

EU Directive 2004/23/EC

Explanatory Paper for IUI and GIFT Establishments

November 2005

Contents

Person Responsible	3
Management of the Service	4
Personnel	5
Premises	7
Consent	8
Procedures and Environment	9
Quality Management	11
Documentation	13
Reporting	15
Regulation	16
Definitions	18

The information provided in this document is based on the latest available information concerning the Technical Commission Directives as of October 2005. There may be changes to requirements before the Directives are finalised. The HFEA will continually update IUI and GIFT establishments about any amendments that will affect their services.

The regulations that will transpose the Directive into UK law will further clarify the regulatory framework and not expected to be drafted before mid 2006. More detailed guidance will be circulated, particularly concerning the regulatory system, once the content of the regulations is known.

Person Responsible

Article 17:

Every tissue establishment shall designate a responsible person (PR) who shall at least fulfil the following conditions and have the following qualifications:

- A diploma, certificate or other evidence of formal qualifications in medical or biological sciences on completion of a university course or a course recognised as equivalent by the Member State;
- At least two years practical experience in the relevant field.

The PR shall be responsible for:

- Ensuring that activities are carried out in accordance with the Directive and the laws in force in the Member State;
- Providing information to the competent authority as required;
- Implementing the requirements of the Directive within the tissue establishment.

In keeping with the HFEA's existing licensing system the "Responsible Person" for the Tissue Directive will be known as the "Person Responsible" (as is the case under the Human Fertilisation and Embryology (HF&E) Act.)

The PR will have the over all responsibility for ensuring that requirements of the Directive are complied with *by all the staff* within the tissue establishment, and will hold the licence for the establishment in his/her name. Similarly, the PR will have to be satisfied that services provided by third parties are in keeping with the requirements of the Directive.

We expect that many of the requirements of the Directive will already be in place to some extent in the majority of IUI and GIFT establishments. However, the PR will have to produce coherent documented evidence that the required systems and procedures are in place, for inspection by the HFEA. The Quality Manual will be one of the key means of achieving this.

The appointment of the PR will form part of the quality management system. The role of the PR should not deter tasks and responsibilities being delegated throughout the team. However, all staff should report to the PR concerning areas of their work that directly involve compliance with the Directive.

The following sections will outline the detailed responsibilities of the PR, who must ensure that the requirements are implemented.

Management of the service

Quality Systems

Article 16:

Each tissue establishment shall put into place and update a quality system based on the principles of good practice.

The documented quality management system is a central theme of the Directive. It encompasses and links together most of the other requirements. The quality system should be documented through a Quality Manual.

This will include an organisational chart clearly defining accountability and reporting relationships, and documented standard operating procedures (SOPs).

SOPs should be maintained for every procedure, including treatment processes and house keeping such as staff induction/training and health and safety measures. SOPs must be appropriately version controlled, regularly reviewed and accessible to all relevant staff.

Guidelines referred to in the quality manual will include the establishment's own policies, professional guidelines such as Control of Substance Hazardous to Health and guidelines produced by professional bodies. Legal requirements such as the Tissue Directive and, when the Directive has been transposed to UK law the relevant sections of the HFE Act, should be accessible and understood by all relevant staff.

Any risks inherent in the use and handling of biological material should be identified and measures taken to minimise them. The risks will include those relating to the equipment, procedures and environment in relation to both staff and patients. Measures to reduce risk should be reflected in the SOPs.

Article 6:

The tissue establishment shall not undertake any substantial changes to activities without the prior written approval of the competent authority.

Establishments will have to notify the HFEA if they wish to start any additional treatments that fall within the scope of the Tissue Directive or the HF&E Act. Also any significant changes to procedures and changes to premises will have to be reported to the HFEA for prior approval.

Third parties

Article 24:

Tissue establishments shall establish written agreements with a third party each time an external activity takes place which influences the quality and safety of tissues and cells. In particular:

- **Where a tissue establishment entrusts one of the stages of tissue or cell processing to a third party;**
- **Where a third party provides goods and services that affect tissue or cell quality and safety assurance;**
- **Where a tissue establishment provides services to a tissue establishment that is not accredited;**
- **Where a tissue establishment distributes tissues or cells processed by third parties.**

Tissue establishments shall evaluate and select third parties on the basis of their ability to meet the standards laid down in the Directive.

Tissue establishments shall keep a complete list of the agreements, which will specify the responsibilities of the third parties and detailed procedures. Copies of the agreements will be provided to the competent authority upon request.

