CONSOLIDATED TEXT

Royal Decree-Law 9/2014 of 4th July establishing the quality and safety standards for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells and approving the coordination andoperational rules for their use in humans.

Head of State
"BOE No. 163 of 5th July 2014 Reference: BOE-A-2014-7065"

CONSOLIDATED TEXT

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I

The transplantation of human tissues and cells has experienced a considerable increase in recent years. Directive 2004/23/EC of the European Parliament and of the Council dated 31st March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells was adopted at European Union level to regulate the increasing clinical use of these elements. Commission Directive 2006/17/EC of 8th February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards specific technical requirements for the donation, procurement and testing of human tissues and cells; and Commission Directive 2006/86/EC of 24th October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse events and reactions and specific technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells.

Royal Decree 1301/2006, of 10th November, establishing the quality and safety standards for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells and approving the coordination and operational rules for their use in humans, transposed the EU regulations into Spanish domestic law. However, the Supreme Court has annulled the aforementioned Royal decree on the grounds of insufficient rank in its recent ruling of 30th May 2014.

The decision of the High Court leaves without legal Regulation, in matters of donation and transplantation of human cells and tissues, necessary aspects relating to the quality and safety of donation such as the voluntary nature, anonymity between donor and recipient, altruism and solidarity that characterize the transplant model of the National Health System; the control systems of the processes that take place from the procurement of the cells and tissues to their implantation; the conditions that must be met by the centers and units of procurement and application as well as the tissue establishments; the systems and channels of information on cell and tissue donation; the objectives and criteria for access, based on an objective evaluation of the medical needs, as well as of the tissue establishments; the participation of the public sector and non-profit organizations in the provision of services for the use of human tissues and cells.

The absence of Regulation in these areas would lead to the abolition of existing requirements applicable to the donation of tissues and cells - often originating not only from EU Member States but also from third countries - and thus to the elimination of measures,with the consequent risk to public health, aimed at preventing the transmission of diseases from donor to recipient through the implantation of tissues, some of which are of considerable quantitative and qualitative importance in terms of use, such as bone marrow, umbilical cord blood, bone tissue or corneas.

Specifically, this lack of Regulation would lead, firstly, to a lack of guarantees of quality andsafety in tissue donations and transplants due to the absence of conditions and requirements for intervention in this field. In terms of donor determinations or tissue processing, the lack of essential requirements would generate a high risk of disease transmission or transplant failure.

Secondly, there would also be a lack of necessary public controls in cell and tissue donation, in particular, around bone marrow donation.

And along the same lines of the lack of necessary public requirements and controls, the lack of control over imports and exports is particularly worrying.

The rule declared null and void required prior administrative authorization to import or export tissues from or to third countries. In this situation, tissues from Spanish donors could be sent, without any control, to any country in the world, or tissues fromdonors from countries without the minimum quality criteria could enter Spain, with the risk of transmitting diseases to the recipients.

II

This Royal Decree-Law responds to the evident need to regulate with the required urgency the legal framework indispensable for the immediate materialization of the use of human cells and tissues, as well as the products made from them, when they are destined to be applied to human beings, in the same terms that were already enshrined in the Royal decree now annulled.

To maintain both the guarantees of control of the import and export of tissues from and to third countries and the establishment and operation of Spanish and foreign entities in this field and the legal security of patients and professionals concerning this type of transplants immediate regulatory action is essential. It is a question of guaranteeing the Regulation of numerous aspects and activities related to the therapeutic application of human cells and tissues to avoid the risk to public health that the current situation entails. This risk to public health no longer allows the Regulation of the matter to be delayed.

At the same time, this Regulation complies with the regulatory rank required by Article 43.2 of the Spanish Constitution, which enshrines as a guiding principle of social and economic policy the obligation of the public authorities to organize and protect public health through preventive measures and health benefits, establishing the "duties and rights of all" in this regard.

The Constitutional Court has pointed out, in judgments such as 182/1997, of 28th October, and 245/2004, of 16th December, that the fact that a matter is subject to the principle of reservation of law does not lead to the conclusion that it is excluded from the scope of Regulation of the Royal Decree-Law. The Royal Decree-Law can legislate on this matter as long as it meets the constitutional requirements of enabling conditions and does not "affect", in the constitutional sense of the term, the issues excluded by Article 86 of the Spanish Constitution, an aspect that is necessarily relaxed as we find ourselves in the presence of a guiding principle of social and economic policy in Chapter III of Title I of the Constitution.

For all these reasons, the Government considers that the necessary assumptions of tremendous and urgent need established in Article 86 of the Spanish Constitution are met, which enable it to approve these measures through the mechanism of a Royal Decree-Law.

III

This Royal Decree-Law consists of thirty-eight articles divided into six chapters, a transitional provision, a derogatory provision, four final provisions and eight annexes.

Chapter I contains the general provisions relating to the purpose and scope of application of the Regulation; definitions; the principles of gratuity and non-profit nature; promotion and publicity; education and training; and confidentiality. This Royal Decree-Law applies to all human tissues and cells, including hematopoietic progenitor cells from peripheral blood, umbilical cord, or bone marrow; reproductive cells, except in the aspects regulated in Law 14/2006, of 26th May, on assisted human reproduction techniques; fetal

cells and tissues, andadult and embryonic stem cells when their purpose is therapeutic use or clinical application. Blood and blood products, except for hematopoietic progenitor cells and human organs, are excluded from its scope. Research procedures involving cells and tissues that do not include application in the human body are also excluded from its scope. This Regulation also provides for the possibility for establishments to be set up in the following areas whose activities include preserving cells and/or tissues for eventual autologous use, laying down the conditions with which such establishments must comply.

Chapter II contains provisions on the donation and procurement of human tissues and cells, differentiating the Regulation according to whether they come from living or deceased donors; on the authorization of activities in tissue and cell procurement establishments and units; on donor selection and evaluation; on the tissue and cell procurement procedure; onthe packaging, labelling and transport of tissues and cells to the tissue establishment; and on the system for the collection and safekeeping of information.

Chapter III regulates the processing, storage and distribution of human tissues and cells and, in particular, the authorization of activities, the general operating conditions and the technical responsible and assigned personnel of tissue establishments; quality management; the reception, processing, storage, labelling, documentation, packaging, distribution, import and export of tissues and cells; the relations between tissue establishments and third parties; and the system for the collection and custody of any information.

Chapter IV regulates the application of tissues and cells and, within this framework, the authorization of the application of tissues and cells in application centers or units; access to tissues and cells and general conditions of application; the system of collection and storage of information and clinical research.

Chapter V regulates the information, monitoring and biomonitoring systems and, in this area, the registers of centers and units for the procurement and application of human tissues and tissue establishments and hematopoietic progenitor donors; the general information system; traceability and coding and biomonitoring systems.

Chapter VI regulates the inspection, evaluation, and accreditation of centers and services, as well as infringements and sanctions.

The sole transitional provision regulates the retroactive application of this Regulation to legal situations arising and procedures initiated before the entry into force of the Royal Decree-Law, except regarding provisions imposing penalties that are not favorable to or restrictive of individual rights. The sole repealing condition provides for the corresponding repeal of the regulations. The final clauses regulate the competence title; the incorporation of European Union law; the power of development and modification; and the Regulation's entry into force.

Finally, the eight annexes regulate, respectively, the minimum requirements and conditions for the authorizations of tissue establishments and tissue and cell procurement establishments or units; the clinical requirements for the evaluation of tissue and cell donors; the laboratory tests required for the assessment of donors, except for donors of reproductive cells; the selection and evaluation of the donor of reproductive cells; the procedures for donation, retrieval of cells and tissues and their reception at the tissue establishment; the minimum information required in the traceability system from origin to destination of human tissues and cells procured for human application; the tissue and cell coding system; and the system of biomonitoring.

This Royal Decree-Law, insofar as it determines essential aspects for the protection of thehealth and safety of human beings, both donors and potential recipients, has the status of basic regulations, under the protection of article 149.1.16 of the Constitution, which attributes to the State the competence over the bases and general coordination of health, and following the provisions of Law 14/1986, of 25th April, General Health. Exceptions to the above are Article 23, which is enacted under the exclusive competence of the State in matters of foreignhealth, and Article 29, which is passed under the provisions of Article 149.1.15, which grants the State exclusive competence in matters of promotion and general coordination of scientific and technical research.

By virtue of the foregoing, making use of the authorization contained in Article 86 of the Spanish Constitution, at the proposal of the Minister of Health, Social Services and Equality, following deliberation by the Council of Ministers, at its meeting of 4th July 2014.

PROVIDED:

CHAPTER I

General provisions

Article 1. *Purpose and scope.*

1. This Royal Decree-Law regulates the activities related to the use of human tissues, cells and the products made from them when they are intended to be applied to human beings. The regulated activities include their donation, procurement, evaluation, processing, preservation, storage, distribution, application, and clinical research.

2. If specific rules regulate the elaboration, transformation, processing, application, and clinical research of products derived from cells and tissues, this Royal Decree-Law shall only apply to their donation, procurement and testing.

3. The following are excluded from the scope of this Royal Decree-Law:

a) Cells and tissues used as autologous grafts within the same surgical procedure.

b) Blood, blood components and blood derivatives as defined in Royal Decree 1088/2005of 16th September 2005 establish the technical requirements and minimum conditions for hemodonation and transfusion centers and services.

c) Organs or parts of organs, if they are intended to be used in the human body with the same function as the whole organ.

4. This Royal Decree-Law shall apply to reproductive cells in all matters not provided forin Law 14/2006 of 26th May, assisted human reproduction techniques, and implemented regulations.

Article 2. *Definitions.*

1. For this Royal Decree-Law, the following definitions shall apply:

a) Storage: maintenance of cells or tissues under controlled and appropriate conditions until distribution.

b) Application: any activity involving the use of cells or tissues in a human recipient and/orin extracorporeal applications (including the activities of implantation, infusion, grafting, application, or transplantation).

c) Cells: individual cells of human origin or cell groups of human origin when any form of connective tissue does not bind them together.

d) Reproductive cells: cells or tissues that can be used for assisted human reproduction.

e) Procurement establishment or unit: a health establishment, hospital unit or any other institution that carries out tissue or cell procurement and retrieval activities, or that mayenable the collection and use of surgical waste for the purposes set out in this Regulation, andwhich does not need to be authorized as a tissue establishment.

f) Human implantation or human application unit or establishment: a health establishment, hospital unit or any other institution that carries out activities involving the application of human tissues or cells to humans.

g) Quarantine: the period during which the removed tissues or cells are kept in physical or other effective isolation pending a decision on their acceptance or rejection for use in humans.

h) Critical: a fact, action or event that can potentially affect the quality and safety of cells and tissues.

i) Distribution: transport and delivery of tissues or cells intended for human application.

j) Donation: the act of donating human tissues or cells intended for human application.

k) Intra-couple donation: the transfer of reproductive cells from a man to a woman of thesame couple who claim to be in an intimate physical relationship.

l) Donor: any human source, living or dead, of human cells and/or tissues.

m) Serious adverse event: any untoward occurrence associated with the procurement, testing, processing, storage, and distribution of tissues and cells that might lead to the transmission of disease, to death or life-threatening, disabling, or incapacitating conditions for the patient, or which might result in, or prolong, hospitalization ormorbidity.

n) Tissue establishment: tissue bank, unit of a hospital or any other establishment where activities of processing, preservation, storage or distribution of human tissues and cells are carried out after procurement and until their use or application in humans. The tissue establishment may also be responsible for the procurement and testing of tissues and cells.

o) "Clinical investigation" means research carried out using protocols involving the procedures for the procurement and application of human tissues and cells in humans, wherethe efficacy or safety of the procedures or the tissues or cells is not sufficiently established or where the therapeutic indication is not sufficiently well established, and the purpose of which is the verification of one of these points.

p) Procurement: process by which human cells and/or tissues may be made available for the purpose referred to in this Royal Decree-Law.

q) Organ: a differentiated and vital part of the human body formed by different tissues, which maintains its structure, vascularization and capacity to develop physiological functions with a significant level of autonomy.

r) Preservation: the use of chemical agents, alteration of environmental conditions or application of other means during the processing of tissues or cells in order to prevent ordelay biological or physical deterioration of tissues or cells.

s) Standard Operating Procedures (SOPs): documented and authorized work instructions that describe how to carry out activities or perform tests that are not usually described in work plans or standards of good practice.

t) Processing: operation(s) involving the preparation, manipulation, preservation and conditioning of tissues and cells intended for human applications.

u) Serious adverse reaction: an unexpected donor or recipient response, including a communicable disease, associated with the procurement or human application of tissues and cells, that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalization or morbidity.

v) Quality system: comprises the organizational structure, definition of responsibilities, procedures, processes and resources, which are intended to develop quality management. It includes any activity that contributes directly or indirectly to total quality.

w) Quality management system: coordinated activities aimed at the direction and controlof an organization in relation to quality.

x) Tissue: any constituent part of the human body made up of cells bound together by some form of connective tissue.

y) Traceability: the ability to locate, trace and identify the cells and/or tissues at any step of the process from donation, procurement, processing, testing, storage and distribution to therecipient or until they are discarded and/or destroyed, which entails the ability to identify the donor, the tissue establishment and the facility receiving, processing or storing the tissues or cells, as well as the ability to identify the recipient(s) to which the tissues or cells are applied. Traceability also covers the ability to locate and identify any relevant data on the products andmaterials that will be in direct contact with the cells and/or tissues, affecting the quality and safety of the tissues and/or cells.

z) Single European Code or "SEC": a unique identifier that applies to tissues and cells distributed in the European Union and consists of a donation identification sequence and a product identification sequence as detailed in Annex VII.

aa) The donation identification sequence is the first part of the unique European code, consisting of the EU tissue establishment code and the unique donation number.

bb) EU tissue establishment code: unique identifier for tissue establishments accredited, designated, authorized, or approved in the European Union consisting of an ISO country code and the tissue establishment number as listed in the EU Compendium of Tissue Establishments, as detailed in Annex VII

(ab) 'Unique donation number' means the unique number assigned to a specific donation of tissues and cells in accordance with the system in force in Spain for assigning such numbers, as detailed in Annex VII.

(ac) Product identification sequence: second part of the unique European code, consisting of the product code, the sublot number and the expiry date.

ad) Product code: identifier for the specific type of tissue or cell in question consisting of the product coding system identifier indicating the coding system used by the tissue establishment ('E' for EUTC, 'A' for ISBT128 and 'B' for Eurocode) and the product number of the tissues and cells provided for in the respective coding system for the product type, as detailed in Annex VII.

(ae) 'Sublot number' means a number that uniquely distinguishes and identifies tissues and cells that have the same unique donation number and product code and originate from the same tissue establishment, as detailed in Annex VII.

(af) 'Expiry date' means the date until which the tissues and cells may be applied, as detailed in Annex VII.

(ag) EU Coding Platform: IT platform, hosted by the Commission, containing the EU Tissue Establishment Compendium and the Cell Products Compendium.

(ah) EU Compendium of tissue establishments: a register of all tissue establishments that have been authorized, approved, designated or accredited by the competent authority or authorities of the Member States and containing the information on these tissue establishments as set out in Annex IX.

ai) EU Compendium of Tissue and Cellular Products: register of all types of tissues and cells circulating in the European Union and the respective product codes according to the three permitted coding systems (EUTC, ISBT128 and Eurocode).

aj) EUTC: product coding system for tissues and cells developed by the European Union, which consists of a register of all types of tissues and cells circulating in the European Union and their corresponding product codes.

(ak) Release into circulation: distribution for human application or transfer to another operator, e.g. for further processing, with or without return.

