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DIRECTORATE GENERAL FOR HEALTH AND FOOD SAFETY

Directorate B - Health systems, medical products and innovation
B4 – Medical products: quality, safety, innovation

Summary of Responses to the Open Public Consultation for the Evaluation of the Blood, Tissues and Cells Legislation

Contents

Executive Summary

This document presents a summary of the open public consultation (OPC) carried out in the context of the evaluation of the EU legal frameworks on blood, tissues and cells, the key messages emerging and the next steps in this evaluation process. The OPC was a key step in the evaluation process, which aims to identify whether the EU legal frameworks on blood[1], and on tissues and cells[2] have achieved their objective of ensuring access to safe blood, tissues and cells of high quality, and whether they have remained fit for purpose.

The consultation was launched online on May 29th 2017 and was open until September 14th. Dedicated questionnaires were available for individual citizens and for administrations and organisations, in both cases based on the five assessment criteria: effectiveness, relevance, efficiency, coherence and EU added value.

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 number of key messages have emerged and are further detailed in this document:

For effectiveness, the **great majority considered that the legislation had made blood, tissues and cells safer in the EU**. However, respondents noted **some requirements to be 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;
- a lack of 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 efficacy in the recipient, particularly in the context of novel, or even experimental, preparation processes for blood, tissues and cells;
- too 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;
- absence of any provisions for ensuring sufficiency of supply, highlighted particularly by patient groups that see lack of access as a key risk to patients.

For relevance, the key message from most stakeholders was that the **legislation is not up-to-date** with scientific, technological, epidemiological or societal developments and that the

[1] 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 implementing legislation

[2] 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

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) was identified as a suitable reference for up-to-date technical standards.

For efficiency, the majority considered that the **legislation has incurred costs but that these had been justified by benefits** for patients. However, a small number of exceptions were identified that will be explored in more depth in by the contractors conducting an independent study under a contract to the Commission.

With regard to coherence, inconsistencies between the SoHO 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**. Respondents pointed to the lack of a common EU-level mechanism to clarify these borders in view of the many innovative developments in biotechnology.

A large majority of 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.

1 The Open Public Consultation

This Open Public Consultation was one element of a comprehensive evaluation of the EU blood and tissues and cells legislation that is being conducted by the European Commission. This is the first formal evaluation of this legislation since the adoption of the basic Acts in 2002 (blood and blood components) and 2004 (tissues and cells). The evaluation aims to assess whether the legislation has achieved its original objectives and whether it is still fit for purpose. The evaluation consists of several steps defined in a Roadmap[3] and including a study by an external contractor and extensive consultation of stakeholders. The Commission Final Evaluation report is expected to be published by the end of 2018.

This document summarises the inputs to the Open Public Consultation (OPC) launched on 29th May 2017 and closed on 14th September of the same year. Preliminary analysis was conducted by ICF Consulting Ltd and this summary report was finalised by DG Santé on the basis of that analysis. Individual submissions are published together with this summary, wherever the appropriate consent was granted by the stakeholder. This summary will be complemented by the outcomes of other stakeholder consultation activities to compile a Synopsis Report that will be annexed to the final Evaluation Report.

1.1 Objectives

The main aim of the OPC was to gather detailed views, opinions and data to support the first formal evaluation of this legislation since the adoption of the basic Acts in 2002 (blood) and 2004 (tissues and cells). In particular, the consultation aimed to gather the views and opinions of organisations and citizens on whether:

- the legislation has been effective in achieving its original objectives (i.e. **Effectiveness**);
- the legislation remains adequate today, taking into account any relevant changes, e.g., technological, epidemiological, organisational or societal, that have occurred since its adoption (i.e. **Relevance**);
- the costs and burdens of implementing the EU legislation have been justified by the results achieved (i.e. **Efficiency**);
- the Directives are coherent and consistent, in regards to their own provisions, other relevant EU legislation and third country/international approaches (i.e. **Coherence**);
- the EU was the most appropriate level at which to regulate these fields and whether the same results could have been achieved with national or global standards or legislation (i.e. **EU Added Value**).

1.2 The questionnaires

Two questionnaires were designed for the consultation. The first was targeted to administrations, associations, tissue and blood establishments, manufacturers of medicinal products using blood, cells or tissues as starting materials, and other organisations. The second questionnaire was addressed to individual citizens. The questionnaire for 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. Respondents were asked to provide information on their main field of work: 1) EU public administration (ministry of health, competent authority etc.), 2) blood/tissue establishment and or/ donor recruitment and procurement/collection, 3) patients, 4) donors, 5) healthcare provision (clinical use of blood, tissues, cells or medicinal products derived from these substances), 6) manufacturers of downstream products using blood, tissues or cells as a starting material, equipment or service provision, 7) academic or scientific research and development, 8) public administration outside the EU, 9) ethics or 10) other. The questions are shown in Annex 1, where the answers to all closed questions are also provided. All closed questions were

[3] http://ec.europa.eu/smart-regulation/roadmaps/docs/plan_2016_154_evaluation_eu_legislation_on_blood_en.pdf

followed by free text fields where respondents could describe their views. The messages that emerged from those comment fields are summarised in the main part of this report.

1.3 The OPC in numbers

One hundred and fifty eight organisations and 43 individual citizens took part in the OPC, with representation from 23 Member States (MS) in total (20 and 16, respectively). Forty nine additional documents were uploaded to support the submissions by organisations. The majority of citizen responses came from Austria (21%); Italy (16%); Germany (14%) and the Netherlands (12%). Stakeholders responding on behalf of organisations, were mostly located in Germany (14%); Italy (11%) and Spain (9%).

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%). Only one organisation identified itself in the category of 'Ethics'.

The majority of organisations (70%) had experience in more than one area, illustrating a diversity of knowledge. Over half of all respondents (51%) had experience of blood and blood components, and a substantial proportion of respondents had knowledge and experience of cells for transplant and tissues for transplant (47% and 46%, respectively). A significant number of respondents were also familiar with blood tissues or cells used for the manufacture of medicinal products, and tissues or cells for assisted reproduction.

Forty eight additional attachments, including position statements and other background information, were uploaded by 25 organisations. They have been reviewed, their content is reflected in this summary report and they have been added to the evidence base for the final report of the Evaluation.

The majority of individual citizens responding to the OPC worked in the public healthcare sector (42%), followed by the private healthcare industry (33%) and the not-for-profit sector (14%). Eighty seven percent of citizens had experience or familiarity in more than one thematic area. Most citizens had experience with the pharmaceutical industry (42%) and with blood collection and/or blood banking (40%), followed by the transfusion of blood and blood components (35%). Fewer citizens were familiar with tissue or cell donation/banking for either transplantation (26%) or assisted reproduction (19%). At least one respondent had experience in other areas including clinical application of tissues or cells and assisted reproduction and government oversight of blood or tissue establishments.

2 Summary of inputs: Organisations

This section summarises the inputs received from organisations, and is structured by evaluation theme, differentiating between blood and tissues and cells legislation in each section. For closed questions, a full analysis of answers is shown in Annex 1. In general, views were convergent between the different stakeholder groups; where there was important divergence, this is specifically mentioned in this summary.

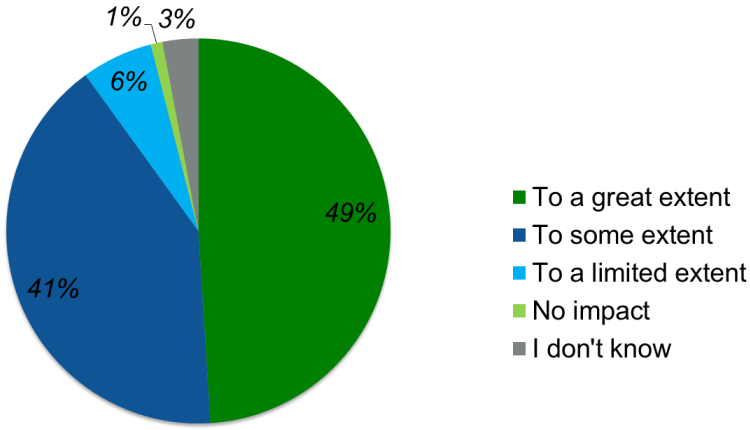
2.1 Effectiveness

2.1.1 Blood and blood components

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, Figure 2.1) and achieved a high level of human health protection for recipients (92% of 87

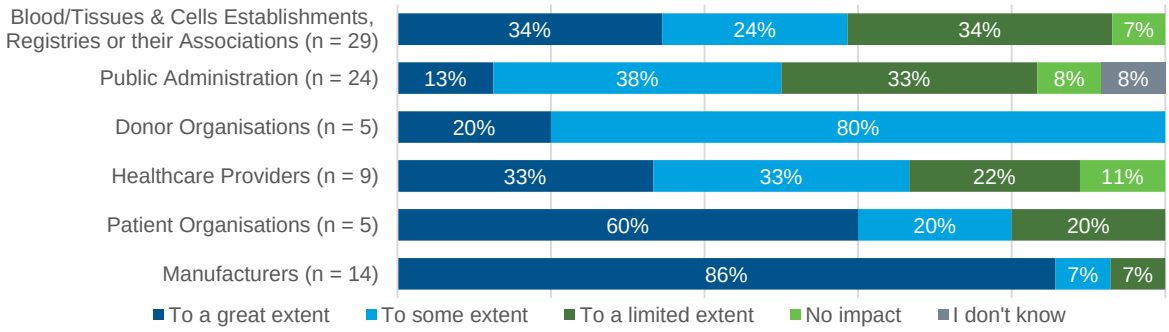
respondents) to a great or to some extent, with only one stakeholder organisation working in healthcare provision responding that there had been no impact in either of these two areas.

Figure 2.1 In your opinion to what extent has the legislation increased the quality and safety of blood and blood components? (n=88)



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 (Figure 2.2).

Figure 2.2 In your opinion to what extent has the legislation achieved a high level of human health protection for donors of blood substances? (n = 86)



Donor safety was highlighted both with respect to donor selection criteria and donation frequency rules and regarding the need for strengthened rules for the monitoring of donor health of frequent donors (particularly of plasma) and for long term follow up. Many respondents considered the current requirement (to report donor reactions only when the safety or quality of the donation is affected) to be inadequate and call for mandatory reporting of all serious donor reactions.

