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REPORT FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL, THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE AND THE COMMITTEE OF THE REGIONS

on the implementation of Directives 2004/23/EC, 2006/17/EC and 2006/86/EC setting standards of quality and safety for human tissues and cells

{SWD(2016) 127 final}
{SWD(2016) 128 final}

1. Introduction

Article 26 of Directive 2004/23/EC requires Member States to submit to the European Commission, before 7 April 2009 and every three years thereafter, a report on the activities carried out in relation to the provisions of the Directive, including an account of the measures taken in relation to inspection and control. The Commission is required to transmit these national reports to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions. The Commission is also required to provide the European Parliament and the Council with an overview report on the implementation of the requirements of the Directive, in particular as regards inspections and monitoring.

In addition, and in accordance with Article 12(1) of Directive 2004/23/EC, Member States also have to submit to the Commission reports on the application of the principle of voluntary and unpaid donation (VUD) every three years. On the basis of these national reports, the Commission is required to report to the European Parliament and the Council and to inform them of any necessary further measures in relation to VUD it intends to take at Union level.

This report is based on the replies to questionnaires that the Commission sent to Member States in 2012 (verification of the completeness of transposition), 2013 (implementation survey)[1,2] and 2014 (implementation of the VUD principle) and follows up on the Commission communication published in January 2010[3] as well as the two reports on the application of the principle of VUD for tissues and cells issued in 2006[4] and 2011[5]. All Member States replied to the transposition questionnaire. The implementation survey was answered by all Member States except Greece, and also by two EEA countries, Liechtenstein and Norway. All Member States, and also Liechtenstein and Norway provided answers to the survey on the implementation of the VUD principle.

The full analysis of the Member States' replies to the 2013 implementation survey and the 2014 survey on the implementation of the VUD principle is included in the two staff working documents accompanying this report.

Besides complying with the legal obligations pursuant to Article 12 (1) and Article 26 of Directive 2004/23/EC, the current report sets out how Directive 2004/23/EC[6] and its implementing Directives 2006/17/EC[7] and 2006/86/EC[8] (hereafter commonly referred to as the EU tissue and cell legislation) function in practice, against a backdrop of significant

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1 Detailed Member States' replies (as well as replies from Norway and Liechtenstein) can be accessed at http://ec.europa.eu/health/blood_tissues_organs/key_documents/

2 In a number of cases clarification requests were sent to Member States. It is important to note that the hyperlinks contain the original replies of Member States, whilst the report reflects the updated information provided by Member States. This can lead to certain discrepancies. In such cases this report contains the updated information.

3 http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2009:0708:FIN:EN:PDF

4 http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1422283594361&uri=CELEX:52006DC0593

5 http://ec.europa.eu/health/blood_tissues_organs/docs/tissues_voluntary_report_en.pdf

6 Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (OJ L102, 07.04.2004, p. 48).

7 Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells (OJ L38, 9.2.2006, p. 40).

8 Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells (OJ L294, 25.10.2006, p. 32).

scientific and organisational developments (internationalisation, commercialisation) that have taken place in the tissue and cell sector over the past decade.

Where appropriate data gathered through other channels and supporting the findings of the two surveys (e.g. exchanges with the national competent authorities during the bi-annual meetings with the Commission, mandatory annual reporting to the Commission of serious adverse reactions and events (SARE), alerts launched in the Rapid Alerts for Tissues and Cells (RATC) platform, Eurobarometer survey exploring the views of EU citizens on tissue and cell donation[9] and the output of a number of relevant EU-funded projects and studies) were also taken into account.

2. Transposition of the EU tissue and cell legislation

A verification of the completeness of transposition into national legislation has been carried out by the Commission and demonstrated that the EU tissues and cells legislation is fully transposed into national legislation in all but two Member (which have failed to fully transpose the requirements of the Directives for reproductive cells). As a consequence, pursuant to Article 258 TFEU, the Commission has brought action against one Member State to the Court of Justice[10], and launched an infringement proceeding against another Member State, which is ongoing.

3. Implementation of the EU tissues and cells legislation

Overall, the implementation of the EU tissues and cells legislation by the Member States is considered adequate and the legislation has resulted in the establishment of a network of competent authorities that oversee the sector through authorisation, inspection, and vigilance. However, some difficulties in interpretation, implementation and enforcement of the legislation have been identified, which in some cases could be explained by the scientific and technological advances since its adoption. As the EU legislation in the tissue and cell does not provide a basis for full harmonisation and as Directives allow the Member States a certain degree of discretion as to how to ensure their implementation, there are accordingly many differences between Member States in the approaches they have taken to implementation. These differences facilitate successful integration of the requirements into national legislation but in some cases they may limit the mutual acceptance of authorisations with consequences on the cross-border movement of tissues and cells.

3.1. Designation of competent authority or authorities responsible for the implementation of Directive 2004/23/EC

All reporting Member States have appointed competent authorities for tissues and cells. Concerning the number of competent authorities, in some Member States only one authority is responsible for the oversight of the tissue and cell sector, whereas in other countries the tasks are divided amongst two or three authorities (based either on type of tissues and cells or on duties e.g. accreditation/authorisation v. inspections/vigilance or the allocation of tasks between federal and regional levels). In some Member States the authorities for tissues and

[9] http://ec.europa.eu/health/blood_tissues_organs/eurobarometers/eb822_en.htm

[10] Case C-29/14, judgment pronounced on 11 June 2015. In 2015 the MS concerned has adopted new legislation for the ART sector and is in process of implementing it.

cells are also responsible for the oversight of other sectors (e.g. organs, blood and/or medicinal products) (Fig.1 and 2), which can be beneficial from an efficiency point of view.