(al) In the same site: means that all steps of the process from procurement to human application are carried out under the same responsible person, the same quality management system and the same traceability system, in a healthcare setting comprising at least one authorized establishment and one organization responsible for human application at the same site.

am) Batching: physical contact or mixing, in the same container, of tissues or cells from more than one procurement from the same donor, or from two or more donors.

(an) 'Emergency' shall mean any unforeseen situation where there is no practical alternative to the urgent importation into the European Union of tissues and cells from a third country for immediate application to a known recipient or to known recipients whose health would be

seriously threatened in the absence of such importation.
añ) "Importing tissue establishment" means a tissue bank, a hospital unit or any other body established in the European Union, which is party to an agreement contract with a third country supplier for the importation into the European Union of tissues and cells from a third country intended for human applications.
(ao) 'Exceptional import' means the import of any specific type of cell or tissue intended for the personal use of a recipient or recipients known to the importing tissue establishment and to the third country supplier prior to importation. Such a specific type of cell or tissue importation shall not normally occur more than once for a given recipient. Imports from the same third country supplier that occur regularly or repeatedly shall not be considered "exceptional imports".
(ap) 'Third country supplier' means a tissue establishment or other body established in a third country responsible for exporting to the European Union tissues and cells through their supply to an importing tissue establishment.

A third country supplier may also carry out one or more of the activities, performed outside the European Union, of donation, procurement, testing, processing, preservation, storage and distribution of tissues and cells imported into the European Union.

2. It shall also mean:

a) Allogeneic use is when cells or tissues are taken from one person and applied to another.

b) Autologous use: process by which cells or tissues are removed and applied to the same person.

c) Eventual autologous use: cells and/or tissues are obtained with the purpose of being preserved for hypothetical future application in the same person, without there being an established medical indication at the time of procurement and initiation of preservation.

d) Direct use: any procedure in which cells are obtained and used without any processingor storage.

e) Validation: documentary evidence that proves, with a high level of assurance, that a given process, piece of equipment or part of an equipment or environmental condition consistently and reproducibly produces a given product that meets predetermined specifications, qualities and attributes. A process is validated with a view to proving its effectiveness for a given use.

Article 3. *Free of charge and non-profit nature.*

1. The donation of cells and tissues shall in all cases be voluntary and altruistic, and no financial consideration or remuneration may be received either by the donor or by any other natural or legal person.

2. The medical procedures related to the removal shall in no case be burdensome for the living donor, nor for the family in the case of the deceased donor, and the living donor shall beguaranteed the necessary assistance for his recovery.

3. Living donors of cells or tissues may receive compensation from the institution responsible for the retrieval, strictly limited to covering expenses and inconveniences incurredin the procurement of cells or tissues, such as subsistence allowances, replacement of lost income or similar.

4. No consideration shall be required from the recipient for the cells and/or tissues used.

5. The activities of tissue establishments shall be of a non-profit nature, and only the actual costs of the services provided for the development of the authorized activities may be passed on.

Article 4. *Promotion and publicity.*

1. The promotion and advertising of the donation or procurement of human tissues and cells shall always be done in a general manner, without seeking a benefit for specific individuals, and shall be of a voluntary, altruistic and disinterested nature.

Organizations that intend to carry out any promotional and publicity activity in support of the donation of human tissues and cells must request prior authorization from the competent health administrations. For this purpose, the competent health administration shall be understood to be that corresponding to the Autonomous Community where the activity is tobe carried out, and the National Transplant Organization when the activities are carried out in the Autonomous Community of origin, and the National Transplant Organization when the activities are carried out in the Autonomous Community of origin activities intended to go beyond this scope. In any case, the procedure for deciding on the authorization or refusal of the development of such activities shall be governed by the

provisions of Law 30/1992, of 26th November, on the Legal Regime of the Public Administrations and Common Administrative Procedure.

2. The promotion and advertising of the centers and services referred to in this Royal Decree-Law shall also be carried out on a general basis and shall be subject to inspection and control by the competent health administrations, in accordance with article 30.1 of the General Health Act 14/1986 of 25th April 1986.

3. The existence and/or persistence of false, misleading or biased advertising and promotion shall be incompatible with the authorization of tissue and cell procurement, preservation, processing, distribution or application activities in Spain by the tissue establishment, institution, unit or establishment that has issued such advertising or has contractual relations with the institution that has issued the advertising.

In particular, misleading advertising shall be deemed to exist in the case of establishments, units and institutions whose advertising is misleading as to the actual usefulness of the procurement, processing and preservation of human tissues and cells for possible autologous uses, according to available knowledge and experience.

Article 5. *Education and training.*

1. The health authorities shall promote public information and education on the donation of cells and tissues for human applications, both in terms of the benefits for the people who need them and the conditions, requirements and guarantees that this procedure entails.

2. They will also promote the continuing training of health professionals in this area.

Article 6. *Confidentiality.*

1. Donors shall be guaranteed the confidentiality of all data related to their health and provided to authorized personnel, as well as the results and traceability of their donations, in accordance with Organic Law 15/1999, of 13th December, on the Protection of Personal Data.

2. Tissue establishments must adopt, in the processing of donor-related data, the high-level security measures provided for in the Regulation on security measures for automated files containing personal data, approved by Royal Decree 1720/2007, of 21st December, approving the Regulation implementing Organic Law 15/1999, of 13th December.

3. The personal data shall be confidential and shall be exclusively at the disposal of the interested parties, in accordance with the provisions of Law 41/2002, of 14th November, the basic law regulating patient autonomy and rights and obligations regarding clinical information and documentation and, where appropriate, of the judicial authority for the exercise of the functions entrusted to it. Its use shall be limited to healthcare purposes or those of interest to public health and shall be collected and safeguarded in accordance with the provisions of article 10 of Law 14/1986, of 25th April, in Organic Law 15/1999, of 13th December, and in Law 41/2002, of 14th November.

4. The duty of confidentiality shall not prevent the adoption of preventive measures when the existence of risks to individual or collective health is suspected under the terms provided for in Articles 25 and 26 of Law 14/1986, of 25th April, or, where appropriate, in accordance withthe provisions of Organic Law 3/1986, of 14th April, on Special Measures in the Field of Public Health, Law 41/2002, of 14th November, and Organic Law 15/1999, of 13th December.

5. Information that would allow the identification of donors and recipients of human tissues and cells may not be provided or disclosed, nor may identifying details of recipientsbe provided to donors or their relatives or vice versa.

CHAPTER II

Donation and procurement of human tissues and cells

Donation and procurement of tissues and cells from living donors.

1. The procurement of cells and tissues from a living person for subsequent allogeneic application in human beings may be carried out if the donor is of legal age, has full capacityto act, is in an adequate state of health and has given his or her informed consent in writing.

The information that the donor will receive from the physician who is to perform the procurement or is responsible for the procurement must cover the purpose and nature of the procurement of the tissues and cells; its consequences and risks; the analytical tests to be performed; the recording and protection of the data; and the therapeutic purposes. It mustalso provide information on the protective measures applicable to the donor and the benefits that the recipient is expected to derive from the use of the retrieved tissue or cell group.

Consent may be revoked at any time prior to the procurement of the cell and/or tissue, except in cases of peripheral blood or bone marrow hematopoietic progenitor procurement, where revocation may only occur prior to the start of conditioning treatment in the recipient.

Cells and tissues may not be obtained from minors or from persons who, due to mental deficiency, mental illness, legal incapacity or any other cause, are unable to give their consent, except in the case of surgical residues or hematopoietic progenitors or other reproducible tissues or cell groups whose therapeutic indication is or may be vital for the recipient. In these cases, consent shall be given by the person legally representing the recipient.

2. The procurement of tissues and cells from a living person for processing and subsequent autologous use or for possible autologous use shall be carried out in accordance with the provisions of the first to third subparagraphs of the previous paragraph.

In the case of eventual autologous use, the content of the information provided prior to procurement must include, in addition to the provisions of the previous paragraph, the indication that the cells and tissues thus procured will be available for allogeneic use in other patients if there is a therapeutic indication; the current, true and complete information on the state of scientific knowledge regarding therapeutic or research uses; the conditions for processing and storage in the authorized establishments; and any other matter relating to the therapeutic usefulness of the procurement of tissues and cells without a medical indication established at the time of procurement and commencement of preservation.

In the case of minors or persons who, due to mental deficiencies, mental illness, legal incapacity or any other cause, are unable to give their consent, such consent shall be givenby their legal representative.

3. Information and consent should be provided in appropriate formats, following the rules of the design-for-all principle, in a way that is accessible and understandable to persons with disabilities.

4. In all matters not provided for in this Article, the procurement of cells and tissues froma living donor shall be governed by the provisions of Chapter IV of Law 41/2002 of 14th November 2002.

Donation and procurement of tissues and cells from deceased donors.

1. The procurement of tissues and cells from deceased persons may be carried out in the event that they have not left an express statement of their opposition, in accordance with the provisions of Article 11 of Law 41/2002, of 14th November.

In the case of minors or persons with judicially modified capacity, the objection to the donation may be made by those who were their legal representatives during their lifetime. In the case of persons with disabilities, account shall be taken of the individual's personal circumstances, their capacity to make such a decision in particular, and the provision of supportfor such decisions should be envisaged.

2. The procurement of reproductive material from deceased persons for reproductive purposes shall be governed by the provisions of Law 14/2006, of 26th May, on assisted human reproduction techniques.

3. Family members and relatives should be provided with information on the need, nature and circumstances of the procurement, specifying what procedures for the restoration and preservation of the body and mortuary health practices will be carried out.

4. The procurement of cells and tissues shall be carried out after the corresponding certification of the death and after the police and judicial proceedings, if any, have been carried out.

Article 9. *Authorization of activities in tissue and cell procurement establishments and units.*

1. The procurement of tissues and cells may only be carried out in those health centers orunits that are duly authorized by the competent health authority, in accordance with the provisions of Royal Decree 1277/2003, of 10th October, which establishes the general bases for the authorization of health centers, services and establishments, and provides that the minimum requirements and conditions set out in Annex I.1 of this Royal Decree-Law are complied with.

Without prejudice to the specific regulations in this respect in each Autonomous Community, the application for authorization must contain:

a) The name(s) of the person(s) responsible for the donor evaluation and procurement process.

b) A detailed report with a description of the means at its disposal and their adequacy with regard to the minimum conditions and requirements set out in this standard.

2. These establishments and health units must have a specific authorization for theprocurement of each type of tissue or cell group, the validity of which shall be for a specific period of no less than two years and not more than four, at the end of which it may be renewed after verification that the conditions and requirements that gave rise to its grantpersist. In no case shall it be understood to be automatically extended.

Any substantial modification in the conditions or requirements that led to the granting of the authorization must be notified to the competent health authority, and may lead to itsreview or even to the revocation of the authorization if the modifications entail a substantial alteration of the circumstances that justified the granting of the authorization.

3. In those cases in which it is feasible and necessary to obtain the tissue or cell group outside the hospital or health care setting or in a health care establishment not authorized for the procurement of tissues and/or cells, such procurement must be carried out by professionals integrated in a procurement team of a duly authorized establishment for such activity and under the conditions laid down by that establishment. In these cases, the tissue and cell procurement teams must be in possession of the appropriate authorization for this specific practice. In any case, the necessary clinical history and samples shall be collected to ensure that the relevant studies and tests specified in the following article are carried out.

Article 10. *Donor selection and evaluation.*

1. Tissue procurement shall be carried out in such a way as to ensure that the evaluation and selection of donors is carried out in accordance with the requirements specified inAnnexes II, III, IV and V of this Royal Decree-Law, and by suitably trained and experienced personnel. The person responsible for the selection and evaluation procedure shall draw up and sign the corresponding report recording compliance with these requirements.

2. The application of selection and evaluation criteria shall be based on the application of a risk assessment analysis in relation to the specific use of each tissue or cell group.

3. The results of the donor selection and evaluation procedures shall be duly documented and, where appropriate, communicated in accordance with the terms of Law 41/2002, of 14th November.

4. In the case of multiple tissue or tissue donations for the purpose of non-deferred transplantation, the unit responsible for the procurement process of the authorized establishment shall be responsible for the custody and archiving of all data derived from the donor selection and evaluation process, as well as for the existence and maintenance of the serum bank.

5. In the event that the procured tissues or cells are to be sent to another tissue establishment for processing, the latter may be responsible for completing the evaluation and selection of the tissues or cells, shall be responsible for determining their final viability and, in addition, shall have access to the data relating to the evaluation of the donors and shall ensure the safekeeping of the information on the additional evaluation. In the same way, he/she shall keep serum samples in case additional tests have been performed in addition to those processed at the procurement establishment.

6. In the case of donations for specific uses other than clinical transplantation, the person responsible for the procurement procedure shall also be responsible for matters relating tothe collection and archiving of donor data and samples.

Article 11. *Procedure for obtaining.*

1. The procurement of cells and tissues must be carried out by duly documented and validated standardized operating procedures that are appropriate for the tissue or cell groupto be retrieved, that in the case of living donors ensure their health and safety and respect their privacy, and that comply with the provisions of Annex V.

2. The procurement procedure must be appropriate to adequately protect those properties of the cells or tissues that are necessary for their clinical use, while minimizing the risks of microbiological contamination.

3. In case the tissues and/or cells are to be sent to a tissue establishment for processing, the procedure for procurement, packaging, labelling, maintenance and transport to the tissue establishment must be laid down in a document agreed between the procurement unit andthe tissue establishment.

Article 12. *Packaging, labelling and transport to the tissue establishment.*

1. The packaging, maintenance, labelling and transport of tissues and cells to the tissue establishment shall be carried out by means of duly documented and validated standard operating procedures and shall comply with the provisions of Annex V.

2. Tissues and cells must be packaged and transported in such a way as to minimize the risks of contamination and prevent deterioration of the biological properties necessary fortheir potential clinical use.

Article 13. *System for the collection and custody of information.*

1. The centers and units authorized for the procurement of cells and tissues must have a system for the collection and custody of information on their activities that allows compliance with the provisions on coding and traceability of this Royal Decree-Law.

2. The centers and units authorized for the procurement of cells and/or tissues must provide the data relating to their activity that are required by the competent health authorities of their Autonomous Community, which will send them to the National Transplant Organization in accordance with the provisions of Chapter V of this Royal Decree-Law.

CHAPTER III

Processing, storage and distribution of human cells and tissues

*Authorization of activities in tissue establishments***.**

1. Activities related to the processing, storage and distribution of human tissues and cells may only be carried out in those health centers or units duly authorized by the competent health authority, following the general bases for the authorization of health centers, services and establishments established in Royal Decree 1277/2003, of 10th October, and provided thatthe minimum requirements and conditions set out in Annex I.2 of this Royal Decree-Law are complied with.

Without prejudice to the specific regulations in this respect in each Autonomous Community, the application for authorization must be accompanied by a report on compliancewith the requirements of this Royal Decree-Law.

2. These establishments and health units must have a specific authorization for thedevelopment of each of the processes and activities in the previous section for each type of tissue or cell group, in accordance with the requirements set out in Annex I.3. The authorizations shall be valid for a specified period of not less than two nor more than four years, at the end of which they may be renewed, subject to verification that the conditions andrequirements that gave rise to their grant persist. In no case shall it be understood to be automatically extended.

Any substantial modification in the conditions or requirements that led to the granting of the authorization must be notified to the competent health authority, and may lead to itsreview or even to the revocation of the authorization if the modifications entail a substantial alteration of the circumstances that justified the granting of the authorization.

