) a too detailed list of deferral criteria which would be impractical and hard to implement for staff in blood collection centres. It was concluded that it is a MS decision, taking into consideration the local epidemiological situation, whether or not to defer neurosurgeries as well as which types of neurosurgery. There was a general preference to keeping deferral criteria simple.

			proposals and their impact on the harmonisation of such criteria in the EU as well as possible impact on blood donation exclusions and resulting supplies of blood and blood components. A questionnaire was sent to NCAs to gather information on existing national blood safety measures in relation to Creutzfeldt-Jakob disease and to estimate the impact of EMA recommendations on blood supply at national level. The Commission services presented the replies to the questionnaire provided by 9 Member States during the May 2011 meeting.	EMA and ECDC were asked for more scientific evidence on how to better define, if possible, the recommended deferral criteria in relation to neurosurgery procedures and transplants. At the meeting of the Competent Authorities on Blood and Blood Components April 2013, the Commission outlined that there is no deferral for neurosurgery at EU level, as the final version of the EMA position paper on plasma derived medicines did not contain any reference to neurological deferrals. Data from one Member State was also presented showing that exclusion of all neurosurgery is not expected to significantly affect blood supply volumes. It was concluded that applying deferral for neurosurgery is a national decision, but one, which would not significantly affect blood supply.
11.	Meeting of the Competent Authorities on Blood and Blood	Directive 2004/33/EC Annex III	HTLVI/II Disease Deferral in donors of plasma intended for fractionation: Directive 2004/33/EC sets out permanent deferral	

	Components May 2011		criteria for donors of allogeneic donations, including HTLV I/II. Some permanent deferral criteria are excluded for donations used exclusively for plasma for fractionation e.g. Babesiosis At the request of the Plasma Protein Therapeutics Association (PPTA), the EC consulted the NCAs whether HTLV I/II positive donors should also be excluded for donations used exclusively for plasma for fractionation. It was concluded that the request letter sent by PPTA should be circulated to all NCAs for analysis and that feedback should be provided in writing to the Commission and that feedback would be provided at the next CA Meeting.	
12.	Meeting of the Competent Authorities on Blood and Blood Components May 2011	Annex III Point 2.2.2 of Directive 2004/23/EC	Definition of "Qualified Practitioner" The NO Competent Authority requested clarification on the different interpretations given to the term "qualified practitioner" in various translations of Directive 2004/33/EC, Annex III. Annex III of Directive 2004/33/EC states under point 2.2.2. that acupuncture should be performed by "a qualified practitioner", otherwise the donor is to be deferred from donating blood for 6 months, or for 4 months provided a NAT test for hepatitis C is negative.	NCAs agreed that "qualified practitioner" as used in Annex III of the Directive 2004/33/EC should be interpreted as "qualified healthcare practitioner". Member States can implement stricter provisions.
13.	Meeting of the Competent	Directive 2004/33/EC	Quality Control Requirements for Blood and Blood Components:	The National Competent Authorities indicated that the quality requirements

	Authorities on Blood and Blood Components May 2011	Annex V Quality Control Parameters	One Competent Authority consulted the other NCAs on their opinion concerning whether the quality requirements for residual cells in fresh frozen plasma are also applicable to plasma for fractionation, or only to fresh frozen plasma for transfusion.	set out in Directive 2004/33/EC are appropriate for plasma for transfusion and not necessarily for blood donations that are collected with the intention to only use the plasma for manufacturing of medicinal products.
14.	Meeting of the Competent Authorities on Blood and Blood Components October 2012	Directive 2002/98/EC Article 2 – Scope	Autologous Serum Eye Drops: One NCA presented information on a new procedure to manufacture eye drops from whole blood and raised the issue of whether this falls within the scope of European legislation on blood. Three MS outlined that they regulate these products as pharmaceuticals.	It was indicated that this procedure 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 …" which is defined in Article 2 of Directive 2002/98/EC. The NCA's however expressed that in practice it would be hard to make this relatively new procedure comply to the provisions of the 2002 blood legislation. This new practice should be considered in future legal changes.
15.	Meeting of the Competent Authorities on Blood and Blood Components October 2012	Directive 2002/98/EC Article 2 – Scope	Interleukin Rich Serum: Two NCAs explained that they do not consider that this product falls under the EU blood directives. One NCA stated that they had received an enquiry about the regulatory status and had determined that it was not a blood component falling within the scope of Directive 2002/98/EC; it was a non-industrially prepared medicinal product that fell outside the scope of Directive 2001/83/EC.	It was indicated that this procedure 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 …" The NCA's however expressed that in practice it would be hard to make this relatively new procedure comply to the

			One NCA compared this technique to eye drops manufactured from whole blood, and considered that it did fall under the EU blood directive.	provisions of the 2002 blood legislation. This new practice should be considered in future legal changes.
16.	Meeting of the Competent Authorities on Blood and Blood Components October 2012	Directive 2002/98/EC Article 3 – Definitions and Article 8 – Inspection and Control Measures	Harmonisation of terminology: Plasma master files (PMF) and EU Blood Directives. Three NCAs had indicated at the last CA meeting that inconsistencies concerning terminology, in particular concerning (mobile) collection sites and the applicable inspection regimes, might lead to different interpretations, which may in turn result in confusion and potential safety risks. This was applicable to both blood and blood components for transfusion but also to plasma for fractionation only. Suggestions were made for terms including: blood establishment, blood centre, satellite site, and relocation. The NCAs agreed to establish a group working on nomenclature and inspection intervals.	At the NCA Meeting in April 2013, the Commission services explained that Article 8(2) of Directive 2002/98/EC makes no distinction between different blood establishments. On the other hand, the definition of inspections in Article 3(m) may be broad enough to also include off-site inspections. This is current practice in the tissues and cells sector based on a guidance document, although there is no similar document in blood sector. The Commission services also explained that quality and safety cannot be jeopardised for the sake of longer inspection intervals.
	Meeting of the Competent Authorities on Blood and Blood Components April 2013		At the NCA Meeting in April 2013, One NCA presented a list of proposed definitions for different types of establishments. This list is based on a working document by EMA. The underlying concern is the practical difficulty of inspecting every blood establishment every two years (including but not limited to plasma collection centres). It was agreed that the definition of a blood	A group of CAs were requested to continue to look at both the proposed definitions of establishments in the PMF and the definitions of inspections and that discussions could continue at the subsequent meetings of the NCAs.

	Meeting of the Competent Authorities on Blood and Blood Components November 2013 Meeting of the Competent Authorities on Blood and Blood		establishment should be linked to its activities and inspection requirements. One NCA agreed that there are insufficient resources to inspect all sites at the same intervals. Four NCAs supported a risk based inspection model. During the previous NCA meeting, MS discussed that inconsistencies concerning terminology, in particular concerning (mobile) collection sites and the applicable inspection regimes. There was a concern that this might lead to different interpretations, which may in turn result in confusion and potential safety risks. It was considered important to further develop common thinking, given the difficulty of inspecting all sites on a 2-year basis, as laid down in Art. 8.2. A small sub-group was therefore asked to look into nomenclature and inspection intervals. A new proposal classifying Blood establishments according to their structure was presented. It was explained that depending on the activities performed the different risk levels could be expected and it could therefore be more suitable with a risk-based inspection systems, better focusing inspection resources. The definition of "inspection" was also discussed in this context.	Discussions are ongoing on the definitions of ‘blood establishment’ and the definition and understanding of the ‘inspection frequency’ in particular as regards a ‘risk based model’.

	Components November 2015		It was noted that the proposal would underline the need to comply with the 2-year inspection/control measure requirement in Directive 2002/98/EC but that the definition of 'inspection' allowed for measures other than on-site visits to be used (e.g. desk-based reviews). A questionnaire was issued to Competent Authorities in an effort to understand the current practice in relation to frequency of inspection/control measures at blood establishments.	
17.	Meeting of the Competent Authorities on Blood and Blood Components April 2013	Directive 2002/98/EC Article 3 Definitions	Apheresis granulocyte collection: As this component is new, no parameters for its quality and safety were laid down in Directive 2002/98/EC and associated Directives. The procedure requires pre-treatment of donors with corticosteroids or growth factors. Optimal collection also requires the use of a sedimenting agent. Granulocyte collection by apheresis was reported as occurring in ten MS. It was requested that CoE should investigate the new component. CoE will discuss the issue, as the European Convention on Human Rights requires the protection of donors as well as the protection of recipients. One NCA underlined the necessity of having a common approach on granulocyte concentrate in the future, and requested that the efficacy of the	A component monograph for granulocyte collection by apheresis was included in the 18th Edition of the Council of Europe Guide to the Quality and Safety of Blood and Blood Components (2015). A proviso was included which stated that the clinical efficacy, indication and dosage of granulocyte transfusions have not been established.

			component be studied.	
18.	Meeting of the Competent Authorities on Blood and Blood Components April 2013	Annex III of Directive 2002/98/EC	Blood component labelling: One NCA requested that the EU remove the requirement to state the original composition of the anticoagulant on the base label of the component. Adding the composition of the anticoagulant does not provide accurate information to the clinician and can even be misleading if the label is read as being an accurate representation of the content of the bag. Another NCA considered it a good idea to shorten this list, and only provide essential information to physicians.	As the requirement is outlined in Annex III of Directive 2002/98/EC, it can only be amended by a new Commission Decision via the comitology procedure. The Commission took note of this request for any future revision of EU blood legislation.
19.	Meeting of the Competent Authorities on Blood and Blood Components November 2013	Annex III of Commission Directive 2004/33/EC	Acceptance criteria of blood donors aged > 65: According to Annex III of Directive 2004/33/EC, donors over the age of 65 can only donate blood and blood components with the permission of the physician in the blood establishment, to be given on an annual basis. One NCA sought clarification as to whether this permission should be given on an individual or group basis. They explained that donors in this country can safely donate blood until at least the age of 71, provided that they meet all other relevant acceptance criteria. Other countries presented their national approaches. Six NCAs have all raised the maximum age from 65.	The Commission services recognised that the wording of the EU legislation is silent on whether a decision is to be made on an individual basis or can be made for a group as a whole, but recalled that such permission should be granted by the physician *in the blood establishment*. The organisational structure of blood establishments within any given country will therefore determine whether such a decision could be taken at a *de facto* national level, which would appear to be the case in certain MS. The Commission services informed the

			In contrast, three NCAs have an upper age limit of 65. One NCA reminded the group of the need to check the impact of anti-coagulants. One NCA also mentioned that they have a list of medicines to verify in older persons, as these give an indication of diseases necessitating exclusion.	group that in the implementation survey seven out of twenty-seven countries indicated they wanted to review the age criteria. The current edition of the Council of Europe Guide to the Quality and Safety of Blood and Blood Components states that the standards set out in the Guide define age limits for donation (Min 18 and Max 65) and provide discretion to the responsible physician to accept donors outside of these limits. It goes on to state that this medical discretion can be applied either on an individual basis for a given donor or else through a systematic approach based on an appropriate medical risk assessment.
20.	Meeting of the Competent Authorities on Blood and Blood Components November 2014	Point 2.2.1 of Annex III to Directive 2004/33/EC	West Nile Virus (WNV) amendment – Directive 2014/110/EU The Commission presented the amendment of Commission Directive 2004/33/EC and informed the group of next steps towards final adoption following approval of the amendment by the Regulatory Committee on the quality and safety of blood. The new Directive would amend the deferral criterion for West Nile Virus set out in the table (second column, last row) of point 2.2.1 of Annex III to Directive 2004/33/EC by replacing it with the following: '28 days after leaving a risk area of	Some participants expressed concern on that a requirement for individual NAT testing is too strict, however it was noted that only few comments were received during the adoption process. Two NCAs and EDQM felt that the requirement for individual NAT testing was too restrictive and pooled testing should have been allowed. See further on this item raised by

			locally acquired West Nile Virus unless an individual Nucleic Acid Test (NAT) is negative'.	European Blood Alliance in 2016
21.	Meeting of the Competent Authorities on Blood and Blood Components November 2014	Directive 2002/98/EC Article 2 - Scope	Lymphocyte immunotherapy: One NCA presented its query on whether the collection of partner immunocytes to treat women who have suffered from multiple miscarriages could be considered to fall under blood or tissues and cells legislation. Although blood is collected, the treatment is carried out in the context of assisted reproduction, a field regulated by the tissues and cells legislation. According to this NCA's evaluation, this therapy should be regulated pragmatically, as tissues and cells or as blood, depending on the professional body that applies the related therapy. It was highlighted that in future, lymphocytes might be used for other treatments, and it was therefore unclear which legal framework would be the most appropriate. MS were requested reflect on this issue and send comments within 2 weeks. Participants pointed to the general need for a body to decide on such borderline issues.	At the meeting of the Competent Authorities on Blood and Blood Components November 2015, the Commission services provided feedback on discussions arising from an interpretation question on the regulation of Lymphocyte immunotherapy used to treat recurrent miscarriage in pregnant woman. It was felt that justifiable arguments could be made for this activity falling under either the blood or tissues and cells legislation. This being the case, based on the specific nature of their national circumstances (assessment of risks to human health / desired level of human health protection / the existence of more stringent protective measures etc…), and given the fact that LIT is typically a local activity not involving cross-border steps, Member States benefit from a certain degree of discretion when deciding whether to classify this activity under either blood or tissues and cells legislation.

22.	Meeting of the Competent Authorities on Blood and Blood Components November 2015 Meeting of the CAs on Blood and Blood Components May 2016	Directive 2004/33/EC, Annex III, Point 2.1	Basocellular Epithelioma as a Donor Exclusion Criterion: One NCA raised the topic of the exclusion of donors with a history of basocellular epithelioma from donation. It was pointed out that Directive 2004/33/EC, Annex III, 2.1. requires permanent deferral for malignant diseases except '*in situ cancer with complete recovery'*. It was explained that in a strict sense a basocellular epithelioma is not a carcinoma in situ, but an invasive carcinoma with a very low metastatic potential. Given the relatively high and increasing frequency of this condition, the exclusion is having a significant impact on the blood supply. It was proposed that such donors should be accepted for donation and arguments to support the proposal were presented. The discussion on the topic was postponed to the next meeting. The NCA presented a discussion on whether donors with basocellular epithelioma should be excluded from donation as is currently the case. Basocellular epithelioma is the most frequent case of skin cancer. The NCA suggested that these donors should not be excluded based on the low metastatic potential (only 0.03%) and the lack of documented cases of transmission and asked for other NCAs views on this. One other NCA supported this suggestion.	At the meeting of the Competent Authorities on Blood and Blood Components in December 2016, one NCA gave an update on deferral of potential donors with a history of basocellular epithelioma. The NCA suggested to consider basocellular epithelioma as a localised cancer and, based on which, following complete recovery, such patients would be free to be blood donors (as stipulated in point 2.1 of Annex III of Commission Directive 2004/33/EC). This suggestion was generally supported in the meeting and it was noted that it is for each Member state to decide on the length of any temporary deferral. A potential need to consider a change in the legislation in the future was raised by the participants, in particular with a view to alignment with the tissues and cells legislation. The Commission took note of this request for any future revision of EU blood legislation.
23.	Meeting of the Competent	Directive 2004/33/EC	Potential amendment of Directive 2004/33/EC as regards temporary deferral criteria for donors of	At the meeting of the Competent Authorities on Blood and Blood

	Authorities on Blood and Blood Components December 2016	Annex III Point 2.2.1	allogeneic blood donations regarding West Nile Virus Directive 2004/33/EC Annex III Point 2.2.1 (as updated by Directive 2014/110/EU) The Commission introduced the request by the European Blood Alliance (EBA) on the potential amendment of Directive 2004/33/EC as regards deferral criteria on WNV. Following amendment in Directive 2014/110/EU, the deferral criterion now reads as*: '28 days after leaving a risk area of locally acquired West Nile Virus unless an individual Nucleic Acid Test (NAT) is negative.*' EBA questioned firstly, whether this wording precluded the use of mini-pool NAT testing and, secondly, whether 'a risk area of locally acquired West Nile Virus' equates to ECDC risk assessment terminology for WNV.It was noted that the topic would be discussed with EBA during the stakeholder meeting of 2nd December organised back-to-back with this competent authorities meeting. All participants had been invited to attend that meeting.	Components June 2017, the Commission services debriefed the group on the discussion in the December 2016 ad-hoc stakeholder meeting on the deferral criterion for West Nile Virus in Directive 2004/33/EC. During this stakeholder meeting, the European Blood Alliance (EBA) pointed out some difficulties for blood establishments in the implementation of the criterion as amended in Directive 2014/110/EU. On the first point (the use of mini-pool NAT), the group agreed that the cost implications put forward by EBA suggested that a broad interpretation of the text should be favoured. The ECDC representative confirmed that the sensitivity level of mini-pool NAT is sufficiently high so as to not warrant a credible safety risk if used. One NCA pointed out that the type of NAT used is not the decisive factor for them but rather the sensitivity level of the individual donor sample, whether this is tested as part of a mini-pool or not. The group supported a working interpretation, which leaves the

				discretion to MS to decide whether to use the deferral period or use NAT. Where NAT testing is permitted, MS would have the discretion to decide which type of NAT testing is permitted and any conditions, which should be placed on its use i.e. whether a risk assessment is necessary to justify the use of a particular type of NAT or to set an acceptable sensitivity level. On the second point (harmonisation of terminology surround 'WNV at risk area'), the Commission services presented the four types of risk area defined in the ECDC terminology for WNV risk assessments. The group agreed that the definition of an 'affected area' in the ECDC risk assessment terminology is consistent with the term 'risk area of locally acquired West Nile Virus' in Directive 2004/33/EC.
24.	Meeting of the Competent Authorities on Blood and Blood Components December 2016	Directive 2002/98/EC Article 2 - Scope	Platelet Rich Fibrin (PRF) Membrane: One NCA raised an issue on Regulation of Platelet Rich Fibrin (PRF)–membrane. It was highlighted that PRF is one of those that falls on the borderline, being a blood component that is used for purposes other than transfusion.	As with previous similar products, the collection and testing of blood are covered by the EU blood legislation 'for whatever the intended purpose'. However, for the rest of the process it is less clear which legal requirements apply. This issue has been raised in the past, also in relation to the preparation of this type of product using bedside

				devices. The participants stressed that clarity is needed on the regulatory status of PRF and that this should be considered in the ongoing evaluation of blood, tissues and cells legislation.