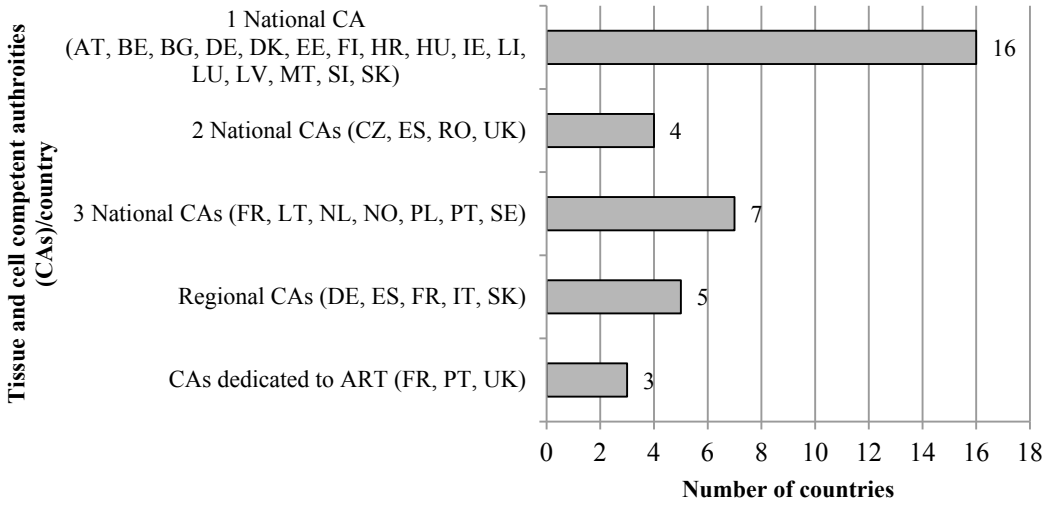


Fig. 1. Tissues and cells competent authorities in the reporting EU Member States and EEA countries (2011 data)

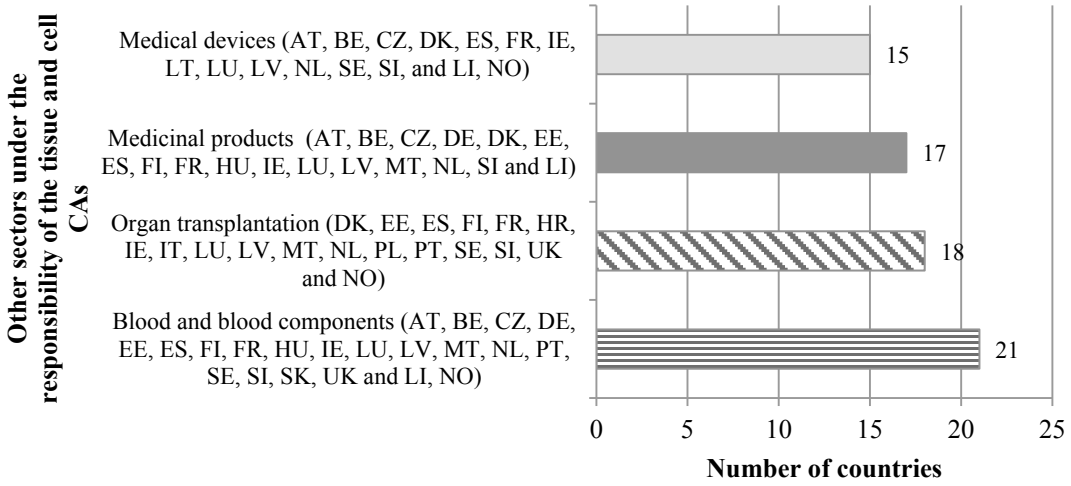


Fig. 2. Other responsibilities of tissues and cells competent authorities in the reporting EU Member States and EEA countries (2011 data)

Wherever accreditation and inspections are undertaken by different authorities, a good communication and coordination between respective authorities needs to be ensured. More generally speaking, it was difficult to assess how divisions of tasks impacts oversight of the sector, especially as some of the national competent authorities did not provide precise/complete information. To facilitate good regulatory communication between Member States, as well as to comply with the annual reporting requirements to the Commission, a well-informed national coordinating contact is essential, even where responsibilities of national competent authorities are shared among multiple organisations or regions. It has to be highlighted that, irrespective of the organisational set up in each country, it is important that authorities have appropriate resources at their disposal in order to ensure their independence from economic operators, in the sector and from other influences.

3.2. Obligations of Member State competent authorities

Supervision of human tissue and cell procurement. The high number of procurement organisations shows that this activity is well developed across the Union. The survey showed that all reporting Member States authorise the conditions of procurement by inspecting procurement organisations and/or by evaluating the procurement-related documentation made available by the tissue establishment working with procurement organisations. Furthermore, besides procurement of replacement tissues, haematopoietic stem cells and reproductive cells, some Member States also reported a significant number of procurement organisations carrying out procurement of tissue and cells to be used for manufacturing of advanced therapy medicinal products (ATMP) (Fig. 3). Concerning testing laboratories, the survey showed that in most of the reporting Member States accreditation/designation/authorisation or licensing of testing laboratories is the responsibility of authorities other than the tissue and cell competent authorities.

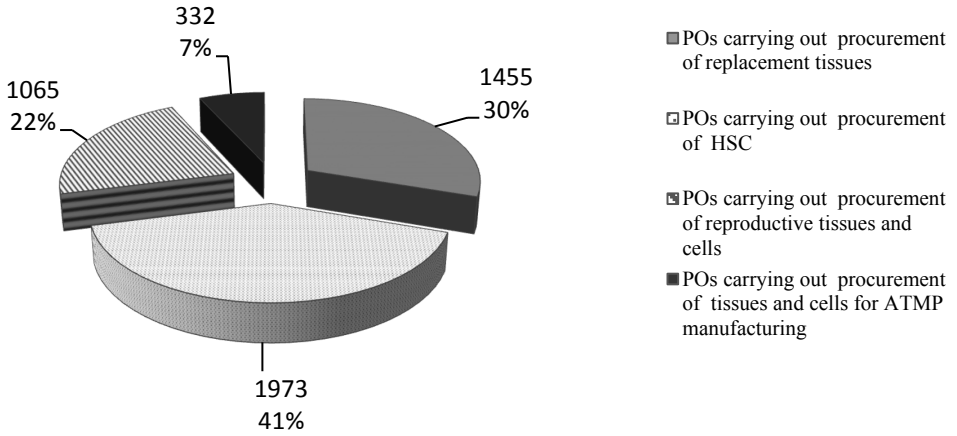


Fig. 3. Number of procurement organisations (POs) reported by the EU and EEA countries (Total POs = 4825; 2011 data)

Accreditation, designation, authorisation or licensing of tissue establishments. The survey confirmed that this core responsibility of competent authorities is well implemented across the Union. At the end of 2011, 2047 tissue establishments were authorised in the EU, showing an almost 20% increase compared to the 2008 data (Fig. 4). It is also interesting to highlight the split between private and public ownership of tissue establishments. In some Member States the sector is fully controlled by public organisations, whilst in others private operators make a significant contribution (Fig. 5). Some mixed models have emerged where, for example, the private sector may take the role of a third party for processing or storage, with all donation, promotion and distribution activities remaining in public hands.