3. Applications for activity authorizations shall set out the actions that the tissue establishment will undertake in the event of termination of the activity for which authorization is requested, including coverage of liabilities incurred and the shipment to another dulyauthorized tissue establishment of stored tissue and cell samples, sera and the information necessary to ensure their traceability.

Article 15. *General conditions for the operation of tissue establishments.*

1. The processing activities carried out in tissue establishments shall be aimed at the preparation, preservation and storage of tissues and cells for clinical use, both autologousand allogeneic, either in therapeutic procedures with established medical indications or in procedures for human application in cases of duly proven usefulness and efficacy, or in duly documented clinical research procedures.

2. Tissue establishments shall process, preserve and store tissues and cells in such a way as to ensure their maximum utilization. In addition, and in accordance with the principleof equitable distribution, they shall ensure access to tissues and cells in cases of insufficient availability and for medical reasons of suitability of recipients.

3. As provided for in Article 3(5), the competent authorities of the Autonomous Communities shall establish the compensation and cost charging regime that may be applied to distributed tissues and cell groups in order to cover the costs arising from their activity. These charges may only be applied to the establishment or unit of application once the processing or preservation activity has been completed and the tissue or cell group has been distributed.

4. Tissue establishments preserving tissues and cells for possible autologous uses are also required to take out insurance to cover the costs of processing, preservation and storagein the event of the transfer or dispatch of those tissues and cells to another establishment, establishment or health unit for allogeneic uses in therapeutic procedures with established medical indications in suitable recipients. The insurance shall also cover the transfer in cases of cessation of the establishment's activity.

Article 16. *Quality management.*

1. Tissue establishments must develop and keep up to date a quality and quality management system integrated into the guidelines and strategies of the tissue establishment and including at least the following documentation:
a) Operating procedure manuals for authorized activities and critical processes.
b) Training and reference manuals.
c) Forms for the transmission of information.
d) Data on the origin and destination of cell groups or tissues.
e) Information on the traceability of cells or tissues.
f) System for detection and reporting of adverse effects and reactions.
2. The documentation referred to must be available for inspection by the competent health authority.

Article 17. *Technical manager and assigned personnel.*

1. Each tissue establishment shall appoint a technical manager who shall meet thefollowing conditions:

a) Hold a higher university degree in the field of medicine or biomedical sciences, awarded after full university studies recognized and accredited in Spain as equivalent to a higher university degree.

b) Have at least three years' proven practical experience in the relevant field of activity.

2. The roles and responsibilities of the line manager include the following:

a) Ensure that within the tissue establishment for which he/she is responsible, tissues and cellsintended for human applications are processed, stored and distributed in accordance with the provisions of this Royal Decree-Law and the applicable regulations.

b) To provide information to the competent authorities on the conditions, requirementsand operating regime demanded of tissue establishments by this Royal Decree-Law.

c) To apply all the conditions and requirements in the tissue establishment and to implement the operating regime regulated in this Royal Decree-Law.

3. Tissue establishments shall notify the competent authority of the name and qualifications of the responsible technical person. Where he/she is replaced on a permanent or temporary basis, such replacement shall be notified immediately to the competent authority. That notification shall include the name and qualifications of the replacement and the exact date of the period of replacement or of their commencement where the replacement is indefinite.

4. Tissue establishment personnel involved in activities related to the processing, preservation, storage or distribution of tissues and cells must be qualified to perform their assigned tasks and trained accordingly.

*Receipt of tissues and cells***.**

1. The tissue establishment must have a documented reception procedure in place to verify that the tissues and cells retrieved at the procurement centers or units comply with the requirements of this Royal Decree-Law.

2. Shipments of tissues and cells that do not meet these requirements must be rejected by the tissue establishment.

3. The reception of tissues and cells must comply with the provisions of Annexes V.2 and V.3. VI.

4. The reception process must ensure that there is no risk of contamination with tissues and cells already deposited and undergoing processing, preservation or storage.

Article 19. *Tissue and cell processing.*

1. Tissue establishments shall include all tissue and cell processing activities in their procedural manuals and ensure that they are carried out under controlled conditions. It shall verify that the equipment used, the working environment and the design, validation andcontrol conditions of the processes comply with the requirements specified in Annex I.3.

2. Any modification of the processes used in the preparation of tissues or cells must comply with the above requirements.

*Storage of tissues and cells***.**

1. Any actions related to the storage of tissues and cells must be documented in the procedure manuals. The storage conditions shall comply with Annex I.3 in such a way as to ensure that the viability, quality and safety of tissues and cells are maintained.

2. In accordance with Article 14(3), in the event of termination of the activity of the tissue establishment, the preserved or stored tissues and cells must be transferred to another duly authorized tissue establishment.

Tissue establishments must guarantee the transfer in case of cessation of activity by means of agreements previously established with other establishments and known by the transplant coordination units of the Autonomous Communities.

3. All information on storage activities shall be duly collected and stored in order toensure that the availability status of stored tissues and cells is known at all times.

Article 21. *Labelling, documentation and packaging.*

Labelling, documentation and packaging procedures shall be in accordance with Annex I.3.

Article 22. *Distribution of tissues and cells.*

1. The conditions for the distribution and transport of tissues and cells shall be in accordance with Annex I.3.

2. Transport from the tissue establishment to the implantation site or to another tissue establishment shall be by the most appropriate means of land or air transport and through systems capable of maintaining the viability and functionality of the cells and/or tissues.These systems must be specified in documented procedures according to the type of cell or tissue to be transferred.

Article 23. *Import and export of tissues and cells.*

1. The Ministry of Health, Social Services and Equality shall authorize, following a report from the National Transplant Organisation, the import and export of the tissues and cells referred to in this Royal Decree-Law. The import, export and transit of these tissues and cells shall only be carried out through the customs areas specified in Annex I of Royal Decree 65/2006, of 30th January, which establishes requirements for the import and export of biologicalsamples.

2. The importation of tissues and cells shall only be authorized under the followingcircumstances:

a) That there is a proven benefit in the use of the tissues and cells to be applied.
b) That the purpose of the tissues and/or cells is for human application.
c) In the case of cells and tissues that are usually processed in one of the national tissueestablishments, there is no availability of such cells and/or tissues at that time.

3. The export of tissues and cells shall be authorized only in the following circumstances:

a) That there is sufficient availability of such cells and/or tissues in national tissueestablishments.

b) There is a medical reason to justify the export.

4. All imports of tissues and cells shall be carried out through the importing tissue establishments regulated in Article 23a, except in the following cases:

a) Importation, with prior and direct authorization by the competent authority, of specific tissues and cells that can be distributed directly for immediate transplantation to the recipient, provided that the supplier has the authorization for this activity.

b) Importation of tissues and cells authorized directly by the competent authority in cases of emergency.

5. Requests for the import and export of cells and tissues shall be addressed to the National Transplant Organisation, as appropriate, by the tissue establishment, the importing tissue establishment, the center or unit involved, with the prior knowledge of the transplant coordination unit of the corresponding Autonomous Community. The National Transplant Organization will forward the requests to the Sub-Directorate General for Foreign Health ofthe Ministry of Health, Social Services and Equality, together with its report, for processing.

6. Requests for the import and export of tissues and cells shall specify the institution of origin and destination, respectively, which must comply with quality and safety standards equivalent to those regulated in this Royal Decree-Law.

7. In order to ensure compliance with the provisions of the previous paragraph, the importing tissue establishment or tissue establishment, as appropriate, shall issue a certificate to accompany the import and export application. In the case of imports of tissues and cells, the certificate shall contain the following information:

a) A documented technical report stating that the tissue or cells or the way in which they have been processed are indispensable for the therapeutic procedure to be applied and that either the tissues and/or cells or the processing method are not available or cannot be provided by the national establishments.

b) Documentation from the institution of origin stating the ethical and health safeguards that are observed.

c) A report from the tissue establishment of origin containing the evaluations and studies carried out (clinical, biological, microbiological and/or immunological), in accordance with the provisions of this Royal Decree-Law regarding the selection and evaluation of the donor.

In the case of exports of tissues and cells, the certificate must contain the followinginformation:

a) A report on the sufficient domestic availability of the tissues and/or cells to be exported.

b) Documentation attesting to the unavailability of the processing method to be usedwhen this is the reason for the departure of the tissues and/or cells.

c) A technical memorandum stating the medical reasons justifying the removal of thetissues and/or cells where this is the reason.

d) Documentation that data protection is ensured.

8. The importation of cells or tissues may be refused or revoked when they do notoriginate from altruistic donations in third countries that meet the appropriate guarantees.

Article 23a. *Authorization of activities of importing tissue establishments.*

1. Importing tissue establishments, prior to requesting authorization for the exercise of their import activities, must take the necessary measures to ensure that imports of tissuesand cells comply with the quality and safety standards equivalent to those established in this Royal Decree-Law and that such tissues and cells can be traced from donor to recipient and vice versa.

They shall also conclude, as provided for in Article 23b, written agreements with suppliers in third countries whenever certain activities of donation, procurement, testing, processing, preservation, storage or export to the European Union of tissues and cells to be imported into the Union are carried out outside the Union.

1. After complying with the provisions of the previous section, and without prejudice to the specific regulations of each Autonomous Community, the importing tissue establishments must submit an application for authorization to the competent authority with the information indicated in Annex X, accompanied by the documentation referred to in section 6 of that Annex. This documentation must include a copy of the written agreements with suppliers in third countries.

They shall also make available and, upon request by the competent authority, submit the documentation referred to in Annex XII.

However, in the case of exceptional imports, the documentation referred to in paragraph 6 of Annex X and Annex XII need not be submitted, provided that the traceability from donor to recipient and vice versa and the non-use of the tissues and cells on a person other than the intended recipients is ensured by the necessary documentation.

In the case of tissue-importing establishments that have been previously authorized as tissue establishments or as tissue-importing establishments, it shall not be necessary to submit information or documentation already provided in the course of the respective procedure.

2. The competent authority shall verify that the importing tissue establishments comply with the requirements for the exercise of their import activities and shall decide on the authorizations indicating, where appropriate, the applicable conditions, such as restrictions on the import of certain types of tissues and cells or on the third country suppliers used.

The competent authority shall issue the certificate provided for in Annex XI to each approved importing tissue establishment.

3. In the case of substantial changes or modifications to the import activities, the importing tissue establishments shall seek prior written authorization from the competent authority.

In particular, any change in the type of tissues and cells imported and in the activities carried out in third countries that may influence the quality and safety of the tissues and cells imported or the third country suppliers used are considered to be substantial modifications.

Where an importing tissue establishment makes an exceptional import of tissues or cells from a supplier in a third country that is not covered by its current authorization, such import shall not be considered as a substantial modification if that establishment is authorized to import the same type of tissues or cells from one or more other suppliers in a third country.

4. Approvals may be revoked or suspended, in whole or in part, if inspections or other control measures show that importing tissue establishments no longer meet the requirements for approval.

5. Importing tissue establishments may at any time inform the competent authority of their decision to terminate, in whole or in part, their import activities.

Article 23b. *Written agreements with third country suppliers.*

1. The written agreements that importing tissue establishments conclude with third country suppliers must specify the quality and safety requirements that must be met to ensure the equivalence of the quality and safety standards of the tissues and cells to be imported with those laid down in this Royal Decree-Law, and must include at least the aspects listed in Annex XIII.

2. Such agreements shall expressly provide for the right of the competent authority to inspect the activities, including facilities, of any third country supplier for the duration of the written agreement and for a period of two years after its termination.

3. Such agreements shall not be necessary in the case of exceptional imports provided that traceability from donor to recipient and vice versa, and the non-use of the tissues and cells on a person other than the intended recipients, is ensured by the necessary documentation.

1. Importing tissue establishments shall notify the competent authority without delay:

a) In whole or in part, any revocation or suspension of the authorization for export of tissues and cells from the third country supplier.

b) In case of non-compliance, any other decision by the competent authority or authorities of the country where the third country supplier is established may influencethe quality and safety of the imported tissues and cells.

Article 24. *Relations between tissue establishments and third parties.*

1. Tissue establishments must conclude written contracts with third parties whenever theycarry out an activity that influences or may influence the quality and safety of the tissues and/ or cells processed, and in particular when:

a) The tissue establishment entrusts a third party with the responsibility for a stage of celland/or tissue processing.

b) A third party supplies materials or products or provides services that may affect thequality and safety of cells and/or tissues.

c) A tissue establishment provides a service to another establishment for which it is notauthorized .

d) A tissue establishment stores and distributes tissues and/or cells processed or treatedby a third party.

2. The tissue establishment shall evaluate the capacity of the third parties and selectthose that guarantee compliance with the standards established in this Royal Decree-Law.

3. Contracts should clearly specify the responsibilities of the third parties in relation to theprocesses to be carried out and a detailed description of these processes.

4. There shall be documented operating procedures specifying the manner of contracting,the relationships between the contracting parties and the protocols to be followed by each in relation to the contracted activity.

5. Tissue establishments shall have a register of contracts concluded with third parties, the information on which shall be available to the competent authority and the transplant coordination unit of the Autonomous Community concerned.

6. In the event of termination of the contract, the contracted entity must forward to the tissue establishment any data and samples that may affect traceability or the quality and safety of tissues and cells. The terms of this sample and information transfer must be detailed in the procurement procedure and must be included in the service contract.

7. Tissue establishments shall send copies of the contracts signed with third parties to thetransplant coordination unit and to the competent authority for the authorization of these activities in their autonomous community.

8. When the contracting of the third party involves access by the latter to personal data, the contract must comply with the provisions of article 12 of Organic Law 15/1999, of 13th December.

Article 25. *System for the collection and custody of information.*

1. Tissue establishments shall have in place a system for the collection and safekeeping of information relating to their activities that ensures the traceability of all tissues and cells processed. In case the system is in electronic format, back-up copies must be ensured.

2. There shall be a documented procedure for the collection and custody of information. The establishment shall designate a person to be responsible for the system for the collectionand custody of information on activities and shall communicate this designation to the transplant coordination unit and to the competent authority of the Autonomous Community in which it is located.

3. Tissue establishments shall send quarterly information on their activities to the transplant coordination unit and to the competent authority of the corresponding Autonomous Community and shall at all times have at the disposal of the latter their system for the collection and custody of information.

4. Importing tissue establishments shall maintain a record of their activities, including the types and quantities of tissues and cells imported, as well as their origin and destination. That record shall include the same information in relation to exceptional imports.

CHAPTER IV

Application of cells and tissues

Article 26. *Authorization of the application of tissues and cells in application centers or units.*

1. The application of human tissues and cells may only be carried out in those health centers or units duly authorized by the competent health authority in accordance with the general bases for the authorization of health centers, services and establishments established in Royal Decree 1277/2003, of 10th October, and provided that the minimum requirements and conditions set out in Annex I.4 of this Royal Decree-Law are met.

2. These establishments and health units must have a specific authorization for each tissue and cell application or implantation activity and for each type of tissues and cells. The competent health authority of each Autonomous Community shall determine the period of validity of the authorizations, which shall not be less than two years or more than four years, as well as the requirements for their possible renewal.

Any substantial modification in the conditions or requirements that led to the granting of the authorization must be notified to the competent health authority, and may lead to itsreview or even to the revocation of the authorization if the modifications entail a substantial alteration of the circumstances that justified the granting of the authorization.

3. Without prejudice to the specific regulations in this respect in each autonomous community, the application for authorization of the application shall be accompanied by a report with a detailed description of the means available to the center to carry out the activity requested and their adaptation to the provisions of this Royal Decree-Law. Likewise, the type of tissue or group of cells for which authorization is requested and the name and training of the person responsible for the implantation team shall be stated.

4. The competent health authority of the Autonomous Communities shall notify the National Transplant Organization in real time of the authorizations granted, refused and revoked.