Establishments must document any agreements that are maintained with third parties. These will specify the terms of the relationship and responsibilities as well as the protocols to be followed to meet the required performance specification.

For example:

- contracts with manufacturers of equipment and media used in the sperm preparation process;
- contracts with maintenance companies involved with the upkeep of the facilities and equipment;
- agreements with pathology, cytology, or haematology labs that carry out sperm analysis tests (where this is not taking place within the tissue establishment itself). These labs would need to be CPA accredited in order to demonstrate that they meet acceptable standards;

All third party agreements will have to be accessible, available during HFEA inspections, and copies must be submitted to the HFEA upon request.

Personnel

Staff

Articles 5 & 18:

All tissue and cell procurement and testing shall be carried out by persons with appropriate training and experience. Personnel directly involved in activities relating to the Directive shall be qualified to perform such tasks and shall be provided with the training referred to in the Directive.

Staff involved in the treatment process must be available in sufficient number and be qualified for the tasks performed. The establishment should have access to a registered medical practitioner to advise on and oversee activities and clinical outcomes, where there is no one of that role within the establishment.

All staff should have clear, documented and up-to-date job descriptions. Tasks, responsibilities and accountability should be clearly documented and understood.

All staff will have to be suitably qualified for their specific role and receive adequate training and development opportunities. The competency of the staff should be evaluated by the PR at intervals specified in the quality system.

Training and Continued Professional Development (CPD)

Staff should be provided with appropriate initial training and update training as required when procedures change or scientific knowledge develops. There should be adequate opportunities for relevant professional development. Training must ensure that each individual:

- has demonstrated competence in the performance of their designated tasks
- has adequate knowledge and understanding of the scientific/technical processes and principles relevant to their designated tasks
- understands the organisational framework, quality system and health and safety rules of the establishment
- is adequately informed of the broader ethical and legal context of their work

Training and reference manuals shall be maintained and accessible to all relevant staff.

Premises

Articles 5 and 6:

Tissue and cell procurement and testing shall take place in conditions licensed for that purpose by the competent authority. All tissue establishments where activities of testing, processing, preservation, storage or distribution of human tissues and cells intended for human applications will be licensed for the purpose of those activities.

Facilities

Facilities must be suitable for the activities for which licensing is sought. Significant changes to facilities and any changes to premises will need to be reported to the HFEA for prior approval. Establishments should take account of legal requirements, professional guidelines, and health and safety rules when designing, maintaining and making amendments to premises.

Equipment

All equipment should be designed, validated and maintained to suit its intended purpose and minimise any hazard to patients and/or staff.

Equipment/technical devices must be regularly inspected and preventatively maintained in accordance with manufacturers instructions and be used in accordance with SOPs. Equipment with a measuring function must be calibrated in accordance to a traceable standard, if available.

New, maintained and repaired equipment should be validated before use. Test results should be documented. Maintenance, servicing, cleaning, disinfection and sanitation of all critical equipment shall be performed regularly and recorded accordingly.

Procedures for the operation of each piece of critical equipment, detailing the action to be taken in the event of malfunctions or failure, should be available. Where equipment or materials affect critical processing or storage parameters (e.g. temperature, pressure, particle counts), the parameters should be identified, monitored and corrected as required.

Health and Safety

Appropriate personal protective equipment and hygiene equipment should be provided along with written hygiene instructions, where necessary.

Consent

Consent

Article 13:

The procurement of human tissues and cells shall be authorised only after all mandatory consent or authorisation requirements in force in Member States have been met.

Before treatment takes place, an authorised person must confirm and record:

- that consent for the procurement and processing of gametes has been obtained
- how the patients have been reliably identified and by whom

The staff member responsible for the consultation process shall ensure that the patients have:

- understood the information provided, had an opportunity to ask questions and been provided with satisfactory responses
- acknowledged that all the information provided by the patient is true to the best of his/her knowledge

Procedures and environment

Article 20:

SOPs shall include all processes that affect quality and safety and ensure they are carried out under controlled conditions. The equipment used, the working environment and process design, validation and control conditions shall be in compliance with requirements. Any modifications to processes in the preparation of tissues and cells shall meet the criteria laid down in the Directive. SOPs shall include special provisions for handling of tissues and cells to be discarded, in order to prevent the contamination of other tissues or cells, the processing environment or personnel.

Every stage of the treatment process must be documented in SOPs, and also in house procedures including validation and quality control.