Part 2: Tissues and Cells

No.	**Meeting:**	**Reference to relevant text of Directive(s):**	**Issue:**	**Outcome:**
1.	Meeting of Competent Authority of Tissues and Cells February 2007	Article 2 of Directive 2004/23/EC: Scope	**Regulation of Donor Lymphocytes (DLI):** Donor Lymphocytes fall within the definition of "blood components" provided by Directive 2002/98/EC, but in practice, Directive 2002/98/EC would not be de facto applicable when DLI are used for haematopoietic stem cells transplants. In this instance, they would fall within the scope of Directive 2004/23/EC.	During discussions at the Blood Competent Authority Meetings, it was recommended that Art. 2 of Directive 2002/98/EC would expressly exclude from its scope of application DLI used in the context of haematopoietic stem cells transplant.
2.	Meeting of Competent Authorities on Tissues and Cells May 2008	Scope Article 2 of Directive 2004/23/EC	**Regulatory Status of Amniotic Membrane used for homologous procedures:** One NCA raised concern regarding the inclusion of some 'tissues and cells for non-homologous use' in the scope of the Advanced Therapy Regulation. In particular the use of amniotic membrane in the eye could be classified as a medical product, subject to	<u>Meeting of the Competent Authorities on Tissues and Cells December 2011:</u> Amniotic membrane is also used as a wound dressing and/or barrier for treatment and management of burn wounds and wounds of various etiology, its preparation and use being

			market approval while many EU tissue banks regulated under Directive 2004/23/EC procure, process, store and supply this tissue for ocular use. It was felt that if this product was to be regulated as a medicinal product it would result in it not being available for many patients in the future. It was considered that amniotic membrane use can be considered as homologous because the function it performs is the same whether on the placenta or on the eye (same essential functions) and therefore within the scope of Directive 2004/23/EC. This coincides with the position taken by the FDA.	similar to the one mentioned during the Meeting of Competent Authorities in May 2008. In this regard, one NCA called for a confirmation that amniotic membrane used as a wound dressing and/or barrier for treatment and management of bum wounds and wounds is covered by the Directive 2004/23/EC. It was concluded that amniotic membrane used as a wound dressing and/or barrier for treatment and management of bum wounds is covered by the Directive 2004/23/EC and that this view should be also communicated to CAT. The NCAs concluded that this issue highlights the need for a mechanism to discuss borderline products such as this and to have a more clear understanding of 'homologous' (i.e. 'same essential function') vs. 'non-homologous' use.
3.	Meeting of the Competent Authorities on Tissues	Definitions of 'Storage', 'Distribution' and 'Transport' within	**Storage of Tissues and Cells for end use:** One NCA requested clarification on the requirement to inspection 'storage' of tissues and cells for end-use i.e. at hospitals/healthcare establishments where the tissues/cells may be stored before final use. This NCA indicated they had adopted	<u>Meeting of the Competent Authorities October 2009:</u> A further discussion was undertaken at this meeting during which the Commission services outlined the various approaches being taken in the

	and Cells May 2009	Directives 2004/23/EC, 2006/17/EC and 2006/86/EC.	a risk-based approach in order to prioritise such establishments to be inspected and accredited/designated/authorised/licensed. At the beginning of the year, another NCA performed a survey among Member States regarding this issues and it seemed that most MS do not expressly accredit/designate/authorise/license storage for end-use.	MS in relation to the regulation of such end-use storage facilities. Some MS do not authorise these facilities in any way, other MS authorise the facilities if storage of tissues and cells occur for greater than 48 hours and other MS designate the responsibility for control of these storage facilities to the supplying tissue establishment. Joint meeting of the Competent Authorities and the Regulatory Committee on Tissues and Cells May 2010: The Commission services explained the provisions relating to the terms of "transport", "storage" and "distribution" within the meaning and scope of Directives 2004/23/EC, 2006/17/EC and 2006/86/EC. Based on these provisions the following may be concluded: Distribution of tissues and cells is an operation to be carried out by the tissue establishment before human application and it is the last point in the chain regulated by the Tissues and Cells Directives. Storage of tissues and cells, being a step before distribution, is regulated by the Tissues and Cells Directives

				only when it is carried out by the tissue establishments before the transport and delivery to the organisations responsible for human application. Storage in organisations responsible for human application is not covered by the Tissues and Cells Directives. In any case, traceability of tissues and cells shall be ensured from the donor to the recipient (Art. 8 of Directive 2004/23/EC). The Commission services noted that, notwithstanding the above and the exclusion of storage after distribution from the scope of the Tissues and Cells Directives, the objective of Directives 2004/23/EC, 2006/17/EC and 2006/86/EC is according to recital 13 of Directive 2004/23/EC to: *"...establish standards for each one of the steps in the human tissues and cells application process'* Therefore, it is important to ensure safety and quality of tissues and cells notably in terms of storage conditions, traceability and effective recall procedures, also for this step which is not covered by Directives 2004/23/EC. 2006/17/EC and

				2006/86/EC.
4.	Meeting of the Competent Authorities on Tissues and Cells May 2009	Scope Article 2 of Directive 2004/23/EC	**Regulatory Status of Pancreatic islets:** The Commission services indicated that it receives recurrent questions on whether pancreatic islets are covered by the Tissues and Cells Directive, the Advanced Therapies Regulation or whether they should be classified as organs.	The NCAs agreed that, without prejudice to an eventual future opinion of the CAT (Committee on Advanced Therapies), pancreatic islets, as far as they are used for the same initial function and as far as they are not substantially manipulated (for instance cultured), should be considered under the scope of the Tissues and Cells Directives.
5.	Meeting of the Competent Authorities on Tissues and Cells May 2009	Point 2.5.b) of Annex II of Directive 2006/17/EC	**Nucleic Acid Testing for Syphilis and the need to retest samples:** A query/clarification was raised in relation to the need to retest after 180 days for syphilis if a NAT was performed at donation. It was highlighted that Point 2.5.b) of Annex II of Directive 2006/17/EC states that "Where tissues and cells of allogeneic living donors can be stored for long periods, repeat sampling and testing is required after an interval of 180 days.". Point 2.6 of the same Annex specifies that "If in a living donor (except bone marrow stem-cell and peripheral blood stem-cell donors) the 'donation sample' is additionally tested by the nucleic acid amplification technique (NAT) for HIV, HBV and HCV, testing of a repeat blood sample is not required".	It was concluded as reasonable to assume that no repeat testing for syphilis after 180 days should be necessary when point 2.6 of annex II of Directive 2006/17/EC applies, as contrarily to HIV, HBV and HCV, Syphilis is not a donation exclusion criterion as such.
6.	Meeting of	Annex III of	**Testing of Partner Donations (not for direct use) in ART:**	Meeting of the Competent Authorities

	the Competent Authorities on Tissues and Cells October 2009	Directive 2006/17/EC	Annex III of Directive 2006/17/EC requires the testing of donors at the time of each donation of gametes in order to assess the risk of cross contamination during cryo-preservation. Some NCAs argued that this is costly and excessive and that testing at a fixed timeframe would be sufficient. The Commission services requested MS to submit scientific evidence in support of these arguments. <u>Joint meeting of the Competent Authorities and the Regulatory Committee on Tissues and Cells May 2010:</u> In the preceding months an expert group had been established as a response as a response to the concerns raised about the requirements of testing for *each* partner donation of reproductive cells as discussed at the Competent Authority Meeting, 19-20 October 2009. The WG included three NCAs and ESHRE. The objective of the group is to collect and analyse the available evidence-base. Key aspects include: potential risk of cross-contamination during cryopreservation; potential risk of cross-contamination during other processing and storage steps, and mix-up of gametes. In parallel, Commission services requested the assistance of the ECDC in examining the potential health risks associated with changing the protocol for testing from each donation to periodic testing (e.g. every 12th or 24th months). <u>Meeting of the Competent Authorities on Tissues and Cells December 2010:</u>	<u>for Tissues and Cells June 2011:</u> The Working Group on Testing of Partner Donations (not for direct use) in ART provided feedback indicating it had taken into account ECDC's risk assessment on change of testing requirements for reproductive cells in partner donation, as well as the experience and studies provided by the participating NCAs. The Working Group considered that it was not needed to maintain the current testing requirements for partner donation as laid down in Annex III of Directive 2006/17/EC and this was agreed by the National Competent Authorities. This will require a future amendment of the Directive, through the regulatory procedure. It is the responsibility of the NCAs to ensure that ART tissue establishments have in place the appropriate safety and quality systems, which does not affect the safety and quality of reproductive cells and/or human health when donors are tested at up to 24-month time intervals.

			The ECDC presented the draft risk assessment on change of testing requirements for reproductive cells in partner donation to the Competent Authorities. It underlined that given the limited data available the findings of the risk assessment should be treated with caution. The Commission services asked the Competent Authorities to review and provide comments on the ECDC risk assessment by 31 January 2011.	<u>Meeting of Competent Authorities for Tissues and Cells December 2011:</u> Taking into account the recommendations in the ECDC's risk assessment on change of testing requirements for reproductive cells in partner donation and following the discussions with NCAs during the meeting in June 2011, the Commission presented a draft decision amending the current legal testing requirements for partner donation as laid down in Annex III of Directive 2006/17/EC. All participants agreed with the draft. Following this outcome, there were also calls to review the screening requirements for sperm and oocyte donors (non-partner) to ensure that the requirements were up to date with scientific knowledge and testing advances.
7.	Meeting of Competent Authorities on Tissues	Annex III of Directive 2006/17/EC	**Starting point for Embryonic Cells Lines:** One NCA queried as to which should be considered the starting point for embryonic stem cell lines derived from frozen embryos, the donors of the gametes or the embryonic stem cell	<u>Meeting of Competent Authorities December 2012:</u> In one NCA, several universities and companies are developing new therapies based on "rest-embryos".

	and Cells October 2009		lines themselves? Such embryonic stem cell lines may end up in clinical trials or in use as advanced therapies. These tissues and cells are subject to the Tissues and cells Directives as far as donation, procurement and testing is concerned; to the Directive 2001/20/EC where used for Clinical Trials and to Regulation 1394/2007 when used as Advanced Therapies Medicinal Products. As these regulations fall under different authorities or bodies (Commission, National Competent Authorities and EMEA), the need for a multi-party discussion was expressed in order to ensure complementarities. One NCA stated that it consider that the starting point for the embryonic stem cell lines are the donors and that testing should be performed in accordance with Directive 2006/17/EC. The Commission services reaffirmed this indicating that as embryos used for stem cell lines have been frozen, there is a legal requirement to test the donors at moment of donation according to Annex III of Directive 2006/17/EC.	Such embryos were originally created through IVF for the purpose of fertility treatment, but are no longer needed by the partner/couple. Years after their creation, these embryos can be donated by the partner couples to research and development. This second donation raises some specific questions: (a)Are the original tests of partner donors, relevant if the embryos are now donated to third parties, potentially for allogeneic use? (b) Are these donated embryos intended for human application? (c) Due to the time window between the 2 donations, additional testing might be needed to check on potential contaminations in processing/storage. (d) As time windows might be around 10 years, national requirements from before transposition of Directive 2004/23/EC might need to be considered. The NCA presented a proposal to amend donor testing requirements in the Directive 2006/17/EC, allowing

				testing to be performed on material other than donor serum (i.e. cell lines) under specific circumstances. Following discussions, it was agreed to further reflect on the proposed amendment. Member States were requested to consult their experts and provide comments.
8.	Meeting of Competent Authorities on Tissues and Cells October 2009	Scope: Article 2 of Directive 2004/23/EC	**Facial transplant:** A question was raised as to whether composite and facial transplant should be considered organs or tissues. It was indicated that in most MS, facial transplants should be considered as composite tissue transplants, multi-tissues or tissues with special status. Composite tissue transplants require processing similar to organs; however, composite tissue transplants are not defined as organs as they fulfil no physiological life-saving function. No conclusion was reached at the meeting. Meeting of Competent Authorities on Tissues and Cell December 2011: The question whether composite tissues, such as facial transplant should fall under the Organs or T&C Directive was again introduced by the Swedish Competent Authority. Since this question was first raised in 2009, Directive 2010/53/EU was adopted and provides for a definition for "organs" in Art 3 (h). Several NCAs considered that facial	<u>Meeting of Competent Authorities on Tissues and Cells December 2012:</u> The issue was brought again to the attention of the NCAs for organ transplantation and during their meeting in September 2012 it was agreed that the face is a vascularised composite tissue requiring similar processing and safety issues to organ transplantation. The group of the Tissues and Cells NCAs agreed with this.

			transplants require similar processing and have similar safety issues to organ transplantation. It was suggested that Commission should have the same interpretation for other multi-tissue transplantation procedures (e.g. hand transplantation). <u>Meeting of the Competent Authorities on Tissues and Cells June 2012:</u> The Commission services indicated that the definition of Organ should prevail in the instance of composite tissues but that a thorough analysis of the technical aspects of such procedures is needed. Several NCAs provided arguments in support of including the transplantation of composite tissues under the Organs Directive (e.g. long-term storage – possible for tissues and cells, but not valid for organs/composite tissues). Other NCAs stated that they have already included composite tissues in their national legislation when transposing the Directive 2010/53/EC (ES). Council of Europe representative mentioned that it was agreed to include transplantation of composite tissues in the last edition of the Guide for Organ Transplantation to be published next year.	
9.	Meeting of Competent Authorities on Tissues and Cells October 2009	Distribution: Definition and concept in Directives 2004/23/EC, 2006/17/EC and 2006/86/EC.	**Commercial Bone Distributors:** One NCA raised a query about the distribution of commercial bone products in the EU indicating that these were generally placed on the EU market through one distributor within one EU MS and how these should/can be managed under the Tissues and Cells Directive. The Commission services stated that Directive 2004/23/EC clearly stipulates that the import/export, storage and distribution	Due to the important safety aspects related to the issues raised, it was agreed that they should be raised in discussion in the Import-Export Working Group with the aim to finding a harmonised approach across EU Member States.

			activities can only be performed by Tissue Establishments. Therefore, all distributors of commercial bone substitutes in all EU MS need to comply with the EU legislation and need to be authorised by the NCA accordingly. <u>Meeting of the Competent Authorities on Tissues and Cells December 2011:</u> The issue regarding commercial bone products was again brought up by one CA who had received several applications from national commercial distributors for authorisation as a Tissue Establishment for "storage" and "distribution" of demineralised bone products. Most often, these are processed outside Europe (USA) and imported through one European country (i.e. the point of entry), where the donor history file review and product release takes place. When distributed in Europe from this point of entry flexibility in relation to qualifications for the designated Responsible Person should be considered. During discussions NCAs shared their experience and problems encountered with commercial distribution of such products. Another concern was raised: the possibility that some of the products may enter into some MS as medicines or medical devices, and thus avoid the national controls by NCAs for tissues and cells. In this regard, the Commission reminded the NCAs that a Working Group to work on import-export legal requirements is being created and called for volunteers. Mutual recognition of the site (authorisation) certificates for distributors of bone substitutes (DBMs) was also introduced by one NCA who suggested that the site certificates issued by the	Many of the issues raised here in relation to the import of commercial bone products in the EU via commercial distributors/brokers were subsequently addressed in Directive 2015/566 as regards the procedures for verifying the equivalent standards of quality and safety of imported tissues and cells, however the issue of brokering services was not addressed in this Directive and was addressed at a national level.

