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

**on the application of Directive 2004/23/EC on setting standards of quality and safety for
the donation, procurement, testing, processing, preservation, storage and distribution of
human tissues and cells**

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1. INTRODUCTION

Article 26 of Directive 2004/23/EC¹ requires Member States to submit to the European Commission, before 7 April 2009 and every three years thereafter, a report on the activities undertaken in relation to the provisions of the Directive, including an account of the measures taken in relation to inspection and control. The Commission is required to transmit these reports to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions, and to provide them with a report on the implementation of the requirements of the Directive, in particular as regards inspections and monitoring.

This report is based on the replies to questionnaires on transposition and implementation that Member States send to the Commission on a yearly basis and is particularly focussed on the one referring to the year 2008. All Member States except Latvia and Luxembourg submitted a report on the activities undertaken in relation to the provisions of the Directive in 2008. Norway, Croatia and Turkey also submitted a report.

This first Commission report provides an overview of the situation in the 27 Member States.

2. RESULTS

2.1. Implementing Directives

Directive 2004/23/EC provides that specific technical requirements should be adopted in accordance with the ‘Comitology’ procedure. In this respect, two Commission Directives supplement the provisions of Directive 2004/23/EC:

¹ Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (OJ L 102, 7.4.2004, p. 48).

- Commission Directive 2006/17/EC of 8 February 2006 as regards certain technical requirements for the donation, procurement and testing of human tissues and cells².
- Commission Directive 2006/86/EC of 24 October 2006 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 cells³.

Member States may maintain or introduce more stringent protective measures than those of Directive 2004/23/EC provided that they comply with the Treaty. For instance, 14 Member States apply additional testing requirements to take into account their specific national epidemiological situation (for more information, see section 2.5.1).

No Member State indicated particular problems in intra-community exchanges of tissues and cells due to more stringent measures in other Member States.

2.2. Designation of competent authorities (Art. 4 of Directive 2004/23/EC)

Under Article 4(1), Member States must designate the competent authority or authorities responsible for implementing the requirements of the Directive. All Member States have designated a competent authority in accordance with this provision. In 21 Member States, the designated competent authority is responsible for all types of tissues and cells. France, Greece, Portugal, Finland and the United Kingdom have a specific competent authority for reproductive tissues and cells.

2.3. Obligations on Member States' authorities (Art. 5-11 of Directive 2004/23/EC)

2.3.1. Supervision of human tissue and cell procurement (Art. 5)

Under Article 5, the competent authority or authorities must ensure that tissue and cell procurement complies with the stipulated requirements. Commission Directive 2006/17/EC established the requirements for the procurement of tissues and cells: selection criteria for donors, testing requirements, consent and donor identification, procurement procedures, reports, labelling and reception at the tissue establishment.

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

² Commission Directive 2006/17/EC 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 L 38, 9.2.2006, p. 40).

³ Commission Directive 2006/86/EC 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 L 294, 25.10.2006, p. 32).

and the United Kingdom) carried out 53 inspections of procurement organisations during 2008.

2.3.2. *Accreditation/designation/authorisation/licensing of tissue establishments and tissue and cell preparation processes (Art. 6)*

Under Article 6(1), Member States must have in place an appropriate mechanism to ensure that all tissue establishments where activities of testing, processing, preservation, storage and distribution of human tissues and cells intended for human applications are undertaken have been accredited, designated, authorised or licensed by a competent authority for the purpose of those activities.

An accreditation/designation/authorisation/licensing system of tissue establishments is in place in 23 Member States (Belgium, Bulgaria, Czech Republic, Denmark, Germany, Estonia, Ireland, Spain, France, Italy, Cyprus, Latvia, Lithuania, Hungary, the Netherlands, Austria, Poland, Portugal, Romania, Slovenia, Slovakia, Finland, and the United Kingdom). The system is decentralised in five Member States (Germany, Spain, France, Italy and Hungary) where the process is channelled through federal states, regions or autonomous communities.

Sweden, Malta and Greece did not have an accreditation/designation/authorisation/licensing system in place at the end of 2008. Sweden intends to implement its system during the course of 2009.

No information has been received from Luxembourg in this respect.