Environment

The draft technical requirements state that:

“Processing of gametes should take place in an environment with specified air quality and cleanliness in order to minimise the risk of contamination, particularly cross contamination between samples. The effectiveness of these measures shall be validated and monitored.”

The draft requirements include exceptions to Grade A air which can be applied to assisted conception.

The HFEA will provide further guidance on air quality in due course. It is likely that the onus will be on establishments to demonstrate that the level of air quality they have in place does not result in contamination of gametes or infection in the recipient (e.g. through the use of settle plates and maintaining data on the incidence of infection in recipients). The use of a class II hood will be a relatively easy way to demonstrate that the risk of contamination to the sample and practitioner is minimised, and also the policy of processing one sample at a time.

The HFEA is keen to convey the message that establishments should not focus attention on attempting to achieve a level of air quality that is unachievable in the context of IUI/GIFT. Establishments should instead focus on implementation of the total quality system of which monitoring and validation around air quality is just one part.

The draft requirements also state that critical reagents and materials should meet documented requirements and specifications and when applicable the requirements of the relevant Directives, namely Directive 98/79/EC on in vitro diagnostic medical devices and 93/42 on Medical Devices.

Procurement and testing

IUI and GIFT patient's will not have to be screened for HIV, Hepatitis B and Hepatitis C if the establishment can demonstrate that the risk of cross contamination and staff exposure has been addressed through the use of validated processes. (E.g. the use of a class II hood and a policy of processing only one patient's sample at a any one time.)

There must be procedures in place to protect the safety of the gamete provider. Also to protect properties of the gametes and minimise cross contamination. Any adverse event occurring during procurement that may cause harm to the gamete provider, and the outcome of any investigation to determine the cause must be recorded and reviewed.

Policies and procedures must also be in place to minimise the risk of contamination by staff who

might be infected with transmissible diseases.

Sterile instruments and devices must be used for procurement. Instruments or devices must be of good quality, validated or specifically certified and regularly maintained for the procurement of gametes. When reusable instruments must be used, a validated cleaning and sterilisation procedure for removal of infectious agents has to be in place. Wherever possible only CE marked medical devices shall be used and all relevant staff should receive appropriate training on such devices.

Storage / packaging for the transport of gametes between premises

Article 21:

All storage processes shall be carried out under controlled conditions. Procedures shall be applied to the control of packaging and storage areas in order to prevent any situation that might adversely affect the functioning or integrity of the tissues and cells.

Storage conditions necessary to maintain the required tissue properties, including relevant parameters such as temperature must be defined. Critical parameters (e.g. temperature, humidity, potential contamination) must be controlled, monitored, and recorded to demonstrate compliance with the specified storage conditions.

Where sperm is moved from one area to another within an establishment (for example by a patient walking with the pot under an armpit etc), establishments will be expected to produce documented validation to support that the practice maintains the critical parameters of the sperm. Alternatively a portable incubator should be used.

Quality Management

Monitoring

In the processing area, critical parameters (e.g. temperature, potential contamination) must be controlled, monitored, and recorded.

Audit and Quality Control

Self-inspections and audit systems should be in place. Trained and competent staff within the organisation should conduct this in an objective way according to approved protocols. Establishments must also arrange for an appropriate professional from another IUI, GIFT or IVF establishment to audit their procedures in order to obtain independent feedback and share learning points.

The self-inspection should encompass all parts of the operation that influence quality and safety of tissues and cells and shall be carried out at least annually, in order to verify compliance with the approved protocols and the regulatory requirements. All results should be documented.

Processes should undergo regular critical evaluation to ensure that they continue to achieve the intended results and the quality control system should be reviewed to ensure continuous and systematic improvement.

Validation

Processing procedures should be validated in order to ensure the process is capable of achieving the required outcome without rendering the gametes clinically ineffective or harmful to the recipient. This validation may be based on previously published studies or by retrospective evaluation of data. There should be a written SOP for the validation and the results should be documented.

When technical procedures cannot be verified at any particular time throughout the process, appropriate parameters must be identified and must be continuously monitored to ensure that the established specifications are met.

New processes must be validated before they are implemented. Where any significant change in processing occurs the validation steps must be repeated and documented.

Traceability

Article 8:

All tissues and cells procured, processed, stored or distributed shall be traced from donor to recipient and vice versa. This traceability shall apply to all relevant data relating to products and materials coming into contact with these tissues and cells.