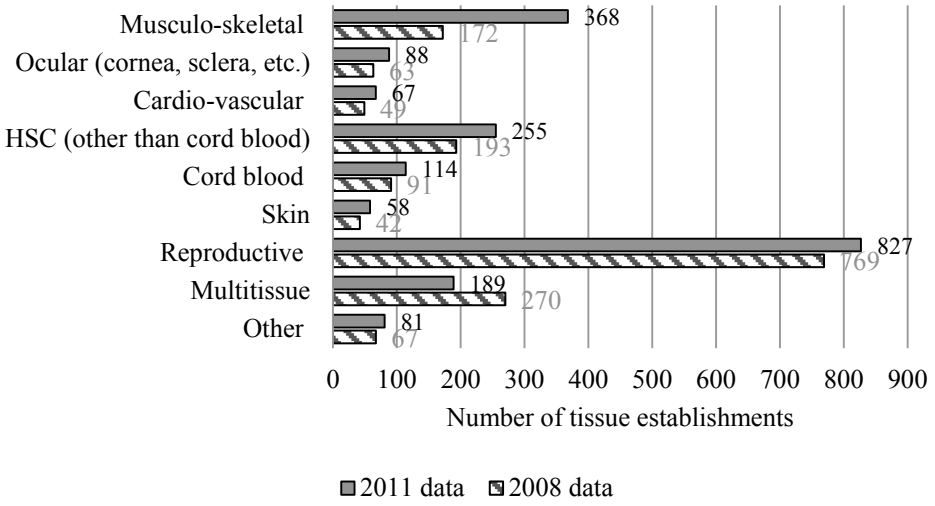


Fig. 4. Number of accredited/designated/authorised/licensed tissue establishments per type of human tissues and cells (comparative data; data submitted by 27 Member States and two EEA countries)
Legend: HSC = haematopietic stem cells

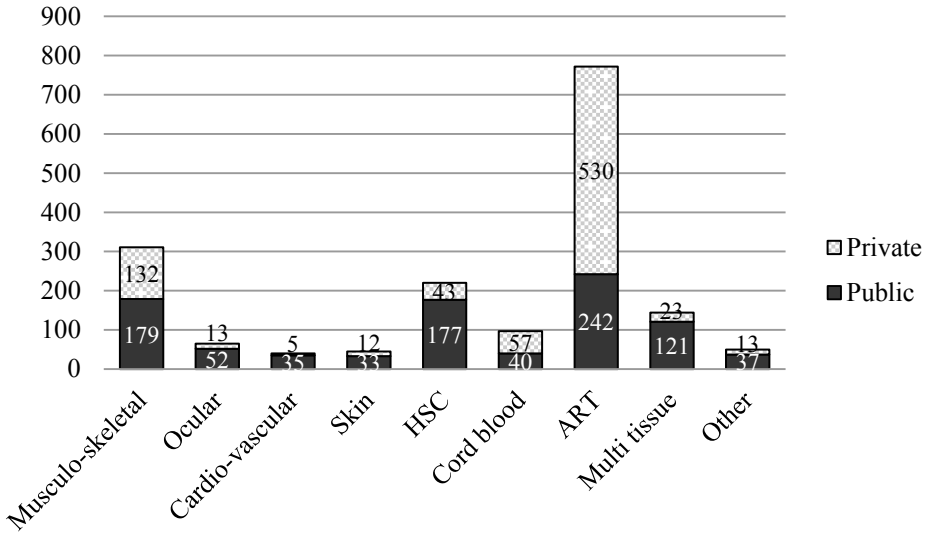


Fig. 5. Tissue establishments' status (public vs. private)/type of tissue (2011 data; data submitted by 25 Member States and one EEA country)
Legend: ART = assisted reproductive technologies

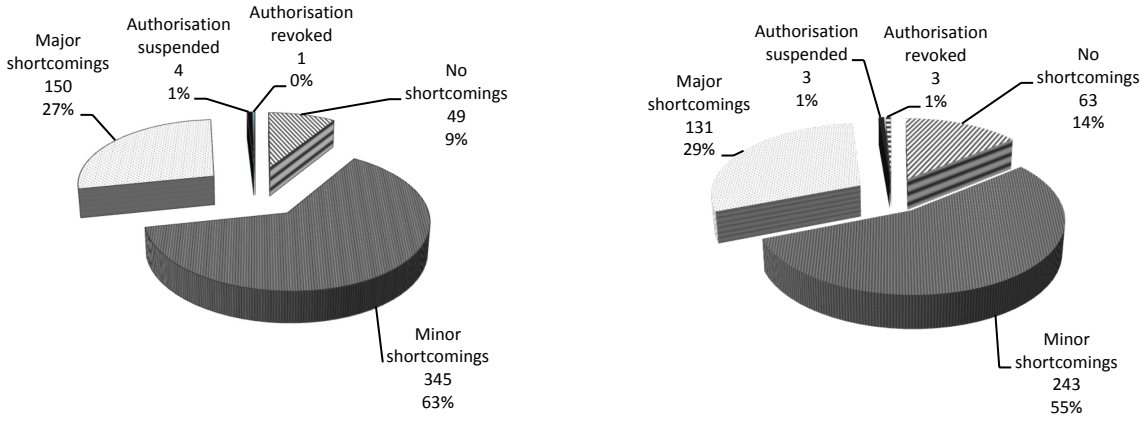
The survey revealed a variety of approaches for the implementation of the procurement requirements laid down in Directive 2006/17/EC, especially when granting authorisation (e.g. prior on-site inspection vs. desk-based review of documentation, differing criteria for major changes requiring a notification of the competent authorities, differing duration of authorisation and conditions of renewal). In addition, in several Member States, only tissue establishments are authorised to procure tissues and cells, with some countries authorising tissue establishments just for procurement activities.

