

Scope of the European Medical Device Directives

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Can a product that incorporates nonviable human tissue be regulated as a medical device in Europe? Is a product that includes viable tissues or cells of animal origin regulated as a medical device? Is a product that incorporates a human blood derivative regulated as a medical device? This article discusses the scope of the medical device Directives and the regulatory status of products that are excluded.

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Establishing the exclusions

Recently, a United States medical device manufacturing company that markets medical devices in Europe decided to introduce a new product composed of human tissue that had been rendered nonviable. It was not until important marketing decisions had been made that it realised that the product was not covered by the Medical Device Directive (MDD) (93/42/EEC). Furthermore, it was unclear whether or not the product would be covered by the new European regulation on tissues and cells, which is discussed later in this article; by other European Directives or regulations; by national regulations; or not covered at all.

In this case, the product was not covered by the new European regulation on tissues and cells, the Advanced Therapy Medicinal Products (ATMP) regulation,¹ because the product did not act principally by pharmacological, immunological or metabolic action. Furthermore, the product was not covered by the European Directives on tissue donation,^{2,3,4} because the product was rendered nonviable before importation into Europe. Thus, to determine the regulatory requirements applicable to the product, it was necessary to check each European market where the product was to be marketed.

This highlights the importance of being aware of the products that are excluded from the MDD and the Active Implantable Medical Device Directive (AIMDD) (90/385/EEC). These exclusions are listed in Table I. Based on this information, a product that includes viable tissues or cells of animal origin is not regulated in Europe as a medical device. Whereas, a product that otherwise meets the definition of a medical device and that incorporates a human blood derivative as an integral part, with action ancillary to that of the device, is regulated as a medical device under the MDD or AIMDD, whichever is applicable.

The In Vitro Diagnostics (IVD) Medical Device Directive (98/79/EC) excludes products for general laboratory use unless those products are specifically intended by the manufacturer to be used for in vitro diagnostic examination. In addition, the IVD Directive does not apply to devices manufactured and used only within the same health institution and on the premises of their manufacture or used on premises in the immediate vicinity without having been transferred to another legal entity.

New Advanced Therapy Medicinal Products regulation

On 10 December 2007, the ATMP regulation was published in the *Official Journal* of the European Communities. The regulation became effective on 30 December 2007 and is to be implemented in Member States by 30 December 2008. The scope of this regulation includes:

- Gene therapy medicinal products, as defined in Part IV of Annex I to Directive 2001/83/EC on medicinal products for human use⁵
- Somatic cell therapy medicinal products, as defined in Part IV of Annex I to Directive 2001/83/EC
- Tissue engineered products, which are defined as products that contain or consist of engineered cells or tissues, and are presented as having properties for, or are used in or administered to human beings, with a view to regenerating, repairing or replacing a human tissue.

The ATMP regulation states that a tissue engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or nonviable. It may also contain additional substances such as cellular products, biomolecules, biomaterials, chemical substances, scaffolds or matrices. Cells or tissues will be considered to be “engineered” if they fulfil at least one of the following conditions: →



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- ■ The cells or tissues have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved
- The cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.

There are also important exclusions in this ATMP regulation. For example, Annex I of the regulation lists manipulations that are not considered “substantial manipulations.” These include, cutting, grinding, shaping, centrifugation, soaking in antibiotic and antimicrobial solutions, sterilisation, irradiation, filtering, lyophilisation, freezing, cryopreservation and vitrification; and cell separation, concentration and purification. This means that any product that is processed using one of these means would not meet the definition of “engineered” tissues or cells. In addition, if the product does not meet the definition of a “gene therapy medicinal product” or a “somatic cell therapy medicinal product,” it is not covered by the ATMP regulation. Products containing or consisting exclusively of nonviable human or animal cells and/or tissues that do not act principally by pharmacological, immunological or metabolic action, are excluded from the definition of “tissue engineered product.”

Table I: Products excluded from the MDD and AIMDD, as specified in Article 1, Definitions, Scope of the Directives.