5. The application of human tissues and cells shall require the consent of the recipient or their legal representatives in accordance with the provisions of Law 41/2002 of 14th November 2002.

Article 27 - *Access to tissues and cells and general conditions of application.*

1. Tissues and cells stored in tissue establishments shall be made available to tissue and cell application establishments or units for allogeneic use in therapeutic procedures with established medical indications in suitable recipients.

In the event that the tissue establishment that has processed and stored the tissues and cells does not have the necessary infrastructure for a complete typing of the tissues and cells to establish compatibility and suitability when necessary, it must send a sample to another duly authorized establishment that does have the appropriate infrastructure and that will be constituted as a reference establishment. The provisions of this Royal Decree-Law shall be taken into account in the distribution of tissues and cells.

2. Autologous application shall be limited to therapeutic procedures of proven efficacy in established medical indications.

In the case of processing activities for possible autologous uses for which there is no current established medical indication, the tissues and cells thus processed shall be available for allogeneic application as provided for in paragraph 1.

3. In the case of a tissue or cell group of limited availability, the data of patients waiting toreceive the implant will be centralized in the transplant coordination unit of the autonomous community and in the National Transplant Organisation.

4. The application for the tissue or cell group shall be made by the person in charge of theestablishment or unit of application to the person in charge of the tissue establishment. A validated copy of the approval as a implant or unit of application for that tissue or cell groupmust be attached to the application. The tissue establishment shall not distribute the tissue or cell group unless the above-mentioned copy is provided.

5. In the absence of tissue processing establishments in the Autonomous Community itself, or in the event that the authorized establishments do not have the tissue requested, the request will be addressed to the transplant coordination unit of that Autonomous Community, which will forward it to the National Transplant Organization for its search at national or international level.

Article 28. *System for the collection and custody of information.*

1. The establishments and units authorized for the application in humans of human tissues or cells must have a system for the collection and safekeeping of information on the activities carried out in this field, with restricted and confidential access, which will record the clinical uses and applications carried out with the data necessary for the identification of the recipients, the tissues and/or cells implanted and their origin, so as to allow adequate follow- up if necessary, in accordance with the provisions of Chapter V.

2. The centers and units authorized for the application of human tissues or cells shallsend quarterly information on their activities to the transplant coordination unit and to the competent authority of the corresponding Autonomous Community and shall at all times have their system for the collection and custody of information available to the latter.

3. Tissue and cell application establishments shall inform the tissue establishment, the importing tissue establishment or, where applicable, the procurement establishment that supplied the tissues and cells, of the final destination of the human application of thosetissues or cells and, in the event that the application does not take place, the reason why it was not possible.

Article 29. *Clinical research.*

1. Clinical research with cells and/or tissues may only be carried out in the procurement and application centers and units and tissue establishments duly authorized for the conductof the research activity.

2. Clinical research projects shall be authorized by the competent authority of the corresponding Autonomous Community. In order for authorization to be granted, the report of the experts appointed for this purpose by the Transplant and Regenerative Medicine Commission of the Interterritorial Council of the National Health System shall be mandatory.

3. Applications for authorization for clinical research projects involving cells and/or tissuesmust include at least the following information and documentation:

a) Justification and detailed description of the clinical research project.

b) Information on related clinical or basic research procedures and information on the tissues/cell groups to be used and the process of processing and/or transformation and utilization of these tissues/cell groups.

c) Designation of the coordinating center and professional responsible for the project acting as principal investigator and description of the research team(s).

d) Identification of the participating centers and units, both in the extraction and implantation phases.

e) Identification of tissue establishments when different from the procurement or implantation sites.

f) The authorizations of the heads of the centers involved.

g) The report of the ethics committee of the coordinating center of the project. If it is notan implantation center, the report of the ethics committees of the implantation centers involved will be required.

h) The informed consent document.
i) The insurance policy for patients where applicable.
j) The cost report of the project and of the promoting body.
k) The project's quality assurance system protocol.

4. The competent authority of each Autonomous Community must notify the National Transplant Organization every six months of those clinical research projects that are authorized and underway in their Autonomous Community.
5. The provisions of this article shall not be applicable to cases of clinical research in cell therapy, which shall be regulated in accordance with the provisions of Royal Decree 223/2004, of 6th February, which regulates clinical trials with medicinal products. In these cases, the Spanish Agency for Medicines and Health Products shall request a report from the National Transplant Organization.

CHAPTER V

Information, monitoring and bio surveillance systems

Article 30. *Register of human tissue procurement and application establishments and tissue establishments.*

1. The National Transplant Organization, without prejudice to the registration powers of the autonomous regional authorities, shall develop and maintain a register of tissue establishments, tissue importing establishments, and authorized human tissue and cell procurement and application units or centers, specifying for each of them the specific activities for which they are authorized. This register shall be accessible to the public.

2. The transplant coordination units of the Autonomous Communities must communicate in real time to the National Transplant Organization the information on tissue establishments, tissue importing establishments and centers or units for the procurement and application of tissues and cells that are authorized within the scope of their competence, in order to includeit in this register. This information must include at least the name and location of the authorized establishment, unit or establishment, the activities for which they are authorized, and the periods for which such authorizations are valid.

3. The National Transplant Organization will designate a technical person responsible forthe maintenance and custody of the register.

Article 31. *Register of hematopoietic progenitor donors.*

1. The National Transplant Organization, without prejudice to the registration competencies of the autonomous regional authorities, will be the competent body for developing and maintaining the register of hematopoietic progenitor donors comprising the aggregate information of the National Health System as a whole.

This register will be a single, public register and will be integrated, together with the donorcollection centers, into the National Health System. The Autonomous Communities will be responsible for donor recruitment, obtaining the progenitors for transplantation and, followinga report by the Transplant Commission of the Interterritorial Council of the National Health System, determining the number of donors susceptible to registration, which must in all casesbe adjusted to the transplant needs of the population.

2. The transplant coordination units of the Autonomous Communities must communicate in real time to the National Transplant Organization information on the hematopoietic progenitor donors included in their respective registers.

3. The head of the Ministry of Health, Social Services and Equality may entrust the management of this information to public or private entities that carry out their activity in the field of promotion and publicity in support of the donation of human tissues and cells.

Article 32. *General information system.*

1. The competent authorities of the Autonomous Communities shall determine the information required in accordance with the provisions of articles 13, 25 and 28 of this Royal Decree-Law, which shall at least include the minimum contents approved by the Transplant and Regenerative Medicine Commission of the Interterritorial Council of the National Health System.

2. The transplant coordination units or, where appropriate, the competent authorities of the Autonomous Communities, shall send the National Transplant Organisation, at least everysix months, the information collected in application of articles 13, 25 and 28 of this Royal Decree-Law.

The National Transplant Organization shall develop and maintain a system for the collection, custody and analysis of this information, to which the transplant coordination units of the Autonomous Communities shall have access under the terms agreed by the Transplantand Regenerative Medicine Commission of the Interterritorial Council of the National Health System.

3. The National Transplant Organization shall draw up an annual report containing information on tissue establishments, tissue importing establishments, units or centers for the procurement and application of human tissues and cells, as well as the activities carried out. This report, which in no case shall contain personal data referring to donors and recipients, shall be accessible to the public and shall be sent to all the establishments and units involved and shall include data of general interest to which due publicity shall be given.

4. The Ministry of Health, Social Services and Equality, through the National Transplant Organisation, shall collaborate with the European Commission and the other Member States of the European Union in the development of a network for the exchange of information between the national registers of tissue establishments, tissue importing establishments, and authorized human tissue and cell procurement centers or units.

5. Access to any of the data contained in the information systems regulated in this Royal Decree-Law shall be restricted to those persons authorized both by the technical heads of thetissue establishments and the heads of the tissue extraction or implantation units, and by the transplant coordination units or the competent authorities of the Autonomous Communities and, within the scope of their competence, by the National Transplant Organisation.

6. All information collection and filing systems must comply with the principles established in Organic Law 15/1999, of 13th December 1999.

Article 33. *Traceability.*

1. The National Transplant Organization and the transplant coordination units of the Autonomous Communities shall establish, under the terms agreed by the Transplant and Regenerative Medicine Commission of the Interterritorial Council of the National Health System, an origin-to-destination tracking system for all human tissues and cells obtained for the purpose of application in humans. This system shall contain the information referred to in Annex VI.

2. In the case of embryonic cells of eventual application in humans, the National Transplant Organization and those responsible for the National Cell Line Bank and the Commission for the Monitoring and Control of the Donation and Use of Human Cells and Tissues shall establish a system that guarantees the monitoring foreseen in the previous section.

3. The information, where appropriate, shall be coded in accordance with the basic standards regulated in Annexes VI and VII, which will allow for uniform traceability. Tissue establishments and tissue and cell procurement and application units and establishmentsshall collect the information in real time.

4. Tissue establishments shall collect information on the destination of tissues and cells distributed for human applications. Such information shall be provided by the tissue and cell establishments, agencies or application units on a case-by-case basis in order to ensure the traceability of tissues and cells.

5. Origin to destination traceability shall apply not only to cell and tissue products, butalso to products and materials that come into contact with those cells and tissues and may have an effect on their quality and safety.

6. The National Transplant Organization, in coordination with the Autonomous Communities, shall ensure that tissues and cells can be traced, in particular through documentation and the use of the single European code, from procurement to human application or disposal and vice versa. Tissues and cells used for advanced therapy medicinal products must be traceable in accordance with this Royal Decree-Law, at least until they are transferred to the manufacturer of advanced therapy medicinal products.

7. The National Transplant Organisation, in coordination with the Autonomous Communities, shall ensure that tissue establishments and organizations responsible for human application keep the data set out in Annex VI securely for at least 30 years in an appropriate and readable storage medium.

8. In the case of tissues and cells that have been recovered from a deceased donor by procurement teams working for two or more tissue establishments, the National Transplant Organisation, in coordination with the Autonomous Communities, shall ensure an appropriate traceability system throughout the procurement.

Article 34. *European coding system.*

1. The single European code will be applied to all tissues and cells distributed in Spain forhuman applications.

For all other situations where tissues and cells are released into circulation, the donation identification sequence of that code, as a minimum, shall be applied in the accompanying documentation.

2. The provisions of the preceding paragraph shall not apply to:

a) The donation of reproductive cells between partners.

b) The import or export of human tissues and cells with prior and direct authorization fromthe competent authority, provided that it is for direct distribution for immediate transplantation to the recipient, and provided that the supplier has the authorization for such activity.

c) The importation of tissues and cells authorized directly by the competent authority or authorities in case of emergency.

d) Tissues and cells other than reproductive cells for donation between partners, where such tissues and cells remain in the same establishment.

e) Tissues and cells that are imported into the European Union, where such tissues and cells remain in the same establishment from importation to application, provided that the establishment encompasses a tissue establishment authorized to carry out import activities.

3. The format and structure of the Single European Code are set out in Annex VII.

4. The application of the single European code does not exclude the additional application of other codes in accordance with the requirements of our legal system.

Article 34a. *Obligations of tissue establishments relating to the implementation of the singleEuropean code.*

Tissue establishments, including importing tissue establishments, shall:

a) Assign a single European code to all tissues and cells that require the application of such a code before being distributed for human application.

b) Assign a donation identification sequence upon procurement of the tissues and cells,or upon receipt from a procurement organization, or upon import from a third country supplier.The donation identification sequence shall include:

1. º Your European Union tissue establishment code, as assigned in the EU Tissue Establishment Compendium.
2. º A unique donation number assigned by the tissue establishment, unless this number is a globally unique number such as those used by the ISBT128 coding system. In the case of reproductive cells, the allocation of the unique donation number shall be established by the Ministry of Health, Social Services and Equality on a centralized basis at national level. Where permitted, in the case of pooling of tissue and cell batches, a new donation identification number shall be assigned to the final product. The tissue establishment in which the batching takes place shall ensure the traceability of individual donations.
a) Do not alter the donation identification sequence once it has been allocated to circulated tissues and cells, unless necessary to correct a coding error; any correction requires proper documentation.
b) Use one of the permitted product coding systems, in this case the corresponding tissue and cellular product numbers listed in the EU Compendium of Tissue and Cellular Products or, failing that, ISBT128, before they are distributed for human application.
c) Use an appropriate sublot number and expiry date. For tissues and cells for which no expiry date has been defined, the expiry date shall be no later than 00000000 before distribution for human application.
d) Apply the unique European code on the label of the product concerned in an indelible and permanent manner and mention this code in the relevant accompanying documentation prior to distribution for human application. The tissue establishment may entrust this task to a third party or parties, provided that the tissue establishment ensures compliance with this Royal Decree-Law, in particular as regards the uniqueness of the code. In the event that the size of the label prevents the application of the single European code on the label, the code will be unambiguously linked to the tissues and cells packaged with such a label in the accompanying documentation.
e) Inform the competent authority when:
f) - There is a need to update or correct information contained in the EU Compendium of Tissue Establishments.
g) - The EU Compendium of Tissue and Cellular Products requires updating.
h) - The tissue establishment identifies significant non-compliance with the requirements relating to the Single European Code for tissues and cells received from other EU tissue establishments.
i) Take the necessary measures in case of incorrect application of the single European code on the label.

Article 34b. *Proceedings by the competent authorities relating to the implementation of the Single European Code.*

1. The competent authorities shall take the following actions:

a) Ensure the allocation of a unique tissue establishment number to all tissue establishments authorized in Spain.

If a tissue establishment has different physical locations but only one system for assigning unique donation numbers, it may be considered to be one and the same tissue establishment.

If a tissue establishment uses two or more systems to allocate unique donation numbers, that entity shall be assigned different tissue establishment numbers corresponding to the number of allocation systems used.

a) Monitor and ensure the effective implementation of the Single European Code in Spain.

b) Ensure validation of the data on tissue establishments contained in the EU Compendium of Tissue Establishments for Spain and update the Compendium without undue delay, in particular in the following situations:

1. º When a new tissue establishment is authorized.

2. º When the information on the tissue establishment changes or is not correctly recorded in the EU Compendium of Tissue Establishments.

3. When the details of the authorization of a tissue establishment listed in Annex IX change, inter alia:

1. authorization of a new type of tissue or cell.

2. authorization of a new prescribed activity.

3. details of any conditions or exceptions to be added to an authorization. 4. The suspension, partial or total, of a specific authorization of an activity, specific tissue or cell type.

5. the partial or total revocation of the authorization of a tissue establishment. 6. situations in which the tissue establishment voluntarily ceases to operate, in whole or in part, the activity or activities for which it has been authorized.

Without undue delay means within a maximum of ten working days for any change that substantially affects the authorization of the tissue establishment concerned.

Where a tissue establishment is authorized by two or more competent authorities for different types of tissues and cells, or for different activities, each competent authority shall update the information relating to those activities for which it is responsible.

a) Alert the competent authorities of another Member State when they detect incorrect information in the EU Compendium of Tissue Establishments in relation to the other Member State or when they detect a situation of significant non-compliance with the provisions relating to the Single European Code in relation to the other Member State.

b) Alert the Commission and other competent authorities when, according to their assessment, an update of the EU Compendium of Tissue and Cell-based Products is necessary.

Article 35. *Biosurveillance system.*

1. From the entry into force of this Royal Decree-Law, a bio-monitoring system will be in operation that will enable the notification, recording and transmission of information on serious adverse effects and reactions that may have influenced or may influence the quality and safety of tissues and cells and that may be attributed to the processes of procurement, testing, processing, storage and distribution of tissues and cells, as well as any serious adverse reaction observed during or following the clinical application of tissues and/or cells, and which may be related to their quality and safety.

