



The European tissue directives and intrauterine insemination



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Introduction: EU Tissue Directives (EUTD)

- • **"Mother" Directive 2004/23/EC** of 31/03/2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells
- • **"Technical" directive 2006/17/EC** of 8/02/2006 implementing the previous one as regards certain technical requirements for the donation, procurement, and testing of human tissues and cells
- • **"Technical" directive 2006/86/EC** of 24/10/2006 implementing the "mother" directive as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells

Mother directive 2004/23/EC

- ❑ Accreditation, designation, authorisation or licensing of tissue establishments and tissue and cell preparation processes
- ❑ Inspections and control measures
- ❑ Traceability
- ❑ Import/export of human tissues and cells
- ❑ Register of tissue establishments and reporting obligations
- ❑ Notification of serious adverse events and reactions
- ❑ Donor selection and evaluation
- ❑ Quality management, responsible persons, personnel
- ❑ Tissue and cell reception, processing, storage conditions
- ❑ Labelling, documentation and packaging, distribution
- ❑ Relations between tissue establishments and third parties
- ❑ Coding
- ❑ Reports
- ❑ Penalties

Mother directive 2004/23/EC



(7) This Directive should apply to tissues and cells including haematopoietic peripheral blood, umbilical-cord (blood) and bone-marrow stem cells, reproductive cells (eggs, **sperm**), foetal tissues and cells and adult and embryonic stem cells.

Principles of gamete donation



- The majority of Member States have legislation in respect of:
 - • **Confidentiality** (measures ensuring that all data collated, including genetic information, has been rendered anonymous so that the donor and the recipient are no longer identifiable);
 - • **Anonymity** (measures regulating the disclosure of the identity of the donor. This could mean either that the donor must by law remain anonymous or, on the contrary, that the donor must by law forego his/her anonymity.);
 - • **Non-Remuneration** for the donation (measures preventing organ trade or trafficking).

TD1: 2006/17/EC – Annex III: **SELECTION CRITERIA AND LABORATORY TESTS** REQUIRED FOR DONORS OF REPRODUCTIVE CELLS AS REFERRED TO IN ARTICLE 3(b) AND ARTICLE 4(2)



- **1. Partner donation for direct use:** Donor selection criteria and laboratory testing do not need to be applied in the case of partner donation of reproductive cells for direct use.
- **2. Partner donation (not direct use):** Reproductive cells that are **processed and/or stored** and reproductive cells that will result in the cryopreservation of embryos must meet the following criteria:

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- 2.1. the clinician responsible for the donor must determine and document, based on the patient's medical history and therapeutic indications, the justification for the donation and its safety for the recipient and any child(ren) that might result;
- 2.2. the following **biological tests** must be carried out to assess the risk of cross-contamination: HIV 1 and 2 (Anti-HIV-1,2); Hepatitis B (HBsAg; Anti-HBc); Hepatitis C (Anti-HCV-Ab). **In case of sperm processed for intrauterine insemination and not to be stored, if the tissue establishment can demonstrate that the risk of cross contamination and staff exposure has been addressed through the use of validated processes, biological testing may not be required;**

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- ❑ 2.3. where HIV 1 and 2, hepatitis B or hepatitis C test results are positive or unavailable, or where the donor is known to be a source of infection risk, a system of separate storage must be devised;
- ❑ 2.4. HTLV-I antibody testing must be performed for donors living in or originating from high-incidence areas or with sexual partners originating from those areas or where the donor's parents originate from those areas;
- ❑ 2.5. in certain circumstances, additional testing may be required depending on the donor's travel and exposure history and the characteristics of the tissue or cells donated (e.g. Rh D, malaria, CMV, T. cruzi);
- ❑ 2.6. **positive results will not necessarily prevent partner donation** in accordance with national rules.

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- 3. Donations other than by partners:** The use of reproductive cells other than for partner donation must meet the following criteria:
- 3.1. donors must be selected on the basis of their **age, health and medical history**, provided on a questionnaire and through a personal interview performed by a qualified and trained healthcare professional. This assessment must include relevant factors that may assist in identifying and **screening** out persons whose donation could present a health risk to others, such as the **possibility of transmitting diseases** (such as sexually transmitted infections), or **health risks to themselves** (e.g. superovulation, sedation or the risks associated with the egg collection procedure or the psychological consequences of being a donor);
 - 3.2. the **donors must be negative for HIV 1 and 2, HCV, HBV and syphilis** on a serum or plasma sample, tested in accordance with Annex II, point 1.1, and **sperm donors must additionally be negative for chlamydia on a urine sample** tested by the nucleic acid amplification technique (NAT);

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- 3.3. HTLV-I antibody testing must be performed for donors living in or originating from high-incidence areas or with sexual partners originating from those areas or where the donor's parents originate from those areas;
- 3.4. in certain circumstances, additional testing may be required depending on the donor's history and the characteristics of the tissue or cells donated (e.g. RhD, malaria, CMV, T. cruzi).
- 3.5. for autologous donors, Annex I, point 2.1.1 applies;
- 3.6. **genetic screening for autosomal recessive genes known to be prevalent**, according to international scientific evidence, in the donor's ethnic background and an assessment of the risk of transmission of inherited conditions known to be present in the family must be carried out, after consent is obtained. Complete information must be provided, in accordance with the requirements in force in Member States. Complete information on the associated risk and on the measures undertaken for its mitigation must be communicated and clearly explained to the recipient.