Respondents were also asked to reflect on **other impacts** of the legislation:

- Over half of 83 respondents (57%) considered that the legislation has led to **unintended effects**. Most of these were negative effects such as the lack of strict requirements for EU self-sufficiency and hence reliance on plasma imports described below; regulatory and administrative pressures, especially on smaller establishments; and reduced supplies and donations in countries due to the fact that the EU legal framework allows for more stringent national legal requirements (which, it was considered, often lack a scientific basis, e.g. donor deferral periods).
- Exactly half of 84 respondents identified **barriers preventing the effective implementation** of the legislation, including unclear legislative definitions and requirements, particularly those

related to payment, compensation and incentives, with the consequent application of differing national regulations to comply with the principle of voluntary unpaid donation.

- Forty-six percent of 83 respondents considered that the **rules on oversight** do not effectively ensure the full application of the legislation. In particular, respondents considered that the rules on oversight are too generic, for example, in regards to the role(s), function(s) and impartiality of national competent authorities and inspectors. Many pointed to resource limitations in competent authorities and inspectorates and some to a lack of training and specialist knowledge. The vigilance requirements were often highlighted as lacking in clear rules regarding denominator reporting and criteria for reporting serious adverse events.
- Sixteen percent of 86 respondents concluded that the legislation had reduced **patient access**, while 21% thought it had increased access. The largest group of respondents (45%) considered that there was no impact on patient access.

Of the 82 respondents 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%). In particular, it was noted that the opening of new blood centres can be delayed by the authorities who struggle to resource the required inspections and that blood authorities also have difficulties to resource third country inspections. 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.

Eighty respondents answered regarding the impacts of blood legislation on the **safety and quality of plasma-derived medicinal products** and over half concluded that the framework was effective in ensuring adequate safety of manufactured products. Nonetheless, 35% considered that requirements in the blood legislation need modification, to varying degrees, with 14% suggesting they require significant modifications.

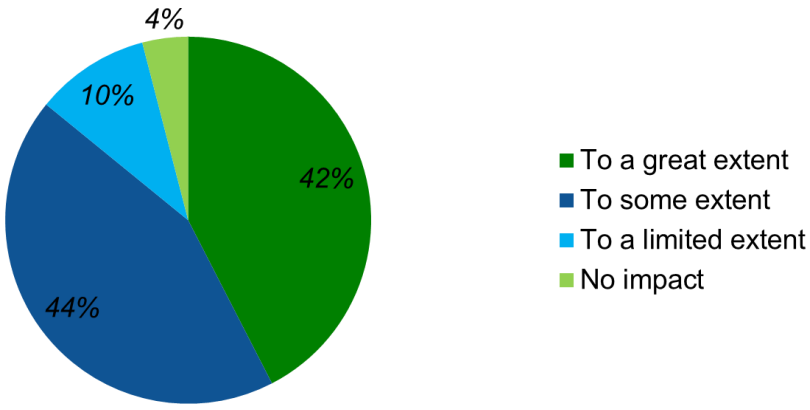
In general comments, some respondents argued that inadequate **access** should be seen as a risk to patients and that the legislation had not addressed access or **community sufficiency**, particularly in the area of plasma derived medicinal products where there is a large degree of dependency on the US for plasma supply. Wastage of plasma was highlighted, with some considering that this occurs due to lack of alignment with the requirements for good manufacturing practice at plasma collecting centres while others argued that the **voluntary unpaid donation** principle had been used as a barrier to access to plasma for manufacturing of medicinal products and to entry to the free market. Some responding organisations, on the other hand, expressed the view that the VUD principle has not been adequately implemented and should be strengthened. This divergence was most notable between the commercial and the public sector stakeholders.

A clear message expressed by many stakeholders was that **donor eligibility criteria need to be risk and evidenced based** and that unjustified criteria can result in the unnecessary loss of donations. This was particularly raised for plasma where some argued that different eligibility rules should apply because of the subsequent microbial inactivation steps applied to the manufactured medicinal products.

2.1.2 Tissues and cells

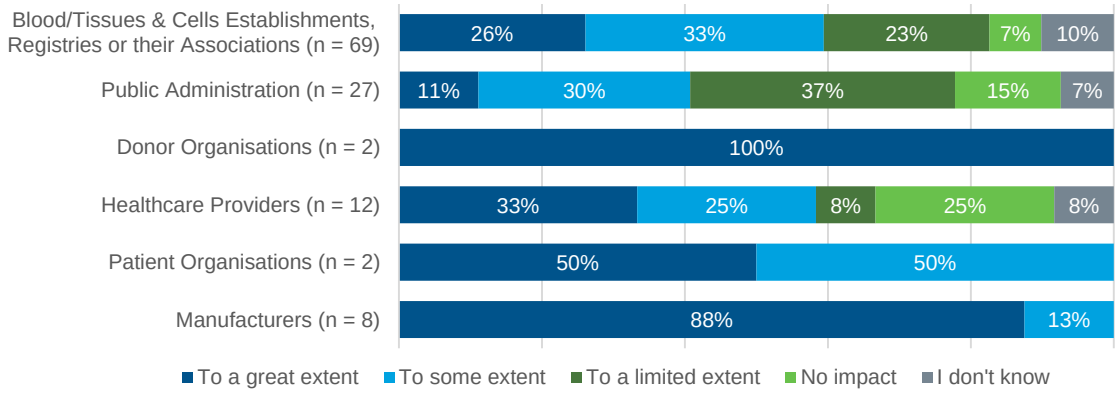
The majority of respondents considered that the tissue and cells legislation has increased **quality and safety** for these substances (85% of 115 respondents, Figure 2.3) to a great or to some extent. Specific improvements included: confidence in quality of imported cells; international formalisation of documentation and traceability; and increased EU harmonisation.

Figure 2.3 In your opinion to what extent has the legislation increased the quality and safety of tissues and cells? (n = 115)



A high proportion of respondents (89% of 117 respondents) also considered that the legislation had achieved a high level of **human health protection for recipients** to a great (40%) or to some (49%) extent, but significantly fewer respondents expressed the same view regarding the legislation achieving a high level of human health **protection for donors** of tissue and cells. As highlighted in Figure 2.4, 34% of the 120 respondents to this question considered that the legislation only had a limited or no impact on protecting donors. Amongst authorities and public administrations, more than half share this view. A specific reflection was that, although the legislation had introduced tests to ensure the safety of the tissues and cells applied to patients, there are no requirements for longer-term follow-up of donor or patient. In particular, it is considered there is not enough emphasis on the clinical safety of the donors and recipients of reproductive tissues and cells. Respondents working in the field of haematopoietic stem cells pointed to the particular need to protect related donors who represent an increasingly important proportion of donors and who are donating in a different context to the traditional unrelated registry donors of bone marrow and peripheral blood stem cells.

Figure 2.4 To what extent has the legislation achieved a high level of human health protection for donors of tissues and cells? (n = 120)



Over half (59%) of 116 respondents considered that the legislation has led to **unintended effects**. Unintended negative impacts related to:

- **Over-regulation**, including the consequences of particularly strict aspects of the legislation in relation to air quality/clean room conditions (which may actually have detrimental effects for the safety and quality of reproductive cells), to time limits for taking blood samples for testing

deceased donors and to the qualification requirements for the responsible person in a tissue establishment;

- **Increased bureaucracy, costs and administration**, and a lack of resources to deal with this. This appears to be especially an issue for establishments handling both blood and tissues and cells, and for those having to handle tissue coding according to the Single European Coding system;
- **Changes to clinical practice** (and therefore longer patient lists) when centres are unable to meet stricter compliance standards, for example due to a lack of resources or resistance from clinicians to perform safety tests; and
- Increased **uncertainty** for some stakeholders regarding which legislative procedures to follow, and when.

In general, where **positive impacts** were listed to this question, these were usually outcomes that had been intended by the legislation. For example, greater information sharing and international consistency and standardisation of requirements for collection, storage and documentation were thought to have improved the exchange of products, as well as transparency and safety. A few respondents suggested more specific impacts which were not initially intended, including: the centralisation of post-mortem banking activities because of the efforts needed to meet legal requirements, and better communication on information regarding genetic diseases in children conceived with sperm from non-partner donors.

Just over half of 117 respondents (51%) **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 (see below). 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.

The majority of respondents (out of 82 respondents) considered that the main challenge to maintaining compliance with tissue and cells legislation was **limited resources** for competent authorities (55%) and tissue establishments (46%), followed by **inadequate definitions** (45%). A similar proportion of respondents considered that requirements were too stringent/detailed (38%), becoming rapidly out-dated, and also that requirements were not specific enough (33%), suggesting a balance in the level of detail of provisions is required to ensure compliance with legislation. One specific reflection was that the legislation does not include the use of tissues and cells for the manufacturing of advanced therapy medicinal products (ATMP), which leads to inconsistencies and divergent interpretation across the EU. Other challenges identified included the high costs associated with Single European Code (SEC) labelling requirements; divergent interpretations on donor testing requirements when collecting white blood cells for further manufacturing of medicinal products; and the lack of consistency and clarity in the definitions of ‘cells’.

A significant proportion (30% of 120 respondents) considered that the legislation had reduced patient **access**, while 16% thought it had increased access and 43% concluded that there was no impact on patient access. One notable reflection was that although patient access has increased due to the increase in the standardisation of legal provisions across the European Union, patient waiting lists are growing for some products due to increased administrative or other costs for centres and tissue banks, and a parallel decline in deceased tissue donors (caused in part by a decline of organ donors in some countries, as well as stricter donor acceptance requirements). The European association representing eye banks expressed the view that the references to the achievement of sufficiency for patients in the current legislation are not adequately supported by provisions that oblige MS to promote donation and to ensure equal access to treatment with donated tissues. This comment was made in the context of a significant level of importation of ocular tissue from the US.

Finally, respondents were asked regarding the impact of Directive 2004/23/EC, together with Directive 2001/83/EC on the **safety and quality of medicinal products manufactured from tissues and cells,** and half of the 111 respondents to this question expressed the view that the framework was

effective in ensuring adequate safety of manufactured products. Nonetheless, 25% considered that requirements in the tissue and cells legislation needed significant or major modification in order to ensure the safety and quality of medicinal products that are manufactured from tissues and cells, indicating that there is a lack of consensus on this issue.