2. Until otherwise regulated, the transplant coordination network of the Autonomous Communities and the General State Administration will function as a biosurveillance network.

3. All establishments or units that procure and apply cells or tissues as well as tissue establishments shall report the existence of any adverse event or reaction in the manner and under the terms set out in Annex VIII, through the above-mentioned transplantation coordination network.

4. Tissue establishments processing or preserving tissues that may be affected by a serious adverse event or reaction must issue a detailed report on the possible causes and consequences, as well as on the measures taken and to be taken.

For their part, importing tissue establishments shall promptly report to the competent authority any suspected or actual serious adverse reactions or serious adverse events thatare brought to their attention by suppliers in third countries and that may influence the quality and safety of the tissues and cells they import. The information referred to in Annex VIII shall be included in such communications.

5. The National Transplant Organization is responsible for notifying the existence ofserious adverse events that could affect other Member States through the notification system established by the European Commission. Likewise, it shall notify the Autonomous TransplantCoordination Units where the tissue establishments affected or that could be affected by a serious adverse event occurring in another country are located of all the information relatingto said event.

6. Tissue establishments are responsible for ensuring that a rapid, accurate and verifiable procedure is in place to recall from distribution any product that may be associated with a serious adverse event.

CHAPTER VI

Inspection, evaluation and accreditation and infringements and sanctions

Article 36. *Inspection and evaluation.*

1. The competent authorities of the Autonomous Communities shall carry out periodic inspections to ensure that the tissue establishments authorized under their jurisdiction complywith the requirements of this Royal Decree-Law and apply the quality control measures required by this Royal Decree-Law.

2. The Interterritorial Council of the National Health System, through its Commission on Transplants and Regenerative Medicine, shall approve a plan of inspections at the initiative ofthe National Transplant Organization and the transplant coordination units of the AutonomousCommunities, which shall include the periodic inspections envisaged in the previous section.

3. The Transplant and Regenerative Medicine Commission shall submit for report to the Interterritorial Council of the National Health System the general criteria that ensure that the conditions for carrying out the inspections, the control measures and the training and qualification of the professionals in charge of them, are carried out with a minimum and homogeneous level of competence and results.

4. The interval between two regular inspections shall be two years.

5. The competent authorities of the Autonomous Communities shall organize the extraordinary inspections and the implementation of the control measures they deem necessary in the event of a serious adverse event or reaction. They shall also organize inspections.

6. The Commission shall take extraordinary measures and apply control measures where necessary, at the justified request of the competent authority of another Member State of the European Union, or of the Commission.

7. The inspection will not only affect tissue establishments but also all third parties with whom there are contractual relations, and will involve the examination, evaluation and verification of any infrastructure, equipment, information, document or register related to what is regulated in this Royal Decree-Law.

8. Requests for extraordinary inspections by another Member State or the Commission shall be channeled through the National Transplant Organization, which shall also be responsible for forwarding the report on the outcome of the inspection and the control measures implemented to the requesting State or the Commission.

Article 36a. *Inspection and other control measures on tissue establishments, importers and suppliers from third countries.*

1. The competent authorities shall organize inspections and other control measures at importing tissue establishments and, where appropriate, at their third country suppliers. The importing tissue establishments shall also carry out appropriate controls in order to ensurethe equivalence of the quality and safety standards of the tissues and cells to be importedwith the standards laid down in this Royal Decree-Law. The interval between two inspections of a given importing tissue establishment may not exceed two years.

2. Such inspections shall be carried out by officials representing the competent authority, who shall:

a) Be empowered to inspect the tissue establishments of importers and, where appropriate, the activities of third country suppliers.

b) Evaluate and verify the procedures and activities carried out in the importing tissue establishments and in the facilities of third country suppliers that are relevant to ensure the equivalence of the quality and safety standards of the tissues and cells to be imported withthe standards laid down in this Royal Decree-Law.

c) Examine any documents or other records relevant to such assessment and verification.

3. The Ministry of Health, Social Services and Equality, through the National Transplant Organization, in coordination with the Autonomous Communities, upon duly justified request from another Member State or the Commission, shall provide information on the results of inspections and control measures in respect of importing tissue establishments and third country suppliers.

4. The Ministry of Health, Social Services and Equality, through the National Transplant Organization, in coordination with the Autonomous Communities, following a duly justified request from another Member State in which the imported tissues and cells are to be subsequently distributed, shall carry out inspections or other control measures, taking appropriate measures after consultation with the Member State that made the request, at the importing tissue establishments and with regard to the activities of third country suppliers.

5. In cases where an on-site inspection is carried out following a request from another Member State, the Ministry of Health, Social Services and Equality, through the National Transplant Organization, in coordination with the Autonomous Communities, must decide, in agreement with the competent authority of the Member State that made the request, whether and how the latter should participate in the inspection. The final decision on such participationrests with the Ministry of Health, Social Services and Equality, through the National Transplant Organization, in coordination with the Autonomous Communities, if the importing tissue establishment is within their territorial jurisdiction. The reasons for a refusal of such participation must be explained to the requesting Member State.

Article 37. *Assessment and accreditation of excellence of centers and services.*

1. The competent authority of each Autonomous Community shall carry out the evaluationand accreditation programs of tissue and cell procurement, processing, distribution and implantation establishments and services in accordance with the criteria referred to in the following section.

2. The Transplant and Regenerative Medicine Commission will submit for report to the Interterritorial Council of the National Health System the general criteria on the conditions for the evaluation and accreditation of centers and services. The competent authority of each Autonomous Community will periodically report to the National Transplant Organization, at least annually, on the evaluation and accreditation activity of the centers and services and their results.

3. In accordance with the provisions of article 70.2.d) of Law 14/1986, of 25 April, the National Transplant Organization, subject to the agreement of the Transplant and Regenerative Medicine Commission of the Interterritorial Council of the National Health System, may act as a technical entity for the evaluation and accreditation of the centers and services authorized under the provisions of this Royal Decree-Law.

Article 38. *Infringements and penalties.*

Without prejudice to other regulations that may be applicable, infringements committed against the provisions of this Royal Decree-Law and its implementing provisions shall be considered as health infringements, in accordance with the provisions of Chapter VI of Title I of Law 14/1986, of 25 April, and other applicable provisions.

The provisions of Title VII of Organic Law 15/1999, of 13th December, shall apply to infringements relating to the use of files containing personal data.

Single transitional provision. *Retroactivity of the rule.*

This Royal Decree-Law shall apply to legal situations that have arisen and to procedures initiated prior to its entry into force, except with regard to provisions imposing penalties that are not favorable or that restrict individual rights.

Sole repealing provision. *Repeal of legislation.*

Any provisions of equal or lower rank that oppose the provisions of this Royal Decree-Law are hereby repealed.

First final provision. *Title of competence.*

This Royal Decree-Law is of a basic nature and is issued under the protection of the provisions of Article 149.1.16 of the Constitution, which grants the State competence over thebases and general coordination of health. Exceptions to the above are Article 23, which is enacted under the exclusive competence of the State in matters of foreign health, and Article 29, which is enacted under the provisions of Article 149.1.15, which grants the State exclusive competence in matters of promotion and general coordination of scientific and technical research.

Second final provision. *Transposition of European Union law.*

This Royal Decree-Law transposes into Spanish law Directive 2004/23/EC of the European Parliament and of the Council of 31st March 2004 on setting standards of quality andsafety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells; Commission Directive 2006/17/EC of 8th February 2006implementing Directive 2004/23/EC of the European Parliament and of the Council as regardscertain technical requirements for the donation, procurement and testing of human tissuesand cells; and Commission Directive 2006/86/EC of 24th October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse events and reactions and certain technicalrequirements for the coding, processing, preservation, storage and distribution of human tissues and cells.

Third final provision. *Power of development and modification.*

The Government is empowered to issue the provisions necessary for the development and application of this Royal Decree-Law. Likewise, the head of the Ministry of Health, Social Services and Equality is empowered to modify the annexes of this Royal Decree-Law.

in order to bring them into line with advances in scientific and technical knowledge or to adaptthem to Community legislation.

Fourth final provision. *Entry into force.*

This Royal Decree-Law shall enter into force on the same day of its publication in the Official Gazette."Official State Gazette.

Given in Madrid, on 4 July 2014.

FELIPE R.

The President of
the Government,
MARIANORAJOY
BREY

ANNEX I

Minimum requirements and conditions for the authorizations of tissue establishments and tissue and cell procurement establishments/units and tissue and cell procurement and application units

1. The minimum requirements and conditions for the authorization of health establishments for the procurement of human tissues and cells for human use are:

a) Have a medical-surgical unit specialized in the removal of the tissue or cell group tobe harvested. The person responsible for the harvesting procedure shall be designated in each case.

b) In case the use or destination of the cells or tissues is an immediate or non-deferred transplantation, there must be an established relationship with the transplantation coordination team.

c) Where the destination of the retrieved tissues or cells is referral to a tissue establishment for processing, there must be a collaboration agreement, including a protocol agreed with that establishment, setting out the conditions for procurement, preparation and transport of the tissues or cells until their arrival at the processing establishment.

d) When the destination of the cells or tissues is their transformation, there must be a collaboration agreement with the entity responsible for such transformation that is known and authorized by the competent authority of the corresponding Autonomous Community.

e) Have the appropriate infrastructure and personnel in place for the correct evaluation of the donor and ensure that the relevant studies are carried out to rule out the presence of transmissible diseases, as stipulated in Annexes II, III and IV. The person responsible for the donor evaluation procedures shall be designated.

f) Have a standard operating procedure in place for the correct verification of:

1.º The identity of the donor.

2.°The authorization requirements.

3.°The selection and assessment criteria.

4. °The performance of the laboratory tests required for evaluation and selection.

g) Have the necessary facilities and means to guarantee the conditions for the collection, preparation and transport of the cells or tissues, in accordance with the protocol referred to in paragraph c).

h) Have adequate facilities and means to ensure the restoration and preservation of the corpse, as well as mortuary practices, in the event that the removal is carried out on a deceased person.

i) Have documented relationships and conditions of retrieval with related tissue and cell processing and/or implantation establishments, which must be communicated to the competent authority.

j) To have a system for the collection and custody of information relating to its activities, with restricted and confidential access, which will record the extractions carried out and the necessary data on the donors, cells or tissues, as well as their final or intermediate destination. Data on the tests performed and the characteristics of the donors shall be kept, specifying the date on which the tests were performed and the results of the tests, in such a way as to allow appropriate follow-up of the information, if necessary, in accordance with the provisions of Articles 13 and 31.

k) Maintain an archive of sera from allogeneic or potentially allogeneic donors (samples collected for hypothetical autologous use with no current therapeutic indication) for at least 10years from the last clinical application or expiry date of the cells/tissues, in order to

perform biological controls if necessary. In the case of reproductive cells, the serum file shall be kept for two years from the last transfer.

l) Have a standardized operating procedure for packaging, labelling and transport of cells and/or tissues to the point of destination (tissue establishments and transplantation teams in the case of direct distribution).

2. The technical requirements for approval as a tissue establishment are as follows:

a) In terms of organization and direction:

1.º In addition to the Director of the establishment, a technical manager must be appointed in accordance with Article 17.

2.º To have an appropriate organizational structure and operating regime which clearly defines the reporting relationships and responsibilities of each job, and which is appropriate tothe activities for which authorization is requested.

3.º There must be standard operating procedures for all activities for which authorization is sought.

4.º The tissue establishment must be equipped with a medical team or have available access to medical support that can review, supervise, analyze and, if necessary, promote certain changes in the establishment's medical activities, such as: donor selection, risk assessment of tissues/cells, availability of tissues or cells in exceptional cases, review and evaluation of the follow-up of tissues/cells distributed for application or relations with application centers or units, among others.

5.º They must have a quality management system applied to all the activities for whichthe tissue establishment is eligible for authorization under the conditions laid down in Article 16.

6.º Procedures must be in place to minimize the risks inherent in the handling of biologicalmaterial while maintaining an adequate level of quality and safety of tissues and cells. All technical activities of the establishment's tissue and cell processing, environmental conditionsand the hygienic and sanitary conditions of the establishment's personnel must be covered here.

7.º A documented procedure must be in place to ensure the identification of all tissuesand cells at any stage of the activity for which authorization is sought. This identification procedure must be compatible with the state coding system set out in Chapter VI.

b) In terms of staff:

1.º Have sufficient personnel sufficiently prepared to carry out the activities for whichauthorization is requested.

2.º Have a detailed description of the job profile, tasks, responsibilities and relations withother jobs.

3.º Have a continuous training program for the personnel of the tissue establishment that ensures that each worker:

i) Has sufficient competence to perform the tasks entrusted to him/her.

ii) Has the appropriate knowledge and experience to understand the technical scientificprocesses involved in the tasks assigned to him/her.

iii) He/she knows the organizational structure, the operating regime and the qualitysystem of the establishment.

iv) Knows the establishment's hygiene and sanitary regulations in relation to the activitiescarried out there.

v) Is adequately informed of the ethical and legal aspects and standards of good practicein relation to the establishment's activities.

c) In terms of equipment and material:

1.º All equipment and material used must be specifically designed and maintained for the purpose intended, minimizing any risk to recipients or staff working in the establishment.

2.º Critical equipment must be identified as such. It must be inspected periodically and/or regularly and appropriate preventive measures must be taken in accordance with the manufacturer's instructions. When the equipment may affect critical processes or parameters marking storage or preservation conditions (temperature, pressure, particle counting, contamination levels, etc.), it must be identified as such. In such cases, the most appropriate monitoring, control and warning systems, alarms and corrective measures required to detecta malfunction, the danger of an unacceptable deviation or a defect shall be established and it shall be ensured that critical parameters are maintained within acceptable limits at all times.

3.º All new or repaired equipment must be assessed at the time of installation and validated before use. Information relating to all the results of these evaluations must be collected and stored.

4.º Maintenance, cleaning, disinfection, sanitization and servicing of critical equipment shall be documented in documented procedures, carried out on a regular basisand information on the performance of these procedures shall be collected and stored appropriately.

5.º Documented procedures must be in place for the operation of each critical piece of equipment detailing the actions to be taken in the event of malfunction or failure.

6.Operating procedures for the activities for which authorization is sought must include specifications for critical equipment and reagents. Specifications for additives (i.e. solutions) and packaging materials shall be included. Reagents and critical materials must comply with the specifications of Royal Decree 1591/2009, of 16th October, which regulates medical devices, and Royal Decree 1662/2000, of 29th September, on medical devices for in vitro diagnostics.

d) In terms of infrastructure and premises:

1.º To have the premises and infrastructures necessary to carry out the activities for whichauthorization is requested.

2.º Where these activities involve the processing of cells or tissues under open exposure conditions, the air quality and cleanliness conditions they require to minimize the risks of contamination including cross-contamination must be specified. The effectiveness of the measures necessary to meet these conditions must be validated and monitored.

3.° Except in the cases specified in point 4, whenever cells or tissues are to be processedin open exposure and without a subsequent microbiological inactivation procedure, a microbiological colony and particulate air quality equivalent to that specified as grade A in Annex I of the European GMP Guide shall be required at the place of processing. Ambient airin the rest of the working area shall be required to be of a quality suitable for the activities to be carried out, but at least equivalent to Grade D of the European GMP Guide for particulate and microbiological colony count.

4.º Less stringent environmental conditions than those specified in point 3 may be permitted in the following cases:

i) When validated microbiological sterilization or inactivation procedures are to beapplied.

ii) Where it is demonstrated that exposure to grade A ambient air has detrimental effectson the biological properties required of the tissue/cell group concerned.

iii) Where it has been demonstrated that the route or procedure of application of the cells or tissues involves a significantly lower risk of transmission of bacterial or fungal diseasesthan the transplantation of cells or tissues.

iv) When it is not technically possible to carry out the processing of the cells or tissues ina grade A environment, e.g. when the operating conditions of the equipment required are not compatible with a grade A environment.