- Transplants or tissues or cells of human origin or products incorporating or derived from tissues or cells of human origin
- Human blood, blood products, plasma or blood cells of human origin
- Devices that incorporate blood products, plasma or cells, with the exception of devices that incorporate as an integral part, a human blood derivative, which is liable to act upon the human body with action ancillary to that of the device
- Transplants or tissues or cells of animal origin, unless the device is manufactured utilising animal tissue that is rendered nonviable, or nonviable products derived from animal tissue
- A combined advanced therapy medicinal product, which means an advanced therapy medicinal product that incorporates, as an integral part of the product, one or more medical devices (as defined in the MDD) or AIMDs and a cellular or tissue part that contains viable cells or tissues, or a cellular or tissue part containing nonviable cells or tissues that are liable to act on the human body with action that can be considered as primary to that of the medical device.
- In vitro diagnostic devices
- Medicinal products covered by Directive 65/65/EEC (now updated as 2001/83/EC), including medicinal products derived from blood as covered by Directive 89/381/EEC
- Cosmetic products covered by Directive 76/768/EEC
- Personal protective equipment (PPE) covered by Directive 89/686/EEC; however, when changes from Directive 2007/47/EC, the Directive revising the MDD and AIMD, are implemented, the relevant basic health and safety requirements of Directive 89/686/EEC will also need to be met when the intended use covers the medical devices and PPE Directives.
- A medicinal product to be administered by a device
- A device that administers a medicinal product, that is placed on the market in such a way that the device and the medicinal product form a single integral product, which is intended exclusively for use in the given combination.

Regulation on tissue donation

Medical technology products that are not regulated under the European medical device Directives or under the forthcoming ATMP regulation may be covered by Directive 2004/23/EC concerning tissue donation.² This Directive came into effect on 7 April 2006, with a one-year transition period for “tissue establishments” that met prior national legislation. The primary purpose of the Directive is to standardise the quality and safety standards for tissues and cells across the European Union with regard to the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells intended for human applications, and of manufactured products derived from human tissues and cells intended for human applications. The Directive specifies requirements for

- the designation of national Competent Authorities
- the accreditation, designation, authorisation or licensing of “tissue establishments” and tissue and cell preparation processes
- import and export of human tissues and cells
- notification of serious adverse events and reactions
- donor selection, evaluation and consent
- quality management
- tissue and cell receipt, processing, storage, labelling, distribution and traceability.

Article 4 of the Directive, however, states that it shall not prevent a Member State from maintaining or introducing more stringent protective measures. In particular, a Member State may introduce requirements for voluntary unpaid donation, which include the prohibition or restriction of imports of human tissues and cells, to ensure a high level of health protection. The Directive also does not affect the authority of Member States to prohibit the donation, procurement, testing, processing, preservation, storage, distribution or use of any specific type of human tissues or cells, or cells from any specified source, including where decisions that concern imports of the same type of human tissues or cells.

Many of the technical requirements for implementation of the Directive were left to decisions made by a committee set up under Article 29 of the Directive, with the result that two additional implementing Directives were adopted in 2006.

Directive 2006/17/EC³ establishes specific technical requirements for each of the steps in the human tissue and cell application process defined in 2004/23/EC. Annex I specifies requirements for the selection criteria for donors, deceased and living; Annexes II and III provide details of the biological tests required for donors; and Annex IV includes requirements for procurement and receipt of cells/tissues at the tissue establishment. This Directive was scheduled to be implemented in Member States by 1 November 2006.

Directive 2006/86/EC⁴ specifies requirements for the accreditation, designation, authorisation or licensing of tissue establishments and cell preparation processes; and requirements for reporting serious adverse reactions; adds details to the traceability requirements of 2004/23/EC;


and, requires a single European identifying code to be allocated to all donated material. This Directive was to be implemented in Member States by 1 September 2007, except for the provision of the European coding system, which is scheduled to be operational by 1 September 2008.

Critical step in product launch strategy

Before any decisions are made with regard to the introduction of a medical technology product onto the European market, the regulatory status of the product should be determined. This is particularly important with products that may contain human or animal tissues and the continuing evolution of regulatory requirements for some types of these products. When the ATMP regulation is implemented in Europe, many products that were previously not regulated under European harmonised regulation will be subject to this regulation. In other cases, other European Directives or regulations may apply. In some cases, only national regulations will apply and in yet other cases, no regulations may be applicable. Prudent manufacturers will understand these issues before making important marketing decisions.

References

1. Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal

- products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. Downloadable from <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev1.htm>
2. Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. The documents in References 2, 3 and 4 are downloadable from http://ec.europa.eu/health/ph_threats/human_substance/legal_tissues_cells_en.htm
3. Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells.
4. Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells.
5. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (*Official Journal* L 311, 28/11/2001 pp. 67–128). Downloadable from <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev1.htm> 

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