			National Competent Authorities for distributors of bone substitutes should be more informative so they are mutually recognised within EU. When a commercial distributor in one MS receives DMBs from a tissue establishment in another EU country, the site certificate of the latter could attest that the specified activities (e.g. donation, procurement, testing, processing, storage, distribution) were authorised and therefore the appropriate regulatory requirements have been fulfilled. The minimum information of name and site address of the tissue establishment, the list of the specified activities and the product descriptions/codes to which it is applicable, should be included and thus, these types of site certificates can assist the principle of mutual recognition and transparency in EU. Several NCAs supported the above proposal. It was also suggested that the principles of the model certificate in the "Manual on inspection of tissue and cell procurement and tissue establishments" published by the Commission in August 2010 should be applicable for all site certificates. <u>Meeting of the Competent Authorities on Tissues and Cells June 2012:</u> Brokers selling T&C without storage; online advertising of demineralised bone products: One NCA again raised the question about authorising/licensing "broker companies" which are not involved in tissues/cells storage, but just import/export of products from third countries and their subsequent distribution in EU Member States. Criteria for authorising/inspecting were discussed. In addition, advertising DBMs over internet with the possibility of ordering and their direct distribution to EU hospitals/professionals was also debated.	

10.	Joint meeting of the Competent Authorities and the Regulatory Committee on Tissues and Cells May 2010	Annex II and III of Directive 2006/17/EC (HTLV Testing)	**Human T-lymphotropic virus (HTLV) I/II testing:** For a number of years the American Association of Tissue Banks (AATB) had required systematic HTLV testing for donations of tissues and cells occurring on US territory. Recently the AATB board had agreed to align with FDA's approach of not imposing an HTLV test for processed human tissues. Directive 2006/17/EC requires that HTLV-I antibody testing is performed for donors living in, or originating from, high incidence areas, with sexual partners originating from those areas or where donor's parents originate from those areas. The Regulatory Committee concluded that the Commission should request the assistance of ECDC to review the elements put forward by the AATB to justify suspending systematic testing for HTLV and to assess the possible risks of the change in HTLV testing for human tissues and cells imported from US into the EU. One NCA informed the participants that it has decided to maintain its requirements for HTLV testing for tissues and cells imported from the US. Commission agreed to set up a small working group of volunteering Member States to discuss and elaborate on recommendations on how to best face this situation.	This issue was again discussed at the Meeting of the Competent Authorities on Tissues and Cells December 2010 and the Meeting of the Competent Authorities on Tissues and Cells June 2011 and December 2011. Following the discussion of the working group on HTLV testing and based on ECDC's risk assessment on HTLV transmission by tissue/cell transplantation, during the NCAs meeting in June 2011, it was recommended to amend Annex 11 and III of the Directive 2006/17/EC by changing from high "incidence" to high "prevalence". This amendment was subsequently implemented.
11.	Joint	Article 2 of	**Pancreatic Islet Cell Transplantation:**	Meeting of the Competent Authorities

	meeting of the Competent Authorities and the Regulatory Committee on Tissues and Cells May 2010	Directive 2004/23/EC: Scope	The Human Tissue Authority in one NCA raised a question in relation to autologous treatment with pancreatic islets in the same surgical procedure, where the pancreas is removed, transported to a separate laboratory for processing and returned to the operating theatre for application. The patient remains in theatre while processing takes place. The question raised was whether this procedure would be excluded from the scope of Directive 2004/23/EC according to its Article 2. In addition, the meaning of the term "banking" in recital 8 was questioned in relation to the above mentioned surgical procedure. The NCA explained that the question relates to other similar treatments e.g. a pelvic sarcoma treatment where part of the pelvis is removed, transported to a different hospital where it is irradiated and then returned back to the patient. Another NCA suggested that the transport of the tissues from the operating room to the place of processing under certain conditions can be considered banking as referred to in recital 18 of Directive 2004/23/EC.	on Tissues and Cells 6-7 December 2010: The Commission services presented the legal framework that applies to the situation as raised in the May 2010 meeting: Tissues and cells used as an autologous graft within the same surgical procedure are excluded from the scope of Directive 2004/23/EC. However, recital 8 explains that the exclusion is justified only because the quality and safety considerations associated with this process (autologous same surgical procedure without any banking process) are completely different (from 'normal' tissues and cells). The considerations are different because it was assumed at the time that in an autologous transplantation within the same surgical procedure, the cells would remain during the whole process in the operation theatre, hence there would be no risks in this case for cross-contamination or mix-up of the cells during transport or during processing. During the

				discussion, several NCAs referred to the next case as a typical example for exclusion: dissection and use of a peripheral vena for immediate use as bypass during cardiovascular surgery. The term 'banking process' is not defined in Directive 2004/23 but needs to be interpreted in the light of COM initial proposal and of the CoE recommendation R(94)/141. Based on the above consideration it was concluded that: The term 'banking process' cannot be considered only as storage and preservation. The processing of autologous grafts in other establishments with a view to their application within the same surgical procedure was considered to be within the scope of Directive 2004/23/EC, as well as the storage (if relevant), transport and distribution operations that are carried out with a view to this processing.

12.	Joint meeting of the Competent Authorities and the Regulatory Committee on Tissues and Cells May 2010	Directive 2004/23/EC Annex II Point 2.4	**Cornea donation in relation to the 24-hour requirement for blood** **Sampling:** In a letter of 8 March 2010, the University Medical Centre of Freiburg (Germany) claimed that, due to the requirement for serological viral testing within 24 hours after the donor's death, the number of cornea donors in Lions cornea donation bank, Baden-Württemberg had dropped by 25% over a year. It was explained that often more than 24 hours are needed to fully explain a corneal donation to the deceased person's relatives. Most of the NCAs informed that to date they had not encountered problems of increased cornea loss because of the testing requirements in Article 4 and Annex II of Directive 2006/17/EC. In addition, many delegations expressed the view that serological viral testing within 24 hours after donor's death is necessary and appropriate.	<u>Meeting of the Competent Authorities on Tissues and Cells 23-24 June 2011:</u> One NCA presented the preliminary results of a national study, which noted that the availability of cadaver corneas in this country may be reduced by over 60% due to the 24-hour limit for post mortal blood sampling. A study of the Charité hospital in Berlin was also quoted. The Group of Competent Authorities considered that further validation of assays and data is required, as well as an improved statistical analysis.
13.	Meeting of Competent Authorities on Tissues and Cells December 2010	Article 2 of Directive 2004/23/EC: Scope	**Human placenta tissues for human consumption:** One NCA raised a question about the legal status of human placenta tissues for human consumption. Human placenta is consumed by some birth mothers either raw (placenta smoothies) or cooked and dehydrated (capsules) or by the baby in a form of tincture. The placenta derived products are prepared by a) the birth mother at her home b) a "placenta expert" at mother's home c) third party (commercial service). The questions raised were 1) whether the placenta processing falls within Directive 2004/23/EC and its implementing measures and 2) whether placenta derived products are covered by the Food	The Commission services presented the legal framework. It could be argued that, although derived from human tissues and cells, the placenta derived product under question are intended to be ingested by humans hence they are covered by the definition of 'food' in Regulation 178/2002/EC on general food law.

			Law.	
14.	Meeting of Competent Authorities tor Tissues and Cells June 2011	Article 2 (a) of Directive 2004/23/EC: Scope	**Procurement of Stem Cells from Autologous Adipose Tissue :** The Commission was asked whether the procurement of stem cells from autologous adipose tissue and re-implantation within the same surgical procedure is considered in or out of scope of the Cell & Tissue Directive 2004/23/EC. The device is currently used for reconstructive surgery (e.g. reconstruction of the breast following mastectomy). The Commission services briefly presented the main features of the CE-marked device, which enables real-time access to adipose-derived stem cells at the bedside. The device automates and standardises the extraction, washing, and concentration of a patient's own adipose-derived regenerative cells (ADRCs).	Several NCAs expressed their opinions on the procedure. Conclusively, the group of Competent Authorities for Tissues and Cells considered that that procurement of stem cells from adipose tissue using the above mentioned procedure, when applied to the same individual within the same surgical procedure, in the same operating room, when cells are used for the same essential function (e.g. adipose derived regenerative cells restoring the adipose mass of the breast following mastectomy for breast cancer), should be exempted from the Cell & Tissue Directive 2004/23/EC, based on Article 2.a.
15.	Meeting of Competent Authorities on Tissues and Cells December 2011		**Regulatory Status of Apheresis of mononuclear cells for preparation of ATMPs:** In order to produce some ATMPs (e.g. autologous tumour vaccines) peripheral blood mononuclear cells are collected by an apheresis procedure. These procedures can be carried out in hospitals and in blood establishments. The question is whether the cell product is in the scope of the Blood Directive or in the scope of the T&C Directive (or both).	Following discussion, it was agreed by NCAs that, similar with Donor Lymphocyte Infusion, mononuclear cells collected by apheresis for ATMP manufacture are considered to be in the scope of the EU tissue and cell Directives.

16.	Meeting of Competent Authorities on Tissues and Cells December 2011	VUD	**VUD; Compensation of Gamete Donors:** One NCA updated the NCAs about the new decisions taken by the Human Fertilisation and Embryology Authority's (HFEA) regarding the financial compensation for gamete donors and the benefits in kind allowed by its legislation (egg sharing). It was highlighted that without these approaches, this Member State would face a major shortage of eggs. 40% of the eggs currently donated in this Member State are ensured through egg sharing, the remaining 60% being provided by known donors (friends, relatives). It was also mentioned that the Member State has a registry of all gametes donors and that counselling before donation is compulsory. During the following discussions, some NCAs provided input on their national legislation and in particular on the types of financial compensation for gametes donation or benefits in kind. Discussions also addressed the issue of financial compensation vs. incentive. The Commission services reminded the NCAs about the requirements of the Charter of Fundamental Rights of the EU, which clearly prohibits on "making the human body and its parts as such a source of financial gain".	It was agreed by the NCAs that this topic requires further work at Union level and that a comprehensive definitions and understanding of 'compensation', 'incentives' and 'benefit in kind' is required.
17.	Meeting of Competent Authorities on Tissues and Cells	Article 2 of Directive 2004/23/EC: Scope	**Regulatory Classification of Autologous Endometrial Cells (Endocell)**: A Competent Authority asked the Commission and the CAs for Tissues and Cells whether the co-culture of autologous endometrial cells to support embryo transfer at blastocyst stage may fall under the provisions of Directive 2004/23/EC and about	NCAs agreed that there is no clear regulatory framework yet for such a product (e.g. endometrial tissue) which is produced in one Member State for use in processing patient cells in other Member States. The

	June 2012		its use in other EU Member States. One NCA stated that this is considered an ancillary therapeutic product in this Member State, requiring authorisations.	issue of mutual recognition of processing authorisations could be discussed at a future date. Some NCAs considered that in this case rather the process in the different sites of utilisation should be authorised, and not the single product. It was stated that authorisation for such processing falls under Directive 2004/23/EC.
18.	Meeting of Competent Authorities on Tissues and Cells June 2012	Article 2&3 of Directive 2004/23/EC: Scope	**Faecal microbiota transplants:** One NCA asked whether faeces donated by partner or close relative transplanted as treatment for *Clostridium difficile* infection may fall under Directive 2004/23/EC and what would be the safety and quality issues to be considered in this case. The group of NCAs concluded that bacterial flora does not fall under the provisions of Directive 2004/23/EC.	<u>Meeting of the Competent Authorities on Tissues and Cells June 2014:</u> The issue of faecal donation/transplant or FMT (Faecal Microbial Transplant) was raised again. <u>Meeting of the Competent Authorities on Tissues and Cells December 2014:</u> The Commission services informed the meeting that, to fall under Directive 2004/23/EC, such substances would need to be considered as a 'tissue' or 'cell' and secondly, would need to be considered as intended for 'human application' as per the definitions of

				these terms in Article 3 of Directive 2004/23/EC. It was clarified that since they do not meet these criteria these substances are not considered as falling within the scope of Directive 2004/23/EC or any particular quality and safety legislative framework at Union level. Thus, 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 national legislative frameworks, including the tissues and cells quality and safety requirements, to these substances. The Commission services further pointed out that Article 168(4) TFEU is unequivocal in laying down a mandate for the adoption of measures setting high standards of quality and safety with respect to all substances of human origin. As both human breast milk and faeces are uncontestably substances of human origin it was concluded in the meeting that this Treaty Article should provide a legal basis for possible future regulation of these substances in terms of their quality and safety.

19.	Meeting of Competent Authorities on Tissues and Cells December 2012	More Stringent Safety Requirements	**NAT HCV testing for tissues imported from third countries and distributed in EU Member States:** One NCA raised the issue of more stringent safety and quality requirements than those requested by the EU legislation (e.g. HVC NAT testing) when importing tissues from third countries (e.g. USA), particularly via other MS where similar more stringent requirements are not in place. The NCAs asked questions, including whether an EU Member State is allowed to prohibit an import when the quality meets minimum requirements of the EU Directives but not the more stringent national requirements. Several NCAs with more stringent testing requirements stated that they already have in place methods to check these additional requirements and in some countries tissues/cells distributed from other EU countries are treated like tissues/cells imported from third countries.	Since Directive 2004/23/EC lays down only minimum safety and quality requirements, it was concluded that it is the responsibility of the Member States with more stringent testing requirements (6-7 EU Member States) to check whether tissues/cells distributed from other EU Member States fulfil their national requirements.
20.	Meeting of Competent Authorities on Tissues and Cells June 2013		**Therapeutic application of blood cellular components separated by cytapheresis:** One NCA asked the Commission and the group of Tissues and Cells CA whether blood cellular components separated by cytapheresis are covered by the Blood or Tissues and cells legislation. This clarification would be needed to decide whether a blood establishment performing such procedures may also require an authorisation as a tissue establishment. Several NCAs considered that such activities are covered by the Blood legislation. One NCA recalled previous discussions in which the Tissues and Cells CA group agreed that donor lymphocytes infusion and mononuclear cells should be covered by the Tissues and Cells legislation. It was mentioned that both	The Commission agreed that this topic should be further analysed.

			pieces of legislation, provide the same level of quality and safety. However, it was underlined that the legal requirements should be clear for all stakeholders, and it would be preferable to have the same approach at EU level.	
21.	Meeting of Competent Authorities on Tissues and Cells June 2013	Article 17 of Directive 2004/23/EC	**Responsible Person – meeting laws in other Member States:** An NCA queried whether the responsibility for meeting any supplementary national requirements for distribution falls under the responsibility of the responsible person (RP) at the receiving tissue establishment in one Member State or of the RP at the sending tissue establishment in another Member State. It was pointed out that Article 17(2)(a) of Directive 2004/23/EC provides that the RP has the duty and responsibility for "ensuring that human tissues and cells intended for human applications in the establishment for which that person is responsible are procured, tested , processed, stored and distributed in accordance with this Directive and with the laws in force in the Member State". It was also recalled that during the Tissues and Cells CA meeting in December 2012, the group concluded that it was the responsibility of the Member States with more stringent testing requirements to check whether tissues/cells sent from other EU Member States fulfil their national requirements. Two NCAs confirmed that in their countries, for tissues/cells received from other MS, the RP needs to confirm that the more stringent requirements were met. Two NCAs stated that collaboration with the RP at the sending tissues/cells do not fulfil the legal requirements of the receiving country whenever they are aware that sent tissues/cells do not fulfil the legal	It was indicated that this issue could possibly be looked at in the context of a potential revision of Directive 2004/23/EC.