As underlined by several national competent authorities, a more harmonised procedure for the accreditation, designation, authorisation or licensing of tissue establishments would foster

mutual trust and acceptance between Member States which are essential for ensuring a prompt supply of tissues and cells to the patients in need for the cases in which tissues and cells are distributed from another Member State than the one where the patient is treated.

Authorisation of tissue and cell preparation processes. Diverse practices related to the implementation of the requirements of Article 4 of Directive 2006/86/EC were reported. These are of particular importance given the numerous technological developments in the field in recent years. New processing methodologies, unthought-of of when the Directives were adopted, are now commonly applied: pre-cutting of corneas with the transplant of only the anterior or posterior segment to one patient, decellularisation of skin and heart valves in the tissue establishment to enhance cellularisation in vivo in the recipient, numerous new pathogen inactivation or sterilisation techniques including the use of radioprotectants to allow treatment with high doses of gamma irradiation, transplantation of highly selected cell populations to be used for the same essential function in the recipient as in the donor, have all increased the importance of robust preparation process authorisation. As suggested by some Member States, a procedure setting higher (minimum) standards for the authorisation of tissue and cell preparation processes at the tissue establishments (as referred to in Article 4 of Directive 2006/86/EC) may encourage mutual trust and acceptance between Member States and thus strengthen the cross-border movement of tissues and cells across EU.

Inspections and control measures. The analysis of the replies concerning inspections of tissue establishments indicates, overall, an adequate implementation of the EU requirements. In terms of inspection outcomes, mostly minor shortcomings were recorded with few suspensions and revocations of authorisations (Fig. 6). This may suggest that tissue establishments are striving to comply with the EU quality and safety requirements, but it may also indicate under-enforcement, e.g. in countries which have never reported any shortcomings. Even though most respondents confirmed respecting the required 2-year interval between inspections, some Member States suggested that prioritising inspections based on factors like the size of establishment, range of activity, experience of inspectors and compliance history may prove valuable especially in a period when financial constraints have a considerable influence on the staffing of departments in charge of inspections.



a b

Fig. 6. Outcome of tissue establishment inspections performed in 2011

a. Non-reproductive tissues and cells. Total inspections = 549; data reported by 22 Member States

b. Reproductive cells (ART sector). Total inspections = 443; data reported by 21 Member States

Another important issue highlighted by some Member States was the need to foster harmonisation of the inspection practices in the Member States. Even though most of the Member States reported using the Operational Manual for Competent Authorities on inspection of tissue and cell procurement and tissue establishments[11], there is no common agreement on the classification of shortcomings identified during inspections (e.g. classification of minor, major and critical deficiencies). As a consequence, identical shortcomings may result in different outcomes for the inspected establishments depending on their geographical location (e.g. penalties vs. revocation or suspension of license for the same deficiency).

Concerning joint inspections by authorities from more than one Member State, a small number have been organised in recent years. Their outcome was in general satisfying and in particular allowed bringing expertise where this might be missing within the own Member State.

Traceability. The survey showed that a donor identification system was implemented by most Member States, with a unique code for each donation being assigned, predominantly at the level of the tissue establishment. It has to be underlined that countries which reported difficulties in implementing the donation identification system were either developing a central allocation system for identifiers or were waiting for the adoption of the implementing legislation introducing a Single European Code for tissues and cells. Moreover, most of the Member States stated that the new coding requirements, now laid down in Directive (EU) 2015/565 amending Directive 2006/86/EC[12], should contribute to a harmonised implementation of the Single European Code for tissues and cells and actively supported their development. Regarding data storage for at least 30 years, almost all Member States and EEA countries comply with the requirements of Article 9 of Directive 2006/86/EC, by requesting both paper and electronic records to be maintained for that period.

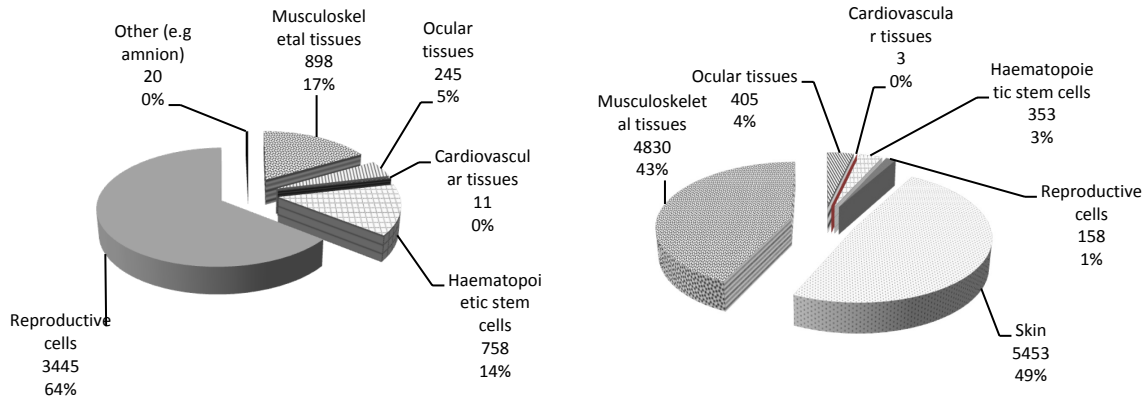
Import/export of human tissues and cells to/from third countries. The data provided, even though incomplete and sometimes not precisely defined, confirm that increasing volumes of human tissues and cells are imported from or exported to third countries (Fig. 7). Nevertheless, it has to be noted that it is difficult to draw firm conclusions regarding the volume of imports and exports of human tissues and cells due the lack of mandatory reporting of such information at national level and absence of a harmonised framework for data collection in the Member States. This may also explain why some Member States have not put in place a coherent policy to ensure national sufficiency at least for some type of tissues or cells.