5.º When any of the cases in section 4 are apply, the conditions of the ambient air in which work is to be carried out must be specified and it must be demonstrated and documented that the required standards of quality and safety of the tissues are achieved under these conditions, bearing in mind the therapeutic object or application and the route or mode of application of the cells and/or tissues and the immunological situation of the recipient. Adequate equipment and clothing must be available, both for personnel protection and for hygiene in all departments where required and must be accompanied by the corresponding written rules of hygiene and use.

6.º When the activities for which authorization is requested involve the storage of cells or tissues, the storage conditions shall be specified and defined in each case, including the ranges of those parameters that are relevant to the maintenance of the properties of the cells or tissues, such as temperature, humidity, or air quality.

7.º Measurements of parameters that are critical must be monitored and controlled and recorded in order to be able to demonstrate that the specifications of the storage conditions are met.

8.º A storage infrastructure must be in place that clearly separates and distinguishesthose tissues and cells that are in quarantine from those that have been rejected, or thosethat have been accepted and are available, in order to prevent cross-contamination and sample mixing. Depending on the tissue or cell, physically separate areas or a secure segregation system may be required but, in any case, the system must be specified and must meet the basic standard of preserving biological, safety and quality conditions.

9.º There should be procedures and standards for access to the establishment's premises, for internal circulation, for hygiene and maintenance, for the disposal of rubbishand soiled or waste material and for the restoration of all services following an emergency situation. These procedures shall be monitored.

e) With regard to documentation, its collection and safekeeping:

1.º All standard operating procedures for the activities for which authorization is sought must be adequately recorded, and documentation must be adequately stored and safeguarded. There must be a system in place to ensure this. The documents must be reviewed periodically, and the procedures must always be in accordance with the basicspecifications of this Royal Decree-Law. The system will ensure that the work is standardized and that all phases can be traced: coding, evaluation of the cells or tissues and the environment where appropriate, procurement, processing, preservation, storage, availability, transport and distribution, and that all aspects related to quality control and management arekept in mind.

2.º Equipment, materials or personnel involved in critical activities must be properly identified and this identification must be documented.

3.º Any changes to operating procedure documents or performance standards must be reviewed, dated, documented and implemented without delay by authorized personnel.

4.º A system shall be in place to ensure that documents are regularly reviewed, that changes are recorded and that only updated versions are in use.

5.º Documentation should be recorded in a way that is a correct and reliable representation of the results.

6.º Records must be legible and indelible; they may be on paper or transferred to any other validated system such as a computer medium or microfilm.

f) In terms of quality systems:

1.º Audits shall be carried out no less frequently than every two years to review all the activities for which tissue establishment has been authorized. The objective of the audits is to verify that work is carried out in accordance with the approved protocols and the requirements of this Royal Decree-Law. Both the findings and the corrective measures must be documented.

2.º The discovery of deviations from the quality standards that have been established will require an investigation to be carried out, which must be documented and include decisionsor suggestions on possible preventive or corrective measures.

3.º The fate of cells and tissues that fall under the definition of "non-conformity" shall be decided in accordance with procedures previously established and supervised by the line manager and the quality area manager. All cells and tissues affected by non-conformities must be identified and accounted for.

4.º Corrective actions shall be initiated and completed in a timely and effective manner.

Allpreventive and corrective actions shall be documented and evaluated for effectiveness.

5.º The quality management system shall be reviewed and there shall be a procedure in place to enable this to be done with the aim of ensuring continuous and systematic improvement of the tissue establishment's performance.

6.. The requirements for the authorization of activities, processing, storage and distribution of tissues and cells are as follows:

a) In terms of processing:

1.º Critical tissue and cell processing processes must be validated. In no case must the tissues and cells be dangerous to the recipient or potentially ineffective. This validation shall be based on studies conducted by the tissue establishment itself or on published data or on the evaluation of the clinical results of the tissues and cells that have been distributed by the establishment in the case of tissue transformation or preparation processes that are consolidated.

2.º It must be demonstrated that validation processes can be carried out in the tissue establishment in an effective and systematic way.

3.º Procedures must be documented as standard operating procedures, hereinafter SOPs, and in accordance with section 2.e), and it must be ensured that activities are carried out in accordance with these SOPs.

4.º Where a microbiological inactivation procedure is to be applied, it must be documented, specified and validated.

5.º Before any changes are made to the processing activities, the modified process must be validated and documented.

6.º Processing activities should be evaluated on a regular basis, to ensure that thedesired results are met.

7.º Activities to discard cells and tissues that do not meet the required standards must be carried out in a manner that avoids contamination of other cells and tissues, personnel, equipment or premises, as well as environmental contamination.

b) Regarding storage:

1.º There must be an inventory system for tissues and cells designed to ensure that they cannot be distributed until all the requirements of this Royal Decree-Law have been met. There must be a SOP detailing the circumstances, responsibilities and procedures for the release and subsequent distribution of tissues and cells.

2.º All storage procedures shall be carried out under controlled conditions so as to ensurethe authenticity, quality and safety of tissues and cells.

3.º There shall be means of environmental control of the conditioning and storage areasin order to avoid any situation that could adversely affect the functionality, integrity or biological conditions of cells and tissues.

4.º The maximum storage time must be specified for each type of tissue or cell and storage condition. The period determined must take into account among other things the possible deterioration of the properties of cells and tissues as well as their intended use.

5.Tissues and cells stored at all stages of processing in the tissue establishment must be clearly identifiable and it must be possible to clearly distinguish between those tissues and cells that are in quarantine and those that are ready for distribution or to be discarded.

6.º The information records must clearly record all data relating to development and processing so that compliance with the specifications of this Royal Decree-Law can be demonstrated prior to the release and distribution of the tissues and cells. All medical data, results of evaluation tests, processing data for all cases where an SOP was necessary must be available, it must be ensured that this has been carried out rigorously by the persons

authorized to do so, and also that all records of the controls of the storage conditions are available.

If at any time, a computer system is responsible for releasing or making available any laboratory test results or validation results, there should be a traceability system that can provide information to the auditor on who is responsible for releasing such information.

7.º The line manager as defined in Article 17 must approve a risk assessment document that determines the fate of all stored tissues and cells. This document shall take into account the donor evaluation and the selection and acceptance criteria of the test results performed, as well as any modifications to the processing steps that may improve the safety and qualityof the tissues and cells.

c) In terms of distribution and removal:

1.º The conditions and maximum transport time must be defined, which allow the biological and functional properties of the cells and tissues to be maintained.

2.º The container must be secure and ensure that the cells and tissues are maintained at the specified conditions. All packaging containers and containers must be validated for the intended purpose.

3.º When distribution is carried out by a third party, there must be an agreed contract document that ensures that the required transport conditions are maintained.

4.º Personnel within the tissue establishment must be designated to be in charge of the recall, to indicate the reasons and need for recall, and to initiate and coordinate the necessary recall activities.

5.º There must be a documented procedure setting out the system for effecting recalls, which must include a clear assignment of responsibilities and actions to be initiated. A corresponding modification according to Annex VII should be included.

6.º Actions must be undertaken within predefined timeframes and must include the tracingand tracking of all tissues or cells that may be involved, with the aim of tracing any donor that may have contributed to an adverse reaction or unwanted effect and recalling all tissues and cells that have been procured from that donor, as well as notifying the consignees and recipients of that donor's tissues and cells who may be at risk.

7.º There must be documented procedures for the handling of tissue and cell requests. The rules for distribution to patients or implanting bodies or establishments must be documented and accessible to those involved on request.

8.º There must be a documented system for the management of tissues or cells returned to the tissue establishment, including inventory acceptance criteria if applicable.

d) On labelling:

1. The tissue establishment must have a labelling system in place to ensure that labels or documents comply with the following information requirements:

i) The labelling of the primary cell/tissue container must show:

1) The identification number or code of the tissue/cell, the type of cells or tissues and the batch where applicable.

2) Identification of the tissue establishment.

3) The expiry date.

4) In the case of autologous use, this must be specified: "for autologous use". In addition,the donor/recipient identification code shall be displayed.

5) In the case of directed donations, the recipient shall be identified.

6) When cells/tissues are known to be positive for any marker of infectious disease, they shall be identified as risk samples: 'biohazard'.

7) The single European code applicable to tissues and cells distributed for human

applications or the donation identification sequence applicable to tissues and cells put into circulation but not distributed for human applications.

If any of the information referred to in points 4, 5 and 7 cannot be included on the label of the primary container, it shall be provided on a separate sheet to be attached to the primary container. This sheet shall be packaged with the primary container in such a way as to ensurethat they remain together.

ii) The following information may be provided on the label or in an accompanying document:

1) Description, definition and, if relevant, dimensions of the tissue or cell product.
2) Morphology and functional data where relevant.
3) Date of cell/tissue distribution.
4) Biological determinations that have been carried out on the donor and their results.
5) Storage recommendations.
6) Instructions for opening the container, for packaging and for any handling orreconstitution.
7) Expiry dates after opening or handling of the container.
8) Instructions for reporting adverse effects or reactions.
9) Presence of potentially hazardous waste (antibiotics, ethylene oxide, etc.).
10) For imported tissues and cells, the country of procurement and the exporting country(if different from the country of procurement).

iii) External labelling for the shipping or transport container.

For shipment, the primary container must be enclosed in an appropriately labelled transport container. This label shall contain at least the following information:

1) Identification of the tissue establishment of origin, including address, telephone number and contact person.
2) Identification of the tissue implantation establishment or tissue establishment of destination, including address, telephone number and contact person.
3) The finding that the package contains human tissues or cells and must be handled withcare.
4) If live cells are shipped and the maintenance of viability is essential for the success of the engraftment, such as hematopoietic progenitors, stem cells, gametes or embryonic cells, the notice "DO NOT IRRADIATE" must be added in a clearly visible place.
5) Recommendations for transport conditions (position, temperature etc.).
6) Safety instructions.
7) Methods of freezing or thawing or any other necessary handling where applicable.

4. The specific requirements for authorization as centers or human tissue implantationunits, depending on the activity to be carried out, are as follows:

a) Hematopoietic progenitor implantation activities, including the implantation of hematopoietic precursors from bone marrow, peripheral blood, umbilical cord or other sources.

1.º The following are established as specific minimum common requirements for the centers to obtain authorization for the three types of transplant mentioned:

1) To have specialized medical staff with accredited experience in bone marrow transplantation.
2) Ensure the availability of a physician with proven expertise in the diagnosis and treatment of bone marrow transplant complications.
3) Having nursing staff trained in this type of care.

4) It must have an Intensive Care Unit, a Diagnostic Imaging Service with the availability of appropriate techniques and adequate general laboratories.

5) Have an adequate anti-infective isolation area.

6) To have a Hematology-Hemotherapy Service or Unit or Blood Bank, which will be responsible for adequate hemotherapy support, mechanized cytapheresis and the collection, cryopreservation and storage of hematopoietic progenitors.

7) Have a Pharmacy and/or Nutrition Service or Unit trained in the preparation of solutions for enteral or parenteral nutrition adjusted to the situation of the patients.

8) To be equipped with an Anatomical Pathology Laboratory with the technical and humanresources necessary for the diagnosis of complications associated with transplantation and tobe able to carry out possible post-mortem studies.

9) To have a microbiology laboratory where the infectious complications presented by patients can be monitored.

2.º Within this group of activities and depending on the different types of transplant for which authorization is requested, the centers will have to comply with the following requirements in addition to all of the above:

1) The authorization of centers to carry out allogeneic transplants will be conditionalupon a minimum number of procedures per year to be determined by the Transplant and Regenerative Medicine Commission of the Interterritorial Council of the National HealthSystem.

2) For the performance of allogeneic implants from family donors, the center must comply, in addition to the common specific requirements and those set out in the previous section, with the following requirements:

i) Have an in-house or contracted histocompatibility laboratory with the capacity to determine major histocompatibility complex (MHC, HLA) polymorphism for A, B, C, DR and DQ loci at low or high resolution.

ii) Have an insulation area that at least applies a reverse insulation system.

3) For allogeneic implants from unrelated donors, the center, in addition to the above requirements (autoimplants and bone marrow implantation from family donors) must guarantee the availability of a histocompatibility laboratory with the capacity to determine theA, B, C, DRB1 and DQ loci by high-resolution DNA.

4) Osteo-tendinous tissue implantation activities: have a specialized Surgical Unit with at least one specialist with proven experience in such transplants.

b) Skin implantation activities: have a specialized Surgical Unit with at least one specialist with proven experience in skin transplantation.

c) Activities involving the implantation of heart valves: to have a specialized surgical unit with extensive and recognized experience in extracorporeal circulation interventions, as well as at least one professional with proven experience in valve implantation.

d) Vascular segment implantation activities: have a surgical unit with at least one specialist with experience in such transplants.

e) Ocular tissue implantation activities, including corneas, limbocorneal, sclera and other ocular tissues: have a specialized surgical unit with at least one specialist with experience in such transplants.

f) Cell group implants: to have the unit and equipment necessary to carry out the specific implants in question.

ANNEX II

Clinical requirements for the evaluation of tissue and cell donors

1. Deceased donors.

1.1. General exclusion criteria: In general, potential donors who meet any of the following criteria will not be considered valid donors:

a) Cause of death unknown, except in cases where an autopsy can be performed and theautopsy shows that no grounds for exclusion are found in the body.

b) History of unaffiliated disease.

c) Ingestion of or exposure to a toxicant that can be transmitted, at toxic doses, to the recipient via tissues or cells (cyanide, lead, mercury, gold, etc.).

d) Presence or history of malignant disease, except for primary basal cell carcinoma, carcinoma in situ of the uterine cervix and some of the primary tumors of the central

nervoussystem where scientific evidence tells us that the risk of transmission is acceptable from the point of view of safety and quality. Donors with malignant diseases can be accepted as corneal donors, except in cases of retinoblastoma, hematological malignancies and other malignant tumors that may affect the anterior pole of the eye.

e) Risk of prion diseases. This risk includes the following examples:

1.º Diagnosis of non-iatrogenic Creutzfeld-Jakob disease or variant Creutzfeld-Jakob disease or family history of non-iatrogenic Creutzfeld-Jakob disease.

2.º History of rapidly progressive dementia or degenerative neurological disease of unknown origin.

3.º Prior treatment with pituitary-derived hormones (i.e. growth hormone). Recipients of dura mater, cornea or sclera. Persons undergoing undocumented surgery where dura mater may have been used.

f) Active and uncontrolled infection at the time of donation, including bacterial infection and systemic viral, parasitic or fungal infection, or localized infection in the tissues to be used.Potential donors with bacterial sepsis may be evaluated and considered for corneal harvesting if corneas are to be stored in cultures that allow detection of bacterial contamination.

g) History, existence of risk factors for transmission, clinical evidence or positive laboratory tests for HIV, hepatitis B, hepatitis C and HTLV I and II.

h) History of chronic autoimmune disease that may have damaged the tissues to beused.

i) Presence of other risk factors for disease transmission, taking into account travel historyand local prevalence of infectious diseases.

j) Risk that biological tests may be invalidated:

1.Due to the existence of hemodilution (see annex III).

2. Due to treatment with immunosuppressants.

k) Presence of physical signs that may pose a risk of disease transmission.

l) Recent history of vaccination with attenuated virus, which may be a source of infection.

m) Xenotransplant recipients.

