European Animal Tissue Directive

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In less than nine months, manufacturers of medical devices containing certain types of tissues of animal origin will need to ensure that their products comply with newly mandated specifications. They should not wait until the last minute to begin this work. This article discusses the important issues that will need to be addressed to ensure effective compliance with the requirements.

Resolving regulatory differences

The risks of infection and contamination that medical devices could pose to patients and users has been addressed in the European medical device Directives, European guidance documents and standards. In spite of these measures, some European national authorities have enacted additional requirements to reduce the risks of transmitting transmissible spongiform encephalopathies (TSE) by medical devices. This has meant that differences exist at the national level, a situation that conflicts with the intent of European regulation.

To respond to the actions being taken at the national level and reinforce the protective measures against the risk of transmitting TSE by medical devices, a Commission Directive[1] was adopted on 23 April 2003. This Directive introduces detailed specifications for medical devices regulated under the Medical Device (MD) Directive (93/42/EEC) that are manufactured using animal tissue rendered nonviable or using nonviable products derived from animal tissue. An important feature of the Animal Tissue (AT) Directive is that it mandates some of the voluntary measures described in the European guidance documents and harmonised standards.

Manufacturers of medical devices subject to the AT Directive must also comply with all applicable provisions of the MD Directive. Manufacturers holding an EC design-examination certification or an EC type-examination certificate issued before 1 April 2004 must obtain a complementary design-examination certificate or EC type-examination certificate attesting to compliance with the specifications of the Annex of the AT Directive no later than 30 September 2004. The AT Directive also specifies that Member States must adopt and publish the provisions necessary to comply with the Directive before 1 January 2004 and apply those provisions with effect from 1 April 2004. Therefore, after 30 September 2004, medical devices subject to the AT Directive will only be able to be placed on the market and put into service if they comply with its requirements.

Materials covered

The AT Directive covers animal tissues originating from bovine (cows), ovine (sheep), and caprine (goats) species, and deer, elk, mink and cats. Animal tissue from porcine (pigs) sources is not covered. Article 1(3) includes another important requirement that collagen, gelatin and tallow used for the manufacture of medical devices should be at least fit for human consumption.

Excluded devices

The AT Directive does not apply to medical devices that are not intended to come into contact with the human body or that are intended to come into contact with intact skin only (Article 1(4)). It should also be noted that medical devices manufactured using nonviable or nonviable products derived from animal tissue, which are regulated →

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under the In Vitro Diagnostic (IVD) Directive (98/79/EC) or the Active Implantable Medical Device Directive (90/385/EEC), are excluded from the AT Directive.

IVD Directive and animal tissues

The IVD Directive contains some provisions for the protection of those coming into contact with IVD devices that include substances of human or animal origin. Essential requirement 8.7(s) of the IVD Directive requires that, where appropriate, instructions for use must contain precautions to be taken against any special, unusual risks related to the use or disposal of the device including special protective measures. In addition, it requires that where the device includes substances of human or animal origin, attention must be drawn to their potential infectious nature.

Need for risk analysis and risk management

The AT Directive contains detailed requirements for risk analysis and risk management activities, which is one of the principal reasons why manufacturers should begin now to ensure full compliance with the Directive within the specified timeframe. Article 3 requires that risk analysis and risk management activities described in the Annex to the Directive be conducted before lodging an application for a conformity assessment pursuant to Article 11(1). These activities are detailed and include

- a justification for the use of animal tissues or derivatives based on an overall risk analysis and risk management strategy for a specific medical device
- an assessment procedure
- review of the assessment.

The assessment procedure includes the

- implementation of an appropriate and well-documented risk analysis and risk management strategy
- identification of hazards associated with the tissues and derivatives
- establishment of documentation on measures for minimising the risk of transmission
- demonstration of the acceptability of the residual risk associated with the device using animal tissues or derivatives.

In addition, a series of factors related to the safety of the device must be analysed, evaluated and managed. These factors include animals as a source of material, geographical sourcing, nature of the starting tissue, inactivation or removal of transmissible agents, quantities of animal starting tissues or derivatives required to produce one unit of the medical device, tissues or derivatives of animal origin coming into contact with the patients and users' route of administration.