In addition, some countries do not distinguish between distribution within the Union and import/export from/to third countries which may be considered an important hurdle, not only against data collection and analysis, but also against optimal circulation of tissues and cells for patient benefit across the EU.

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11 http://ec.europa.eu/health/blood_tissues_organs/docs/manual_en.pdf

12 Commission Directive (EU) 2015/565 amending Directive 2006/86/EC as regards certain technical requirements for the coding of human tissues and cells (OJ L 93, 9.4.2015, p. 43).



a b

Fig. 7.

a. Volume of tissues and cells (units) imported in 2011 (data reported by 15 Member States)

b. Volume of tissues and cells (units) exported in 2011 (data reported by 11 Member States)

Register of tissue establishments and reporting obligations. In line with the requirements in Article 10 of Directive 2004/23/EC, national registers of tissues establishments appear to be available in most of the responding Member States. However, the tissue establishment reports are not always publicly available, mainly due to different interpretations of this provision by the Member States authorities. The new legal provisions for the application of the Single European Code[13] shall also satisfy the requirement in Article 10(3) of the Directive 2004/23/EC, by establishing the EU Tissue Establishment Compendium including all tissues establishments with their coordinates and the status of their accreditation/designation/authorised or licence[14]. By updating the data in this Compendium, the tissues and cells competent authorities demonstrate full transparency and provide support to healthcare professionals searching for an authorised tissue or cell provider within the Union. Moreover, the inclusion in the EU Tissue Establishment Compendium will reinforce the credentials of the EU tissue establishments to their partners and customers around the world.

Notification of serious adverse reactions and events (SARE). The analysis of the annual SARE reports submitted by the Member States demonstrates notable efforts to comply with the requirements in Article 7 of Directive 2006/86/EC. In spite of this, both the Commission and national competent authorities for tissues and cells acknowledge that there is still a high degree of under-reporting requiring careful consideration when analysing the data. The importance of SARE reporting is confirmed by the interest of the Member States in collaborating with the Commission to improve the current reporting system (e.g. refining the SARE reporting templates for improving collection of data in the sector of assisted reproduction technology (ART)) and to expand communication with other countries and other sectors (e.g. fostering cooperation with relevant third countries with regard to SARE

[13] Commission Directive (EU) 2015/565 of 8 April 2015 amending Directive 2006/86/EC as regards certain technical requirements for the coding of human tissues and cells. OJ L 93, 9.4.2015, p. 43–55

[14] EU Tissue establishment compendium is part of the EU Coding platform that was introduced by the Directive (EU) 2015/565 amending Directive 2006/86/EC as regards certain technical requirements for the coding of human tissues and cells.

reporting). It should be noted that, although much has been achieved and reporting improves every year, challenges related to under-reporting by organisations responsible for human application and the lack of accurate data remain. The overall aim of the annual reporting, to identify the most frequent causes of SARE and provide appropriate corrective measures, has not yet been fully achieved. In this regard, more training of both healthcare professionals and vigilance officers in tissue establishments and competent authorities will be needed for an appropriate identification and analysis of the "root causes" of these SARE, which should lead to the identification and correction of systematic errors.

Even though the current requirements in Directive 2006/86/EC refer only to reporting of serious adverse reactions (SAR) in recipients of tissues and cells, the voluntary reporting of SAR in donors has gradually improved in the past years, suggesting the Member States' increasing interest in the protection of living donors. Some national competent authorities considered that it would be useful to strengthen the consideration of pharmacovigilance data regarding medicinal products that are used in the context of donations of tissues and cells. Additionally, for cases in which tissues/cells from one donor will be used for both transplantation and manufacturing of ATMP, consideration should be given on how to best exchange relevant data between the pharmacovigilance and biovigilance systems (e.g. donation of cells from a living donor which may be found to develop a tumour after donating cells to an ATMP manufacturer or recipient developing a tumour/communicable disease following therapy with donated cells from a donor who may have donated cells transplanted in another recipient).

3.3. Donor selection and evaluation

Consent, data protection and confidentiality. Overall, the survey showed that regardless of the consent system, all responding countries have put measures in place for verifying donor consent. An alert issued in RATC accompanied by recall of products from an EU tissue establishment revealed that the consent form and its verification may be very different from one Member State to another, depending also on the legal framework under which the EU tissue and cell legislation has been transposed. Even though only trained personnel are allowed to provide appropriate information to donors, this information has been standardised at national level in a small number of countries. Concerning donor anonymity, most countries rely on the EU and national data protection legislation, but also on coding. In this context, the new requirements on the application of the Single European Code for tissues and cells laid down in Directive (EU) 2015/565 may be considered an additional tool for ensuring that donor data are not disclosed to the recipient[14]. No problems were reported regarding the implementation of the provisions related to data protection.

Donor selection and evaluation. The current survey showed that in addition to the requirements in the Directive 2006/17/EC, the more stringent selection criteria required by Member States are usually justified for local reasons, such as the increased prevalence of a certain disease. Divergent criteria might however also create barriers for exchanging tissues and cells between Member States for healthcare professionals requesting tissues or cells from another Member State. Such difficulties were also reported by operators manufacturing ATMP from human tissues and cells. Several of the selection criteria, as well as the tasks of the responsible persons in Member States with more stringent requirements, have been subject to discussion during the bi-annual national competent authority meetings. It was underlined that Member States introducing more stringent safety and quality requirements should inform the other Member States and EEA countries, as well as the Commission, regarding these

measures, in a transparent manner. It was also suggested that the full list of these more stringent requirements could be made available by the Commission.

When verifying the compliance of tissues establishments with the EU donor evaluation and selection requirements, inspections are the most important verification method used by the Member State competent authorities. Nevertheless, it has to be underlined that a small number of countries rely only on the medical records of the donor and/or the autopsy report without interviewing the donor's family or his/her treating physician/general practitioner. The application of selection criteria should be transparent and subject to continuous evaluation in order to minimize safety risks.