			requirements of the receiving MS. The Commission highlighted that this question needs also to take into account cases of "direct distribution".	
22.	Meeting of Competent Authorities on Tissues and Cells June 2013		**Autologous keratinocytes suspension:** An NCA asked whether Directive 2004/23/EC applies to autologous keratinocyte suspensions. From the technical point of view, autologous epithelial tissue is collected from a patient in a hospital and distributed immediately to a laboratory (outside the hospital). In the laboratory, the keratinocytes are separated mechanically and enzymatically from the collected tissue, and the intermediate product is diluted with a physiological sodium chloride solution. It was clarified that keratinocytes are not manipulated or cultured and the entire processing takes about two hours. After processing, the product is sprayed on the same patient's burned area or wound. In relation to the above question, one NCA described a similar case, in which adipose cells are transported for processing to an outside laboratory in a sealed container, which is closed/opened only in the operating theatre.	It was noted that with regard to similar question during the Tissues and Cells CA meeting in December 2010 (pancreatic islets processed in a laboratory for use in the same surgical procedure") the advanced answer was that the exemption foreseen under Article 2.2(a) of Directive 2004/23/EC should not apply if the tissues or cells are taken out of the operating room to a laboratory for processing. It was considered that using a "sealed container" does not provide any additional safety benefit, and the risk of mix-up or mislabelling remains unchanged.
23.	Meeting of Competent Authorities on Tissues and Cells June 2013	Partner Donation in ART	**Definition of Partner Donation:** A question was raised on the use of the term 'partner donation' in ART defined solely as an intimate relationship between a male and female partner. They referred to 'known donors' e.g. in a lesbian relationship where one partner donates oocytes to the other for IVF following fertilisation with donor sperm or where	It was concluded that the definition of partner donation could be looked at in the context of a potential future revision of the Directive.

			a female relation or friend may do similar for another female relation or friend. Two NCAs confirmed that such 'known' donors must be treated as non-partner donors and tested/processed as such.	
24.	Meeting of Competent Authorities on Tissues and Cells June 2013	Genetic Screening of Egg Donors	**Genetic Screening of Gametes:** A question was raised concerning the national practices with regards to genetic screening of egg donors.	Following some discussion, it was agreed that further reflection was required on the development of a list of genetic screening requirements for donors of non-partner sperm and oocytes.
25.	Meeting of Competent Authorities for Tissues and Cells December 2013	Article 9 of Directive 2004/23/EC: Import	**Import and distribution of starting materials for ATMPs:** One NCA introduced the issue of the import and subsequent EU distribution of starting materials for ATMPs with a view to clarifying whether such activities fall within the scope of the tissues and cells legislation. Article 9 of Directive 2004/23/EC lays down that imports of tissues and cells from third countries are undertaken by tissue establishments authorised to import while Article 3 of Regulation 1394/2007 on ATMPs states that the donation, procurement and testing of tissues and cells contained in ATMPs shall be in accordance with the tissues and cells legislation but makes no mention of their import. The question concerned circumstances when donation, procurement and testing takes place in a third country and whether the subsequent import of starting materials for ATMPs must be authorised under the tissues and cells legislation. As shown by the presentation, different approaches were	

			adopted across the MS often depending on the level of processing the tissues and cells have undergone in the third country.	
26.	Meeting of Competent Authorities for Tissues and Cells December 2013	Directive 2006/86/EC: Annex I Point C(6)	**Use of CE marked medical devices – 'when applicable / wherever possible / when appropriate'** One NCA requested clarification of the meaning of 'Critical reagents and materials must meet documented requirements and specifications and when applicable the requirements of Council Directive 93/42/EEC of 14 June 1993 concerning medical devices and Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices'. Directive 2006/17/EC, Annex IV, point 1.3.10 states that 'wherever possible, only CE marked medical devices must be used…' while Annex II, point 2.1 to the same Directive lays down that 'tests must be carried out by a qualified laboratory, authorised as a testing centre by the competent authority in the Member State, using EC-marked testing kits where appropriate.'	The general opinion during the discussion which followed this presentation was that while such phrasing creates ambiguity it also leaves some room for some much-needed flexibility in interpreting the meaning. .
27.	Meeting of Competent Authorities for Tissues and Cells	Article 2 of Directive 2004/23/EC: Scope	**Breast Milk Banking:** The question of how to regulate the allogeneic 'application' of breast milk has arisen following the proliferation of breast milk banks across the EU. As the Council of Europe have produced a questionnaire for its CD-P-TO members on the issue, it was decided that DE, rapporteur within the CoE group, would	<u>Meeting of the Competent Authorities on Tissues and Cells June 2014:</u> The issue of breast milk banking was raised again.

	December 2013		present the questionnaire as a way of initiating a preliminary discussion on this issue within the CA group. During the discussion it was suggested that a majority of MS regulate such activity through food safety authorities although the emergence of applications of breast milk for therapeutic purposes may require a reassessment of such regulatory structures and closer cooperation between food safety and T&C CAs in order to ensure that disease transmission risks and ethical issues linked to donation are suitably dealt with.	<u>Meeting of the Competent Authorities on Tissues and Cells December 2014:</u> In the meeting the Commission stated that such substances would need to be considered as a 'tissue' or 'cell' and secondly, would need to be considered as intended for 'human application' as per the definitions of these terms in Article 3 of Directive 2004/23/EC to fall under Directive 2004/23/EC. It was clarified that if these substances are not considered as falling within the scope of 2004/23/EC or any particular quality and safety legislative framework at Union level, 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 national legislative frameworks, including the tissues and cells quality and safety requirements, to these substances. The Commission services further pointed out that Article 168(4) TFEU is unequivocal in laying down a mandate for the adoption of measures setting high standards of quality and

				safety with respect to all substances of human origin. As both human breast milk and faeces are uncontestably substances of human origin it was concluded that this Treaty Article should be able to provide a legal basis for future regulation of these substances in terms of their quality and safety.
28.	Meeting of Competent Authorities for Tissues and Cells December 2013	SARE Reporting Requirements	**Reporting of a serious adverse reaction (SAR) upon the birth of a child from a sperm or egg donor with a genetic disease:** The issue concerned reporting of SAR following sperm donations from non-partner donors where a genetic disease is transmitted to the new-born child from the donor. Technically speaking this SAR does not occur in the recipient but in the new-born child and therefore does not need to be reported if the wording of the legislation is followed strictly. Two NCAs felt that such cases should be reported as SAR.	
29.	Meeting of Competent Authorities for Tissues and Cells December 2013	Directive 2006/17/EC Annex III	**Identifiable genetic diseases in non-partner donors:** One NCA called for a discussion on what should or could be done in terms of guidance or conditions on the use of such reproductive cells once a genetic disease in a donor has been identified following sperm donation. Other than the requirement laid down in Annex III to Commission Directive 2006/17/EC that complete information on the associated risk of genetic disease transmission must be communicated and explained to the	<u>Meeting of Competent Authorities on Tissues and Cells June 2015:</u> One NCA informed the group about two changes in national legislation regarding procedures related to sperm donors identified as carriers of a hereditary genetic disorder, effective from April 2015.

			recipient where there is an identified history of genetic disease in the donor's family, there are no rules in the EU legislation on the use or non-use of such reproductive cells. One NCA explained that the terms used in its country are 'temporary block' and 'conditional block' however the conditional block is permanent in its nature except that the donated cells may continue to be used for siblings of children already born from that donor only. Another NCA pointed out that, other than on public health grounds, a complete ban on the use of such cells may be difficult in light of fundamental / human rights provisions on the right to start a family and stated that in the case of a potential use for siblings it would expect a risk assessment to be carried out and the recipient couple to receive counselling on the risks of genetic disease transmission.	According to these current requirements, such donors are no longer placed in either quarantine or permanent block, but the sperm bank must update the donor profile/status on their website each time such information becomes available. Customers (clinics and private individuals) can purchase sperm straws from these donors only after having read and accepted a declaration (even without reading the donor information with the case description and risk assessment, with reference to Convention on Human Rights and Biomedicine). The sperm bank must also inform all customers that already purchased straws from such donors. The NCA also confirmed that, after reintroducing the "permanent block" status, it will continue informing CAs about such cases via the RATC platform.
30.	Meeting of Competent Authorities for Tissues and Cells	Distribution: (Directives 2004/23/EC, 2006/17/EC and 2006/86/EC)	**Direct distribution of reproductive cells to end users:** Following discussions on this subject in previous CA meetings (June 2013), one NCA gave an update of the latest situation and informed the group that they had come to the conclusion that, under its national law, sperm banks could not be prevented from	<u>Meeting of Competent Authorities on Tissues and Cells June 2015:</u> Following a request for clarification from the NCAs, the Commission informed the group that it has

	December 2013		distributing directly to end users as they felt that this would infringe free movement of goods rules. Several NCAs pointed out that they have more stringent rules in place on who can purchase /use such reproductive cells or the permission needed from the NCA prior to cross-border distribution into their MS. However, this was not the case in all MS. This provoked the question of how potential end-users and / or the distributing sperm bank should be made aware of such additional national rules. A further question was raised querying the extent of such situation and whether it would be possible to get data from the distributing TEs in order to establish the true extent of this issue. CAs were therefore called on to try to obtain and provide generic data on this situation to be presented at the next NCA meeting.	considered whether a requirement to distribute sperm to an authorised tissue establishment or authorised organisation responsible for human application (i.e. a restriction on direct distribution to natural persons) is in line with Union law and if such a restriction is in line with Union law, can Member States with such restrictions in place require the cooperation of the MS of origin in enforcing them. The Commission services indicated that not only would such a restriction seem to be admissible in order to implement EU quality and safety standards, the lack of such a restriction may be regarded as not being in line with Union legislation and in particular the provisions on traceability and the obligation to report (serious) adverse reactions. <u>Meeting of Competent Authorities on Tissues and Cells February 2017:</u> One MS subsequently amended its legislation to fully comply with EU requirements for traceability and vigilance.

31.	Meeting of Competent Authorities for Tissues and Cells December 2014	Article 2 of Directive 2004/23/EC: Scope	**Regulation of lymphocyte immunotherapy (in treatment of recurrent miscarriage):** One NCA introduced the topic of lymphocyte immune therapy (LIT) to the group and raised the question of how the steps leading to its human application should be regulated across the Union. LIT is used as a treatment for recurrent miscarriage and involves the application of allogeneic human cells (lymphocytes) which are separated from the whole blood collected from a donor, often the husband or partner of the recipient. In such a situation both the EU tissues and cells legislation, the EU blood legislation or a combination of both could be relevant. Prior to the NCA meeting a survey was conducted on how activities leading to LIT were currently regulating. While a considerable majority of respondents indicated that these activities were regulated under T&C legislation, a variety of responses were received with some MS also indicating a combination of both blood and T&C legislation. Other replies also stated that other regulatory frameworks were used or that the therapy was not used within their MS. The NCA itself indicated that, in the absence of legal clarity on the issue, it was currently adopting a pragmatic approach allowing for the procurement to take place by establishments authorised to carry out procurement under the tissues and cells legislation or to carry out collection under the blood legislation. The NCA also pointed out that a cross-sector decision-making process is needed at EU-level to deal with such classification issues.	<u>Meeting of Competent Authorities on Tissues and Cells June 2015:</u> The Commission services considered the following three issues: whether withdrawal of whole blood leading to extraction of lymphocytes falls within the scope of blood or tissues and cells legislation, whether Member States may choose to regulate this activity under either their national blood or tissues and cells legislation and finally whether within a Member State, its authorities have the discretion to regulate the activity under both their national blood and tissues and cells legislation. The Commission services put forward the following view for the group's consideration: It was felt that justifiable arguments could be made for this activity falling under either the blood or tissues and cells legislation. This being the case, based on the specific nature of their national circumstances (assessment of risks to human health / desired level of human health protection / the existence of

			In the discussion which followed one NCA declared that it considered the initial steps of donation, procurement (collection) and testing to fall under the blood legislation and stated its interest in hearing why a number of NCAs indicated that they regulate it under the T&C legislation. One NCA pointed out that both donor lymphocytes for infusion and haematopoietic stem cells fall entirely under T&C legislation. In particular, a parallel could be drawn with donor lymphocytes infusion where identical processing techniques are applied although the actual procurement method is different. This NCA also pointed out that a greater number of tissue establishments were equipped to carry out the procurement and then processing than blood establishments. From a practical point of view it thus made more sense to allow TEs to oversee the donation, procurement (collection) and testing rather than restrict this to BEs many of which are not further equipped to carry out the further stages leading to LIT. While a majority in the group were in favour of allowing procurement under the tissues and cells legislation, one NCA asked for further clarity.	more stringent protective measures etc…), and given the fact that LIT is typically a local activity not involving cross-border steps, Member States benefit from a certain degree of discretion when deciding whether to classify this activity under either blood or tissues and cells legislation. On the final point the Commission services reminded the group of the importance of maintaining legal certainty within any given national legislative framework but did not exclude the possibility that in this specific case authorities within one Member State could allow the same activity to be governed under both sets of legislation, depending on the establishment which performs it, provided that this is justified by an assessment of the risks to human health and the desired level of protection specific to that Member State focusing in particular on largely equivalent levels of quality and safety assured under both sets of national legislation.
32.	Meeting of	Directive	**Testing Requirements for Non-Partner Sperm Donors:**	Meeting of the Competent Authorities

	Competent Authorities for Tissues and Cells February 2017	2012/39/EU, Annex III point 4.2.	On the subject of testing requirements for donations other than by partners, one NCA explained that its country requires non-partner sperm donors to be tested at the time of their first sperm collection and each 3 months subsequently. One NCA referred to the wording and the history of Directive 2012/39/EU, Annex III point 4.2. In this context, the Commission services agreed to request ECDC to assess any risks associated with the donor testing practices for non-partner donations according with this practice.	<u>on Tissues and Cells November 2017:</u> ECDC had assessed the risks associated with the donor testing protocol for non-partner donations currently being applied in one MS. The preliminary conclusions of the ECDC technical report suggest that the national protocol largely ensures an equivalent level of safety. However, under certain circumstances a minor increased risk of missing a window period infection remains, which could be mitigated by restricting release for a specified period. In that case, the protocol could be considered as more stringent than the Directive requirement. <u>Meeting of the Competent Authorities on Tissues and Cells June 2018:</u> The Commission services reported back that, based on the conclusions of the ECDC technical report, that the Danish serological testing protocol can be considered as safe as, or safer than, the protocol in Directive 2006/17/EC, therefore, it may be argued that the protocol can be considered as a more stringent national requirement as permitted in Article 4 of Directive 2004/23/EC and

				article 168 (4)(a) TFEU. With regard to the NAT testing protocol, the Commission services concluded that this could also be considered as a more stringent national requirement provided that the national legislation was changed in line with the recommendation of ECDC to defer release of the donated sperm until the longest diagnostic window period has lapsed. This change to the legislation was subsequently implemented.
33.	Meeting of Competent Authorities for Tissues and Cells November 2017	Article 2 of Directive 2004/23/EC: Scope	**Same Surgical Procedure – A Case Study:** One NCA described a case concerning the use of autologous tissue/cells that are removed from a patient, immediately processed in a device at the patient's side and returned to the same patient. Directive 2004/23 excludes from its scope tissues/cells that are used in 'the same surgical procedure'. Some stakeholders now suggesting that such the Same Surgical Procedure exclusion is no longer appropriate as the 'close to the patient/bedside' technologies are becoming more and more important and there should be an authorisation of the process, not just a CE-marking of the device in which the substance is processed. This particular case also involved a 'claim' that fat cells improve conditions such as chronic cystitis, asthma, stroke, etc. CAs	The NCAs considered that a careful consideration should be given to this case in the context of the ongoing Blood, Tissues and Cells Evaluation.

			considered that such claims highlight the need for a requirement for demonstrating 'efficacy'.	
34.	Meeting of Competent Authorities for Tissues and Cells June 2018		**Rapid Alerts relating to Sperm Donors:** One NCA issues rapid alerts in the RATC system on gamete donors being permanently blocked following the identification of potentially serious genetic disease or hereditary genes for such diseases in a donor. The NCA reported regarding a recent recommendation from the 'Over-implementation Board' under the Ministry of Employment to the Government Committee on Over-Implementation indicating that the NCA should not issue alerts to other EU MS when a child with a genetic condition has been born from a particular sperm donor and sperm from that donor, potentially or certainly carrying the responsible gene, has been distributed to other EU MS. The NCAs were unanimously supportive in their efforts to use the RATC platform to share information of this kind rapidly. The representatives considered that transmission of genetic diseases should indeed be seen as 'serious adverse reactions' and that this kind of communication is important for patient safety and that the practice should not be changed. The representatives also noted that the RATC platform is an effective way for such a rapid communication among the MS authorities.	The Commission services reminded the participants that in the current 2004 legal framework, genetic transmissions to children from gamete donors are not explicitly mentioned, but that this issue had been raised in the evaluation exercise as a sector development on which EU legislation needs to be aligned for clarity.

Annex IX: List of Public Health Programme Actions funded to support the implementation of the BTC legislation

The European Commission provides funding for Actions in the area of SoHO through the EU Health Programme[410], in the form of projects or joint actions with national authorities.