Reference documents

The Directive refers to a number of important reference documents. One of these includes Regulation (EC) No 1774/2002, which lays down health rules concerning animal by-products not intended for human consumption.[2] Reviewing these documents will take time and is another reason why manufacturers should not wait until the last minute to begin efforts to comply with the AT Directive.

Notified Body responsibilities

Additional responsibilities are specified for Notified Bodies involved in the conformity assessment of medical devices subject to the AT Directive. These are described in Article 5 and Section 2 of the Annex. For example, Article 5 requires that Notified Bodies evaluate the manufacturer's risk analysis and risk management strategy, including the information provided by the manufacturer, justification for the use of animal tissues or derivatives, the results of elimination and/or inactivation studies or of the literature search, the manufacturer's control of the sources of raw materials, finished products and subcontractors, and the need to audit matters related to sourcing, including third-party supplies.

If a TSE certificate of suitability issued by the European Directorate for the Quality of Medicines has not been issued for starting materials used in the manufacture of medical devices, Notified Bodies must take the following action. They are obliged, through their Competent Authority, to seek the opinion of Competent Authorities of other Member States on their evaluation of, and conclusions on, the risk analysis and risk management of the tissues or the derivatives intended to be incorporated in the medical device.

Under Section 2 of the Annex, Evaluation of Class III Medical Devices by Notified Bodies, manufacturers must provide Notified Bodies with any new information on TSE risk that is collected by the manufacturer and relevant to the devices. Also, an additional approval must be obtained from the Notified Body for any change in relation to processes of sourcing, collection, handling and inactivation/elimination that could modify the result of the manufacturer's risk management dossier.

European guidance document

In an effort to address the risks associated with medical devices incorporating materials of animal origin, the European Commission published a guidance document in February 1999 on assessment of medical devices incorporating materials of animal origin with respect to viruses and transmissible agents.[3] The AT Directive clearly reflects the issues and approaches that it describes regarding TSE-related controls. Manufacturers should ensure that their medical devices fully comply with the AT Directive, as transposed by national authorities, and then consider the information contained in the Guideline. According to industry trade association sources, another European guidance document to assist in complying with the AT Directive may be issued in future.

Harmonised standards

There are three harmonised standards on medical devices containing animal tissues and their derivatives:

- EN 12442-1:2000, Animal Tissues and Their Derivatives ➔

Utilised in the Manufacture of Medical Devices, Part 1: Analysis and Management of Risk

- EN 12442-2:2000, Animal Tissues and Their Derivatives Utilised in the Manufacture of Medical Devices, Part 2: Controls on Sourcing, Collection and Handling
- EN 12442-3:2000, Animal Tissues and Their Derivatives Utilised in the Manufacture of Medical Devices, Part 3: Validation of the Elimination and/or Inactivation of Viruses and Transmissible Agents.

Efforts are underway to develop a series of international standards on animal tissues and their derivatives used in the manufacture of medical devices employing the existing European harmonised standards as a basis. Based on discussions with European industry representatives and a press release issued by the United States Association for the Advancement of Medical Instrumentation on 11 June 2003, these new standards will be developed by International Organisation for Standardisation (ISO) Technical Committee (TC) 194, Biological evaluation of medical devices, working in co-operation with European Committee for Standardisation (CEN) TC 316, Medical Devices Utilising Tissue. CEN TC 316 developed the existing European standards. The successful development of ISO standards that continue to include provisions that support compliance with the European essential requirements will contribute to the continuing efforts toward worldwide harmonisation of medical device requirements, including those that incorporate animal tissues.

References

1. Commission Directive 2003/32/EC of 23 April 2003 introducing detailed specifications on the requirements laid down in Council Directive 93/42/EEC with respect to medical devices manufactured utilising tissues of animal origin, <http://europa.eu.int/comm/enterprise/medical_devices/index.htm>
2. Regulation (EC) No 1774/2002 of the European Parliament and of the Council of 3 October 2002 laying down health rules concerning animal by-products not intended for human consumption < http://europa.eu.int/eur-lex/en/index.html>
3. European Commission Medical Devices: Guidance document, Guidelines on assessment of medical devices incorporating materials of animal origin with respect to viruses and transmissible agents, MEDDEV 2.5-8 rev 2, February 1999 <http://europa.eu.int/comm/enterprise/medical_devices/meddev/index.htm> mdt

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