1.2.Pediatric age-specific exclusion criteria: In addition to the above, which is equally applicable to pediatric age donors, any child born to a mother who is HIV positive or ill orwho may fall under the above should be excluded, unless it can be demonstrated that there isno risk of transmission:

a) Donors under 18 months of age born to mothers with positive markers for HIV, hepatitisB or C or who have risk factors for these diseases, who have been breastfed in the previous 12 months, should be ruled out regardless of serological testing.

b) Donors under 18 months of age born to mothers with positive markers for HIV, hepatitisB or C who have not been breastfed in the previous 12 months and who have no clinical evidence or history compatible with having been infected, and whose serological tests are negative for HIV, hepatitis B or C may be accepted as donors.

1.3.External physical examination. A detailed physical examination of the cadaver should be carried out to detect signs that may indicate a risk of disease transmission: tumors (e.g. melanoma), infections (e.g. genital ulcers or anal condylomas), risk factors for transmission ofinfectious disease (signs of venipuncture, tattoos or piercings that are not affiliated).

2. Living donor.

2.1. Autologous living donor: The physician responsible for the therapeutic procedure must determine, on the basis of the medical history, therapeutic indication and available documentation, the justification for donation and the safety criteria.

If the cells or tissues obtained are to be stored, cultured or subjected to any "ex vivo" transformation process, the same biological tests as those required for allogeneic donors shall be performed. Positive results of any of the tests shall not preclude re-implantation ofthe cells, tissues or derived products.

Both the patient or his legal representative and the responsible physician must sign the donation document in accordance with the legal provisions in force and the provisions of

Article 7. In this document, the patient must acknowledge that the information he has provided is true to the best of his knowledge.

2.2. Allogeneic living donor: The donor will be selected on the basis of knowledge of his/her medical history and the personal interview conducted by the responsible medical professional. This evaluation will include those points that are relevant in the identification andselection of potential donors whose donation could represent a risk to the health of third parties, such as the possibility of disease transmission, or to their own health. In the case of umbilical cord blood or amniotic membrane donation, there must be no interference orcompromise with the care and safety of the mother or newborn.

The criteria for the selection of living donors of tissues or cells for allogenic use shall be established and documented at the tissue establishment that is to receive them, or at the transplantation unit, in the case of a direct referral of the cells or tissues from the procurementestablishment to the implantation establishment. These criteria shall include those specific to each tissue or cell group plus those referring to the donor's general condition, medical and social history, and the results of clinical and laboratory tests designed to verify the donor's state of health.

The same general exclusion criteria as specified for deceased donors shall be followed. In selected cases of hematopoietic stem cell transplantation, donors with positive viral markers B and C may be accepted. In cases of in-couple gamete donation, the criteria specified for this purpose shall be followed (according to Annex IV).

Depending on the tissue or cell group, further exclusion criteria will be added:

a) Pregnancy: Except for donation of hematopoietic progenitors and amniotic membrane.

a) Breastfeeding.

b) The possibility of transmitting hereditary diseases in the case of hematopoietic progenitors and gametes.

Both the donor or his legal representative and the responsible physician must sign the donation document in accordance with the legal provisions in force and with Article 7. In this document, the donor must acknowledge that the information he/she has provided is true to the best of his/her knowledge.

ANNEX III

Laboratory tests required in the evaluation of donors (except donors of reproductive cells)

1. Required biological tests for donors.

1.1.The following tests shall be required, as a minimum, in all cases of tissue and celldonation:

HIV 1 and 2: Anti HIV-1, 2
antibodies. Hepatitis B: HBs Ag.
Anti. Hbc.
Hepatitis C: Anti-HVC antibodies (in cases of hematopoietic progenitors, PCR is also required).
Syphilis: See 1.4.

1.2. Anti-HTLV I and II antibody tests should be performed on donors living in or coming from areas with a high prevalence of the disease. They shall also be performed in donors whoare sexual partners or offspring of persons living in or coming from areas with a high prevalence of the disease.

3. When the anti-HB-C antibody test is positive and HBsAg negative, further testing will be necessary to determine whether the tissues and/or cells can be used or should be

discarded.

4. In some circumstances additional tests will be performed depending on the donor's history or the characteristics of the cells or tissue to be used (CMV, T. cruzi, toxoplasma, malaria, Dengue, EBV, HLA, RhD).

5. A diagnostic algorithm shall be applied to exclude the presence of active TreponemaPallidum infection:

a) Non-reactive test, specific or not: allows the use of tissues or cells.

b) Non-reactive non-specific test: a specific test must be performed which, if nonreactive,will allow the use of tissues or cells.

c) Specific reactive test: a specific risk assessment is required to determine whether ornot to use the cells and/or tissues.

6. For autologous donors, account shall be taken of Annex II, point 2.2.1.

2. General requirements for biological tests.

3. Tests shall be carried out in qualified laboratories authorized by the competent authorities of the relevant autonomous community. CE marked kits shall be used, when available on the market. Thetype of test used shall be validated for its intended purpose, according to scientific knowledge and following the manufacturer's instructions.

3.1. Biological tests shall be performed on donor serum or plasma. They should not be performed on other fluids, such as vitreous or aqueous humor, unless specifically justified.

3.2.When deceased donors have received transfusions of blood or blood components and/or colloids in the 48 hours preceding death or crystalloids in the hour preceding death,the hemodilution calculation algorithm must be applied. Tissue establishments may accept tissues or cells from donors with hemodilution rates above 50% only if laboratory tests are validated for hemodiluted samples or if any plasma or serum samples collected prior to transfusions/infusions are found.

a) Pre-mortem" blood samples: if blood components, blood or colloids have been infused in the 48 hours preceding sampling or crystalloids in the preceding hour.

b) Post-mortem blood samples: if blood components, blood or colloids have been infusedin the 48 hours preceding death or crystalloids in the hour preceding death.

3.4.In the case of deceased donors, blood samples must be obtained before death. Otherwise, samples shall be obtained as soon as possible, and in any case within 24 hours of death.

3.5.Other assumptions:

a) In the case of living donors (except for bone marrow progenitor cells and peripheral blood progenitor cells, for practical reasons), blood samples for serology must be obtained at the time of donation or within 7 days of donation (from 0 to +7).

b) When cells and/or tissues are to be stored for long periods, a second determination at 180 days is required. In these cases, the "donation sample" may be taken in the interval between 7 days before and 30 days after donation (-7 to +30).

c) Where cells and/or tissues from an allogeneic donor are not to be stored for long periods and the second determination cannot be carried out, point (a) shall apply.

3.6.If DNA amplification techniques are applied for the determination of the presence of HIV, HBV and HLV, a second determination is not required. It is also not required if avalidated viral inactivation process is included during the tissue and/or cell pool processing step.

3.7.In the case of allogeneic hematopoietic progenitor donors, blood samples shall be tested within 30 days pre-donation.

3.8. In the case of hematopoietic progenitors from umbilical cord blood, both the mother's blood and the cord blood will be tested.

3.9. In the case of neonatal donors, the sample shall be obtained from the mother to avoidunnecessary medical procedures for the child.

ANNEX IV

Reproductive cell donor selection and evaluation

1. Donation between partners for direct use.

The criteria for clinical or laboratory evaluation shall not apply to cases of donation ofreproductive cells between partners for direct use.

2. Donation between partners for deferred use.

Where reproductive cells are to be stored or processed, the following criteria must bemet:

2.1. The physician responsible for the gamete donation process must determine anddocument, on the basis of the clinical history and therapeutic indication, the justification forthe procurement and the safety criteria for the mother and the children that may result from the process.

2.2.The following serological tests shall be carried out to assess the risk of cross-contamination:

HIV 1 and 2: Anti HIV-1, 2 antibodies.
Hepatitis B: HBs antigen / Anti-HBC antibodies.
Hepatitis C: Anti-HCV antibodies.

When test results for HIV 1 and 2 or Hepatitis B or C are positive or unavailable, or when the donor is known to have a risk factor for transmission of these infections, an isolated storage system should be scheduled.

2.3.Testing for anti-HTLV I and II antibodies will be performed on donors who live in or come from areas with a high prevalence of disease or whose sexual partners or parentscome from or live in areas with a high prevalence of disease.

2.4. In some circumstances additional tests may be required (malaria, toxoplasma, Trypanosoma cruzi, dengue, CMV, EBV, RhD) depending on the existence of travel, or exposure to risk of infection, or the characteristics of the cells obtained.

2.5. The fact that the tests are positive does not necessarily prevent the cells obtained, or the products derived from them, from being used in cases of donation between people of the same couple, always in accordance with the regulations in force.

2.6. When HIV 1 and 2 or hepatitis B or C tests are positive or the results are notavailable, or when the donor presents any infection risk criteria, an isolated storage system shall be used.

2.7. In the case of partner donation for deferred use, blood samples must be obtained within three months before the first donation. For new donations by the same donor between partners, blood samples must be obtained within 24 months after the collection of the deferred-use sample.

3. Donations outside the couple.

The use of reproductive cells from donors other than the regular partner must meet the following criteria:

a) Donors shall be selected on the basis of their medical history, to be taken by the responsible physician. This assessment shall include any factors that may be relevant to the identification and selection of those whose donation may pose a risk to the health of others, such as the possibility of transmitting a disease, or to themselves (i.e. ovulation induction and/or stimulation, sedation, risks associated with egg retrieval, or psychological consequences).

b) Donors must have negative serological markers for HIV 1 and 2, HVC and HVB and syphilis. Sperm donors must also have negative markers for chlamydia in a urine sample and by PCR determination.

c) Tests for anti-HTLV I and II antibodies will be performed on donors who live in or comefrom areas with a high prevalence of disease or whose sexual partners or parents live in or come from areas with a high prevalence of disease.

d) In some circumstances additional tests may be required depending on the donor's medical history or the characteristics of the cells or tissues (i.e. malaria - CMV - Trypanosomacruzi, RhD).

e) In the case of autologous donations, the provisions of Annex II point 2.1.

f) An assessment of the genetic load in relation to the existence of autosomal recessivegenes will be carried out according to scientific knowledge and the known prevalencein the donor's ethnicity.

a) An assessment of the risk of transmission of known hereditary diseases present in thefamily will be carried out. Those involved shall be informed of the results obtained in accordance with the provisions of Law 41/2002, of 14th November, basic law regulating patient autonomy and rights and obligations regarding clinical information and documentation and Law 14/2006, of 26th May, on assisted human reproduction techniques. This information must be as complete as possible in relation to the associated risks and the measures adopted or that may be adopted and must be clearly transmitted and explained to the recipient.

b) Basic requirements for the performance of biological tests.

Biological tests shall be carried out as specified in points 2.1. and 2.2.

2. of Annex III:

1.Blood samples shall be obtained at the time of each donation.

2.The semen samples shall be kept in quarantine for at least 180 days, after which the biological tests shall be repeated. This second evaluation may be avoided if the first determination was made by nucleic acid amplification test. Similarly, the second biologicaltest determination may be avoided if the cells will undergo a validated viral inactivation process in the transformation or subsequent handling process.

ANNEX V

Tissue and cell donation, retrieval and reception procedures at the tissue establishment

1. Donation and removal.

1.1.Donor consent and identification. Before proceeding with the removal of the cells and tissues, the person responsible for the procedure or person authorized to do so must confirm and record:

a) That consent for the extraction has been obtained in accordance with the provisions of the legislation in force.

b) How donor identification has been carried out.

c) That, in the case of living donations, the donor has understood the information provided, has been informed of his or her right to receive the confirmed results of theanalytical tests performed clearly explained, has had the opportunity to ask questions and hasobtained satisfactory answers, and has confirmed that the information he or she

has provided, with regard to his or her medical history, is true to the best of his or her knowledge.

1.2.Donor evaluation.

1.2.1. The person responsible for the procurement procedure or person authorized to do so must collect and record all clinical and social information from the donor that is relevant to the evaluation as described in section 1.4 of this annex (donor documentation).

1.2.2.In the case of living donors, a personal interview will be conducted during which a structured questionnaire will be completed. In the case of deceased donors, the questionnaireshall be completed with the help of the following:

a) The family or relatives (social and habit anamnesis).
b) The doctor who treated you.
c) The donor's general practitioner (if applicable).
d) Medical records / autopsy results.

1.2.3.A physical examination of the donor will be carried out to detect any signs or marks that may be suspicious of disease transmission or that are complementary to the information in the medical history and that may require further evaluation before accepting the donor: tumors (melanomas), infections (genital ulcers or anal condylomas), risk factors for transmissible diseases (venipunctures), trauma or scars from recent or old operations.

1.3.Extraction of cells and tissues.

1.3.1.The procurement procedures shall be appropriate to the type of donor and the type of cells/tissues to be procured, as well as to ensure donor protection.

1.3.2.The procedures used must ensure that the properties of these cells or tissues required for clinical use are protected and minimize the risks of microbiological contamination,especially if the cells or tissues are not to be subjected to subsequent sterilization treatment.

1.3.3.In the case of deceased donors, the collection site should be recorded (or describedin the collection report) and should be a restricted area. The medical team performing the retrieval should take the most appropriate contamination preventive measures in each case.In general, this should include washing work surfaces with antiseptic solutions, preparing a sterile field, performing surgical hand washing, and using sterile gloves and gowns, as well asa mask and cap.

1.3.4.In the case of retrievals from deceased donors, the time of death and the time of retrieval must be recorded, the interval must be recorded, and care must be taken to ensure that the limits guaranteeing that the biological characteristics and properties of the cells and tissues are preserved are not exceeded.

1.3.5.Once tissues or cell groups have been removed from a deceased donor, reconstruction of the affected areas will be carried out, so that they are as close as possibleto their previous anatomical appearance.

1.3.6.Any events occurring during the procurement procedure that may be or have been detrimental to the donor, as well as any further investigation arising from these events to determine their cause, should be properly collected and evaluated.

1.3.7.Standardized procedural guidelines should be available to minimize the risk ofcontamination by staff members who may be infected with communicable diseases.

1.3.8. High quality sterile instruments and systems, validated and/or specifically certified and regularly maintained for their intended use, shall be used for the collection of cells and tissues.

1.3.9. Where multiple-use instruments are used, validated standardized procedures for

cleaning and sterilization of such equipment should be available.

1.3.10. Wherever possible, EU-certified materials shall be used and the staff involvedshall be adequately trained in the handling of such instruments.

1.4.Donor documentation.

1.4.1.For each donor, a file containing the following information must be prepared:

a) Identification of the donor (name, surname and date of birth with equivalent identification).

b) In the case of neonatal donations or cord blood or any other tissue or cell group obtained at the time of delivery, the name and date of birth of the mother, the date of birth of the donor, and the donor's name if known, shall be recorded.

c) Sex, age, medical and social history.

d) Summary of physical examination.

e) Hemodilution calculation formula (if applicable).

f) Consent document for the collection.

g) Clinical data, results of laboratory tests and any other determinations or testsperformed.

h) Result of the report if a post-mortem examination has been carried out.

i) In the case of hematopoietic progenitors, documentation of the donor's suitability for agiven recipient shall be recorded.

The harvesting team shall prepare a report of the harvesting procedure, a copy of which shall be sent to the tissue processing establishment. This report shall contain at least the following information:

a) Identification, name and address of the destination establishment that is to receive the removed cell group and/or tissues.

b) Identification of the donor, including how the identification was carried out and by whom.

c) Cause, date and time of death (in deceased donor).

d) Description and identification of tissues and cells removed and samples obtained for evaluation.

e) Identification and signature of the person in charge of the extraction group.

f) Date and time (start and end), location of collection and procedure used (SOP, if applicable). Description of the area and conditions under which the collection was performed (if applicable).

g) Incidents occurring during extraction.

h) In the case of deceased donors, information on the methods and conditions of preservation of the body: whether the body has been refrigerated or not, temperature, time, start and end of refrigeration.

i) Reagents and preservation solutions used (Batch identification).

j) Donor information must be archived and protected against unauthorized modifications, appropriately stored and accessible to the competent authority, for at least 30years after the clinical use or expiry of the procured tissues or cells.