Part A: Blood and Blood Components

CATIE	Training sessions for inspectors in the field of blood and blood Components https://www.catie-europe.eu/	A project promoting common standards and organising training workshops to disseminate these standards
Creative Ceutical	Creative Ceutical report https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/2017_eupbm_authorities_en.pdf	An EU-wide mapping exercise of the market for blood, blood components and plasma derivatives, focusing on their availability for patients
CORDIS	Rapid SPR for parallel detection of pathogens in blood Improving the safety of blood and organ supply by creating the research infrastructure to monitor emerging pathogens and develop new screening tests.	A project on blood testing, for the development of reliable and comparable testing procedures across the EU.

[410] Website Commission- EU Health Programme.

DOMAINE	DOnor MAnagement IN Europe https://www.sanquin.org/research/donor-studies-projects/domaine	A project creating a safe and sufficient donor population in Europe: comparing and recommending good donor management practice
EU - Q - Blood SOP	Pan-European standard operating procedure methodology http://ec.europa.eu/health/ph_projects/2004/action2/docs/action2_2004_inter_04_en.pdf	A project developing a pan-European standard operating procedure (SOP) for best practice in ensuring the quality and safety of blood
Eurobarometer	Eurobarometer https://ec.europa.eu/health/blood_tissues_organs/eurobarometers/eb822_en	A report outlining the European public's attitude to blood and tissue and cells donation and transfusion and/or application
EuBIS	Development of pan-European standards and criteria for the inspection of Blood establishments (EU-Blood-Inspection) https://www.eubis-europe.eu/	A project laying down a standard operating procedure methodology on quality and safety of blood.
EUOBU	EU Optimal Blood Use http://www.optimalblooduse.eu/	A guide on EU Optimal Blood Use
PBM	Patient Blood Management https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/2017_eupbm_authorities_en.pdf https://ec.europa.eu/health/sites/health/files/blood_t	A project developing Patient Blood Management

	issues_organs/docs/2017_eupbm_hospitals_en.pdf	
SoHO V&S	Vigilance and Surveillance of Substances of Human Origin http://www.notifylibrary.org/content/vigilance-and-surveillance-substances-human-origin-project-sohovs	A project supporting the Member States in the establishment of vigilance and surveillance systems for tissues and cells in transplantation and assisted reproduction
VISTART	Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction and Transplantation https://vistart-ja.eu/	A project promoting and facilitating the harmonisation of inspection, authorisation and vigilance systems for blood, tissues and cells.

Part B: Tissues and cells

Euro-GTP II	European Good Tissue Practices http://www.goodtissuepractices.eu/	Projects to develop European Good Tissue Practice Guidance and other tools for TEs, to improve mutual recognition and support harmonisation of practices across the EU, and help facilitate the movement of tissues and cells between Member States
Eurobarometer	Eurobarometer https://ec.europa.eu/health/blood_tissues_organs/eurobarometers/eb822_en	A report outlining the European public's attitude to blood and tissue and cells donation and transfusion and/or application
SoHO V&S	Vigilance and Surveillance of Substances of Human Origin http://www.notifylibrary.org/content/vigilance-and-surveillance-substances-human-origin-project-sohovs	A project supporting the Member States in the establishment of vigilance and surveillance systems for tissues and cells in transplantation and assisted reproduction
EQSTB	European Quality System for Tissue Banking Project http://www.eqstb-sanco.org/	A project creating the 'Guide of recommendations for Tissue Banking' and a prototype of an online European multinational musculoskeletal tissue registry
SANCO/2008/C6/051	Comparative analysis of medically assisted reproduction in the EU: regulation and technologies	A project carrying out a comparative analysis of medically assisted reproduction in the EU

POSEIDON	Promoting optimisation, safety, experience sharing and quality implementation for donation organisation and networking in unrelated HSC transplantation in Europe https://webgate.ec.europa.eu/chafea_pdb/health/projects/2006210	A project promoting the optimisation, safety, experience sharing and quality implementation for donation organisation and networking in unrelated HSC transplantation in Europe
EUSTITE	EU standards and training for the inspection of tissues establishments	A project promoting the standardisation and training for the inspection of tissues establishments across the Member States, in compliance with the tissues and cells Directive
EUROCET	European registry for organs, tissues and cells project http://www.eurocet.org	A project creating a European registry for the data collection on organ, tissue and cell donation and transplantation activity
EAHC/2012/Health/19	Economic landscapes of human tissues and cells for clinical application in the EU https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/economiclandscapes_humantissuescells_en.pdf	A project identifying key activities and costs, key players in public and private sectors, legislative and reimbursement schemes across Member States, and finally emerging technological trends and associated ethical, legal, and social issues.
ECCTR	The European Cornea and Cell Transplantation Registry http://www.ecctr.org/ecctr-database	A project building a common assessment methodology and establish an EU web-based registry and network for academics, health professionals and authorities to assess and verify the safety quality and clinical effectiveness of (new) human tissue transplantations and in ophthalmic surgery.

VISTART	Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction and Transplantation https://vistart-ja.eu/	A project promoting and facilitating the harmonisation of inspection, authorisation and vigilance systems for blood, tissues and cells
ARTHIQS	Assisted Reproductive Technologies and Haematopoietic Stem cells for transplantations http://arthiqs.eu/	A project developing guidance for establishing a hematopoietic progenitor cells donor follow-up registry and inspection guidance in Assisted Reproductive Technologies (ART)
Jacie	Joint Accreditation Committee ISCT Europe & EBMT www.jacie.org/	A project developing and maintaining global standards for the provision of quality medical and laboratory practice in cellular therapy. JACIE offers accreditation to transplant programmes in order to encourage health institutions and facilities to establish and maintain quality management systems
SANCO/2008/ C6/051	Comparative Analysis of Medically Assisted Reproduction in the EU: Regulation and Technologies https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/study_eshre_en.pdf	A project comparing regulatory frameworks at Member State level for Medically Assisted Reproduction and comparing reimbursement among Member States

Annex X: ECDC – Support for EU Activities on Substances of Human Origin 2012 – 2018

The European Centre for Disease Prevention and Control (ECDC) is an EU agency aimed at strengthening Europe's defences against infectious diseases. ECDC works in three key strategic areas: it provides evidence for effective and efficient decision-making, it strengthens public health systems, and it supports the response to public health threats.
In 2012, ECDC appointed its first Senior Expert dedicated to vigilance of infectious safety of substances of human origin (SoHO), based today within the Epidemic Intelligence and Response unit. The work of ECDC on this topic underlines the important role of transfusion, transplantation and medically assisted reproduction in the secondary spread of infectious diseases. Since the appointment, there is continuous communication between DG SANTE and ECDC.

Expert consultation meetings

1. Assessing the risk of communicable diseases transmissible through substances of human origin, prioritisation exercise, ECDC, Stockholm, 20–21 September 2012;
2. Satellite consultation meeting on blood donation screening for evidence of malaria infection ECDC, Stockholm, 12-13 February 2013;
3. Consultation on spatial definition of areas affected by malaria, Strasbourg, 04 October 2013
4. Consultation expert meeting on areas with the high prevalence of HTLV – I infection, ECDC, Stockholm, 22nd September 2014;
5. 2nd Meeting of the Working group on prequalification of new blood donors, ECDC, Stockholm, 20 October 2014;
6. Priority setting for a risk assessment of bacterial infection transmission through substances of human origin. Stockholm, 24 – 25 September 2015;
7. Assessing the risk and prevention of hepatitis E transmission through substances of human origin, 27 May 2015, Lisbon, Portugal;
8. Enhanced epidemiological data collection and analysis by establishments for substances of human origin, Stockholm, 29 – 30 September 2016;
9. Expert meeting related to the Guide for preparedness activities on the prevention of Zika virus transmission through SoHO in EU/EEA , ECDC, Stockholm, 11-12 May 2017;
10. WNV and blood donations, Vienna, 15-16 March 2018.

External Tenders and Contracts

1. Service contract: Validation and Evaluation of the Risk assessment tool for contamination of blood donations during outbreaks of infectious diseases (EUFRAT) ref. no: OJ/10/05/2012-PROC/2012/043.
2. Risk Assessment and Prevention of Infectious Disease Transmission through Substances of Human Origin (West Nile virus, dengue and malaria) Tender Reference: OJ/25/04/2013-PROC/2013/011.
3. Systematic Review of Scientific Evidence on the Prevalence of HTLV-I Infection, ref: SRS-14-0098.
4. Risk Assessment and prevention of Chikungunya, Chagas diseases and Leishmaniasis transmission through SoHO" Tender Reference: SRS-2015-OUT-0499—DCLiGr/ Id 4942.
5. Framework contract ECDC/2016/012 "Assessing the risk of bacterial disease transmission by substances of human origin" – ID 5676, Specific contract 1 – 2017, specific contract 2 – 2018, Specific contract 3 – 2019.
6. Tender for the Framework contract "Assessing the risk of parasitic and fungal diseases transmission by substances of human origin" in preparation.

Scientific Advice on Microbial Safety of SoHO

Maintaining SoHO safety during communicable disease outbreaks

1. 2012 – 2013 – not recorded
2. 2014 – 2018 – 57 Rapid Risk Assessments

Scientific advice

1. Framework for action plan in prevention and control of Hepatitis B and C in EU/EEA (EU -HEPFRAME)-2013
2. Ebola and SoHO
3. Screening algorithm – sperm donors
4. Syphilis testing
5. TBE transmission through SOHO

Preparedness plans

1. WNV Blood safety preparedness plan and update
2. Zika virus SoHO safety preparedness plan
3. Zika virus SoHO safety preparedness plan-update

Annex XI: COLLABORATION WITH COUNCIL OF EUROPE

The work of the Council of Europe in the blood transfusion area started in the 1950's. The relevant Committees are the European Committee on Blood Transfusion (Steering Committee) (CD-P-TS); and the Committee on Quality Assurance in Blood Transfusion Services (Expert Committee) (GTS) that drafts and updates the Guide to the Preparation, use and quality assurance of Blood Components (currently in its 19th edition). The relevant section within the Council of Europe is the European Directorate for Quality Management (EDQM). EDQM focuses on the ethical, legal and organisational aspects of blood transfusion with a view to ensuring quality, increasing availability, avoiding wastage, ensuring optimal use of blood supplies and analysing the possible ethical and organisational impact of new scientific developments.

The work of the Council of Europe (EDQM) in the area of organ, tissue and cell transplantation started in 1987, contributing actively to the implementation of high standards for the protection of public health and for the promotion of human rights and dignity. The relevant Committee is the European Committee on Organ Transplantation (Partial Agreement) (CD-P-TO) and its Tissue and Cell Guide Drafting sub-group. The principles guiding the work of the EDQM in this field are ensuring human dignity, maintaining and fulfilling human rights and fundamental freedoms, non-commercialisation of substances of human origin and protecting donors and recipients of organs, tissues and cells.

A current (2019-2021) grant agreement between the European Commission and EDQM includes a commitment to collaboration by EDQM to work on the following topics:

- Development and regular updating of technical SoHO guidance
- A proficiency testing scheme for blood establishments
- Quality management, auditing and training for blood establishments
- Analysis of EU SARE data for blood, tissues and cells, annually
- Standardisation of tissue and cell activity data reporting
- Development of strategies for increasing plasma collection in Europe
- Training of EU vigilance officers to improve SARE reporting
- Support for assessment of BTC standards and practices in EU applicant and neighbouring countries.

Annex XII: Stakeholder Consultation Synopsis

1. Consultation Strategy

The intention of the stakeholder consultation activities conducted as part of this evaluation was to gather views and opinions on the implementation of the BTC legislation and factual information on what works well and where there is a room for improvement. The key elements of the consultation included:

- A Public Consultation addressing general questions to the public and specific questions to targeted stakeholders
- A large-scale stakeholder event to present the preliminary findings of consultation and to identify any remaining information gaps
- Targeted Consultation with relevant stakeholders to gather specific inputs, to fill remaining gaps and to explore certain emerging issues in more depth.
- This included: bilateral Meetings with key stakeholders; meetings with relevant EU agencies and with third country BTC Regulators, multi-lateral topic-specific meetings with selected stakeholders, including donor and patients associations, industry and professionals working in the sector and Member State authorities.
- Validation of emerging evaluation outcomes through discussions with the representatives of the Competent Authorities on Substances of Human Origin Expert Group.

The key stakeholder groups identified:

1. Member State competent authorities for blood, tissues and cells;
2. Member State Ministries of Health and other relevant regulatory bodies;
3. professionals working in blood, tissue and cell donation and transfusion and their professional associations (see Table below);
4. healthcare professionals using blood, tissues and cells in their clinical practice;
5. blood and tissue establishments and procurement organisations and their professional associations;
6. upstream / downstream service and equipment suppliers and users;
7. donors and their associations;
8. patients and their associations;
9. manufacturers of medicinal products / medical devices that use blood, tissues and cells as starting materials;

10. other EU and national authorities, including authorities for medicinal products and medical devices, and agencies such as the European Medicines Agency and the European Centre for Disease Control;
11. relevant international organisations such as the Council of Europe and the World Health Organisation;
12. ethics bodies;
13. third country regulators and professionals;
14. research and academia;
15. any interested citizen.

Many of the stakeholders listed above are represented by a number of large associations, all of which engaged actively in the evaluation process. They are described in the following Table.

TABLE 1: KEY BTC PROFESSIONAL ORGANISATIONS[411]

Consortium of BTC representative societies **(CoRE SoHO)**	CoRe SoHO is a consortium of four Scientific Associations (European Association of Tissue Banks, The European Eye Bank Association, The European Society for Blood and Marrow Transplantation and the European Blood Alliance) formed with the goal of providing expert opinion and supporting data to European Union decision-makers and their respective organisations in the field of SoHO. In particular, the consortium aims to actively contribute to legal and regulatory discussions affecting the SoHO field.
European Blood Alliance **(EBA)**	The European Blood Alliance represents non-profit Blood Services in Europe. Together these organisations collect the majority of EU blood donations, around 17 million annually, and supply blood and blood components for around 470 million EU citizens. More information at: http://www.europeanbloodalliance.eu/
The European Group for Blood and Marrow Transplantation **(EBMT)**	EBMT represents over 4700 physicians and scientists in 568 centres in 55 countries in the EU and beyond. Through a structure of committees and working parties, EBMT promotes research, education, harmonisation of practices and quality improvement through standards and accreditation. www.ebmt.org
The European Haemophilia Consortium **(EHC)**	EHC is a non-profit umbrella patient organisation representing around 90,000 patients dependent on clothing factors and other types of plasma derivatives (PD) supplied by manufacturers. More information at: www.ehc.eu
The European Plasma Alliance	EPA represents 12 European private sector companies that collected

[411] This is not a comprehensive list of BTC stakeholders, others are mentioned in this Synopsis.