Although the accreditation/designation/authorisation/licensing system is for the most part established in the Member States, around half of them indicated that they have yet to finalise the accreditation/designation/authorisation/licensing of each individual tissue establishment in their territory.

Inspections play a key role in the accreditation/designation/authorisation/licensing system which varies from prior compulsory on-site inspections to desk-based review of documentation.

Under Article 6(2), the competent authority or authorities must authorise the tissue and cell preparation processes which the tissue establishment is entitled to carry out. Fourteen Member States have specific systems for authorising tissue and cell preparation processes (Belgium, Bulgaria, Czech Republic, Germany, Ireland, Spain, France, Cyprus, Lithuania, the Netherlands, Austria, Poland, Portugal and Slovenia). In the other Member States, in the absence of specific authorisation systems, tissue and cell preparation processes are normally verified and authorised during a general inspection for the purpose of accreditation/designation/authorisation/licensing of a tissue establishment. In some Member States, a different institution, independent from the competent authority or authorities, is responsible for validating and authorising of the preparation process. This is the case in Romania, where the Medical College of Physicians is responsible for the approval of the preparation processes.

Only three Member States (France, Germany and Ireland) conducted inspections solely for the purpose of authorising preparation processes in 2008.

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

Under Article 6(4), the competent authority or authorities may revoke or suspend the accreditation/designation/authorisation/licensing of a tissue establishment if it is found to no longer comply with the requirements of the Directives. Five Member States (Denmark, France, the Netherlands, Poland and Romania) indicated that some initial approvals given to tissue establishments were revoked for various reasons such as lack of traceability systems, suspicion of illegal or fraudulent activities, problems with sterilisation processes, or lack of compliance with the accreditation/designation/authorisation/licensing requirements.

2.3.3. *Inspections and control measures (Art. 7)*

Under Article 7(1), Member States must ensure that the competent authority or authorities organise inspections and that the tissue establishments carry out appropriate control measures.

Comprehensive inspection systems are in place in 23 Member States (Belgium, Bulgaria, Czech Republic, Denmark, Germany, Estonia, Ireland, Spain, France, Italy, Cyprus, Latvia, Lithuania, Hungary, the Netherlands, Austria, Poland, Portugal, Romania, Slovenia, Slovakia, Finland and the United Kingdom). Only 15 Member States conducted initial or regular inspections of tissue establishments in 2008.

Sweden, Malta and Greece do not yet have inspection systems in place. Sweden intends to implement an inspection system in the course of 2009.

No information has been received from Luxembourg in this respect.

Article 7(5) provides that ‘Guidelines concerning the conditions of the inspections and control measures and on the training and qualification of the officials involved in order to reach a consistent level of competence and performance, shall be established in accordance with the *Comitology* procedure’.

Although Member States already have inspection systems in place, there is a need to provide guidance to them so as to reach a consistent level of competence and performance. The Commission is currently working on the development of such inspection measures. The envisaged measures aim at guiding Member States towards a consistent and equivalent way of performing inspections in the field of tissues and cells. This would foster mutual trust and recognition between Member States. The measures on inspections should not be seen as a tool for the development of harmonised inspection systems in the Member States, but rather as specific guidance for gradually reaching equivalent performance.

2.3.4. *Import/export of human tissues and cells (Art. 9)*

(a) Imports

Under Article 9(1), Member States must take all necessary measures to ensure that all imports of tissues and cells from third countries are undertaken by tissue establishments accredited/designated/authorised/licensed for the purpose of those activities and that imported tissues and cells can be traced from the donor to the recipient and vice versa. In this respect, only 11 Member States have clearly identified tissue establishments explicitly authorised to import tissues and cells (Bulgaria, Czech Republic, Denmark, Germany, Ireland, France, Italy, the Netherlands, Austria, Slovenia, and the United Kingdom). Eight Member States (Bulgaria, Denmark, Germany, Greece, France, Hungary, Italy, and Romania) have a register of tissue establishments in third countries from which imports are performed.

Sixteen Member States reported that they imported tissues and cells from third countries during 2008 (Belgium, Bulgaria, Denmark, Germany, Estonia, Ireland, Greece, Spain, France, Italy, Lithuania, the Netherlands, Portugal, Romania, Slovenia, and the United Kingdom).