Procurement of tissues and cells. In most of the Member States compliance with the requirements for tissue and cell procurement set by Directive 2006/17/EC is verified by the competent authorities when performing inspections, but also by auditing procurement organisations and centres of human application. Responses to the survey showed that this is also the case for procurement of tissues and cells for ATMP manufacturers, in line with Article 3 of the ATMP Regulation. Provisions associated with procurement, but also with donation and testing, are regulated by the tissue and cell legislation and verified during tissue establishment inspection.

Donor testing. The data reported show that the EU and EEA countries comply with the minimal testing requirements stipulated in the Directive 2006/17/EC. Several countries have introduced more stringent testing requirements such as nucleic acid testing (NAT) for hepatitis B (HBV), hepatitis C (HCV) and/or human immunodeficiency virus (HIV) for non-reproductive and/or reproductive tissue and cells, whereas in most Member States and EEA countries the use of this type of testing is not required on the basis of a cost-benefit analysis and/or the epidemiological context. Additional tests required by Member States are usually justified for local reasons, like e.g. the increased prevalence of a certain infectious disease. Several of the testing requirements (e.g. no requirement for NAT testing, the 24 hours limit for blood sample collection from a deceased donor, testing of gamete donors at the time of donation) have been subject to debate at the bi-annual national competent authorities meetings[15] and the various practices shared by the competent authorities showed the need for an evidence-based risk assessment of some practical situations which were not clearly defined/foreseen in Directive 2006/17/EC. It has to be noted that similar to donor selection, more stringent testing requirements introduced by some Member States are sometimes perceived by healthcare professionals ordering tissues or cells from other Member States as barriers hampering development and the cross-border movement of tissues and cells between Member States. Several Member States suggested that a common list of diagnostic tests (panel) for some genetic diseases may be valuable for increasing safety in the EU ART sector.

3.4. Voluntary and unpaid donation (VUD)

This report shows that Member States overall comply with Article 12 of Directive 2004/23/EC requiring Member States to take the necessary measures to endeavour to ensure VUD of tissues and cells. However, the ways in which Member States have implemented the principle of VUD are difficult to assess in a comprehensive manner. It has to be highlighted that VUD is a factor which is not only ethical in nature, but which may contribute to higher safety standards for tissues and cells and therefore to the protection of human health. If donor

[15] http://ec.europa.eu/health/blood_tissues_organs/docs/tissues_mi_20110623_en.pdf

payment were allowed, some individuals could find the monetary remuneration so important that they might hide relevant medical and/or behavioural information. Additional screening and testing may reduce, but cannot completely eliminate, the possibility of a transmission from donor to recipient. Therefore information provided by the donor or his/her family contributes to an accurate assessment of all risks associated to the application of donated tissues or cells.

The large majority of the responding countries (28) reported that the principle of VUD is mandatory at national level. However, one Member State who reported that the VUD principle is mandatory indicated that payment of gamete donors is allowed at national level. Another Member State and one EEA country have not yet defined national provisions on the application of the VUD principle.

Although the principle of VUD is mandatory in the large majority of the Member States, its concrete application varies across the Union. Only 17 Member States reported having guiding principles regarding the possibility to compensate tissue and cell donors, but in many cases these principles were just a description of the practices allowed at national level. This may explain the considerable heterogeneity across the EU in the practices vis-à-vis tissue and cell donors, with some practices being regarded as compensation in one country and incentives or other practices in others. The differences in purchasing power between Member States might also explain why a measure is considered a "compensation" in one country and an "incentive" in another.

An important issue is how and by whom the decision concerning the value and form of compensations for tissue and cell donors is taken. Most Member States allow compensation to be offered to living donors (22 countries for living donors of non-reproductive tissues and cells; 17 countries for donors of reproductive cells). Only in a small number of Member States is the value of the compensation provided to tissue and cell donors connected to national economic indicators (e.g. monthly income, purchasing capacity). Giving lump sums to reproductive cell donors, as practised in some countries, may alleviate administrative burden, but it also raises questions when the value is determined solely by tissue establishments or when the value is significantly high in relation to average national monthly income. Reimbursement of costs linked to travel and medication based on actual costs/receipts are among the most commonly used type of compensation for living donors. Other practices include compensation for the inconveniences related to the donation. Limited information was provided on the value of most of the practices related to tissue and cell donation, probably because the costs vary considerably depending on the donation circumstances (e.g. need of prior testing/medical treatment, duration of hospitalisation, effects on the overall health and capacity to work) or depend on the clinic where the donation takes place.

Verification by the competent authorities of the implementation of the VUD principle in tissue establishments is focused on inspecting documentation related to donor consent. Only 15 Member States reported putting in place additional measures like examination/inspection/approval of advertising materials, training of professionals to spot illegal and fraudulent activities, verification that the VUD principle is also respected for imported tissues and cells. Verification during inspections of standard operating procedures (SOP) prepared by the tissue establishments and inspecting patient and donor information provided by licensed fertility clinics were reported only by two Member States.

Development of follow-up registries as an additional tool for ensuring safety of living donors was also addressed in the survey. In this regard, 18 Member States and one EEA country

reported to have a follow-up registry or database of haematopoietic stem cell donors, but the type of the follow-up examinations, their periodicity and the responsible healthcare facilities/professionals may vary from country to country. Only six Member States have national registries of oocyte and sperm donors. Five Member States have both central oocyte and sperm donor registries. On the other hand, ten Member States indicated that, especially for sperm donors, such registries are maintained by the tissue establishments. It should be highlighted that several Member States indicated that there is no national legal requirement for organising national follow-up registries for living donors.

Regarding practices vis-à-vis deceased donors of tissues and cells, only three Member States reported that they provide compensation to donor relatives. These consist mainly in providing administrative support for the funeral and ensuring full or partial coverage of the cost of the funeral/burial/cremation. Even though this practice is considered as compensation by the competent authorities, it may be perceived as an incentive by the family/relatives of the deceased donors, especially in the absence of an expressed consent of the deceased person or when, due to financial constraints, the relatives have difficulty covering the costs of the funeral/burial/cremation.