(EPA)	2.5 million litres of plasma for the manufacturing of plasma derived medicinal products in 2017. Their companies operate in Germany, Austria, the Czech Republic and Hungary. Their mission is to promote safe plasma collection practices in the EU with focus on donor health and donor safety to ensure patients access to safe products. For more information: epa@pptaglobal.org
The European Hematology Association **(EHA)**	EHA is a non-governmental and not-for-profit membership organisation that promotes excellence in patient care, research and education in European haematology. https://ehaweb.org/
The European Society for Human Reproduction and Embryology **(ESHRE)**	ESHRE is a pan European/ OECD professional organisation of 6,000 members that are clinicians, embryologists, psychologists, nurses, midwifes and lab technicians. It also supports a European Patients Association. Its aims are to promote interest in, and understanding of, reproductive science and medicine by teaching and training, development and maintenance of data registries and research and dissemination. The EBMT registry contains information on close to 600.000 transplants, and the JACIE accreditation scheme aimed at improving quality and safety of HCT. It also aims to inform policy makers in Europe. https://www.eshre.eu/
The International Federation of Blood Donor Organisations **(FIODS)**	FIODS represents 18 million blood donors from 81 countries in 5 continents and promotes regular, anonymous, voluntary, non-remunerated blood donation in all countries of the world. More information at: http://www.fiods-ifbdo.org/
The International Haemovigilance Network **(IHN)**	IHN is a network of professionals, bringing together 38 national haemovigilance programmes and many interested individuals. Its aims are sharing experience and knowledge, benchmarking, the development of international definitions and international collaboration on haemovigilance. More information at: http://www.ihn-org.com/
The International Plasma Fractionation Association **(IPFA)**	IPFA represents not-for-profit plasma fractionators and national blood services collecting plasma for the manufacture of medicinal products. It supports the supply of plasma from Voluntary Non-Remunerated Blood Donors. http://www.IPFA.org
The International Patient Organisation for Primary Immunodeficiencies **(IPOPI/PLUS)**	IPOPI/PLUS: The International Patient Organisation for Primary Immunodeficiencies, is an association of national patient organisations dedicated to improving awareness, access to early diagnosis and optimal treatments for primary immunodeficiency patients worldwide. IPOPI has 61 National Member Organisations, 23 of which are in the EU and it represents 60.000 patients worldwide. The same participant represented the platform of plasma protein user (PLUS), an umbrella for patient organisations bringing together patients dependent on plasma Derived Medicinal Products (PDMP)

	supplied by manufacturers. More information at: https://ipopi.org/
MedTech Europe	MedTech Europe is the European trade association representing the medical technology industries. It is an alliance of European medical technology industry associations representing Diagnostics and Medical Devices manufacturers operating in Europe. It was founded jointly by EDMA, representing the European in vitro diagnostic industry, and Eucomed, representing the European medical devices industry. More information is available at https://www.medtecheurope.org/
The Plasma Protein Therapeutics Association **(PPTA)**	PPTA is a global trade and standards setting association representing commercial manufacturers of plasma-derived and recombinant biological therapies, collectively known as plasma protein therapies. PPTA also represents for-profit collectors of Source Plasma. Their members provide around 70% of the world's needs for Source Plasma (600 plasma collection centres based in North America and more than 100 in the EU) and >80% of the world's plasma protein therapy products. More information at: http://www.ppta.org/
World Marrow Donor Association **(WMDA)**	WMDA provides access to the global database to search for potentially matched bone marrow or peripheral blood haematopoietic stem cell donors or cord blood products. Their focus is on unrelated volunteer donors and they maintain standards and run accreditation and training programmes. The Bone Marrow Donors Worldwide registry included 94 organisations listing 30,168,410 donors and cord blood products for international search on February 17th, 2016 www.bmdw.org

The outcome of the consultation activities and an overview of the stakeholder input is summarised below.

2. Consultation Activities and Key messages

2.1 Roadmap Feedback

The Evaluation Roadmap was published on 17 January 2017[412]. Stakeholders were invited to submit comments on the Roadmap during a 4-week period. Feedback was received from 16 stakeholders and published at the SANTE website[413].

The respondents focused on shortcomings seen in the BTC legislation rather than on the planned evaluation methodology. The issues raised in their responses were further elaborated in the subsequent stakeholder consultation activities.

[412] Evaluation and Fitness Check (FC) ROADMAP by the Commission.
[413] DG SANTE Website on the Evaluation.

2.2 Public Consultation

The Online Public Consultation (OPC) was launched on 29 May 2017 and ran for 14 weeks. A summary of the consultation was published in all official EU languages. A Questionnaire for Citizens, available in all EU official languages and a more detailed Questionnaire for administrations, associations and other organisations were made available. The questionnaire for administrations, associations and organisations included a section with questions on blood and blood components and a section with questions on tissues and cells, so that respondents could choose to answer for one or both sections.

There were 43 responses from individual citizens and 158 from organisations. The latter included a broad range of organisations impacted by the legislation, including all of the key professional societies, donor and patient organisations, national authorities and industrial associations. Many individual blood and tissue establishments also responded. Around a third of respondents uploaded additional documents, either position statements or relevant publications.

A factual summary report of the OPC was published on the DG SANTE web pages along with the individual submissions[414].

The respondents came from 23 Member. Stakeholders responding on behalf of organisations were mostly located in Germany (14%); Italy (11%) and Spain (9%). The majority of citizen responses came from Austria (21%); Italy (16%); Germany (14%) and the Netherlands (12%).

Over half of the organisations were national (53%), over a third (35%) had an International or European reach and the remainder worked at a regional or local level. Organisations responding to the OPC were mostly Blood and Tissues Establishments/Registries or their professional associations (51%). Public Administrations, mainly national competent authorities for blood, tissues or cells, made up the second largest group (22%). There were also respondents representing Manufacturers of Medicinal Products or Medical Devices (11%); Healthcare Providers (9%); Donor Organisations (3%); and Patient Organisations (4%).

A number of key messages emerged from the OPC that are detailed in the published summary. In particular, the following views and issues were highlighted for each of the Evaluation Assessment Criteria.

For **effectiveness**, the majority of respondents expressed the view that the EU legislation on blood and blood components has increased quality and safety for these substances (93% of 85 respondents,) and achieved a high level of human health protection for recipients (92% of 87 respondents) to a great or to some extent, with only one

[414] DG SANTE Website on the Evaluation- Public Consultation.

stakeholder organisation working in healthcare provision responding that there had been no impact in either of these two areas (Figures 1 and 2).

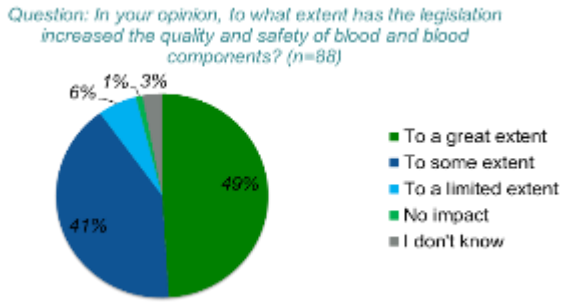


FIGURE 1: RESPONSES FOR BLOOD AND BLOOD COMPONENTS

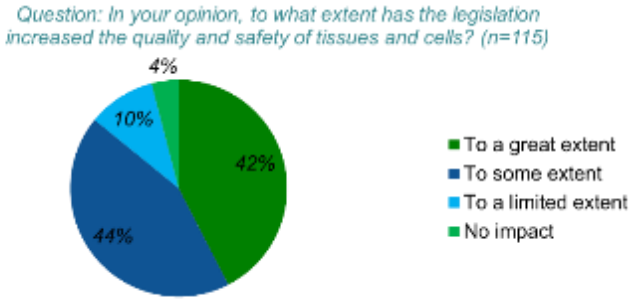


FIGURE 2: RESPONSES FOR TISSUES AND CELLS

However, several provisions are considered to be inadequate or missing. In particular, on donor protection, out of 86 respondents who answered this question, 32% considered that the legislation only had a limited or no impact in this area, which is an important view amongst public authorities and establishments. In summary, the representatives of donor and patient organisations, public administration, blood and tissue establishments and other organisations pointed to a number of requirements they considered missing or inadequate. These included:

- inadequate provisions for the protection of the living donor, including donor evaluation, reporting of adverse reactions and long-term donor follow-up. These are considered essential for certain types of donation involving unknown health risks;
- limited requirements to ensure quality of blood, tissues and cells, as opposed to safety, including the need to verify the quality criteria of these substances before release for clinical application; - lack of demonstration of safety and clinical effectiveness in the recipient, particularly in the context of novel, or even experimental, preparation processes for blood, tissues and cells;

- overly limited descriptions of scope, missing a number of substances that are applied to patients or are donated and used for other purposes but are not currently regulated at EU level;
- inadequate and/or unclear key definitions;
- inadequate provisions for ensuring sufficiency of supply, highlighted particularly by patient groups that see lack of access as a key risk to patients.

Of the 82 respondents representing the blood sector who answered regarding the challenges to maintaining compliance with blood and blood component legislation, the majority (61%) stated that the main challenge was inadequate definitions, followed by limited resources for competent authorities (57%) and blood establishments (44%). While 35% of respondents considered that requirements were too stringent or detailed, exactly the same proportion of respondents answered that requirements were not specific enough.

Over half of 117 respondents (51%) representing the tissues and cells sector identified barriers preventing the effective implementation of the legislation, including financial burdens; continuing inconsistencies, in large part due to differing interpretations between MS; and a lack of coherence with other relevant EU legislation. A majority of respondents (58% of 115 respondents) also considered that the rules on oversight do not effectively ensure the full application of the tissues and cells legislation. In particular, respondents detailed that differing national authorities have varying interpretations of the tissues and cells legislation, and suggested that oversight activities require further harmonisation.

For **relevance**, the key message from most stakeholders representing blood and tissue and cells fields was that the legislation is not up-to-date with scientific, technological, epidemiological or societal developments and that the process of updating is not flexible or quick enough to adapt to them; many examples were provided. It was considered by many respondents that the more technical aspects of the current legislation should be moved to guidance that can be rapidly updated, in line with changing risks and technologies. Particularly, the guidance of the Council of Europe (EDQM) and of ECDC were identified as suitable references to up-to-date technical standards.

The majority of respondents representing the blood sector considered that the developments were not significantly addressed, and a notable proportion considered that the legislation was not suited to the current situation. For instance, the important impact and potential of pathogen inactivation technologies during processing was considered not to be addressed and the availability of more sensitive donor testing by nucleic acid technology was not considered to be adequately reflected. Nearly half of all respondents (44% of 81 respondents) considered there were gaps in scope of the blood and blood components legislation, for example: for blood components used for therapeutic purposes other than transfusion (e.g. serum eye drops, fibrin glue, platelet rich plasma, platelet lysate, lyophilised plasma); and, for other substances of human origin used

therapeutically (e.g. human faeces, breast milk and urine for the manufacture of medicinal products).

Similarly to above, the majority of respondents representing the tissues and cells sector considered that the developments are not significantly addressed, or not suited to the current situation. For example, only 31% of 113 respondents considered that the legislation is fully adapted to scientific developments relating to processing, and only 29% of 112 respondents considered that the legislation is fully adapted to epidemiological developments. Similarly to the field of blood and blood components, those responding on the relevance of the legislation for tissues and cells pointed to the important developments in donor testing and microbial inactivation technologies that are not currently addressed and to the risks brought by multiple epidemiological outbreaks but not mitigated by provisions in the legislation.

For **efficiency**, the majority considered that the legislation has incurred costs but that these had been justified by benefits for patients.

Concerning blood and blood components, most respondents (80% of 87 respondents) considered that the application of the EU blood and blood components legislation brought regarding costs – which would not have been incurred otherwise – for themselves, their organisation or stakeholders represented by their organisation. Donors, manufacturers of downstream products, and public administrators outside the EU particularly indicated that they had incurred significant costs, while the majority of respondents considered there were no additional costs. A minority of respondents (11% of 53 respondents) considered that these costs were not justified by the benefits of the legislation for patients; most respondents considered they were either partially (58%) or fully (28%) justified.

For tissues and cells, most respondents, representing a range of fields and organisations, considered that the application of the EU tissues and cells legislation brought significant or minor additional costs (59% and 25% from 114 respondents, respectively) – which would not have been incurred otherwise – for themselves, their organisation or other stakeholders represented by their organisation. Only a minority of respondents (21% of 94 respondents) considered that these costs were not justified by the benefits of the legislation for patients; most respondents considered they were either partially (34%) or fully (43%) justified.

With regard to **coherence**, inconsistencies between the BTC legal frameworks were identified, along with inconsistencies related to the borderlines with the EU legal frameworks on medicinal products and medical devices and with international frameworks regulating these substances. In general, respondents pointed to the lack of a common EU-level mechanism to clarify these borders in view of the many innovative developments in biotechnology.

Concerning blood and blood components, a higher proportion of respondents (49% of 82 respondents) considered that there were also minor (37%) or significant (12%)

inconsistencies with medicinal products legislation. In both cases, less than a third of respondents considered that blood and blood components legislation was fully consistent and coherent with those legislative frameworks. Similar to medical devices, issues concerning the consistency of the Directives with medicinal product legislation included inconsistent requirements (e.g. in the testing of plasma for fractionation compared with for blood intended for transfusion); borderline issues when blood cells are used as starting materials for ATMP manufacture; an absence of provisions for international controls on the quality of certain blood products which limits trade; and inconsistencies with regards to the regulation of plasma and the definition of 'industrial' processing.

For tissues and cells, 19% of 114 respondents report significant inconsistencies with the EU legal framework for medicinal products. The main issues highlighted concerned vigilance and surveillance communication requirements within or between MS, as well as the role and mandate of EU agencies. Respondents also expressed their view that, similar than with medical devices, greater clarity is required on borderlines between tissues and cells and ATMP legislation pointing to heterogeneous implementation of legislation in/between MS, with implications for safety and quality. Several respondents pointed to the lack of a common EU-level mechanism to clarify the borders between different EU legal frameworks, in view of the many innovative developments in biotechnology.

Regarding **EU added value**, in general most respondents considered that the positive impact of the legislation could not have been achieved, or would have been achieved more slowly, without EU legislation. However, many pointed to the more stringent national requirements adopted by many Member States as limiting the added value of the legislation at EU level.

For blood and blood components, the majority of the 86 organisations that responded to this question, considered that EU legal provisions have added value to regulating the safety and quality of blood and blood components by greatly (53%) or somewhat (13%) improving or accelerating what could have otherwise been achieved at a national or global level.

For tissues and cells, around a third (34%) of 110 respondents considered that EU legal provisions have added value to regulating the safety and quality of tissues and cells across all MS in a manner that could not have been achieved by national or global level measures. Furthermore, 44% of all respondents considered that the provisions greatly (21%) or somewhat (23%) improved or accelerated what could have otherwise been achieved at a national or global level, and only 14% considered that the same outcomes could have been achieved without EU tissue and cells legislation in place.

The summary of the OPC, together with the individual submissions, was published by DG SANTE[415]. The Annex published together with this summary includes a detailed analysis of replies to the OPC questions covering the BTC evaluation criteria.

2.3 Targeted Stakeholder Consultation

Meetings with CASoHO Expert Group

The Competent Authorities for Substances of Human Origin Expert Group E01718 (CASoHO Expert group) includes the representatives, from competent authorities responsible for overseeing the implementation of the BTC legislation. The World Health Organisation, the Council of Europe (EDQM), the European Centre for Disease Control (ECDC), CHAFEA and European Medicines Agency (EMA) were invited as observers[416,417].

Aspects of the evaluation were discussed during 10 meetings of the SoHO authorities, including 4 of the blood competent authorities, at 3 of the tissue and cell competent authorities, and at expert sub-groups, on vigilance and traceability[418].

Ad-hoc multi-lateral meetings with EU authorities and stakeholders

Five ad-hoc meetings between invited stakeholders and the BTC competent authorities were organised to explore specific topics where data or detailed information were lacking.

Table 2: Topics discussed at meetings with stakeholders and competent authorities

Sub-sector	**Date (footnote reference to minutes online)**	**Topics addressed**	**Stakeholders Present – see Abbreviations and descriptions at the beginning of this document.**
Blood	02/12/2017[419]	• West Nile Virus testing • Clinical follow-up of recipients	European Blood Alliance European Haematologists Association
Key messages: - **Despite recent revision of Directive 2006/33/EC, stakeholders presented evidence that the new provisions were too specific and that equivalent safety could be achieved at a lower cost.** - **The EHA argued for the need for systematic follow up of patients following**			

[415] Summary of Responses to the Open Public Consultation for the Evaluation of the Blood, Tissues and Cells Legislation.
[416] DG SANTE Website-Blood, tissues, cells and organs- Events.
[417] https://ec.europa.eu/health/blood_tissues_organs/events_en#anchor3.
[418] Meeting of the SoHO Vigilance Expert Sub-Group 7 APRIL 2017.
[419] Ad-Hoc Meeting between Stakeholders and representatives of members of the Competent Authorities on Substances of Human Origin Expert Group (CASoHO E01718) 2 December 2017.

transfusions and HPC transplantation			
Tissues and cells	22/02/2017[420]	• Donor safety • Clinical follow-up of recipients	European Association of Tissue Banking European Society for Human Reproduction and Embryology European Eye Bank Association European Society for Blood and Marrow Transplantation
Key messages: - **Broad consensus on the inadequacy of current tissue and cell donor protection and follow up provisions** - **Many professionals conduct recipient follow up studies.** - **General consensus that recipient follow up should be mandated in certain circumstances, in addition to the follow-up of children born of medically assisted reproduction.**			
Blood	22/06/2017[421]	Donor safety Plasma Supply	European Blood Alliance PPTA IPFA FIODS
Key messages: - **Broad consensus on the inadequacy of current blood donor protection and follow up provisions** - **Strong concern from all sectors and patients regarding the EU plasma collection rates and the reliance on the US for EU supply.**			
Tissues and cells	16/11/2017[422]	Assisted Reproduction: • Genetics • Defining quality in ART • Medical devices and ART	ESHRE Fertility Europe Donor conception network Cryos sperm bank European Sperm bank
Key messages : - **The possibilities for genetic screening have changed dramatically since the legislation was adopted and these changes should be reflected in provisions.** - **For the field of assisted reproduction, quality should be defined with clear criteria relating to successful pregnancy and healthy offspring** **Greater communication with the regulatory framework for medical devices in needed due to the reliance for safety and success on those devices.**			
Blood	10/10/2018[423]	• Essential medical	Medtech Europe

[420] Ad-Hoc Meeting between Stakeholders and representatives members of the Competent Authorities on Substances of Human Origin Expert Group (CASoHO E01718) 22 February 2017.
[421] Ad-Hoc Meeting between Stakeholders and representatives of members of the Competent Authorities on Substances of Human Origin Expert Group (CASoHO E01718) 22 June 2017.
[422] Ad-Hoc Meeting between Stakeholders and representatives of members of the Competent Authorities on Substances of Human Origin Expert Group (CASoHO E01718) 16 November 2017.
[423] Ad-Hoc Meeting between Stakeholders and representatives of members of the Competent Authorities on Substances of Human Origin Expert Group (CASoHO E01718) 10 October 2018.

		devices for continuity of supply • Pathogen reduction technologies	European Blood Alliance European Plasma Association PPTA IPFA
Key messages : - **High level of dependence of the blood sector on a sustainable supply of medical devices** - **Pathogen inactivation during blood processing can bring increased safety but costs should be justified and balanced with alternative strategies for achieving equivalent safety levels.**			

The evidence (data and references) collected at these meetings were used in the BTC evaluation.

