EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

Single Market : regulatory environment, standardisation and New Approach
Pressure equipment, medical devices, metrology

MEDDEV. 2.11/1 rev.1
February 2004

GUIDELINES ON MEDICAL DEVICES

APPLICATION OF COUNCIL DIRECTIVE 93/42/EEC TAKING INTO ACCOUNT THE COMMISSION DIRECTIVE 2003/32/EC FOR MEDICAL DEVICES UTILISING TISSUES OR DERIVATIVES ORIGINATING FROM ANIMALS FOR WHICH A TSE RISK IS SUSPECTED

A GUIDE FOR MANUFACTURERS AND NOTIFIED BODIES

Note

The present Guidelines are part of a set of Guidelines relating to questions of application of EC-Directives on medical devices. They are legally not binding. The Guidelines have been carefully drafted through a process of intensive consultation of the various interest parties (competent authorities, Commission services, industries, other interested parties) during which intermediate drafts were circulated and comments were taken up in the document. Therefore, this document reflects positions taken by representatives of interest parties in the medical devices sector.

This guidance is based on Commission Directive 2003/32/EC dated 26.04.2003 in O.J.E.C.

Introduction

Commission Directive 2003/32/EC makes provision for the management of risks arising from medical devices that utilise tissues or derivatives originating from animals for which a TSE risk is suspected. The Directive requires that such devices, whether new or already on the market, be subject to a risk management scheme which incorporates a risk assessment. For all new and existing devices within the scope of the Directive the manufacturer is required to submit the risk assessment to a Notified Body for an evaluation prior to certification.

Member States are responsible for ensuring that those Notified Bodies who are designated to evaluate devices utilising animal tissues or derivatives, are appropriately experienced and qualified to evaluate the risk control measures adopted by the manufacturer and to verify conformity with Commission Directive 2003/32/EC. In addition, Member States are responsible for facilitating verification of the Notified Body's evaluation of the manufacturer's risk management activities. Such verification is not necessary when the suitability of all the susceptible starting materials has been certified by the European Directorate for the Quality of Medicines (EDQM).

It should be kept in mind that the requirement in this Commission Directive 2003/32/EC does not alter the provisions of the Medical Devices Directive (93/42/EEC) and both are applicable to relevant products to achieve conformity with the regulations.

Scope

The scope of this Directive applies to medical devices in Directive 93/42/EEC that utilise animal tissue (from bovine, ovine, caprine species or deer, elk, mink or cats) rendered non-viable or non-viable products (e.g. collagen, gelatin). These may comprise a major part of the device (e.g. bovine cardiac valves, bovine bone for orthopaedic surgery or collagen as a wound dressing) a coating/impregnation of the product (e.g. gelatin impregnated vascular graft) or an aid to the manufacturing stages of production (e.g. foetal calf serum used in microbial cell culture for the production of hyaluronic acid in ophthalmic products).

Products that "do not come into contact with the human body" and those that "are intended to come into contact with intact skin only" are excluded by Article 1.4 Directive 2003/32/EC. Whilst these two categories, of *in-vitro* diagnostic medical devices and products such as leather orthopaedic footwear, are excluded from this Directive the application of a risk management scheme by the manufacturer is appropriate under all circumstances.

Tallow derivatives (e.g. stearates) may be utilised as a plasticiser or mould releasing agent in the production of some medical devices (e.g. blood bags). Whilst these are considered excluded from this Directive the application of a risk management scheme and the requirements of Directive 93/42/EEC by the manufacturer is still relevant[1].

[1] For example, tallow derivatives such as glycerol and fatty acids should be produced by vigorous processes which have been subject to specific consideration, see Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products, OJ, C 24, 28.01.2004, p 6 - 19.

Therefore this Directive is applicable to all medical devices which utilise animal tissue rendered non-viable or non-viable products derived from animal tissue, including non-invasive devices such as those used for channelling or storing blood, body liquids or tissues, liquids or gases for subsequent infusion, administration or introduction into the body.

Purpose

The purpose of this guidance is to aid the common application of Commission Directive 2003/32/EC by clarifying some aspects of its interpretation. In particular it addresses the evaluation performed by the Notified Body, the activities of the coordinating Competent Authority and the verification role of the other Competent Authorities.

Evaluation by the Notified Body

The Notified Body's evaluation is expected to focus on the primary aim of the Commission Directive, namely the justification for the use of non-viable animal tissue or derivatives from a TSE-susceptible species. Such a justification should be based on an overall risk:benefit assessment for the product that compares the risks and benefits arising from the use of the animal-derived material with those relating to the available alternatives. The risk analysis should thus consider both similar materials sourced from non-TSE-susceptible species and any synthetic materials. The Notified Body should ensure that the overall risk assessment for the product takes into account the TSE risk and that this risk assessment has been undertaken as part of a documented risk management process.