It is important to note that a recent Eurobarometer survey on blood and cell and tissue donation[16] showed that only 13% of EU citizens considered acceptable to receive cash amounts in addition to the reimbursement of the costs related to the donation. However, a significant percentage of the respondents (48%) considered that receiving refreshments, free testing, or a free physical check-up seem suitable when donating human tissues and cells.

In relation to the supply-demand balance, 17 Member States and one EEA country reported experiencing regular shortages of tissues and cells on a national level, mostly for bone marrow and haematopoietic stem cells, corneas and bone. The main reasons for shortages were the lack of donors, followed by insufficient procurement capacity at national level and technical reasons (e.g. practical difficulties in finding a compatible match for patients in need of an HSC transplantation). In addition, the survey showed that nineteen countries (17 Member States and two EEA countries) did not put in place national policies for promoting national self-sufficiency/sufficiency[17] for tissues and cells and do not always collect data on cross-border movement of tissues and cells at national level. This may suggest a role for the EU in supporting Member States to develop national sufficiency policies although the exact impact of such policies on cross-border exchanges and the supply of starting materials for medicinal product manufacture would need to be carefully analysed.

The findings of the VUD survey suggest that Member States should collect more information on the day-to-day practices vis-à-vis donors in both procurement organisations and tissue establishments, especially when these operators are responsible for deciding the type and/or value of the compensation provided to donors.

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16 http://ec.europa.eu/COMMFrontOffice/PublicOpinion/index.cfm/Survey/getSurveyDetail/search/426/surveyKy/2030

17 For the purpose of the survey, in order to facilitate a consistency in replies, those terms were defined as follows:

- 'National self-sufficiency' was defined as fulfilling the needs of human tissue and cell products for medical application (e.g. transplantation, ART procedures) of the resident population by accessing resources from within the country's population.
- 'National sufficiency was defined as fulfilling the needs of human tissue and cell products for medical application (e.g. transplantation, ART procedures) of the resident population by accessing resources from within the country and through regional/international cooperation.

On the basis of the information collected, the Commission will follow up with the Member States in order to promote, where desirable, a common understanding of Article 12 in the Directive 2004/23/EC. Issues to be addressed include transparency of the decisions regarding donor compensation, the type and value of the compensations for donors, especially for the situations when such decisions were conveyed to procurement organisations or tissue establishments. Best practices to ensure tissue and cell sufficiency/self-sufficiency or measures to reduce shortages might be addressed as well as best practices on verification of the implementation of the VUD principle by the competent authorities. There is a need to find the most appropriate solutions to ensure both the respect of the Article 12 of Directive 2004/23/EC and an adequate supply of tissues and cells to the patients in need across the Union.

3.5. Quality and safety of tissues and cells

It has to be highlighted that safety and quality is a major concern for EU citizens, with 56% of respondents to the Eurobarometer survey on blood and cell and tissue donation[18] citing the risk of contracting a disease as a major concern when accepting donated substances. A majority also supported European legislation to ensure the safety and quality of blood, tissues and cells.

Quality management, responsible person and personnel. The present implementation survey confirmed that Member States are trying to ensure an appropriate level of training for their tissue establishment personnel, and the compliance with the requirements of Directive 2004/23/EC is systematically verified during inspections and also before granting authorisation/accreditation/licence to tissue establishments. It is noted that an additional support on training of tissue establishment personnel was given through EU-funded projects such as European Quality System for Tissue Banking (EQSTB)[18] and European Good Tissue Practices (EuroGTPs)[19]. Good practices developed by the EU-funded initiatives were also included by the Council of Europe in a dedicated Guide to the Quality and Safety of Tissues and Cells[20]. In this regard, several national competent authorities have called for an EU-level endorsement of Good Tissue Practice guidelines (GTP), similar to Good Manufacturing Practice guidelines (GMP) approach in the pharmaceutical sector and for continuing to provide support for training of inspectors at the EU level.

Tissue and cell reception, processing, storage, labelling and packaging. The importance of inspections was highlighted again in the context of compliance with the requirements in the Directive 2006/86/EC, as the most frequent approach to verify their implementation. Mandatory SOPs are also required during the authorisation/accreditation/designation or licensing process in most of the responding countries. Developing more detailed requirements for these activities as part of GTP was supported by several national competent authorities for tissues and cells.

Distribution of tissues and cells for human application. As demonstrated by the Member State replies, there are important cross-border movements of human tissues and cells within the EU and EEA countries (Fig. 8). Even though such movements may be explained by the globalisation of healthcare products and services, the common quality and safety standards laid down in the EU tissues and cells legislation have created the framework for facilitating

[18] http://ec.europa.eu/chafea/projects/database.html?prjno=2003209
[19] http://eurogtps.com/
[20] https://www.edqm.eu/en/organ-tissues-cells-transplantation-guides-1607.html

trans-national movements within the Union. However, it has to be noted that, as for import and export, data collected by the Member States probably serve different purposes and use various methodologies, so it is very difficult to draw a clear conclusion on the importance of EU distribution compared to import/export from/to third countries and therefore to evaluate tissue and cell sufficiency at EU level.

One concern raised during national tissue and cell competent authorities meetings was direct distribution of gametes (i.e. sperm) to individuals for self-application without the involvement of a health professional. Several authorities underlined that in such situations there is a significant risk of losing traceability, including inappropriate reporting of pregnancy rate and serious adverse reactions following medical application (e.g. children born with genetic diseases not reported back to the distributing tissue establishment). The competent authorities allowing such practices were requested to evaluate if and/or how traceability and reporting requirements are ensured by the tissue establishments distributing gametes to individuals and to take the necessary measures in case such practices do not fulfil the safety and quality requirements laid down in the EU tissue and cell legislation. The Commission is closely following this case.