Bilateral meetings with EU stakeholders

Twenty-one organisations attended bilateral meetings with representatives of the European Commission in the course of the BTC evaluation.

Overall, the following organisations or companies participated in bilateral meetings with DG SANTE:

Blood	**Tissues and Cells**
- **European Blood Alliance** - **European Hematology Association** - **International Plasma Fractionation Association Plasma Protein Therapeutics Association** - **Biotest AG** - **CSL Behring** - **NHS Blood and Transplant** - **Etablissement Francais du Sang** - **Agence nationale de sécurité du médicament et des produits de santé** - **Medtech Europe**	- Cryos International - European Society for Blood & Marrow Transplantation - Nordic Cryobank Group/ European Sperm Bank - European Society for Human Reproduction and Embryology - Alliance for Regenerative Medicine - European Eye Bank Association - Confederation of Danish Entreprise - International Society for Cell and Gene Therapy - Agora Consortium - European Association of Tissue Banks - ICCBBA (ISBT 128 coding standard) - Eurocode

The stakeholders representing blood sector, highlighted that there is a lack of adequate provisions in the EU blood legislation to encourage the Member States to establish or increase plasma collection for PDMP manufacture, a lack of key definitions of plasma

components and the lack of a definition of compensation. The stakeholders also pointed that the regulation of the collection of human plasma should be consistent with wider SoHO regulations and a definition for SoHO should be included in the legislation for greater clarity and the concept of Voluntary Unpaid Donation lacks of clarity in the legislation.[424]

In the meetings, the tissue and cells stakeholders underlined a series of issues that have, for their members, as described in the following points[425].

- Some technical requirements to ensure safe tissues of high quality are outdated or too limited in the Directives. The new Good Practice Guidance and the new monographs to be published in 2019 by EDQM, as part of the Guide to the Safety and Quality of Tissues and Cells, are seen as more effective and up to date.
- An absence of legal provisions for the authorisation of clinical users or their hospitals/clinics to receive and use human tissues for transplant.
- New types of substances of human origin are now used clinically but do not fall within with the scope of the existing SoHO legislation because of the way the scope is defined in the BTC directives. These substances remain un-regulated or regulated differently in Member States.
- Some existing provisions are not evidence based, including those relating to air quality requirements for processing facilities and some donor selection criteria; borderlines with ATMPs are not adequately clear.

Bi-lateral meetings with International stakeholders

In meetings with US FDA/CBER[426] with the American Association of Blood Banks[427] and the American Association of Tissue banks [428] participants highlighted the inter-Member State different approaches to interpretation in the EU, and the challenges that causes for those wishing to export to the EU, the challenges of keeping legislation up to date and the ways in which guidance can be recognised by regulators and the mechanisms for defining regulatory borderlines.

Exchanges were also held with regulatory authorities in in third jurisdictions (e.g. Korea and Japan)[429] to consult with some key international regulators in the field of BTC to explore commonalities and differences between the EU regulatory system and those applies elsewhere for these substances. The discussions focused on approaches to classification of BTC and BTC-based medicinal products and on the best approaches to balancing legal requirements with good practice standards.

[424] Meeting between PPTA and DG SANTE B4 19 June 2018.
[425] Meeting between the Board of the European Association of Tissue Banks and DG SANTE B4 18 September 2018 Meeting between the International Society for Cell Therapy and DG SANTE B4 14 June 2018.
[426] Meeting with the U.S. FDA 8 March 2018.
[427] Meeting between American Association of Blood Banks (AABB) and the European Commission (DG SANTE B4) 9 March 2018 .
[428] Meeting between American Association of Tissue Banks (AATB) and the European Commission (DG SANTE B4) 9 March 2018.
[429] Teleconference meeting between the South Korean Ministry of Food and Drug Safety and DG SANTE B4 15 November 2018.

2.4 Stakeholder Event

A Stakeholder Event was organised by the European Commission services on 20 September 2017. The main purpose of the event was to provide an opportunity to validate the main messages that had emerged from open and targeted consultation activities, and to explore remaining evidence gaps. The meeting was open to all interested stakeholders. The event was attended by 205 participants bringing together members of the public, national authorities, patient and donor groups, professionals working with blood, tissues and cells, industry representatives and other relevant stakeholders, who had the opportunity to express their views on key topics regarding the EU Blood, Tissues and Cells legislation. The majority were from EU Member States (21 Member States were represented) and 10 were from non-EU countries (USA, Norway, Switzerland and the Russian Federation).

The audience represented a variety of sectors and stakeholders, as shown in Figure 3.

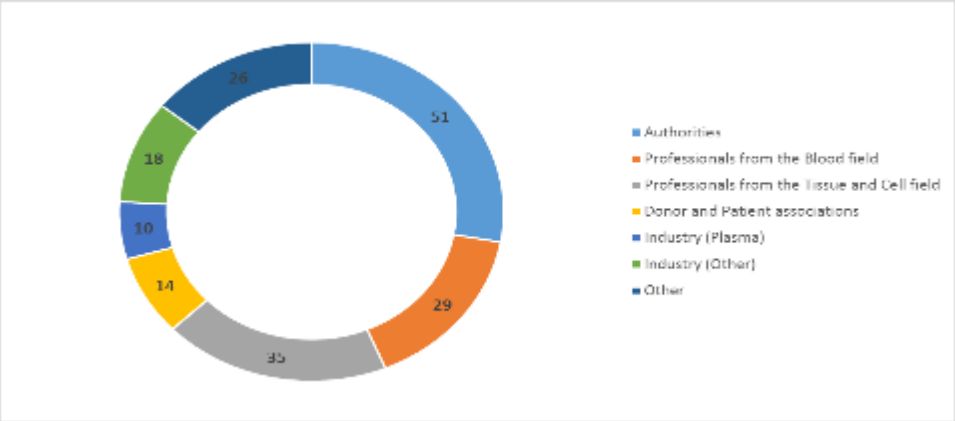


Figure 3: Stakeholder groups at the stakeholder event of 20 September 2019.

The meeting was structured around five main themes relating to the BTC legislation. The key messages that emerged from the presentations and discussions were the following:

THEME	**KEY MESSAGES**
The key importance of donors: The gift of life	The current BTC legislation provides inadequate protection and health monitoring in donors.
Regulatory oversight of the sectors - How to ensure safety and quality?	There are gaps and shortcomings in the oversight provisions relating to new therapies not included in the current scope, the lack of mandated recipient follow up, many technical provisions being outdated, 2-yearly inspection frequency considered as not cost-efficient and a lack of provisions for emergency preparedness.
Availability and	Strong concerns were expressed regarding the reliance of the

sufficiency - Are patients getting the blood, tissues and cells that they need?	EU on the United States for meeting its needs for plasma for medicinal product manufacture with many advocating for EU 'Strategic Independence' for plasma. Other sufficiency concerns related to wastage of BTC due to outdated or unjustified donor eligibility provisions.
Legal consistency and coherence - Regulatory pathways for Substances of Human Origin	Concerns were expressed regarding definitions that lack clarity and result in divergent interpretations and legal uncertainty, including with regards to the regulatory classification of BTC substances/products. A case study was presented that demonstrated how a lack of legal certainty and harmonisation resulted in an ATMP developer limiting its area of activity to the UK rather than across several MS. Challenges of exporting tissues to the EU from the US due to diverging Member State requirements were highlighted.
A changing world – Technological, societal, epidemiological and international developments.	There was broad consensus that the changes in epidemiology and technology that have occurred mean that many provisions are outdated. Concerns were expressed regarding increasing commercialisation (or commodification) and there was a call for cost-effectiveness analysis of any future safety and quality measures.

A Summary of this Stakeholder Event was published by DG SANTE[430].

3. Representativeness of Stakeholder Participation

Looking across all stakeholder consultation activities, a total of 288 organisations participated in the process (see Figure 4) with many taking part in multiple of all activities.

[430] Summary of the Blood, Tissues and Cells Stakeholder Event 20 September 2017.

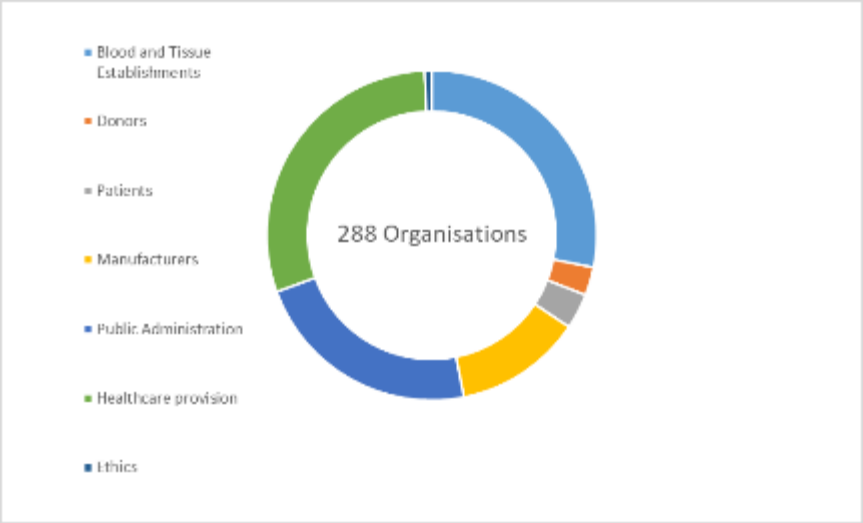


FIGURE 4: TYPES OF ORGANISATIONS PARTICIPATING IN STAKEHOLDER CONSULTATION ACTIVITIES.

The organisations that responded to the OPC were evenly distributed between blood, tissues and cells in terms of experience (Figure 5) and represented a mix of local, national and international organisations (Figure 6).

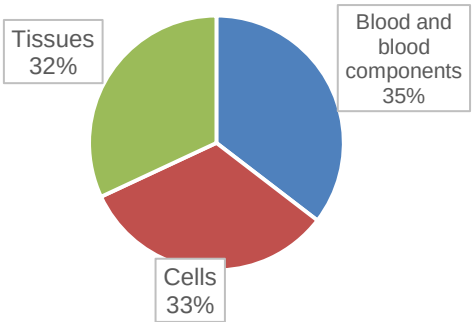


FIGURE 5: SUB-SECTOR OF OPC RESPONDERS

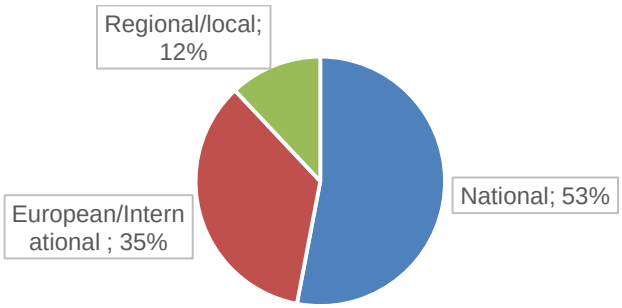


FIGURE 6: OPC RESPONDER GEOGRAPHICAL REACH

Target groups of stakeholders identified in the consultation strategy were reached by the OPC (Figure 7). DG SANTE reached out more actively to some that were less represented, particularly donors and patients, inviting them to participate in ad-hoc multilateral stakeholder meetings.

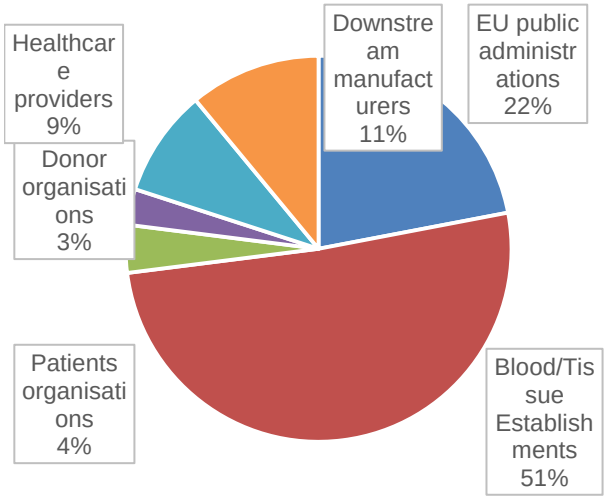


FIGURE 7: OPC RESPONDER CATEGORIES

Of the 43 individual citizens that responded to the dedicated OPC questionnaire, the great majority (87%) were interested in the consultation because of having direct experience in one of the sectors concerned. They represented a balanced mix of individuals working in the public sector (42%), private healthcare industry (33%) and the non-profit sector (14%).

Only one submission to the OPC was received from an Ethics organisation (The Nuffield Council of Bioethics). However, a number of the professional associations that participated, and are categorised under a different heading, also have a mandate for ethical aspects of the sectors and submitted comments on ethics related topics.

Although a number of organisations classified themselves as Academic/research, it was agreed with them that, on the basis that their submissions addressed issues for tissue establishments within the institutions they represent, that they would be grouped with blood and tissue establishments. However, it should be noted that the European Society of Blood and Marrow Transplantation and the European Society for Human Reproduction and Embryology, in particular, also represent the organisations that carry out the largest amount of research in those fields. The same applies to some extent to a number of other organisations. It is not, therefore, considered that research and academia perspectives are missing.

Targeted stakeholder consultation was the tool used to reach out to and engage those stakeholders that were less well represented in the OPC. The most challenging group of

stakeholders to reach were donors and patients and international authorities. Exceptions to this were blood donors that were represented by the International Federation of Blood Donors and patients that rely on plasma derived medicinal products, represented by IPOPI and PLUS. The latter organisations participated actively in the OPC, in the major stakeholder event and in multi-lateral stakeholder meetings. Patients relying on fertility treatment or on donor gametes to have children were actively contacted and two societies, Fertility Europe and the Donor Conception Network, participated in an ad-hoc multilateral stakeholder meeting. There are no organisations representing replacement tissue and cell donors. Patients that receive tissue transplants are very diverse, from cornea transplant recipients to orthopaedic and cardiovascular surgery patients and they are not organised as tissue recipients.

As international authorities did not submit to the OPC they were actively contacted and both face-to-face meetings and teleconferences were used to present and discuss the legislation with them. The United States is the main country involved in exporting plasma, tissues and cells into the EU, and therefore, efforts were focused there as described above. A mission by Commission personnel to the United States included an in-depth workshop with a large number of FDA experts where all of the key issues of common concern were explored.

The authorities regulating other areas of relevance in the EU, particularly medical devices and medicinal products, were represented in the OPC submissions but usually in their capacity of also regulating blood, tissues and cells and usually they commented from that perspective. To ensure that this sector had its views taken into account Commission personnel presented the evaluation and invited discussion at a routine meeting of the Pharmaceuticals Committee and a meeting of the Borderline and Classification expert group in medical devices. Dedicated meetings were also held with the European Medicines Agency and the European Centre for Disease Control.

The inputs and contributions received from the stakeholders in the BTC stakeholder consultation was indispensable to crystallise the key findings of the BTC evaluation which highlights that the BTC legislation has substantially improved safety and quality of blood, tissues and cells in the EU. While public confidence in the sectors remains high, there are important and growing gaps and shortcomings to address.