Slightly less than 50% of Member States importing tissues and cells use bilateral agreements to verify the equivalence of standards for quality and safety of the tissues and cells. International standards like EATB⁴, AATB⁵, JACIE⁶, WMDA⁷ and NETCORD⁸ are also used, depending on the tissue and/or cell involved.

In many cases data concerning volumes of imports are not available; Member States indicated that 1 122 units of haematopoietic stem cells (HSC), 2 281 units of musculo-skeletal tissue, 4 units of skin and 7 units of reproductive tissues and cells were imported during 2008. The competent authorities should be able to collect more comprehensive data on imports through the tissue establishments' compulsory annual reports in accordance with Article 10(1).

(b) Exports

Under Article 9(2), Member States must also take all necessary measures to ensure that all exports of tissues and cells to third countries are undertaken by tissue establishments accredited, designated, authorised or licensed for that purpose.

Only nine Member States (Bulgaria, Denmark, Ireland, France, Italy, Hungary, Slovenia, Slovakia and the United Kingdom) have a register of tissue establishments authorised to export tissues and cells to third countries.

⁴ European Association of Tissue Banks.

⁵ American Association of Tissue Banks.

⁶ Joint Accreditation Committee-ISCT & EBMT.

⁷ World Marrow Donor Association.

⁸ Foundation dedicated to cord blood banking and transplantation.

Fourteen Member States exported tissues and cells during 2008 (Belgium, Bulgaria, Czech Republic, Denmark, Germany, Ireland, Spain, France, Italy, Cyprus, the Netherlands, Portugal, Romania and the United Kingdom). In many cases data concerning volumes of exports are not available, but Member States indicated that 269 units of HSC, 489 units of ophthalmic tissue, 6 225 units of musculo-skeletal tissue and 10 units of amniotic membrane were exported. The competent authorities should be able to collect more comprehensive data on exports through the tissue establishment's compulsory annual reports in accordance with Article 10(1).

The competent authority or authorities may authorise the import or export of tissues and cells in case of emergency. Bulgaria, Denmark and Cyprus performed this type of direct distribution to the recipient of specific tissues and cells during 2008, in particular for 29 units of HSC and 18 units of ophthalmic tissue.

2.3.5. *Register of tissue establishments and reporting obligations (Art. 10)*

Under Article 10(1), tissue establishments must keep a record of their activities and submit an annual report to the competent authority or authorities, which should be publicly available.

Nineteen Member States have created an annual report model on the activities of tissue establishments that makes the reporting of the yearly activities by tissue establishment easier (Belgium, Bulgaria, Czech Republic, Denmark, Germany, Ireland, Spain, France, Italy, Cyprus, Lithuania, Austria, Poland, Portugal, Romania, Slovakia, Finland, Sweden and the United Kingdom).

Sixteen Member States received annual reports from their tissue establishments corresponding to 2008 activities (Belgium, Bulgaria, Czech Republic, Denmark, Germany, Ireland, Spain, France, Italy, Lithuania, Poland, Romania, Slovenia, Slovakia, Finland and the United Kingdom).

It should be borne in mind that the reports obtained from the tissue establishments are crucial in providing an adequate indication of the activities carried out in the field as well as reference data for assessing needs and risks in the tissue and cell transplantation field.

Only 12 Member States had made the tissue establishments' reports publicly available during 2008 (Bulgaria, Czech Republic, Spain, France, Italy, Cyprus, Austria, Poland, Portugal, Slovenia, Romania and Sweden).

Under Article 10(2), the competent authorities are responsible for maintaining a publicly accessible register of tissue establishments specifying the activities for which they have been accredited/designated/authorised/licensed. Twenty Member States indicated that they have a public register available (Belgium, Bulgaria, Czech Republic, Denmark, Germany, Estonia, Ireland, Spain, France, Italy, Cyprus, Lithuania, the Netherlands, Austria, Poland, Portugal, Slovenia, Romania, Finland and the United Kingdom).

In most cases the annual reports and the register are accessible through the competent authorities' web pages.

Under Article 10(3), Member States and the Commission should establish a network linking the national tissue establishment registers. Currently this network linking is achieved by EURO CET (European Registry for Organs, Tissues and Cells, <http://www.eurocet.org/>), which is a registry of national tissue establishments and activity reports managed by the Italian Competent Authority.