In reaching a decision on the suitability of the product for its intended use and the acceptability of the TSE risk, Notified Bodies should take into account at least the following information, where applicable:

- a critical analysis of pre-clinical and clinical data to support any specific advantages claimed;
- an evaluation of the characteristics and performance of alternative materials (e.g. materials of animal origin that are not susceptible to TSE infection and synthetic materials) to determine their ability to achieve the desired product characteristics and intended purpose;
- an evaluation of the measures adopted to minimise the risk of infection, including sourcing and veterinary controls[2], feeding restrictions, harvesting practices, significant processing stages, elimination and/or inactivation studies, or of literature searches;
- whether or not the product complies with relevant standards[3];
- confirmation that any collagen, gelatin or tallow used meets the requirements "fit for human consumption" [4];

[2] Essential Requirement 8.2 of the MDD (93/42/EEC) requires Notified Bodies to retain information on the geographical origin of the animals, and these materials originate from animals subject to veterinary controls and surveillance.
[3] EN ISO 14971, Medical devices - the application of risk management to medical devices and EN 12442, Animal tissues and their derivatives utilized in the manufacture of medical devices Parts 1, 2 & 3, are considered to be relevant.
[4] The material of animal origin intended for utilisation in the medical device should have originated from animals confirmed by a veterinarian as being fit for human consumption. For species not usually consumed by humans a status equivalent to "fit for human consumption" is required. Tallow should be prepared by a recognised processing method, see Regulation (EC) 1774/2002.

- any evaluation and certification of the suitability of raw materials by the European Directorate for the Quality of Medicines (EDQM).

The Notified Body should document the key elements of its evaluation as a "Summary Evaluation Report". The purpose of this report is to provide confirmation that the relevant supporting documentation has been evaluated by the Notified Body and is deemed sufficient to demonstrate compliance to the TSE-relevant parts of Commission Directive 93/42/EEC and the whole of Commission Directive 2003/32/EC. The Summary Evaluation Report should briefly characterise the TSE hazard, estimate the risk and outline applicable risk control measures. It should include:

- a product description, including information on intended use and composition. This should include information on the nature of the starting tissue [5], the species and geographical origin;

- a description of the key elements adopted to minimise the risk of infection;

- a qualitative or quantitative estimate of the TSE risk arising from the use of the product, taking into account the likelihood of contamination of the product, the nature and duration of patient exposure;

- a justification for the use of animal tissues or derivatives in the medical device, including a rationale for the acceptability of the overall TSE risk [6] estimate, the evaluation of alternative materials and the expected clinical benefit;

- the approach to the auditing of source establishments and/or third party suppliers for the animal material used by the medical device manufacturer;

- a conclusion statement.

Verification by the Competent Authorities

The role of the Competent Authorities is to verify that ;

- the procedures set out in Commission Directive 2003/32/EC have been followed and that sound judgements have been made;

If the device utilises only EDQM certified starting materials, the opinion of the other Competent Authorities need not be sought.

Some Competent Authorities may choose to approach other Member States or a relevant National Authority (e.g. a national committee of specialists) for assistance. Where this is the case, it will be necessary for the Competent Authority to ensure that there are no conflicts of interest, that all data are maintained in confidence and that the consultation is carried out in a timely manner.

[5] The infectivity classification table of materials for sheep and goats should continue to be considered indicative for the selection of source materials from other species (e.g. deer, elk, mink, cat) known to be susceptible to TSEs. See WHO Guideline on Transmissible Spongiform Encephalopathies in Relation to Biological and Pharmaceutical Products (February 2003).

[6] This must take into account any evaluation and certification by EDQM, to demonstrate conformity with relevant monographs on the reduction of TSE risk in respect of starting materials.

National Competent Authorities are requested to provide an update on the progress of these conformity assessments at the Medical Devices Experts Group meetings.

Coordinating Competent Authority

The Notified Body is required to approach its National Competent Authority, who will then seek the opinion of the Competent Authorities of the other Member States on the evaluation and conclusions in the Summary Evaluation Report. As the designating authority, the Notified Body's National Competent Authority is also responsible for verifying that the Notified Body has sufficient knowledge to assess conformity for these devices.

The role of the Coordinating Competent Authority is thus to ensure that :

- the opinions of the Competent Authorities of the other Member States are sent to the Notified Body within twelve weeks of the date of the receipt of information from the Notified Body.

- Notified Bodies undertaking the evaluation of products subject to Commission Directive 2003/32/EC have appropriate knowledge and experience to perform the risk assessment.

The Coordinating Competent Authority should acknowledge receipt of any request for an opinion, act as a channel for all communications between Competent Authorities and the Notified Body, collate the opinions of the National Authorities, including their own, and pass them on to the Notified Body. Competent Authorities should complete their review on the evaluation and conclusions in the Summary Evaluation Report within nine weeks of its receipt from the Coordinating Competent Authority. This should allow sufficient time to collate the opinions and pass them directly to the relevant Notified Body.

The designating Competent Authority should amend the scope of activities of any Notified Body not deemed to posess the knowledge and experience necessary for assessing conformity of these products.

Review of the opinions from the Competent Authority

The Notified Body is required to give due consideration to any comments received through their National Competent Authority. It should document the final decision on the certification of the product and the rationale for any disagreement with the opinion of any Competent Authority. Where this occurs the Notified Body should consult with their device Competent Authority.[7] This decision should be notified to the manufacturer and the National Competent Authority, and will be made available to other Competent Authorities upon request.

If the Notified Body receives no opinions within 12 weeks of the confirmed receipt of the Summary Evaluation Report by its Competent Authority, it can finalise its decision on the certification of the product, without further reference to the Competent Authority.

[7] This approach is similar to the procedures in MEDDEV 2.1/3 for the situation of a negative opinion from a medicinal authority on a medicinal substance when its action is ancillary to the medical device.