As general comments, many stressed that the legislation **focuses on safety** for the recipient, while it **addresses quality inadequately**, with almost no reference to the quality criteria that should be ensured for each type of tissue or cell applied to a patient. A lack of requirements for demonstrating safety and **efficacy** of tissues and cells in the patient (clinical follow-up) was also raised.

The exclusion of **autologous tissues and cells used in 'the same surgical procedure'** was considered by some correspondents as one of the important gaps, particularly in the light of the increasing use of these procedures. Similar comments were made regarding **bedside processing** of cells using medical devices; it was argued that these should be regulated by this legislation. It was also highlighted that ensuring appropriate and timely responses to emerging **disease outbreaks** or other crises is lacking in the legislation. Some commented that the scope of the legislation should be extended to the **clinical centres** applying tissues and cells, with mandatory activity data and adverse outcome reporting; some suggested that the absence of a requirement for the authorisation of centres that clinically apply tissues and cells represents an important gap and others, particularly in the ocular tissue banking field, considered that the exclusion of tissues for research from the scope of the legislation is an important gap.

2.2 Relevance

2.2.1 Blood and blood components

The OPC respondents were asked to comment on the extent to which the EU blood and blood component legislation is sufficiently adapted to four categories of development: i) donor eligibility developments, ii) scientific/technical developments related to donor testing for transmissible diseases, iii) scientific developments related to blood and blood component processing (preparation and microbial inactivation), storage and distribution and iv) Epidemiological developments.

Eighty six respondents answered regarding donor eligibility (history screening) and scientific and technical developments related to donor testing for transmissible diseases; 84 respondents answered regarding scientific developments related to blood and blood component processing, storage and distribution; and 85 respondents answered regarding epidemiological developments.

In general, the majority of respondents considered that all four **developments were not significantly addressed**, and a notable proportion considered that the legislation was not suited to the current situation. In particular, only 14% of 85 respondents considered the legislation is fully adapted to **epidemiological** developments. In addition, only 21% of 84 respondents considered it was fully adapted to **scientific** developments relating to processing and only 24% of 86 respondents had the same view regarding donor testing. In particular, 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.

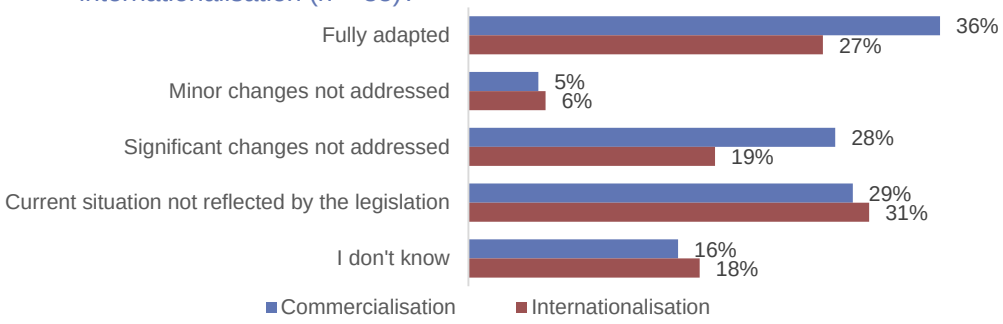
In addition, 48% of 82 respondents considered that there were other specific areas to which blood and blood component legislation has not sufficiently adapted, including: the large increase in coverage of the HBV vaccination; ongoing debates on paid or compensated donation; and not taking account of newer IT-solutions in the requirement for assessing health and medical history .

As shown in Figure 2.5, approximately two-thirds of respondents (67% of 86 respondents) considered, to varying degrees, that the blood and blood components legislation had not sufficiently adapted to the **commercialisation** of the sector, with particular reference to the growing role of the for-profit plasma industry that compensates plasma donations. Just over half (55% of 85 respondents) considered the legislation had also not sufficiently adapted to the **internationalisation** of the sector. Just one

organisation identified itself in the category 'Ethics' and expressed strong concerns regarding the adaptation of the legislation to commercialisation. In their view, the provisions for voluntary unpaid donation and the current situation in the EU are not in line.

One particular reflection concerned the recent confusion in some MS regarding which **VAT regime** should be applied to plasma for manufacturing, as this would have had important consequences for the private plasma collectors in EU, potentially also affecting access to PDMPs. Furthermore, 44% (out of 78 respondents) also stated that other changes were not adequately reflected or addressed in the legislation, including demographic changes such as the **ageing population and migration** (given this impacts the donor/recipient balance and has implications for donor acceptance criteria).

Figure 2.5 To what extent do you think the blood and blood component legislation is sufficiently adapted to societal changes in the sector such as commercialisation (n = 86) and internationalisation (n = 85)?



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). Further, a smaller proportion of respondents (19% of 84 respondents) considered that there were substances or activities that should be removed from specific pieces of legislation, such as donor lymphocyte cells from Directive 2002/98/EC.

The overall key message emerging from the responses is that the **EU blood legislation is not considered sufficiently adaptable to the evolution** of scientific knowledge, changing epidemiological risk and technological innovation as it is not subject to regular review and updating.
In this context, the technical annexes (2004/33/EC, 2005/61/EC and 2005/62/EC) were perceived by many respondents as being insufficiently adaptable to changes and developments and, in that context, to include technical requirements that are too detailed. It was proposed by many respondents that the legislation should provide general principles, while technical requirements that are subject to continuous change should be defined in guidance which can be updated more regularly. The view was expressed that such guidance should be cross-referenced in the legislation in a manner equivalent to the recent experience where Directive 2016/1214 of 25 July 2016 amended Directive 2005/62/EC, introducing a legal reference to Good Practice Guidance published by EDQM (Council of Europe).

Tissues and cells

The OPC respondents were asked to comment on the extent to which tissue and cells legislation is sufficiently adapted to four developments: i) donor eligibility developments, ii) scientific/technical developments related to donor testing for transmissible diseases, iii) scientific developments related to blood and blood component processing (preparation and microbial inactivation), storage and distribution and iv) Epidemiological developments. One hundred and sixteen respondents answered regarding donor eligibility (history screening); 114 respondents answered regarding scientific and technical development related to donor testing for transmissible diseases; 113 respondents answered regarding scientific developments related to tissue and cell processing, storage and distribution; and 112 respondents answered regarding epidemiological developments.

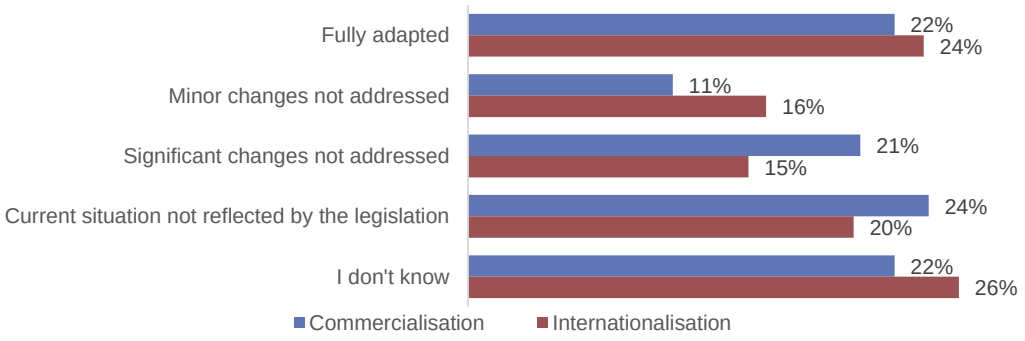
In general, the majority of respondents considered that all four **developments are not significantly addressed**, or not suited to the current situation. For example, only 31% of 113 respondents considered that the legislation is fully adapted to **scientific** developments relating to processing, and 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.

In addition, a third of 106 respondents indicated that there are other areas that tissue and cells legislation has not sufficiently adapted to, including: progressive technological developments (e.g. decellularisation of tissues, successful preservation of ooctyes and gonadal tissues) and the subsequent implications on donor exclusion, and the need for authorisation of new or experimental preparation processes. It was pointed out that increasing complexity of tissue and cell processing requires appropriate oversight rules. Particular concerns were expressed regarding donor eligibility; respondents made comments concerning the lack of genetic testing requirements for reproductive cell donors, varying selection criteria for donors generally, absence of limits on frequency of living donation, particularly for oocytes and a lack of evidence for the 24-hour limit for taking blood samples for testing of deceased tissue donors.

As shown in Figure 2.6, only a small proportion of respondents considered that the tissue and cells legislation had fully adapted to the **commercialisation** (22% of 112 respondents) and **internationalisation** (24% of 109 respondents) of the sector, and importantly a similar proportion of respondents considered that the current situation was not at all reflected by the legislation in both cases (24% and 20%, respectively); the organisation specialised in ethics was among those that considered the situation in relation to commercialisation not to be reflected in the legislation. Some described consequences of some of these developments, such as the negative impact of commercialisation on academic or smaller research groups, and the impact of internationalisation on harmonisation of definitions and procedures. Specific comments regarding commercialisation concerned a lack of regulation and monitoring of brokering activities, and of for-profit sales of tissues and cells, as well as heterogeneous interpretations amongst MS leading to different treatment options being available in different MS.

Additionally, 26% of 105 respondents stated that other **societal changes** were not adequately reflected or addressed in the legislation, including the recognition of same sex partnership and marriage, the aging population and the increased advertisement and promotion of tissue and cell treatments accompanied by unproven claims made by suppliers. The lack of legal provision for **demonstrating efficacy** was considered an important gap in this context, particularly in the area of stem cells. Global developments, including results of new clinical therapies and trials; long-term follow-up of donors and offspring; and serological screening were all highlighted as areas not adequately addressed in the legislation.

Figure 2.6 To what extent do you think the tissue and cells legislation is sufficiently adapted to societal changes in the sector such as commercialisation (n = 112) and internationalisation (n = 109)?



Twenty percent of 109 respondents considered that there were substances or activities that should be removed from specific sub-sections of legislation, such as reproductive tissues and cells (suggesting that they should have their own legislation).