2.3.6. *Notification of serious adverse events and reactions (Art. 11)*

Under Article 11(1), Member States must ensure that there is a system in place to report, investigate, register and transmit information about serious adverse events⁹ and reactions¹⁰ which may influence the quality and safety of tissues and cells and which may be attributed to the procurement, testing, processing, storage and distribution of tissues and cells, as well as serious adverse reactions observed during or after clinical application which may be linked to the quality and safety of tissues and cells. The procedures for notifying serious adverse events and reactions were adopted by Commission Directive 2006/86/EC.

All Member States except for Greece and Latvia have a vigilance system in place to report, investigate, register and transmit information about serious adverse events and reactions which may influence the quality and safety of tissues and cells.

No information has been received from Luxembourg in this respect.

Criteria for the reporting of adverse events to the competent authority have been laid down by 22 Member States.

Criteria for the reporting of adverse reactions to the competent authority have been laid down by 21 Member States.

In accordance with Article 7(1) of Directive 2006/86/EC, Member States must submit to the Commission an annual report on the serious adverse reactions and events notified to the competent authority. The first annual report on this subject, covering the period from 1 September to 31 December 2007 was submitted to the Commission by only 13 Member States (Belgium, Denmark, Spain, Ireland, Lithuania, the Netherlands, Poland, Portugal, Romania, Slovenia, Slovakia, Finland and the United Kingdom). The second annual report covering the year 2008 was submitted by Member States in the course of August 2009.

Under Article 7(6) of Directive 2004/23/EC, the competent authority or authorities must organise inspections and carry out control measures as appropriate whenever there is a serious adverse reaction or event. Twelve inspections were conducted in this respect during 2008.

⁹ According to Article 3(m) of Directive 2004/23/EC, ‘Serious adverse event’ means any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity.

¹⁰ According to Article 3(n) of Directive 2004/23/EC, ‘Serious adverse reaction’ means an unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity.

2.4. Donor selection and evaluation (Art. 12-15 of Directive 2004/23/EC)

2.4.1. Principles governing tissue and cell donation (Art. 12)

Under Article 12(1), Member States must endeavour to ensure voluntary unpaid donations of tissues and cells. Donors may receive compensation strictly limited to making good the related inconveniences. In such cases Member States must define the conditions under which compensation may be granted. Member States must regularly submit reports on these measures to the Commission. On the basis of these reports the Commission will inform the European Parliament and the Council of any necessary measures it intends to take.

The latest Commission report to the European Parliament and the Council is available on the Commission website¹¹.

In most Member States, the principle of voluntary and unpaid donation is ensured by law. Some Member States place the responsibility for respecting this principle on the tissue establishments. Additionally some Member States organise campaigns to promote donation while others do not see this as necessary because they have a presumed consent system.

2.4.2. Data protection and confidentiality (Art. 14)

Under Article 14(2), Member States must ensure that data and confidentiality are protected and that no unauthorised disclosure of information occurs, whilst guaranteeing the traceability of donations. Article 14(3) provides that Member States will take all necessary measures to ensure that the identity of the recipient(s) is not disclosed to the donor or his family and vice versa without prejudice to legislation in force in Member States on the conditions for disclosure, notably in the case of gametes donation. In 13 Member States, the conditions for disclosure of the identity of a recipient and/or a donor are specified in law (Belgium, Bulgaria, Czech Republic, Spain, France, Italy, Cyprus, Hungary, Malta, Poland, Portugal, Sweden and the United Kingdom).

2.5. Provisions on the quality and safety of tissues and cells (Art. 16-24 of Directive 2004/23/EC)

2.5.1. Tissue and cell reception (Art. 19)

Under Article 19(1), tissue establishments must ensure that all donations of human tissues and cells are subject to the required tests and that selection and acceptance requirements are met. Commission Directive 2006/17/EC established the testing, selection and acceptance requirements in respect of tissues and cells, as well as associated documentation and packaging requirements prior to reception at the tissue establishment.

¹¹ http://eur-lex.europa.eu/LexUriServ/site/en/com/2006/com2006_0593en01.pdf

All the reporting Member States comply with the minimum testing requirements of Directive 2006/17/EC. However, Italy, Lithuania, Malta and the United Kingdom do not perform NAT Chlamydia testing for sperm donors (other than partners)¹².