Annex XIII: Examples of technological changes in the processing of tissues and cells

Sub-sector	Examples of technological advances
Replacement tissues	**Corneas**: transplanted whole as standard in the early 2000s are now routinely laser cut to allow the supply of thin lamellar grafts, sometimes with more than one patient treated from one cornea[431].
	Skin: the epidermis can be removed or the cells can be removed from the skin leaving a matrix structure into which the recipient cells will migrate and grow [432] or the epidermal cells can be separated and used in suspension (without culturing)[433].
	Bone and tendons: 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[434].
	Heart valves: increasingly decellularised to improve recellularisation with the patient's own cells when implanted[435].
Haematopoietic stem cells	**Bone marrow**, peripheral blood stem cells and cord blood: preparation often includes sophisticated methods for cell selection, cell depletion and volume reduction before transplant[436].
Medically assisted reproduction	**Oocytes**: now routinely preserved by vitrification, a process that was considered highly experimental at the time that Directive 2006/86 was adopted[437].
	Ovarian and testicular tissue: now successfully cryopreserved to preserve fertility in patients with cancer[438]. Future perspectives include the use of ovarian tissue to postpone menopause or delay osteoporosis[439]

[431] Boynton GE and Woodward MA (2015) Evolving techniques in Corneal Transplantation. Curr Surg Rep. 3(2). Published online 1 Feb 2015.
[432] Hogg P[1], Rooney P, Ingham E et al. (2012) Development of a decellularised dermis. Cell Tissue Bank. 2013 Sep; 14(3):465-74.
[433] Section 18.10 Guide to the Quality and Safety of Tissues and Cells for Human Application. EDQM, 3rd Edition 2017.
[434] 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 JN and Wolfinbarger L.
[435] Chapter 19, Guide to the Quality and Safety of Tissues and Cells for Human Application. EDQM, 3rd Edition 2017.
[436] Section 21.4 Guide to the Quality and Safety of Tissues and Cells for Human Application. EDQM, 3rd Edition 2017.
[437] Chian R, Wang Y and Li Y (2013) Oocyte vitrification: advances, progress and future goals J Assist Reprod Genet (2014) 31:411–420.
[438] Chapter 25, Guide to the Quality and Safety of Tissues and Cells for Human Application. EDQM, 3rd Edition 2017.
[439] Andersen C, Kristensen SG () Novel use of the ovarian follicular pool to postpone menopause and delay osteoporosis. Reproductive BioMedicine Online (2015) 31, 128–131.

	where recent developments include mitochondrial replacement therapy[440] and germline genome editing[441].
	Embryos: Mitochondrial replacement therapy[442], and germline genome editing[443] represent two highly innovative developments that might become important for preventing serious genetic conditions in the future, although ethical concerns related to these technologies are considerable[444],[445].

[440] In mitochondrial replacement therapy, genomic DNA (nuclei, mitotic spindle or polar body(ies)) from an oocyte with mitochondria affected by a genetic condition is transferred to a donor oocyte. The oocyte is fertilised in vitro, resulting in an embryo with genomic/mitochondrial DNA from three individuals.
[441] Germline genome editing can be applied to correct genetic defects in gametes or embryos.
[442] In mitochondrial replacement therapy, genomic DNA (nuclei, mitotic spindle or polar body(ies)) from an oocyte with mitochondria affected by a genetic condition is transferred to a donor oocyte. The oocyte is fertilised in vitro, resulting in an embryo with genomic/mitochondrial DNA from three individuals.
[443] Germline genome editing can be applied to correct genetic defects in gametes or embryos.
[444] Vogel G. (2015) Embryo engineering alarm - Researchers call for restraint in genome editing. Science 347(6228): 130.
[445] The Scientist (2017) "Opinion: Ethical Considerations of "Three-Parent" Babies".

Annex XIV: Emerging/Increasing Commercial Activities

Sector	Commercial/non-public sector activity
Haematopoietic stem Cells	Cord blood banking for future possible family use ('insurance against future illness') – fee basis
	Offering treatments for diseases not traditionally treated by cell transplantation (often without proof of clinical effectiveness[446])
Other sources of stem cells	Banking of other sources of stem cells for future family use e.g. teeth, umbilical cord tissue, adipose tissue
Replacement tissues	Musculoskeletal processing in subsidiaries of commercial US banks established in the EU
	Import of musculoskeletal tissues from commercial companies in the US
	Import of skin products from commercial companies in the US
	Marketing of tissue grafts by surgical instrument companies
Medically assisted reproduction	Banking of oocytes for supply to IVF clinics (equivalent to model for sperm banking) Online distribution of sperm direct to patients
	Banking of gametes or reproductive tissue for own future use (social freezing to allow postponement of family planning)
Corneas	Trend in international cornea banking towards commercialisation[447]. Suggestions that within 5 years, 50% of all corneas worldwide could be supplied by a single US commercial company, if current trends continue[448].
Plasma collection	Increasing reliance on the commercial sector to collect plasma in the EU

[446] See item 34 in Annex VIII, part 2.
[447] Mannis MJ, Sugar J (2018) Is This the Future of Eye Banking? Cornea (editorial) Cornea 37(7): 811-812.
[448] M Moshirfar JL Goldberg TW Brown WD Wagner YC Ronquillo (2019) A paradigm shift in eye banking: how new models are challenging the status quo. Clinical Ophthalmology 2019:13 63–67.

Annex XV: A non-exhaustive list of clinical outcome registries in the BTC sectors

No	Data Registry	Geographical scope	Follow-up focus	Source
1.	European Society for Blood and Marrow Transplantation (EBMT) patient registry	Europe	Patients who have undergone a haematopoietic stem cell transplantation (HSCT) procedure; patients with bone marrow failures receiving immunosuppressive therapies; and patients receiving non-haematopoietic cell therapies.	https://www.ebmt.org/ebmt-patient-registry
2.	The IVF monitoring consortium (EIM) hosted by European Society of Human Reproduction and Embryology ESHRE	EU and Non EU countries	Children born after ART	https://www.eshre.eu/eim
3.	European Cornea and Cell Transplantation Registry ECCTR	Europe	New human tissue transplantations and ophthalmic surgeries (cornea transplantations)	http://www.ecctr.org/about-the-ecctr-project
4.	Registry of Committee of Nordic Assisted Reproductive Technology and Safety (CoNARTaS)	Denmark, Finland, Norway, Sweden	Health in mothers and children born after ART	http://www.conartas.com/about/
5.	Scandinavian donations and transfusions (SCANDAT)	Sweden, Denmark	Blood donors, blood transfusions and transfused patients	http://www.scandat.se/
6.	International Surveillance of	Worldwide	Recipients of blood and blood products that can	https://ihn-org.com/istare

	Transfusion-Associated Reactions and Events (ISTARE)		certainly, probably or possibly be imputed to blood transfusion. Also, blood donors	

Annex XVI: Inconsistencies between EU-legal frameworks

TABLE 1: INCONSISTENCIES BETWEEN THE BLOOD AND TISSUE AND CELL PROVISIONS.

Topic	Inconsistency
Donor testing for syphilis	This test is mandated for tissue and cells donors (apart from donors of reproductive tissues and cells) but not for blood donors, where the risk of transmission is likely to be higher.
Donor testing for Human T-cell leukemia virus (HTLV)	There are specific provisions for performing this test for tissue and cell donors but none for blood donors, without clear evidence of a rationale for this difference.
Preparation Process Authorisation	Directive 2006/86/EC provides for an authorisation for the processes applied to tissues and cells before they are distributed for clinical application. There is no such authorisation process provided for blood and blood components. In contrast, Annex V of Directive 2006/33/EC defines a series of blood component specifications that indicate which preparation processes are permitted.
Traceability/Coding	The tissue and cell legislation provides for a specific Single European Code that has involved the construction of a public compendium of authorised tissue establishments, with their associated codes, and a compendium of tissue and cell product codes, that must be used to construct the Single European Code to appear on tissue and cell labels (with some exemptions and exceptions). There are no specific rules for the coding of blood and blood components, apart from generic provisions for traceability and unique identification of donors and their donations.
Rules on import from third countries	The tissue and cell legislation has detailed rules for import from third countries with a requirement for competent authorities to issue a specific import authorisation to tissue establishments meeting certain criteria[449]. There is no such provision in the blood legislation.

[449] Commission Directive 2015/566 implementing Directive 2004/23/EC concerns the procedures for verifying the equivalent standards of quality and safety of imported tissues and cells.

Quality System	There is an obligation on the Commission to provide standards and specifications for the activities related to a quality system in blood establishments[450] while no such obligation exists for tissues and cells.
Immutability[451] of adverse reactions	This concept is included in the blood legislation where an imputability grading scale is provided in Directive 2005/61/EC and reporting requirements are dependent on the imputability level while no such concept or reporting requirements are included in the tissue and cell legislation. Additionally, the requirements for reporting of blood related serious adverse reactions according to imputability level are somewhat incoherent within the blood legislation[452].

TABLE 2: EXAMPLES OF INCONSISTENT OR UNCLEAR CLASSIFICATIONS BETWEEN BTC AND MEDICINAL PRODUCTS

Substance/therapy	Borderline issue	Reference
Pancreatic islets **Used as an alternative to pancreas transplantation in patients with type 1 diabetes.**	The Commission has received recurrent questions on whether pancreatic islets are covered by the Tissues and Cells Directive, the Advanced Therapies Regulation or whether they should be classified as organs. Although they are separated by enzymatic digestion, both CAT [453] and the Tissue and Cell competent authorities have considered that these fall under the tissues and cells legislation.	See Part 2, item 4 in Annex 9.
Isolated hepatocytes (without expansion) **Used as a 'bridge' to liver transplantation in patients on the transplant waiting list.**	A Commission survey of EU tissue and cell authorities indicates the following current situation for cells separated from tissue by enzymatic digestion without expansion (including keratinocytes, hepatocytes etc.): 9 Member States regulate as tissues and cells 7 regulate as a medicinal product (ATMP) 2 decide on a case-by-case basis depending on manipulation and use. 3 do not have this therapy or do not regulate it.	Presentation to the meeting of T&C competent authorities 2019[454].

[450] Directive 2002/98/EC Article 11 paragraph 2.
[451] Imputability is defined in Directive 2005/61/EC as 'the likelihood that a serious adverse reaction in a recipient can be attributed to the blood or blood component transfused or that a serious adverse reaction in a donor can be attributed to the donation process'.
[452] Article 5 of Directive 2005/62/EC requires reporting of serious adverse reactions to the competent authority if they are graded as imputability of 2 or 3 while the reporting form included in Annex II part D of the same Directive implies that reactions of all imputability levels much be reported.
[453] The ATMP Regulation introduced a mechanism for requesting scientific recommendations on whether a medicinal product meets the definition of an ATMP from the Committee of Advanced Therapies (CAT)[453], based on scientific criteria.
[454] Summary reports of the Tissue and Cell Competent Authority meeting of 13-14 May 2019.

Platelet rich plasma (and platelet rich fibrin) Produced, in high volumes, in hospitals using a medical device but unclear if the blood legislation or tissue and cell legislation should also apply. Not used 'for transfusion' but in other procedures such as orthopaedic or cosmetic.	Directive 2002/98 would seem to be applicable, in any case, to collection and testing. Divergent regulatory systems and quality and safety rules are applied. A Commission survey of EU tissue and cell authorities indicates the following current situation: 7 Member States do not regulate 5 apply blood safety and quality requirements 4 apply tissue and cell safety and quality requirements 2 regulate as a medicinal product (non-ATMP) 3 regulate in another way.	See Part 1, items 9 and 25 in Annex 9
Isolated keratinocytes – sprayed onto patient skin to promote healing of burns and other wounds (without cell expansion).	A Commission survey of EU tissue and cell authorities indicates the following current situation for cells separated from tissue by enzymatic digestion without expansion (including keratinocytes, hepatocytes etc.): 9 Member States regulate as tissues and cells 7 regulate as a medicinal product (ATMP) 2 decide on a case-by-case basis depending on manipulation and use. 3 do not have this therapy or do not regulate it.	Presentation to the meeting of T&C competent authorities 2019[455].
Serum eye drops Autologous serum prepared for patients with dry eye syndrome – usually stored and applied at home by the patient.	Commission services indicated that this procedure could fall under the scope blood directive as it applies "to the collection and testing of human blood and blood components, whatever their intended use …" as defined in Article 2 of Directive 2002/98/EC. Many blood and tissue establishments prepare and supply the product. A Commission survey of EU tissue and cell authorities indicates the following current situation: 7 regulate under the blood legislation 3 apply tissue and cell requirements 3 regulate as a medicinal product (non-ATMP) 8 Member States do not regulate	See Part 1, item 15 in Annex 9 Presentation to the meeting of T&C competent authorities 2019[456].
Amniotic membrane patches Transplanted in the eye to promote corneal healing or in some cases as a membrane or skin replacement therapy. In some cases, fragments are dispersed in autologous serum	Although the anatomical site of application (the eye) is different to the original site in the donor (the placenta), tissue and cell competent authorities considered that the essential function was the same as in the original site and therefore that this tissue should be regulated under Directive 2004/23/EC. At least one Member State regulates as a medicinal product when fragments care dispersed in serum considering that the fragmentation of the membrane means that it cannot carry out the same essential function.	See Part 2, item 2 in Annex 9. FDA also consider this to be 'the same essential function'.
Autologous adipose tissue (prepared in	A Commission survey of EU tissue and cell authorities indicates the following current situation:	Presentation to the meeting of T&C

[455] Summary reports of the Tissue and Cell Competent Authority meeting of 13-14 May 2019.
[456] Summary reports of the Tissue and Cell Competent Authority meeting of 13-14 May 2019.

hospital)	11 Member States regulate as tissues and cells 2 Member States regulate as medicinal product (ATMP) 2 do not regulate. 3 decide on a case-by-case basis or regulate in another way.	competent authorities 2019[24].

TABLE 3: EXAMPLES OF SUBSTANCES CONTAINING BTC WHERE THE BORDERLINES WITH MEDICAL DEVICES HAVE BEEN DISCUSSED

Substance/therapy	Borderline issue	Reference
Platelet rich plasma (PRP, and platelet rich fibrin, PRF) **Produced, in high volumes, in hospitals using a medical device but unclear if the blood legislation or tissue and cell legislation should also apply. Not used 'for transfusion' but in other procedures such as orthopaedic or cosmetic.**	Directive 2002/98 is applicable to collection and testing. Divergent regulatory systems and quality and safety rules are applied for the subsequent steps. A Commission survey of EU tissue and cell authorities indicates the following current situation: 7 Member States do not regulate 5 apply blood safety and quality requirements 4 apply tissue and cell safety and quality requirements 2 regulate as a medicinal product (non-ATMP) 3 regulate in another way. In all cases, the device to prepare the PRP and PRF are regulated by the medical device regulation.	See Part 1, items 9 and 25 in Annex 9 Presentation to the meeting T&C competent authorities 2019[24].
Decellularised dermis (skin) **Used for a range of skin replacement treatments, including burns and for aesthetic surgery. The removal of donor cells is considered to**	There has been discussion at the MDCG subgroup Borderline and Classification on whether tissues from which cells have been removed (or rendered non-viable) should be considered as 'derivatives' and should therefore fall under the new Medical Device Legislation. A Commission survey of EU tissue and	Presentation to the meeting of T&C competent authorities 2019[457].

[457] Summary reports of the Tissue and Cell Competent Authority meeting of 13-14 May 2019.

accelerate the repopulation of the tissue with recipient cells after application.	cell authorities indicates the following current situation: 13 regulate under the tissues and cells legislation 7 have no current regulation or do not have the therapy.	
Decellularised heart valves **Used for heart valve replacement. The removal of donor cells is considered to accelerate the repopulation of the tissue with recipient cells after application.**	There has been discussion at the MDCG subgroup Borderline and Classification on whether tissues from which cells have been removed (or rendered non-viable) should be considered as 'derivatives' and should therefore fall under the new Medical Device Legislation. A Commission survey of EU tissue and cell authorities indicates the following current situation: 15 regulate under the tissue and cell legislation 5 do not regulate or do not have the therapy.	Presentation to the meeting T&C competent authorities 2019[27].
Demineralised bone (with or without the addition of gel or putty) **Used in large volumes for a wide range of applications where the stimulation of new bone growth is required. The removal of minerals from bone makes the naturally occurring bone-growth-stimulating proteins more exposed and functional.**	There has been discussion at the MDCG subgroup Borderline and Classification on whether tissues from which cells have been removed (or rendered non-viable) should be considered as 'derivatives' and should therefore fall under the new Medical Device Legislation. A Commission survey of EU tissue and cell authorities indicates the following current situation regarding demineralised bone combined with putty or gel: 11 regulate under tissue and cell legislation 1 regulates as a medical device 1 regulates as a medicinal product (non-ATMP) 3 do not have the therapy	Presentation to the meeting T&C competent authorities 2019[24].