The overall key message emerging from the responses is that the **EU tissues and cells legislation is not considered sufficiently adaptable to the evolution** of scientific knowledge, changing epidemiological risk and technological innovation as it is not subject to regular review and updating. In the context of this rapidly evolving field, respondents suggested that a more high-level 'framework' legislation would be more appropriate, with 'delegation' of the development of technical requirements to other bodies such as the European Directorate for the Quality of Medicines and Healthcare (EDQM) at the Council of Europe and/or professional associations that are better placed to perform more frequent revisions of technical aspects based on expert opinion and best practice and supported by research and data. In the field of haematopoietic stem cells and assisted reproduction technology particularly, the quality improvements achieved by professional standards and accreditation schemes were considered to be undervalued or absent in the legislation.

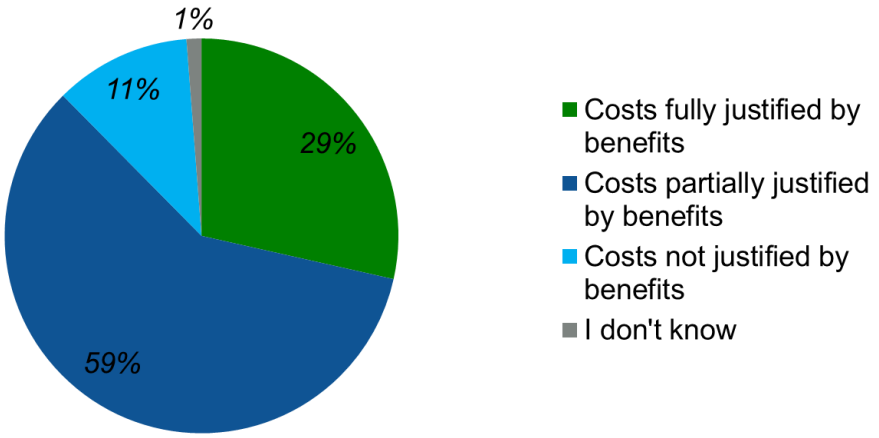
2.3 Efficiency

2.3.1 Blood and blood components

In general, respondents expressed the view that the blood regulation and subsequent EU-wide standardisation has increased EU patient access to safe products, but some considered that shortfalls in self-sufficiency and patient access to transfusion still remain, along with concerns regarding a lack of cost-benefit analysis when new safety measures are introduced.

The overall view expressed was that the EU legislation has brought **additional costs, but that these were justified by the benefits** (Figure 2.7). 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.

Figure 2.7 Do you consider that the costs [incurred by the legislation] were justified by the benefits for patients? (n = 53)



A particular concern of authorities was the requirement to **inspect all blood establishments every two years**, without differentiation between those centres with large scale activities from donation to

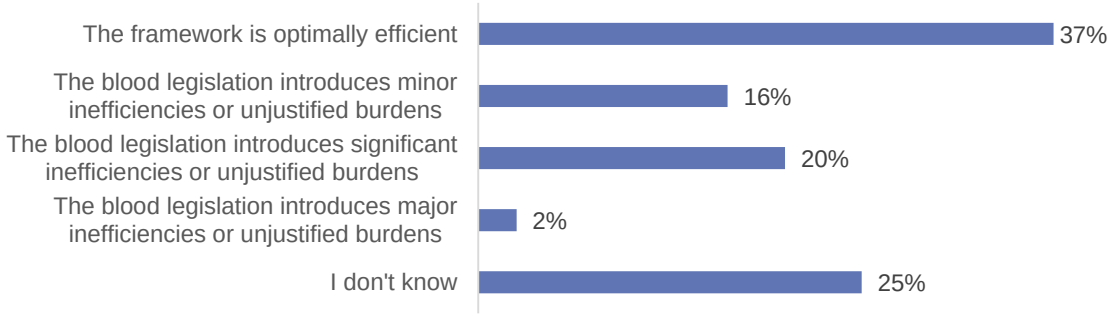
distribution and those that carry out very limited activities such as plasma collection. Many argue that it would be more cost-effective to inspect on the basis of a risk assessment.

The respondents, on the whole, were unfamiliar with administrative or other burdens for specific groups of operators (excluding the organisation(s) they represented), though a small proportion considered there were significant or minor additional costs (23% and 21% of 82 respondents, respectively) that were mostly justified by the benefits for patients. In this instance, only three respondents considered that the administrative or other burdens were not at all justified by the benefits for patients.

Respondents expressed the view that the implementation of **new measures should always be evaluated against the benefits** for patients, donors and the healthcare system as a whole, especially given the increasingly cost-constrained healthcare environment. Measures should only be implemented if they improve safety beyond existing measures or practices and do not have unjustifiable significant operational or financial impacts. For example, imposing stricter requirements for blood donation has both administrative and operational implications (i.e. when introducing new tests) but also may lead to fewer donations, ultimately reducing patient access. Some suggest that certain tests performed do not contribute to blood transfusion safety and some argued that the level of detail in the legislation (e.g. the requirement that West Nile Virus testing be performed on single donor samples rather than on pooled samples) causes costs and the loss of donations without a justified increase in safety.

Finally, a group of respondents (22% of 81 respondents) considered that the blood and blood components legislation, together with the medicinal products legislation, introduce significant or major inefficiencies for ensuring the safety and quality of **plasma derived medicinal products** (Figure 2.8).

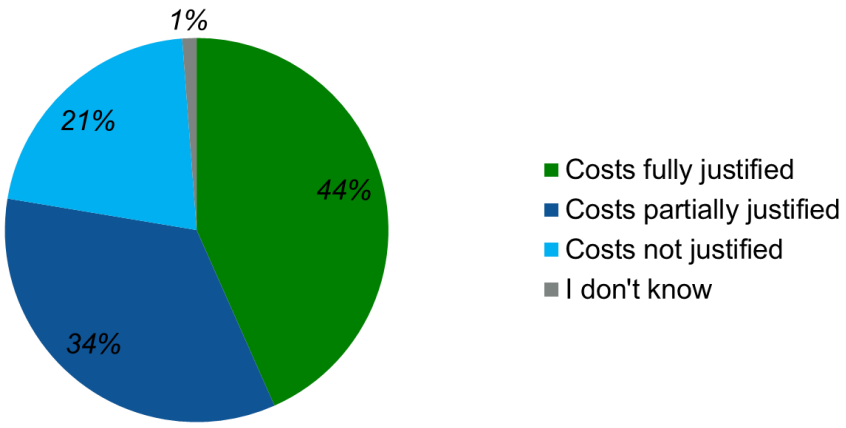
Figure 2.8 To what extent do you consider that Directive 2002/98/EC, together with Directive 2001/83/EC, form an efficient (cost effective) framework for ensuring the safety and quality of plasma derived medicinal products? (n = 81)



2.3.2 Tissue and cells

The overall view expressed was that the EU legislation has brought **additional costs, but that these were justified by the benefits** (Figure 2.9). 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. Reasons identified for these costs are the introduction of new 'elaborate' procedures and activities, and the need to implement IT systems to conform to labelling requirements. 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. As with the blood and blood components legislation, respondents considered new measures should always be evaluated against the benefits for patients, donors and the healthcare system.

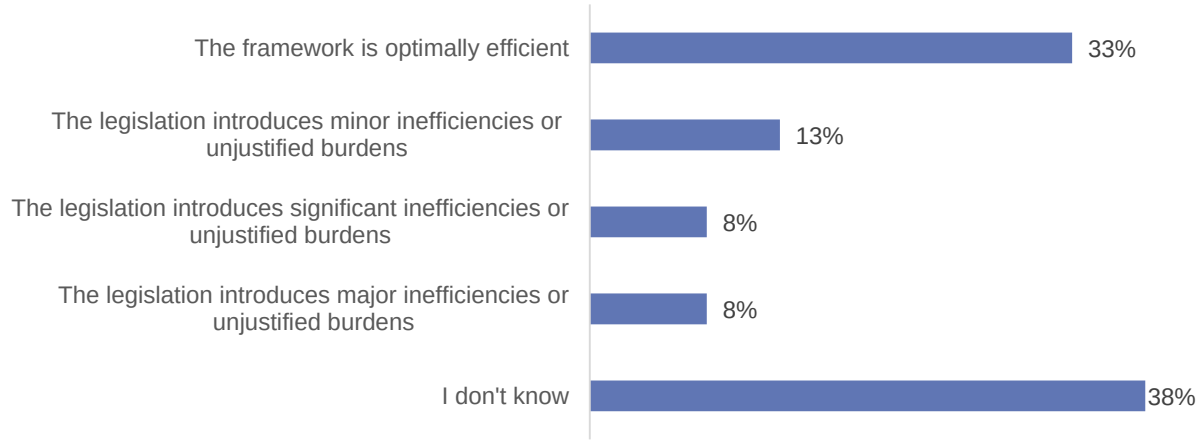
Figure 2.9 Do you consider that the costs [incurred by the legislation] were justified by the benefits for patients? (n = 94)



A particular point was made by many respondents regarding the costs of implementing the air quality requirements to process tissues and cells and, for certain substances, such as reproductive cells and ocular tissue; these requirements were not considered justified by quality or safety improvements. These costs were identified as being especially burdensome for smaller centres. The costs of implementing IT systems to comply with coding and labelling requirements were also highlighted as significant. As for blood and blood components, authorities identified the 2-year inspection requirement as a costly burden that was not justified by improved safety that would, in their view, be better achieved through risk-based inspection scheduling.

Finally, 16% of 112 respondents considered that Directive 2004/23/EC, together with Directive 2001/83/EC, introduces significant or major inefficiencies or unjustified burdens when ensuring the safety and quality of **medicinal products manufactured from tissues and cells** (Figure 2.10).