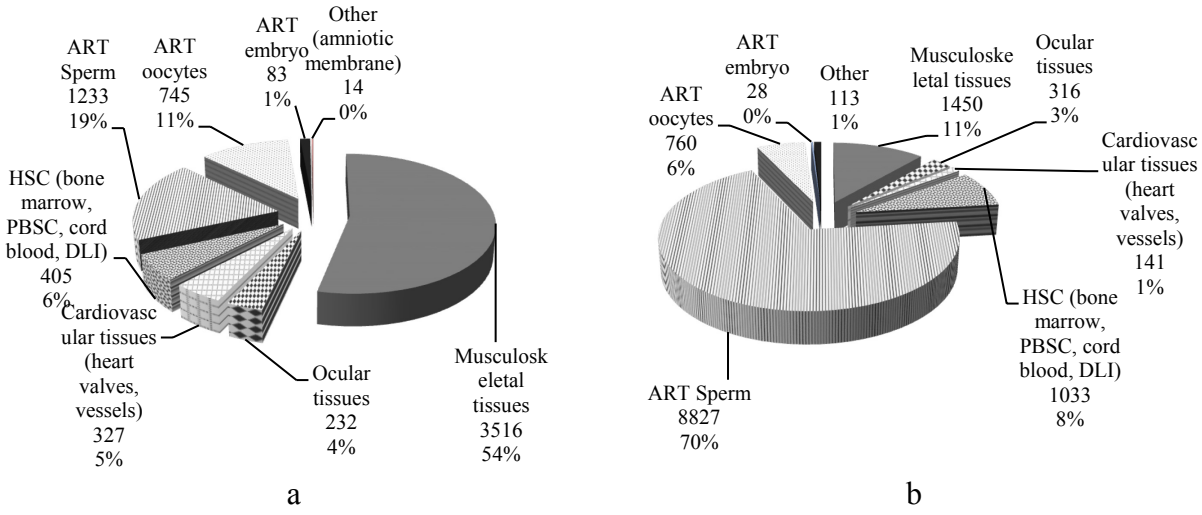


Fig. 8.

a. Volume of tissues and cells (units) distributed from one MS to other EU MS and/or EEA countries in 2011 (Data reported by 18 countries)

b. Volume of tissues and cells (units) received by MS from other EU MS and/or EEA countries in 2011 (Data reported by 15 Member States)

Relations between tissue establishments and third parties. The fact that third parties may be involved in all steps of the chain from donation and procurement to distribution in most Member States highlights the importance that needs to be given to the written agreements established by tissue establishments and their verification by the national competent authorities. In this respect, it should be highlighted that the new Directive (EU) 2015/566[21] provides for the harmonisation of the minimum requirements in terms of contents of written agreements between importing tissue establishments and their third country suppliers.

[21] Commission Directive (EU) 2015/566 implementing Directive 2004/23/EC as regards the procedures for verifying the equivalent standards of quality and safety of imported tissues and cells (OJ L 93, 9.4.2015, p. 56).

Penalties. The penalties foreseen in national legislation, their criteria for implementation and their effective implementation can differ significantly between Member States. There is no harmonisation in defining or applying such penalties, therefore it is difficult to evaluate whether similar measures are applied by all the Member States in case of a specific breach of the legislation in this area. In any event, the number of penalties imposed is very low.

4. Support for the implementation of the EU tissue and Cell Directives

The European Commission has been supporting the implementation of the legislation by the Member States by encouraging the active participation of national Competent Authorities in a series of actions, from bi-annual expert group meetings to EU-funded projects.

The regular meetings of the national competent authorities as part of the Competent Authorities on Substances of Human Origin Expert Group (CASoHO E01718) developed into a well-appreciated platform for discussions, allowing for sharing best practices and clarification of common difficulties encountered at national and EU level.

Since 2003, a number of projects have been funded under the multi-annual programmes for Union action in the field of health[22] addressing the area of human tissue and cells for clinical application. Projects such as EUSTITE, EuroGTP, SOHO V&S, and the on-going joint actions ARTHIQS and VISTART[23] have provided a strong support to Member States in their efforts to implement the requirements of the EU tissue and cell legislation. These actions allowed for the development of guidelines and manuals in areas of common interest such as inspections and vigilance, included training courses for Member States Competent Authorities and their inspectors and brought together professionals in the tissue banking sector for the development of detailed technical guidance in line with the EU legal requirements.

As regards the risk of transmission of communicable diseases thorough tissues and cells, the collaboration with ECDC proved extremely valuable. In addition to providing regular updates during the bi-annul meeting of the tissue and cell expert sub-group on the epidemiological situation relevant to the tissue and cell sector, the development of risk assessments (e.g. for HTLV, malaria, dengue and chikungunya) and preparedness plans (e.g. for WNV outbreaks) provided a valuable contribution to policy and decision making in this sector at both national and EU level.

Finally the Commission developed - in close cooperation with Member States - a Rapid Alert Platform for Tissues and Cells (RATC) which facilitates web-based communications between Member States in case of alerts relating to human tissues or cells transferred across borders.

5. Conclusions

In conclusion, this Report reveals an overall adequate application of the current quality and safety requirements of the EU tissues and cells legislation in most of the responding EU Member States and EEA countries. Significant progress has been made in many areas, also

[22] http://ec.europa.eu/chafea/documents/health/leaflet/transplantation-transfusion.pdf
[23] http://ec.europa.eu/health/blood_tissues_organs/projects/index_en.htm

through the active support by Commission funded projects and other initiatives. However, the report points to some gaps and difficulties in relation to the application and enforcement of the existing provisions (e.g. definitions, requirements on the safety aspects regarding living donors, inspections framework), some of them owing to the different approaches taken by the Member States when transposing and implementing the current EU legislation and others due to the scientific and technologic developments since the adoption of the Directives. The Commission will follow-up with Member States to address situations where the legislation might not have been fully or correctly implemented.

As regards the implementation of the VUD principle, the Commission survey showed that Member States overall comply with Article 12 of Directive 2004/23/EC requiring them to take the necessary measures to encourage VUD. However, Member States interpretation of what is considered compensation and incentive vary.

The gaps and difficulties identified suggest that a further in-depth evaluation might be useful. The Commission will consider the need for an evaluation in order to assess the relevance, effectiveness, efficiency, coherence and the EU added value of Directive 2004/23/EC and its implementing Directives.