Data relating to traceability must be accessible for 30 years. Records should include:

- gamete provider identification
- identification of the establishment
- unique donation ID number
- Date of procurement and application
- Place of procurement

- Type of donation (e.g. allogenic)

Adverse events / reactions

Article 11:

The PR shall ensure that the competent authority is notified of any serious adverse events and reactions and is provided with a report analysing the cause and ensuing the outcome.

The PR should notify the competent authority of any serious adverse event or reaction as soon as practically possible. Under the Directive the HFEA is likely to require reporting within 12 working hours in line with existing Code of Practice requirements.

Establishments will be required to report any cases of transmission of infection through gametes or any other suspected serious adverse reaction which may be attributable to the procurement. The HFEA will provide a reporting template, based on a generic template provided by the European Commission. The HFEA will also provide guidance on our interpretation of what is covered under the definition of 'adverse event' and 'adverse reaction' under the Directive.

The HFEA will compile and monitor reports of adverse events and reactions, and will investigate incidents as necessary. This may involve an inspection of the premises or may be done purely through correspondence. The HFEA encourages incident reporting and the investigation system is intended to provide practical support to the staff and share learning points, in addition to addressing any regulatory issues.

The establishment should have SOPs in place for reporting and dealing with adverse events and reactions.

Documentation

Confidentiality

Article 14:

All data collated within the scope of the Directive and to which third parties have access will have been rendered anonymous.

This will mean documentation transferred between the establishment and any third parties *that are not licensed and directly involved in the patient's care* will have to have patient names anonymised.

Record keeping

Articles 8 and 16:

The quality system should include at least the following documentation:

- Standard operating procedures
- Guidelines
- Training and reference manuals
- Reporting forms

Donor records and Information on the final destination of tissues or cells

The clinician responsible for the gamete provider must determine and document, based on medical history and therapeutic indications, the justification for the 'donation' and its safety for the recipient and any children that might result. Information on the destination of the gametes should be documented in the patient records.

For each treatment there must be a record containing:

- Consent; including the purpose for which the gametes are used and any specific instructions for disposal if the gametes are not used for the purpose for which consent was obtained
- Gamete provider identification and characteristics; type of donor, age, sex, presence of risk factors
- Partner identification
- Place of procurement
- Gametes obtained and relevant characteristics

This documentation will be available for inspection by the competent authority. Tissue establishments shall keep the data necessary to ensure traceability. Data required for full traceability shall be kept for a minimum of 30 years after clinical use. Data storage may be in electronic form.

Document management

There must be a system in place that results in clearly-defined and effective documentation, correct records and registers and authorised SOPs. The system should ensure that work is standardised, and that all steps are traceable

Documents should be regularly reviewed and changes acted upon promptly. Amendments should

be dated and signed by an authorised person. A document control procedure should log the history of document reviews and adjustments, and ensure that only current versions of documents are in use.

Records should be reliable and a true representation of the results. They must be legible and may be hand-written or transferred to another system, such as a computer or microfilm.

All records, including raw data, which are critical to the safety and quality of the tissues and cells, should be kept for 30 years after expiry date or disposal. Establishments may wish to archive old records in off site storage facilities until the expiry date. This is acceptable providing the PR is satisfied that confidentiality will be maintained, a documented third party agreement is in place, and the data is accessible if needed.

Reporting

Article 10:

Tissue establishments shall keep a record of their activities and shall submit an annual report to the HFEA. This report shall be publicly accessible. A publicly assessable list will be compiled by the HFEA detailing the establishments that hold a licence and the licensable activities that they offer.

This will mean a record must be kept to include:

- The types of licensable treatments carried out by the establishment;
- The numbers of treatment cycles carried out by the establishment.

The HFEA will clarify the reporting period and the type of data required. Templates of all reporting forms should be kept centrally.

The HFEA is obliged under the Directive to compile a publicly assessable list detailing the establishments that hold a licence and the licensable activities that they offer.

Regulation

Inspection and Licensing

Article 6:

Member States shall ensure that all tissue establishments where activities of testing, processing, preservation, storage or distribution of human tissues and cells intended for human applications are undertaken have been licensed by a competent authority for the purpose of those activities.

The licensing process will be based on evidence submitted to the HFEA, and through on site inspections.

Article 7:

Agreements between tissue establishments and third parties shall be examined within the framework of the licensing procedure. The competent authority shall be empowered to:

- **Inspect tissue establishments and the facilities of any third parties;**
- **Evaluate and verify the procedures and activities of the tissue establishment and the facilities of any third parties;**
- **Examine any documents or other records relating to the requirements of the Directive.**

The HFEA will have the power to examine third party agreements during the inspection process and to request that copies are sent to the HFEA upon request. The HFEA will have the power to inspect the premises of third parties where it is considered necessary, but this will not be a routine part of the inspection process for every establishment.