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- **Sperm donations other than by partners** will be **quarantined for a minimum of 180 days**, after which repeat testing is required. If the blood donation sample is additionally tested by the nucleic acid amplification technique (NAT) for HIV, HBV and HCV, testing of a repeat blood sample is not required. Retesting is also not required if the processing includes an inactivation step that has been validated for the viruses concerned.

- **Annex IV**: The organisation performing the procurement must produce a procurement report, which is passed on to the tissue establishment. **Where sperm is procured at home, the procurement report must state this and must contain only:**
 - (a) the name and address of the tissue establishment to receive the cells/tissues;
 - (b) the donor identification.
- The **date and time** of procurement may be included, where possible.

Serology : Lab requirements

- Separate storage of samples necessary:
 - when positive tests
 - when results unknown at moment of storage
- Systems for separate storage:
 - High security straws
 - Separate storage tanks



TD2: 2006/86/EC



- **Quality Management System:** ISO 9001/15189
- **Air quality conditions:** A in D except when air quality requirements have detrimental effect on tissues or cells, there is a low additional risk of transmitting infection upon application to the human body, technical incompatibility (However; the air quality always needs to be documented)
- **Traceability:** of everything !
- **Coding:** EU code only for non-partner donation
- Notification of **adverse reactions and events**

[http://www.eshre.com/binarydata.aspx?type=doc/
ESHRE_position_paper_on_the_EU_Tissues_and_Cells_Directive_EC_final.pdf](http://www.eshre.com/binarydata.aspx?type=doc/ESHRE_position_paper_on_the_EU_Tissues_and_Cells_Directive_EC_final.pdf)



european society of human reproduction & embryology

**ESHRE position paper on the
EU Tissues and Cells Directive EC/ 2004/23**

November 2007

ESHRE position paper



- In an ART perspective the EUTD involves basically **minimizing the risk** of two severe adverse events, namely **transmission of infections** and **prevention of gamete/zygote/embryo exchange** (mix-up). The directive is not concerned with pointing at specific ways of increasing "performance" such as success rates. Instead, the directive aims at increasing quality through **mandatory implementation of a quality management system**. This involves the presence of adequately trained and certified staff, full documentation and formulation of standard operating procedures, quality control and quality assurance at all units performing assisted reproduction.

ESHRE position paper



- The EUTD will have a profound impact on all units conducting assisted reproduction. All units will have to be **licensed or accredited** as decided by the national authorities. Further, all units must implement a **quality management system** with **written standard operating procedures** and ensure **full documentation** of all activities in the clinic/unit - including full traceability for all materials used in each treatment. This documentation must be kept for 30 years.
- “Donor” means every human source, whether living or deceased, of human cells and tissues. **Partner donation** means the donation of reproductive cells between **a man and a woman** who declare to have an **intimate physical relationship**. In a couple, man and woman are considered donors to each other.

ESHRE position paper

- Cells and tissues have to be traceable from donor to acceptor and vice versa. Traceability is also mandatory to all products and materials coming into contact with tissues and cells. This includes for instance all culture media, all culture media supplements and all disposables,
- A unique European coding system is not applicable to reproductive tissues and cells for partner donation. A unique code guaranteeing traceability remains however required.
- The EU has ordered a workshop at CEN, the European Committee of Standardization, to propose a unique European coding system which will apply in case of non -partner donation.
- In assisted reproduction every misidentification or mix-up of gametes, zygotes or embryos is to be considered a serious adverse event.

ESHRE position paper: problems

- Frequency of screening for HIV and Hepatitis: (Commission Directive 2006/17/EC, Annex III.4.2.): It is specified in the directive that all donors (patients) shall be tested for HIV and Hepatitis B and C **at the “time of donation”**. It is however not specified if it is **required to re-test** the patient prior to each treatment or whether a **specified interval** will be acceptable. This will have a profound impact on the financial consequences of the directive. “
- Member states shall ensure that tissue establishments have agreements and procedures in place to ensure that, in the event of termination of activities for whatever reason, stored tissues and cells shall be transferred, according to the consent pertaining to them, to other tissue establishment or establishments accredited, designated, authorized or licensed...” This paragraph specifies what is to be done if a clinic/unit closes. **ESHRE considers this the responsibility of the local authorities.**
- **Intra uterine insemination:** IUI is included in the directive as it involves processing of gametes and this may have a profound impact on insemination performed outside of regular fertility clinics/units.



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ESHRE Pages

Revised guidelines for good practice in IVF laboratories

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Revised guidelines for good practice in IVF laboratories

- **Staffing and direction**
- **Policies and procedures**
- **Laboratory safety (design, equipment, Infectious agents, Protective measures)**
- **Identification of patients and their gametes, zygotes and embryos**
- **Culture media preparation and quality control testing**
- **Handling of embryos, zygotes, oocytes and spermatozoa**
- **Oocyte retrieval**
- **Sperm preparation**
- **Insemination of oocytes**
- **Scoring for fertilization**
- **Embryo culture and transfer**
- **Cryopreservation of gametes, zygotes and embryos**
- **Assisted hatching**
- **Preimplantation genetic diagnosis**
- **Quality control and quality assurance**

European Assisted Conception Consortium



- Representatives from all member states:
 - Clinicians, embryologists, regulators
- Communicates with ESHRE, European Commission, HFEA



COMMISSION OF THE EUROPEAN COMMUNITIES

Health and Consumers Directorate-General

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**Meeting of Competent Authorities
On Tissues and Cells**

27-28 May 2009

Thank you for your attention !