Figure 2.10 To what extent do you consider that Directive 2004/23/EC, together with Directive 2001/83/EC, form an efficient (cost-effective) framework for ensuring the safety and quality of medicinal products manufactured from tissues and cells? (n=111)

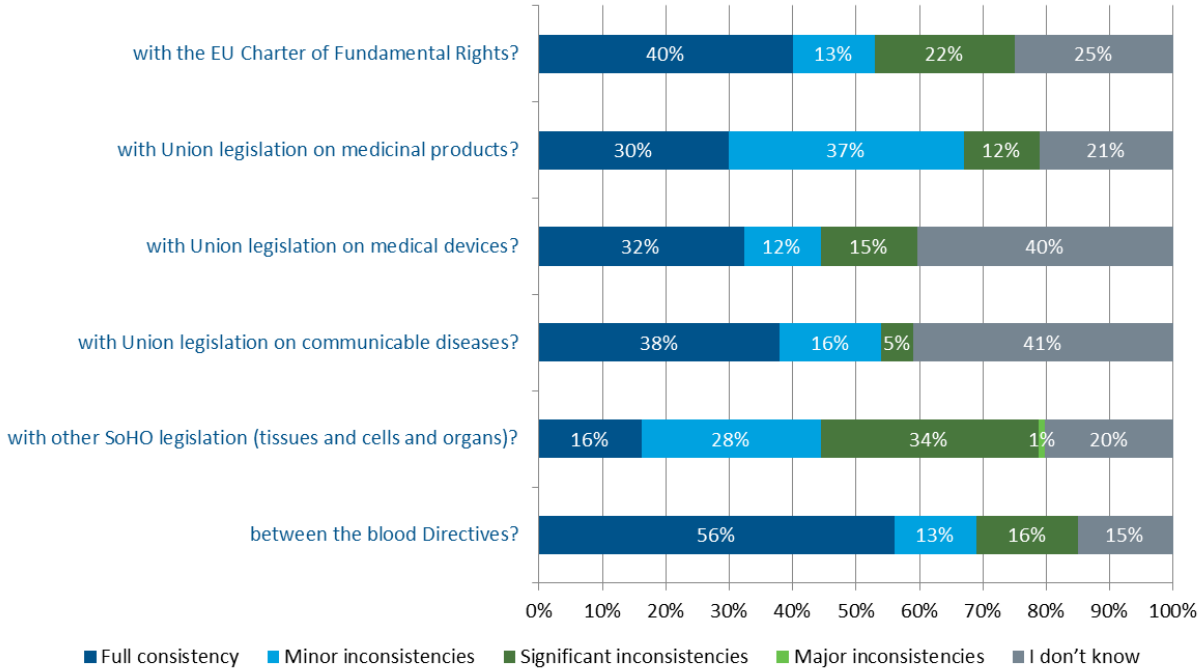


2.4 Coherence

2.4.1 Blood and blood components

Inconsistencies between the SoHO legal frameworks were identified, as were the borderlines with the EU legal frameworks on medicinal products (Figure 2.11). Respondent organisations also pointed to inconsistencies with the Charter of Fundamental Rights.

Figure 2.11 To what extent do you consider Directives 2002/98/EC, 2004/33/EC, 2005/61/EC and 2005/62/EC to be consistent and coherent:



The largest part of respondents considered that EU blood legislation is fully consistent and **coherent within its own provisions**, while 29% point out there are minor or significant inconsistencies between Directive 2002/98/EC, Directive 2004/33/EC and Directive 2005/61/EC. Over a third of 88 respondents also concluded that there are significant inconsistencies between blood and blood components legislation and legislation regulating other substances of human origin (i.e. on organs and tissues and cells), and a further 28% replied that there are minor inconsistencies. Comments from respondents suggest that the main inconsistencies concern donor selection provisions (particularly in relation to voluntary and unpaid donation), definitions, and regulatory borderlines.

Regarding the consistency of blood and blood components legislation with **medical devices legislation**, 27% (out of 84 respondents) considered there were minor (12%) or significant (15%) inconsistencies. Issues raised concerning the consistency of the Directives with medical devices legislation included the difference of schemes to assess risks which mean a higher risk level is accepted in the production of medical devices than in the processing of blood products, with a potential negative impact on the quality and safety of blood components. An additional issue reported relates to substances derived from blood and used in hospital settings/intra-operatively that are covered under the medical devices legislation, while this only guarantees the safety of the device used to produce the product, and not the quality and safety of the product itself.

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.

Only a small proportion of respondents (21% of 86 respondents) also considered there were minor or significant inconsistencies between blood legislation and other relevant union legislation such as the **communicable diseases legislation**, specifically regarding testing or reporting requirements and vigilance and surveillance communication requirements within or between MS. A higher proportion of respondents (35% of 85 respondents) considered there were minor or significant inconsistencies between the blood legislation and the EU **Charter of Fundamental Rights**, particularly in relation to voluntary unpaid donation and the role of the for-profit industry.

Finally, 61% of 80 respondents agreed that blood and blood components legislation is coherent and compatible with other **international** and/or third country approaches to the regulation of the quality and safety of these substances. Most respondents pointed to a high degree of coherence, especially with the US FDA, but respondents also stated that for some products e.g. autologous products, donor testing requirements are different (i.e. in the US, Japan, Australia or Canada), and there is also variation in some important quality and safety requirements.

2.4.2 Tissues and cells

While some inconsistencies between the SoHO legal frameworks were identified, the most frequent significant inconsistencies mentioned relate to the borderlines with the EU legal frameworks on medicinal products and medical devices (Figure 2.12). Respondents pointed to the lack of a common EU-level mechanism to clarify these borders in view of the many innovative developments in biotechnology.

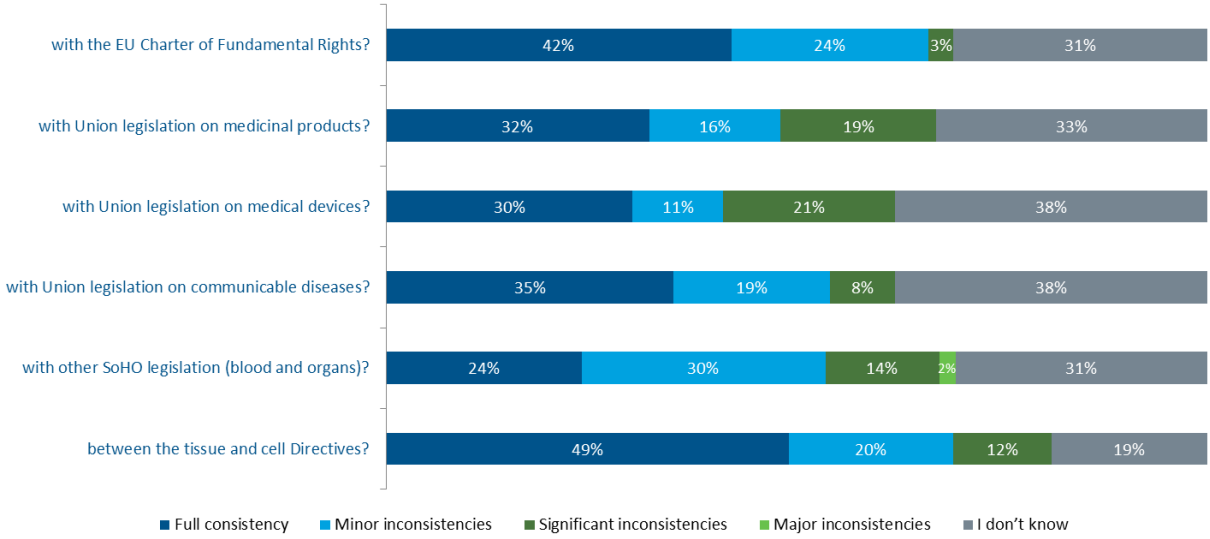
Almost half of respondents (49% of 116 respondents) considered that the tissues and cells Directives are fully **consistent and coherent within their own provisions** and around a third point out minor (20%) or significant (12%) inconsistencies between Directive 2004/23/EC, Directive 2006/17/EC and Directive 2015/566/EC, caused mainly by technological and scientific developments. Some of these respondents questioned for example whether substances such as reproductive cells should be regulated under the tissue and cell directives. Another reflection pointed to a lack of consistency in the definition of ‘validation’ between Directive 2006/17/EC and the other Directives.

Forty-four percent of 108 respondents consider that there are minor (30%) and significant (14%) inconsistencies between tissue and cell legislation and legislation regulating other substances of human origin (i.e. on **organs and blood and blood components**), and a further two stakeholders suggest there are major inconsistencies. Respondents suggest that the main inconsistencies relate to definitions and donor selection provisions, and further note specific inconsistencies such as the minimum period of record keeping for blood/blood components and tissues and cells (15 and 30 years, respectively). Some respondents reported the importance of maintaining coherence between Directives governing different types of substances of human origin is important because donors many donate many different kinds of substances, sometimes at the same time.

Twenty-one per cent of 112 respondents report significant inconsistencies with the EU legal framework for **medical devices**. Respondents brought forward issues with the use of many medical devices in tissue establishments, and how to handle related alerts on safety/quality issues, as well as the need for clarity on classifications of borderline products like demineralised bone matrix or collagen fillers.

Nineteen per cent 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.

Figure 2.12 To what extent do you consider Directives 2004/23/EC, 2006/17/EC, 2006/86/EC and 2015/566/EC to be consistent and coherent:



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. Others considered that additional investment (resources and time) were needed to understand what companies or hospitals need to do to remain compliant with legislative procedures defined in other legislation which can result in costs and delays to patients' accessing new, innovative therapies made from tissues and cells.

Respondents considered that the regular review and updates of standards and guidelines would be helpful for the sector, as would the harmonisation of national legislation on medical devices and medicinal products in particular. One particular suggestion was to create a new and specific regulatory framework for substances used as starting materials for ATMPs, covering all processes and steps, as well as commercialisation.

Twenty seven percent of 106 respondents considered there were minor or significant inconsistencies between the tissues and cells legislation and the EU **Charter of Fundamental Rights** (Charter). A particular issue raised concerned the principle of the non-commercialisation of the human body in the Charter, which prohibits making the human body and its parts a source of financial gain, and the lack of obligation in the tissue and cell legislation to enforce voluntary and unpaid donation, and to ensure procurement organisations work on a not-for-profit basis.

Forty one of 95 respondents consider that the tissue and cell legislation is not coherent and compatible with other **international and/or third country** approaches to the regulation of the quality and safety of these substances. As with blood and blood components, donor testing requirements for autologous products are different (i.e. in the US, Japan, Australia or Canada), and respondents note the legal complexities in importing and exporting products to non-European countries. One important concern noted by a respondent was the need to ensure consistent global regulation to prevent "stem-cell tourism" and ill-informed access to unproven therapies being provided by clinics across the world.

Finally, a few respondents commented on the **VAT Directive** 2006/112/EC in relation to the tissue and cell legislation, as this states that "the supply of human organs, blood and milk" shall be exempted from VAT. This statement was considered to be outdated; the absence of any reference to tissues and cells has resulted in confusion regarding the interpretation of the article in question (Art. 132(d)) which has resulted in some MS considering that tissues and ells should not be exempt from VAT.