Article 4:

The Directive does not prevent a member state from maintaining or introducing more stringent measures.

Most of the requirements are taken directly from the two commission technical directives. However, in some circumstances the HFEA will go into greater detail when providing guidance to establishments through the HFEA Code of Practice. This is for two reasons; firstly to help establishments implement the requirements by providing practical guidance. Secondly to ensure that the UK implements the Directive in a way that is consistent with existing regulation under the HF&E Act 1990. For example, HFEA will require that adverse events/reactions are reported within 12 working hours, whereas the Directive does not specify exactly when events/reactions should be reported. This is to streamline incident reporting requirements under the Directive with existing HFEA procedures relating to adverse incidents.

Inspections shall be organised and control measures carried out by the competent authority. The interval between two inspections shall not exceed two years.

The competent authority may suspend or revoke the licence of a tissue establishment or of a tissue or cell preparation process if inspections or control measures demonstrate that an establishment or process does not comply with the requirements.

The competent authority shall organise inspections or carry out control measures as appropriate whenever there is any serious adverse reaction or event.

We hope that the regulations that bring the Directive into force will allow establishments to obtain a licence prior to the implementation date of the detailed requirements. This will enable establishments to continue offering treatment legally. In due course the HFEA will provide an application form and details on how to apply. The initial licence is likely to include a self assessment by the prospective PR. We are currently planning to a timetable of physical inspections taking place after April 2007. All establishments will have to have undergone formal inspection by April 2009.

Some establishments may be inspected more frequently than once in two years and this will be determined by risk analysis. After the initial licensing process it is possible that there will be a greater emphasis on self assessment and audit of documentation rather than on site interviews.

The HFEA will investigate adverse events and reactions, and in some cases this may include an inspection of the establishment.

The HFEA will have the power to revoke licences where the legal requirements are not being met. Where areas of guidance are breached the HFEA may impose licence conditions that must be met in order for a licence to continue.

Member States shall, upon request of another Member State or the Commission, provide information on the results of inspections and control measures.

The outcome of HFEA inspection and licensing procedures are already publicly accessible under the Freedom of Information Act 2000, and this will include previously unlicensed establishments under the Directive.

Penalties

Article 27:

Member States shall lay down rules on penalties and shall take all measures necessary to ensure they are implemented. Penalties must be effective, proportionate and dissuasive.

Penalties under the Directive may include licence conditions, more frequent inspections, and the HFEA will have the power to revoke licences in extreme cases. The precise measures to be taken will be determined by the Department of Health as they draft the regulations that will transpose the Directive to UK law.

Definitions

The following definitions are taken from the text of the 'parent' Directive and the two commission technical directives.

Distribution

Transportation and delivery of tissues and cells intended for human applications;

Donation

Donating human tissues or cells intended for human applications. 'Partner donation' means donation of gametes between partners who have an intimate physical relationship;

Donor

Every human source of human tissues and cells;

Processing

All operations involved in the preparation, manipulation, preservation and packaging of tissues or cells intended for human applications;

Procurement

Process by which tissues or cells are made available;

Quality management

The co-ordinated activities to direct and control an organisation with regard to quality;

Quality system

The organisational structure, responsibilities, procedures, processes, and resources for implementing quality management, including all activities contributing to quality, directly or indirectly;

Serious adverse event

Any untoward occurrence associated with procurement, testing, processing, storage and distribution of tissues or cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity;

Serious adverse reaction

An unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity;

Standard operating procedures (SOPs)

Written instructions describing the steps in a specific process including the materials and methods to be used and the expected end product;

Storage

Maintaining the product under appropriate controlled conditions until distribution;

Tissue establishment

A tissue bank or a unit of a hospital or another body where activities of processing, preservation,

storage or distribution of human tissues and cells are undertaken. It may also be responsible for procurement or testing of tissues and cells;

Traceability

The ability to identify and locate the tissue/cell during any step between its donation, procurement, processing, testing, storage, and distribution, whether to recipient or disposal. It implies the capacity to identify the donor and the tissue establishment, or the manufacturing facility receiving the tissue/cells and, at the medical facility/facilities, the ability to identify the recipient(s). Traceability also concerns all relevant data relating to products and materials coming into contact with these tissues/cells;

Validation

Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality attributes. A process is validated to evaluate the performance of a system with regard to its effectiveness based on intended use.