No information has been received from Luxembourg in this respect.

Some Member States apply other tests in addition to those established as minimum requirements in the Directive, in particular:

- Ag HIV testing¹³: Four Member States (Czech Republic, France, Malta, Romania)
- NAT HIV1 testing¹⁴: Six Member States (Denmark, Estonia, Italy, Hungary, Portugal, Slovakia)
- NAT HBV testing¹⁵: Five Member States (Denmark, Spain, Italy, Hungary, Portugal)
- NAT HCV testing¹⁶: Six Member States (Denmark, Germany, Spain, Italy, Hungary, Portugal)
- HTLV-1 testing¹⁷: Eight Member States (Bulgaria, Germany, Greece, Spain, France, Italy, Hungary, Romania)

2.5.2. *Relations between tissue establishments and third parties (Art. 24)*

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

2.6. **Exchange of information, penalties, transposition (Art. 25-31 of Directive 2004/23/EC)**

2.6.1. *Coding of information (Art. 25)*

Article 25 of Directive 2004/23/EC requires the Member States to establish a system for the identification of human tissues and cells, in order to ensure the traceability of all human tissues and cells. The minimum requirements of a European coding system were adopted by Commission Directive 2006/86/EC.

An efficient coding system is a crucial, but not exclusive, element in the traceability chain and ultimately in any vigilance system for human tissues and cells. The human tissue and cell chain is dependent on a robust codification system, which will secure

¹² Sperm donors other than partners must be negative for Chlamydia on a urine sample tested by the nucleic acid amplification technique (NAT).

¹³ Testing for presence of HIV antigens.

¹⁴ Nucleic acid amplification technique for testing HIV1.

¹⁵ Nucleic acid amplification technique for testing Hepatitis B.

¹⁶ Nucleic acid amplification technique for testing Hepatitis C.

¹⁷ Human T-lymphotropic virus.

the information flow from donation to transplantation and vice versa. The European coding system should ensure that the pre-existing traceability/coding systems can be maintained and further developed by the Member States, whilst ensuring a minimum level of compatibility between them.

The Commission, in cooperation with the Member States, is working on the design of a single European coding system to provide information on the main characteristics and properties of tissues and cells.

2.6.2. *Exchange of information*

The Commission has convened three meetings with the competent authorities designated by the Member States to exchange information on the experience acquired with regard to the implementation of Directives 2004/23/EC, 2006/17/EC and 2006/86/EC. The last meeting took place on 27-28 May 2009. Some of the difficulties identified by Member States were linked to the implementation of testing requirements, in particular in the Medically Assisted Reproductive Technologies (MART) sector. The interpretation of the air quality standards that tissue establishments need to apply while tissues and cells are being processed is also a matter of concern among Member States. More guidance on coding systems, inspections, import/export and vigilance requirements was also sought by Member States.

The Commission is endeavouring to provide Member States and competent authorities with appropriate support in these areas.

2.6.3. *Penalties (Art. 27)*

Member States must lay down rules on penalties applicable to infringements of the national provisions, and take all measures necessary to ensure that they are implemented and notified to the Commission. France, Poland and the United Kingdom reported that they had imposed penalties on some tissue establishments in this respect.

2.6.4. *Transposition (Art. 31)*

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

3. CONCLUSIONS

Overall, the implementation of the Directives by the Member States is satisfactory.

This concerns in particular the requirement to designate a competent authority or authorities and to establish accreditation/designation/authorisation/licensing systems of tissue establishments; inspections systems; registries of tissue establishments;

systems to report, investigate, register and transmit information about serious adverse events and reactions; and testing requirements.

The degree of implementation of some other measures suggests that further efforts and actions by Member States are needed. This concerns the development of specific systems for authorising the tissue and cell preparation process; finalisation of the accreditation/designation/authorisation/licensing process in respect of each individual establishment; the carrying out of inspections in all Member States; monitoring of imports/exports; fulfilment of the reporting requirements (tissue establishments' annual reports on activities, register of accredited/designated/authorised/licensed tissue establishments at the level of the Member States and at EU level -EUROCET-); preparation of annual reports on adverse events and reactions for the Commission.

The Commission is working with the Member States to help them develop operational solutions in response to the remaining challenges.