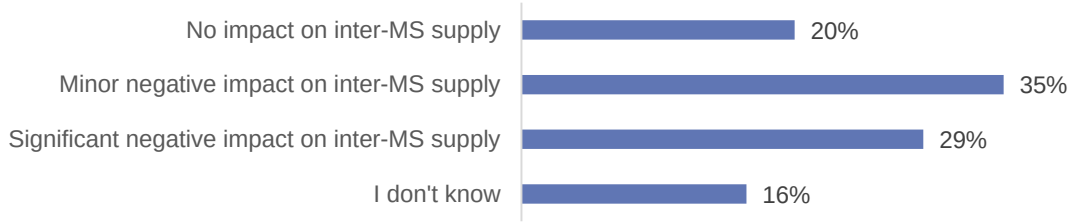
2.5 EU added value

Overall, most respondents generally believe **legislation at an EU level has helped to improve the quality and safety** of blood, tissues and cells. However, the majority of respondents considered that the **potential EU added value has been significantly limited by allowing for more stringent national legislation,** which generates differences between Member States and therewith barriers for cross-border exchange. As a result, a number of respondents called for improved harmonisation across MS in the interpretation and implementation of the EU regulatory framework.

2.5.1 Blood and blood components

In general, 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. Notably, around a fifth of respondents (21%) considered only EU legal provisions could have achieved current safety and quality outcomes, while only two respondents considered that these outcomes could have been achieved without EU blood legislation in place. Nevertheless, as shown in Figure 2.13, around two thirds of 86 respondents considered that the stricter national legal provisions have had a minor (35%) or significant (29%) negative impact on inter-MS supply. Some respondents expressed the view that one area of improvement for EU provisions would be in increasing the flexibility of technical requirements in line with scientific and technical developments.

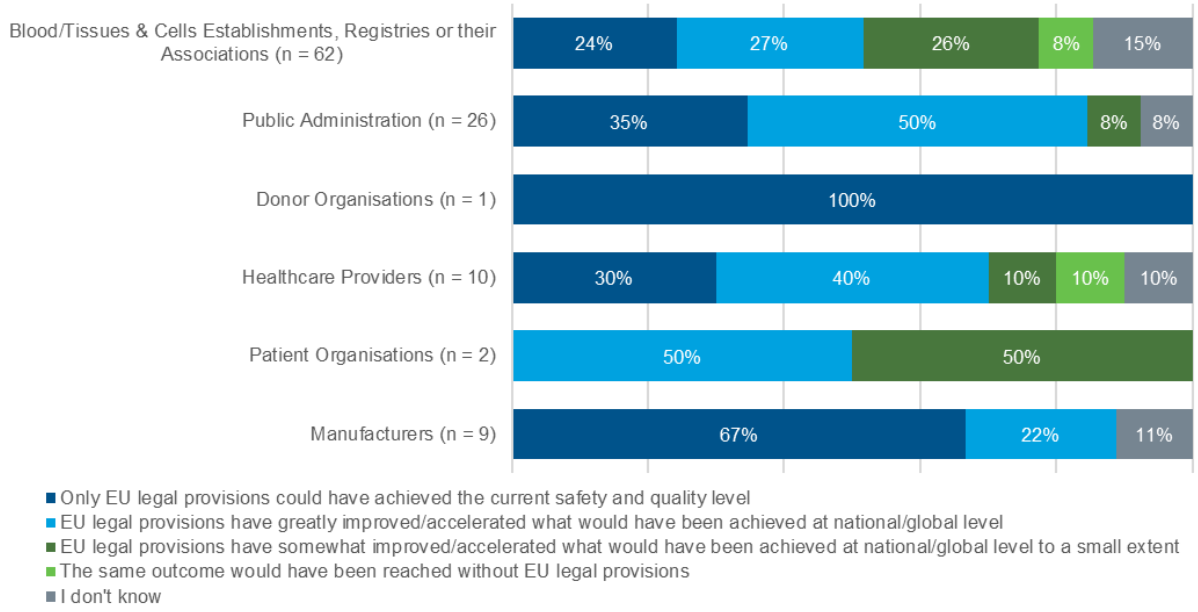
Figure 2.13 To what extent do stricter national measures pose an obstacle to exchange of supplies between Member States? (n = 86)



2.5.2 Tissues and cells

In general, 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. Figure 2.14 illustrates that stakeholders from the same types of organisations have quite diverse views regarding the extent to which EU legislation has added value. Importantly, 61% of 111 respondents considered that stricter national legal provisions have had a minor (31%) or significant (30%) negative impact on inter-MS supply of tissues and cells, limiting the potential EU added value.

Figure 2.14 To what extent has the legislative framework at EU level added value to the regulation of tissues and cells across the EU-28 in a manner that could not have been achieved by measures taken at national or global level? (n = 110)



3 Summary of inputs: Citizens

This section summarises the inputs received from individual citizens, and is structured by evaluation theme.

3.1 Relevance

Respondents were asked to consider whether there have been technological advances that could increase the quality or safety of blood transfusions, tissue and cell transplantation or assisted reproduction, and that should be introduced into the EU rules. Nearly half of all the 26 respondents answered 'yes' (42%), with NAT testing, DNA sequencing, de-cellularisation of valved homografts and pathogen inactivation methods cited as examples of advancements by respondents.

Over three-quarters (77%) of the 26 respondents answered 'no' to the suggestion that EU safety and quality rules could be made less stringent because the level of risk has fallen since the blood, tissues and cells legislation was adopted. Suggestions by respondents for less stringent regulations included the complete removal of deferral procedures for men having sex with men (MSM) as they considered that this is no longer scientifically justified, and the exclusion of reproductive cells from tissue and cells legislation as they are "mostly in-couple donations and do not cure a disease".

Just under half of the 26 respondents (42%) considered there were no epidemiological changes missing from the current EU legislation, with an equal amount answering 'I don't know'. Additional feedback concerned the lack of pan-EU harmonisation on testing and risk assessment (beyond what is laid down in Directive 2006/17/EC) Exactly half of the 26 respondents to this question responded that there were societal changes that also needed to be taken into account. This predominately related to the impact of an ageing donor base and resulting increased needs of elderly patients for both blood and tissues and cells, which might require adjustments to donor eligibility criteria, particularly to meet increasing demand.

Just under a quarter of respondents (23%) suggested other substances of human origin should be included under EU legislation. One respondent mentioned breast milk as an example of what could be covered, and another respondent reflected that biological products obtained from blood for treatment in traumatology, ophthalmology or other autologous and allogeneic uses, should also be included in the legislation. Another suggestion was that the blood, tissues and cells legislation could improve clarity over which regulations cover the use of substances of human origin for specifically research and/or training purposes. Finally, exactly half of the 26 respondents considered that there were no substances of human origin being used to treat patients in the EU that should be removed from the blood, tissues and cells legislation.

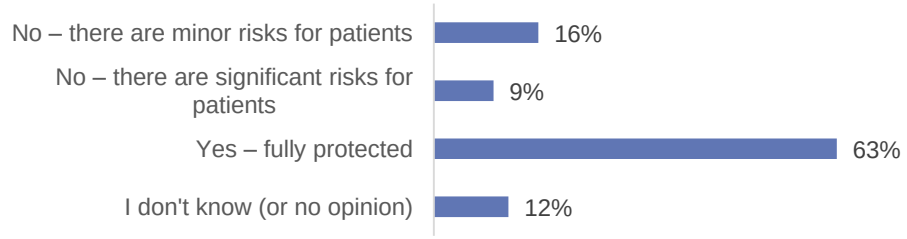
3.2 Effectiveness

As Figure 3.1 indicates, 63% of 43 respondents considered that patients treated with blood transfusions in the EU are adequately protected from risk by the EU safety and quality rules. Likewise, over half of respondents (53%) responded that patients treated with tissue or cell transplantation are fully protected. This differs in the case of assisted reproduction, with only 37% considering patients are 'fully protected' and with respondents predominately answering 'I don't know' (42%). One respondent reflected that there may always be a minor risk for patients left (e.g. mismatch of blood group) but the legislation has enabled quality and safety standards to improve in Europe.

Almost three-quarters of the 43 respondents to this question answered that donor protection is adequate for blood and blood components. This majority falls slightly to just over half of respondents (56%) in the context of tissues and cells and an important reflection was that the tissues and cells directives consist of a "limited list of donor selection criteria without further guidance regarding proper handling of testing samples, types of tests to be performed or the interpretation of test results".

In addition, 40% of the 43 respondents answered that donor protection is adequate for donors of gametes or embryos, with 47% answering 'I don't know'. Issues flagged included: lack of information and informed consent forms, DNA databases reducing donor anonymity, a lack of technical details in the tissue and cells legislation regarding the conditions under which procurement of tissues and cells should be performed, and a lack of EU governance of national policies or registries.

Figure 3.1 Do you think that patients treated with blood transfusions in the EU are adequately protected from risk by the EU safety and quality rules? (n = 43)



Responses varied as to whether EU legislation on blood, tissues and cells had an outcome that was not intended when it was adopted. An equal proportion of the 26 respondents (38%) answered either 'No' or 'I don't know', compared with 23% selecting 'Yes'. Unintended impacts for blood included issues arising due to the legislation's scope being too broad, and the omission of a differentiation between blood and plasma meaning "requirements developed for blood (intended for transfusion) also apply to plasma (intended for further fractionation to manufacture products)". For tissues and cells, the ambiguity of ATMP definitions was noted as causing wide regulatory heterogeneity.

3.3 Efficiency

Most of the 43 respondents (47%) considered the supply of blood, blood components and blood-derived medicinal products as adequate to meet EU patients' needs. Out of the 18 (42%) respondents who responded that supplies are inadequate, almost a third saw this as being due to a shortage of blood/blood component donations and a quarter applied this conclusion to plasma-derived medicinal products. Additionally, respondents mentioned the ban to remunerate donations as one possible barrier to an adequate supply of blood and blood components.

Conversely, in the case of tissues and cells, the majority (42% of 43 respondents) viewed supplies as inadequate to meet EU patients' needs. Of these responses, the majority (29%) considered that shortages are caused by a lack of tissue or cell donations, with most referring to bone marrow or other types of blood stem cells. A lack of effective quality control, as well as a severe lack of fairness for tissue allocation (e.g. due to a lack of uniform criteria for heart valve allocation), were mentioned as potential causes of tissue and cell shortages.