1.5.Packaging.

1.5.1.After retrieval, all tissues and cells shall be packaged in a manner that minimizesthe risks of contamination and ensures the required temperature to preserve the biologicaland functional characteristics and properties of the tissues and cells. The packaging mustalso prevent contamination of those carrying out the packaging and those transporting the tissues and cells.

1.5.2. Packaged cells and tissues must be transported in containers suitable for the transport of biological material and which maintain their quality and safety.

1.5.3. Tissue or blood specimens accompanying those obtained for ultimate use for the purpose of further testing or analytical determinations must be appropriately labelled. These labels must include the identification of the donor and information on where and when the specimen was collected.

1.6. Labelling of extracted tissues or cells.

1.6.1. Internal containers of cells and/or tissues for human use must be labelled with atleast the following information:

a) Donor identification code.
b) Type of cell and/or tissue.

1.6.2. If the container allows it, by virtue of its dimensions, it must also be included:

a) Date and time of collection.
b) Precautions (if applicable).
c) Additives used (if applicable).
d) In the case of direct donations, the recipient must be identified.
e) In case of autologous donations: "For autologous use only" should be stated.

1.7. Labelling of the outer transport container. The transport container of the cells and/or tissues must be labelled with the following information:

a) "Biological sample of cells/tissues-Handle with care”.

b) Identification of the tissue establishment of origin of the tissue and/or cell group,including address and telephone number and contact person for any contingency.

c) Identification of the tissue establishment of destination, including address and telephone number, as well as the contact person to whom the container should be delivered.

d) Date and time of commencement of transport.

e) Specifications for maintaining the biological characteristics of cells or tissues duringtransport (if applicable).

f) Storage specifications if applicable (i.e. DO NOT FREEZE).

g) If tissues or cells may be affected by X-rays, "DO NOT IRRADIATE" must be clearly marked.

h) In cases of products which are known to be potentially contaminating or for which the results of serological tests are unknown: "RISK OF BIOLOGICAL CONTAMINATION" must be specified.

i) In the case of autologous donations, "For autologous use only" must be clearly stated.

2. Reception of the tissue and/or cell group in the tissue establishment.

2.1. General conditions. When the tissue and/or cell group retrieved arrives at the tissue establishment, a documented procedure shall be followed to verify that the consignment received complies with all the requirements, both in this Royal Decree-Law and in the specifications of the tissue establishment itself, in relation to the conditions of transport, packaging and labelling, and in relation to the samples for subsequent controls and the information and documentation that must accompany the tissues and/or cells.

The tissue establishment must ensure that the tissues and/or cells received remain in quarantine until they and all accompanying documentation have been subjected to the analyses, controls, inspections or verifications required in this Royal Decree-Law and in the establishment's own specifications. The review of the documentation, as well as the subsequent decision on its acceptance, must be made by the authorized or designated person at the tissue establishment.

Each tissue establishment must have a documented procedure to ensure that consignments of tissues and/or cells received that do not comply with the established requirements, or whose documentation is incomplete or awaiting completion of donor evaluation results, are stored in such a way that there is no risk of contamination to other tissues and/or cells preserved, stored or processed in the same establishment.

2.2.Data recording. The data to be recorded at the tissue establishment (except in the case of reproductive cell donation between partners) shall be at least the following:

a) Consent or authorization for collection, stating the purpose of use (therapeutic use or research or both) and any specific instructions for destruction when not used for the purpose for which they were obtained.

b) Those relating to donor identification and characteristics, including the type of donor and cause of death, if applicable, as described in the section:
"Documentation".

c) Those relating to the donor's medical history and the procurement procedure, asoutlined in the relevant annex.

d) Those relating to the physical examination of the donor, the results of laboratory testsor any other tests carried out on the donor, including necropsy results if performed.

e) The full donor evaluation report signed by the person responsible for the

evaluationand selection process or authorized person.

f) Those relating to the removal procedure, as set out in the relevant annex, including theplace of removal and the person responsible.

g) The tissues and/or cells received and their characteristics.

h) In case of autologous tissue, it is necessary to specify in addition:

1.º The characteristics of the lesion or pathological process to be treated.

2.º Allergies to medicines or products that may be used in preservation and processing.

2.2.1. In the case of cell cultures for autologous use, information on possible allergies of the recipient (e.g. antibiotics) shall also be provided.

2.2.2.In the case of reproductive cell donations outside the normal partnership, the following donor data shall also be recorded: height, weight, race, skin color (pale, brown), eye color (brown, green, amber, blue, black), hair color (blond, light brown, dark brown, red, black), hair texture (straight, wavy, curly), blood group and Rh.

2.2.3.In the case of reproductive cells to be used within the regular couple, the data to be recorded are:

a) Consent/authorization for collection, stating the purpose of use (therapeutic/research use or both) and any specific instructions for destruction when not used for the purpose for which they were obtained.

b) Donor identification data: type of donor, age, sex, presence of risk factors and causeof death in case of deceased donors.

c) Partner identification data: age, sex and presence of risk factors.

d) Location of cell group procurement.

e) Cells or tissues obtained and their most relevant characteristics.

3. Requirements for direct distribution of specific tissues and/or cells to the implantation center.

Exceptionally, the Autonomous Transplant Coordination Unit and/or the National Transplant Organization may authorize the direct shipment of some specific cells or tissues from the center where the extraction is performed to the implantation center for immediate use. (i.e. hematopoietic progenitor cells, corneas, etc.). In any case, the requirements specified in these annexes for identification, collection, packaging, shipping, preservation and labelling shall apply.

ANNEX VI

Minimum information required in the traceability system from origin to destination of human tissues and cells procured for human application

1. For tissue establishments:

a) Donor identification.

b) Identification of the donation, including as a minimum:

1.Identification of the procurement agency (including contact information) or tissueestablishment.

2.Unique identification number of the donation.

3.Date obtained.

4.Place of procurement.

5.º Type of donation (e.g. single or multiple tissue; autologous or allogeneic; living ordeceased donor).

c) Identification of the product, including at least:

1stIdentification of the tissue establishment.
2.º Type of tissue and cell/product (basic nomenclature).
3.Batch group number (if applicable).
4.ºSublot number (if applicable).
5.º Expiry date (if applicable).
6.Status of the tissue/cells (e.g. quarantined, suitable for use, etc.).
7.º Description and origin of products, processing steps applied, materials and additivesthat come into contact with tissues and cells and have an effect on their quality and/or safety.
8.º Identification of the facility issuing the final label.

d) Single European Code (where applicable).
e) Identification of the human application, including, as a minimum:

1.º Date of distribution/disposal.
2.º Identification of the doctor or end user/facility.

2. By the organizations responsible for human application:

a) Identification of the supplier tissue establishment.
b) Identification of the medical practitioner or end user/facility.
c) Type of tissues and cells.
d) Product identification.
e) Identification of the recipient.
f) Date of implementation.
g) Single European Code (where applicable).

ANNEX VII

Format and structure of the Single European Code.

1. FORMAT OF THE SINGLE EUROPEAN CODE

The unique European code shall be in a legible format and preceded by the letters "SEC". The parallel use of other labelling and traceability systems shall be possible.

The unique European code shall be printed together with the donation identificationsequence and the product identification sequence, separated by a single space or on two successive lines.

2. STRUCTURE OF THE SINGLE EUROPEAN CODE

ANNEX VIII

1. SERIOUS ADVERSE REACTIONS.

2. SERIOUS ADVERSE EFFECTS

ANNEX IX

Data to be recorded in the EU Compendium of Tissue Establishments

1. Information on tissue establishment:

fax a) Name of the tissue establishment.

· b) National or international code of the tissue establishment.

c) Name of the organization in which the tissue establishment is located (if applicable).

d) Address of the tissue establishment.

e) Publishable contact details: functional e-mail address, telephone number and

2. Data on the authorization of the tissue establishment:

a) Name(s) of the competent authorizing authority (ies).

b) Name(s) of the responsible national competent authority (ies)

for the maintenance of the EU Compendium of Tissue Establishments.

c) Name of the authorization holder (if applicable).

d) Tissues and cells for which authorization was granted.

e) Activities actually carried out for which the authorization was granted.

f) Authorization status (authorized, suspended, revoked, partially or totally,

voluntarycessation of activity).

g) Details of conditions and exemptions added to the authorization (if any).

ANNEX X

Minimum requirements for information and documentation to be submitted by importing tissue establishments when applying for authorization for the purpose of their import activities

When applying for authorization to conduct import activities, the importing tissue establishment shall provide, unless already provided as part of previous applications for authorization as a tissue establishment or as an importing tissue establishment, the following updated information and, for Part 6, the documentation indicated.

1. General information on importing tissue establishment (ETI):

a) Name of the ETI (name of the company).
b) Physical address of the ETI.
c) Postal address of the ETI (if different from above).
d) Status of the applicant TIE: indicate whether this is the first application for authorization as a TIE or, if applicable, a renewal application. In case the applicant has already been authorized as a tissue establishment, its compendium code must be provided.
e) Name of the applicant unit (if different from the name of the enterprise).
f) Physical address of the requesting unit.
g) Postal address of the applicant unit (if different from above).
h) Name of the place of receipt of imports (if different from the name of the company andthe requesting unit).
i) Physical address of the place of reception.
j) Postal address of the place of receipt (if different from above).

2. Contact details for the application:

a) Name of the contact person for the application.
b) Telephone number, e-mail address.
c) First name and surname of the responsible person (if different from the contact person).
d) Telephone number.
e) E-mail address.
f) URL of the ETI website (if available).

3. Detailed information on the tissues and cells to be imported:

a) List of the types of tissues and cells to be imported, including exceptional imports ofspecific types of tissues or cells.
b) Product name (if applicable, according to the EU generic list) of all types of tissues andcells to be imported.
c) Trade name (if different from the product name) of all types of tissues and cells to beimported.
d) Name of the third country supplier for each type of tissues and cells to be imported.

4. Location of activities:

a) List indicating the donation, procurement, testing, processing, preservation or storage activities performed prior to importation by the third country supplier, by type of tissue or cell.
b) List indicating the donation, procurement, testing, processing, preservation or storage activities performed prior to importation by subcontractors of the third country supplier, bytype of tissue or cell.
c) List of all post-import activities performed by the ETI by tissue/cell type.
d) Names of third countries where activities are carried out prior to importation, by type

of tissue or cell.

5. Data from third country suppliers:

a) Name of the supplier/suppliers in the third country (name of the company).
b) Name of contact person.
c) Physical address.
d) Postal address (if different).
e) Telephone number (including international dialing code).f) Emergency contact number (if different).
f) E-mail address.

6. Documentation attached to the application:

a) Copy of the written agreement with the third country supplier(s).
b) Detailed description of the flow of imported tissues and cells from procurement to reception at the importing tissue establishment.
c) Copy of the export authorization certificate of the third country supplier or, if no specific export authorization has been issued, a certificate from the competent authority or authorities of the third country concerned authorizing the activities of the third country supplier in the tissues and cells sector, including exports. This documentation must also include the contact details of the competent authority or authorities of the third country. In third countries where such documentation is not available, other documentation, such as reports of audits carried out on the third country supplier, shall be provided.

ANNEX XI

Certificate of approval issued by the competent authority or authorities to the importing tissue establishment(s)

ANNEX XII

Minimum requirements for the documentation to be submitted to the competent authority or authorities by tissue establishments wishing to import tissues and cells from third countries

Except in the case of exceptional imports as defined in Article 2, which are exempted fromthese documentation requirements, the importing tissue establishment shall make available and, unless already provided as part of previous applications for authorization as an importingtissue establishment, provide, upon request by the competent authority or authorities, the most up-to-date version of the following documents relating to the applicant and his third country supplier(s).

1. Documentation relating to the importing tissue establishment:

a) Description of the functions of the responsible person and details of his/her qualifications and training, as laid down in Article 17 for the technical responsible persons of tissue establishments.
b) Copy of primary label, repackaging label, outer packaging and transport container.
c) List of relevant and updated versions of the Standard Operating Procedures (SOPs) related to the import activities of the establishment, including SOPs for the implementation of the Single European Code, the receipt and storage of tissues and cells at the importing tissueestablishment, the management of adverse events and reactions, the management of product retrievals and their traceability from donor to recipient.

2. Documentation relating to the third country supplier(s):

a) Detailed description of the criteria used for the identification and evaluation of the donor, the information provided to the donor and/or the donor's family, the manner in which the consent of the donor and/or the donor's family was obtained, and whether or not the voluntary and unpaid nature of the donation was confirmed.

b) Details of the assessment center(s) used by the third country supplier(s) and the tests carried out by these center(s).

c) Detailed information on the methods used during the processing of tissues and cells, including details of the validation of the critical processing procedure.

d) Detailed description of the critical facilities, equipment and materials and the criteria used for quality control and environmental control for each of the activities carried out by the third country supplier.

e) Detailed information on the conditions of delivery of tissues and cells by the third country supplier(s).

f) Details of subcontractors used by third country suppliers, including name, location and activity performed.

g) Summary of the most recent inspection of the third country supplier by the competent authority or authorities of the third country, including the date and type of inspection and the main findings.

h) Summary of the most recent audit of the third country supplier carried out by or on behalf of the importing tissue establishment.

i) Any relevant national or international accreditation.

ANNEX XIII

Minimum requirements for the content of written agreements between importing tissue establishments and their suppliers in third countries

Except in the case of exceptional imports as defined in Article 2, which are exempted fromthese requirements, the written agreement between the importing tissue establishment and the third country supplier must include at least the following:

1. Detailed information on the specifications of the importing tissue establishment inorder to ensure that the quality and safety standards laid down in this Royal Decree-Law are met and the roles and responsibilities mutually agreed by both parties to ensure that importedtissues and cells meet equivalent quality and safety standards.

2. A clause ensuring that the third country supplier shall provide the information required in Annex XII, Part 2 to the importing tissue establishment.

3. A clause ensuring that the third country supplier shall inform the importing tissue establishment of any suspected or confirmed serious adverse reaction or event that may influence the quality and safety of the tissues and cells that have been or will be imported by the importing tissue establishment.

4. A clause ensuring that the third country supplier shall inform the importing tissue establishment of any substantial change in its activities, including the revocation or suspension, in whole or in part, by the competent authority or authorities of its authorization toexport tissues and cells or other decisions in case of non-compliance, which may influencethe quality and safety of the tissues and cells that have been or will be imported by the importing tissue establishment.

5. A clause giving the competent authority or authorities the right to inspect the activitiesof the third country supplier, including on-site inspections if they so wish, as part of their inspection of the importing tissue establishment. The clause must also guarantee the

importing tissue establishment the right to audit its third country supplier on a regular basis.

6. The agreed conditions to be met for the transport of tissues and cells between the third country supplier and the importing tissue establishment.

7. A clause ensuring that the third country supplier or its subcontractor will retain data relating to imported tissue and cell donors, in line with EU data protection standards, for a period of 30 years after procurement and that appropriate arrangements will be made for theirretention in the event that the third country supplier ceases its activity.

8. Provisions for the periodic review and, if necessary, revision of the written agreementto reflect possible changes in the requirements of the EU quality and safety standards set out in this Royal Decree-Law.

9. A list of all standard operating procedures of the third country supplier relating to the quality and safety of imported tissues and cells and an undertaking to make them available onrequest.