Almost half of respondents (49% of 43 respondents) did not know, or had no opinion, regarding whether or not provisions for assisted reproduction therapies are adequate. From those perceiving inadequate supplies (23%), this was most commonly attributed to restrictive national rules based on ethics (as mentioned by seven respondents). An absence of anonymous donation in certain MS was also identified as limiting adequate provision of assisted reproduction therapies.

Finally, the majority of respondents did not feel that there were any particular EU safety and quality requirements that had high costs, without equivalent benefits for patients. However, two specific examples of requirements of high costs and no equivalent benefit were given: requirements for clean rooms for reproductive cells were deemed unnecessary, and the high costs for EU inspections required for plasma from outside the EU were also mentioned.

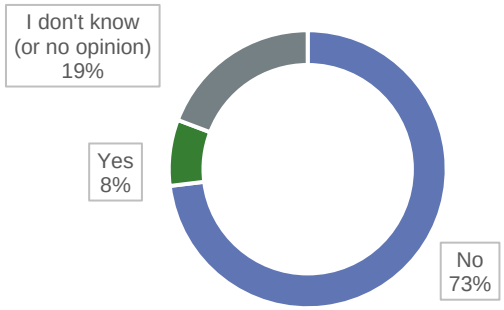
3.4 Coherence

Most respondents (42% of 26 respondents) were not familiar enough with the EU legislation for blood, tissues and cells to identify aspects that do not fit logically with other EU legislation. Only 31% of respondents suggested there were aspects of legislation that do not appear to fit clearly and logically with other EU legislation, for example with regards to the inspection of blood establishments, "as suppliers of plasma for fractionation may overlap with inspection as a blood establishment". In relation to tissues and cells, ambiguities in terms of terminology and inconsistences in regulation of borderline products (e.g. de-cellularised heart valves which have been nationally regulated as an ATMP or a tissue) were cited. Other ambiguities included the terminology and provisions for absence of financial gain for the donor, particularly in the case of blood, plasma and gametes; inconsistent regulation of tissues and cells initially derived from organs for organ transplantation; and plasma master file (PMF) requirements for the authorisation of plasma derived medicinal products.

3.5 EU added value

As Figure 3.2 indicates, almost three-quarters of respondents replying to this question considered that legislation on blood, tissues and cells at the EU level, as opposed to national measures, is necessary to achieve the required results. One specific reflection was that there is still no harmonisation across all EU MS on inspection systems, which prevents the regulations from being as effective as they could be.

Figure 3.2 If you have experience in applying EU legislation for blood or tissues and cells, do you consider that the results could have been achieved through measures at national level and without EU legislation? (n = 26)



4 Next Steps

The Commission will duly consider the views expressed by stakeholders in this open public consultation, as well as in the views and information gathered in other consultation activities including the Public Stakeholder Event held on September 20th 2017[4] and the many meetings held with stakeholders during the evaluation process[5]. The results of the online public consultation will be complemented with the stakeholders views collected in these other consultation activities and will be summarised in a Consultation Synopsis Report that will be annexed to the final Evaluation Report to be published by the Commission. The Evaluation process can be followed on the relevant pages of the European Commission website[6].

[4] https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/ev_20170920_sr_en.pdf

[5] https://ec.europa.eu/health/blood_tissues_organs/events_en

[6] https://ec.europa.eu/health/blood_tissues_organs/policy/evaluation_en

Part A: ANNEXES

Annex 1 Survey of organisations – answers to closed questions

A1.1 Relevance

A1.1.1 Blood and blood components

To what extent do you think the legislation is sufficiently adapted to:	Fully adapted	Minor developments not addressed	Significant developments not addressed	Not suited to current situation	Don't know	Total respondents
Developments related to donor eligibility	28%	26%	31%	9%	6%	86
Scientific/technical developments related to donor testing for transmissible diseases	24%	24%	37%	10%	3%	86
Scientific developments related to blood and blood component processing (preparation and microbial inactivation), storage and distribution?	21%	23%	30%	15%	11%	84
Epidemiological developments	14%	27%	31%	19%	9%	85

Question	Yes (%)	No (%)	Total respondents
Have there been developments to which the legislation is not adequately adapted other than those listed above?	48%	52%	82

To what extent do you think the legislation is sufficiently adapted to societal changes in the sector such as commercialisation / internationalisation?	Fully adapted	Minor changes not addressed	Significant changes not addressed	Current situation not reflected by the legislation	I don't know	Total respondents
Commercialisation	36%	5%	28%	29%	16%	86
Internationalisation	27%	6%	19%	31%	18%	85

Question	Yes (%)	No (%)	Total respondents
Have there been societal changes in the sector other than commercialisation or internationalisation which are not adequately reflected or addressed in the legislation?	44%	56%	78

Question	Yes (%)	No (%)	Total respondents
Are you aware of any gaps in terms of substances of human origin	44%	56%	81

Question	Yes (%)	No (%)	Total respondents
(substances not listed in Section 1 question 1.4) or activities (e.g. research, biobanking or other activities not listed in Section 1 question 1.5) that are not regulated by the Directives or other EU legislation?			
Do you consider that there are substances or activities falling within the scope of the Directive 2002/98/EC that should be removed?	19%	81%	84

A1.1.2 Tissues and cells

To what extent do you think the legislation is sufficiently adapted to:	Fully adapted	Minor developments not addressed	Significant developments not addressed	Not suited to current situation	Don't know	Total respondents
Developments related to donor eligibility	31%	29%	22%	7%	10%	116
Scientific/technical developments related to donor testing for transmissible diseases	38%	19%	28%	8%	7%	114
Scientific developments related to tissue and cells processing (preparation and microbial inactivation), storage and distribution?	31%	19%	33%	11%	6%	113
Epidemiological developments	29%	18%	24%	6%	22%	112

Question	Yes (%)	No (%)	Total respondents
Have there been developments to which the legislation is not adequately adapted other than those listed above?	33%	67%	106

To what extent do you think the legislation is sufficiently adapted to societal changes in the sector such as commercialisation / internationalisation?	Fully adapted	Minor changes not addressed	Significant changes not addressed	Current situation not reflected by the legislation	I don't know	Total respondents
Commercialisation	22%	11%	21%	24%	22%	112
Internationalisation	24%	16%	15%	20%	26%	109

Question	Yes (%)	No (%)	Total respondents
Have there been societal changes in the sector other than commercialisation or internationalisation which are not adequately reflected or addressed in the legislation?	26%	74%	105

Question	Yes (%)	No (%)	Total respondents
Do you consider that there are substances or activities falling within the scope of the Directive 2004/23/EC that should be removed?	20%	80%	109

A1.2 Effectiveness

A1.2.1 Blood and blood components

In your opinion to what extent has the legislation:	To a great extent	To some extent	To a limited extent	No impact	I don't know	Total respondents
Increased the quality and safety of blood and blood components?	49%	41%	6%	1%	3%	88
Achieved a high level of human health protection for recipients of these substances	44%	47%	7%	1%	1%	87
Achieved a high level of human health protection for donors of these substances?	36%	31%	25%	6%	2%	88

Question	Increased patient access	No impact on access	Reduced patient access	I don't know	Total respondents
To what extent, if any, has the legislation impacted on patient access to blood or blood components?	21%	45%	16%	17%	75

Question	Adequately ensures the safety of the manufactured products	The requirements in the blood legislation need minor modification to ensure safety and quality of manufactured products	The requirements in the blood legislation need significant modification to ensure safety and quality of manufactured products	I don't know	Total respondents
To what extent do you consider that Directive 2002/98/EC, together with Directive 2001/83/EC, form an effective framework for ensuring the safety and quality of plasma derived medicinal products?	54%	21%	14%	11%	77

Question	Yes (%)	No (%)	Total respondents
To your knowledge has the legislation led to any unintended effects (positive or negative)?	57%	43%	83
In your experience, have there been barriers preventing effective implementation of the legislation?	50%	50%	84
In your opinion, do the rules on oversight (inspection, authorisation, vigilance) effectively ensure full application of the legislation?	54%	46%	83

A1.2.2 Tissues and cells

In your opinion to what extent has the legislation:	To a great extent	To some extent	To a limited extent	No impact	Total respondents
Increased the quality and safety of tissues and cells?	42%	43%	10%	4%	115
Achieved a high level of human health protection for recipients of these substances	40%	49%	9%	3%	117
Achieved a high level of human health protection for donors of these substances?	32%	33%	25%	11%	110

Question	Increased patient access	No impact on access	Reduced patient access	I don't know	Total respondents
To what extent, if any, has the legislation impacted on patient access to tissues and cells?	16%	43%	30%	12%	120

Question	Adequately ensures the safety of the manufactured products	The requirements in the tissue and cell legislation need minor modification to ensure safety and quality of manufactured products	The requirements in the tissue and cell legislation need significant modification to ensure safety and quality of manufactured products	The requirements in the tissue and cell legislation major modification to ensure safety and quality of manufactured products	I don't know	Total respondents
To what extent do you consider that Directive 2004/23/EC, together with Directive 2001/83/EC, form an effective framework for ensuring the safety and quality of medicinal products manufactured from tissues and cells?	50%	9%	20%	5%	17%	111

Question	Yes (%)	No (%)	Total respondents
To your knowledge has the legislation led to any unintended effects (positive or negative)?	59%	41%	116
In your experience, have there been barriers preventing effective implementation of the legislation?	51%	49%	117
In your opinion, do the rules on oversight (inspection, authorisation, vigilance) effectively ensure full application of the legislation?	58%	42%	115

A1.3 Efficiency

A1.3.1 Blood and blood components

Question	No additional costs	Minor additional costs	Significant additional costs	I don't know	Total respondents
Did application of the legislation bring costs for you, your organisation or the stakeholders represented by your organisation that would not have been incurred without EU legislation?	20%	18%	45%	17%	87
Question	**Costs fully justified by benefits**	**Costs partially justified by benefits**	**Costs not justified by benefits**	**I don't know**	**Total respondents**
If you answered B or C to the previous question, do you consider that the costs were justified by the benefits for patients?	28%	58%	11%	2%	53
Question	**No additional costs**	**Minor additional costs**	**Significant additional costs**	**I don't know**	**Total respondents**
Are you aware of particular administrative or other burdens for specific groups of operators apart from your organisation or the organisations you represent?	15%	21%	23%	41%	82
Question	**Costs fully justified by benefits**	**Costs partially justified by benefits**	**Costs not justified by benefits**	**I don't know**	**Total respondents**
If you answered B or C to the previous question, do you consider that the costs were justified by the benefits for patients?	43%	46%	9%	4%	35

Question	The framework is optimally efficient	The blood legislation introduces minor inefficiencies or unjustified burdens	The blood legislation introduces significant inefficiencies or unjustified burdens	The blood legislation introduces major inefficiencies or unjustified burdens	I don't know	Total respondents
To what extent do you consider that Directive 2002/98/EC, together with Directive 2001/83/EC, form an efficient (cost effective) framework for ensuring the safety and quality of plasma derived medicinal products?	37%	16%	20%	2%	25%	81

A1.3.2 Tissues and cells

Question	No additional costs	Minor additional costs	Significant additional costs	I don't know	Total respondents
Did application of the legislation bring costs for you, your organisation or the stakeholders represented by your organisation that would not have been incurred without EU legislation?	9%	25%	59%	7%	114
Question	**Costs fully justified by benefits**	**Costs partially justified by benefits**	**Costs not justified by benefits**	**I don't know**	**Total respondents**
If you answered B or C to the previous question, do you consider that the costs were justified by the benefits for patients?	43%	34%	21%	2%	94
Question	**No additional costs**	**Minor additional costs**	**Significant additional costs**	**I don't know**	**Total respondents**
Are you aware of particular administrative or other burdens for specific groups of operators apart from your organisation or the organisations you represent?	15%	17%	35%	33%	115
Question	**Costs fully justified by benefits**	**Costs partially justified by benefits**	**Costs not justified by benefits**	**I don't know**	**Total respondents**
If you answered B or C to the previous question, do you consider that the costs were justified by the benefits for patients?	37%	32%	30%	2%	60

Question	The framework is optimally efficient	The legislation introduces minor inefficiencies or unjustified burdens	The legislation introduces significant inefficiencies or unjustified burdens	The legislation introduces major inefficiencies or unjustified burdens	I don't know	Total respondents
To what extent do you consider that Directive 2004/23/EC, together with Directive 2001/83/EC, form an efficient (cost effective) framework for ensuring the safety and quality of medicinal products manufactured from tissues and cells?	33%	13%	8%	8%	38%	112

A1.4 Coherence

A1.4.1 Blood and blood components

Question	Full consistency	Minor inconsistencies	Significant inconsistencies	Major inconsistencies	I don't know	Total respondents
To what extent do you consider Directives 2002/98/EC, 2004/33/EC, 2005/61/EC and 2005/62/EC to be consistent and coherent within their own provisions?	56%	13%	16%	0%	15%	86
To what extent do you consider the legislation on blood and blood components to be consistent and coherent with other legislation on substances of human origin (i.e. on organs and on tissues and cells)?	16%	28%	34%	1%	20%	88
To what extent do you consider that the legislation to be coherent and consistent with other relevant Union legislation - legislation on Communicable Diseases?	38%	16%	5%	0%	41%	86
To what extent do you consider that the legislation to be coherent and consistent with other Union legislation – Legislation on Medical Devices?	32%	12%	15%	0%	40%	84

To what extent do you consider that the legislation to be coherent and consistent with other Union legislation – Legislation on Medicinal products	30%	37%	12%	0%	21%	82
To what extent do you consider that the legislation to be coherent and consistent with other relevant Union legislation regarding EU Charter of Fundamental Rights?	40%	13%	22%	0%	25%	85

A1.4.2 Tissues and cells

Question	Full consistency	Minor inconsistencies	Significant inconsistencies	Major inconsistencies	I don't know	Total respondents
To what extent do you consider Directives 2004/23/EC, 2006/17/EC, 2006/86/EC and 2015/566/EC to be consistent and coherent within their own provisions?	49%	20%	12%	0%	19%	116
To what extent do you consider the legislation on tissues and cells to be consistent and coherent with other legislation on substances of human origin (i.e. on organs and on blood)?	24%	30%	14%	2%	30%	108
To what extent do you consider that the legislation to be coherent and consistent with other relevant Union legislation - legislation on Communicable Diseases?	35%	19%	8%	0%	38%	110
To what extent do you consider that the legislation to be coherent and consistent with other relevant Union legislation - Legislation on Medical Devices?	30%	11%	21%	0%	38%	112
To what extent do you consider that the legislation to be coherent and consistent with other relevant Union legislation - Legislation on Medicinal Products?	32%	16%	19%	0%	33%	114
To what extent do you consider that the legislation to be coherent and consistent	42%	24%	3%	0%	31%	106

with other relevant Union legislation regarding EU Charter of Fundamental Rights?						

Question	Yes (%)	No (%)	Total respondents
To your knowledge, is the legislation coherent with other relevant international / third country approaches to the regulation of the quality and safety of tissues and cells?	59%	41%	95

A1.5 EU Added Value

A1.5.1 Blood and blood components

Question	Only EU legal provisions could have achieved the current safety and quality level	EU legal provisions have greatly improved / accelerated what would have been achieved at national / global level	EU legal provisions have somewhat improved/accelerated what would have been achieved at national / global level to a small extent	The same outcome would have been reached without EU legal provisions	Total respondents
To what extent has the legislative framework at EU level added value to the regulation of blood and blood components across the EU-28 in a manner that could not have been achieved by measures taken at national or global level?	21%	53%	13%	2%	86

Question	No impact on inter-MS supply	Minor negative impact on inter-MS supply	Significant negative impact on inter-MS supply	I don't know	Total respondents
To what extent do stricter national measures pose an obstacle to exchange of supplies between Member States?	20%	35%	29%	16%	88

A1.5.2 Tissues and cells

Question	Only EU legal provisions could have achieved the current safety and quality level	EU legal provisions have greatly improved / accelerated what would have been achieved at national / global level	EU legal provisions have somewhat improved/accelerated what would have been achieved at national / global level to a small extent	The same outcome would have been reached without EU legal provisions	Total respondents
To what extent has the legislative framework at EU level added value to the regulation of tissues and cells across the EU-28 in a manner that could not have been achieved by measures taken at national or global level?	34%	23%	25%	14%	110

Question	No impact on inter-MS supply	Minor negative impact on inter-MS supply	Significant negative impact on inter-MS supply	I don't know	Total respondents
To what extent do stricter national measures pose an obstacle to exchange of supplies between Member States?	21%	31%	30%	19%	111

Annex 2 Survey of citizens – answers to closed questions

A2.1 Relevance

Question	Yes	No	I don't know / no opinion
Are there technological advances (e.g. new tests for donors, new ways to process blood, tissues or cells) that could increase the quality or safety of blood transfusions, tissue and cell transplantation or assisted reproduction and that should be introduced into the EU rules?	11	5	10
Could any of the EU safety and quality rules could be made less stringent (e.g. donor acceptance rules, donor testing rules) because the level of risk has fallen since the Directives were adopted?	4	20	2
Are you aware of technological advances that might imply risks to the quality or safety of blood transfusions, tissue and cell transplantation or assisted reproduction that are not adequately regulated under current EU legislative?	1	10	15
Are you aware of epidemiological changes (e.g. the spread of Zika, Ebola) that	4	11	11

Question	Yes	No	I don't know / no opinion
are not adequately regulated under current EU legislation on the quality or safety of blood transfusions, tissue and cell transplantation or assisted reproduction?			
Are you aware of societal changes (e.g. commercialisation, internationalisation, changing family units, and increased life expectancy) that might affect the quality, safety or availability of blood, tissues and cells and that should be taken into account in EU legislation?	13	11	2
Are there substances of human origin that should be included under this EU legislation but currently are not (e.g. donated breast milk, tissues or cells for laboratory research)?	6	8	12
Are there any substances of human origin being used to treat patients in the EU that are covered by the two Directives but that should not be?	2	13	11

A2.2 Effectiveness

Question	Yes – patients are fully protected	No – there are minor risks for patients	No – there are significant risks for patients	I don't know / no opinion
Do you think that patients treated with blood transfusions in the EU are adequately protected from risk by the EU safety and quality rules?	27	7	4	5
Do you think that EU safety and quality rules adequately protect patients treated with tissue or cell transplantation (e.g. bone marrow, corneas, skin grafts, heart valves) in the EU?	23	10	1	9
Do you think that EU safety and quality rules adequately protect patients treated with assisted reproduction techniques such as in vitro fertilisation (IVF) in the EU?	16	8	1	18

Question	Yes – donor protection is adequate	No – donor protection could be improved in minor ways	No – donor protection is inadequate	I don't know / no opinion
Do you think that EU safety and quality rules adequately protect donors of blood and blood components in the EU?	30	7	1	5
Do you think that EU safety and quality rules adequately protect donors of tissues and cells for transplantation in the EU?	24	6	3	10
Do you think that EU safety and quality rules adequately protect donors of gametes (sperm or eggs) or embryos in the EU?	17	3	3	20

Question	Yes	No	I don't know
In your opinion, has EU legislation on blood, tissues and cells had an outcome/impact that was not intended when it was adopted (positive or negative)?	6	10	10

A2.3 Efficiency

Question	Yes	No	I don't know / no opinion
Do you consider that the supply of blood, blood components and blood-derived medicinal products is adequate to meet the needs of patients in the EU?	20	18	5
Do you consider that the supply of tissues and cells for transplantation is adequate to meet the needs of patients in the EU?	12	18	13
Do you consider that there is adequate provision of assisted reproduction therapies to patients in the EU (e.g. in-vitro fertilisation, IVF)?	12	10	21
To your knowledge, are there particular EU requirements for safety and quality that have high costs without equivalent benefits for patients?	4	12	10

A2.4 Coherence

Question	Yes	No	I don't know / no opinion
If you are familiar with the EU legislation for blood, tissues and cells, are you aware of any aspects that do not appear to fit clearly and logically with other EU legislation (e.g. organs, medicinal products, medical devices, communicable diseases, the Charter of Fundamental Rights)?	8	7	11

A2.5 EU Added Value

Question	Yes	No	I don't know / no opinion
If you have experience in applying EU legislation for blood or tissues and cells, do you consider that the results could have been achieved through measures at national level and without EU legislation?	2	19	5