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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, OJ EC N° L 105, 26.4.2003, p.18.

Application of Council Directive 93/42/EEC taking into account Commission Directive 2003/32/EC for medical devices utilising tissues or derivatives originating from animals susceptible for TSE

1.0 - Introduction

1.1 - 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.

1.2 - Member States are responsible for ensuring that those Notified Bodies that are verified[1] 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, all the Member States are responsible for facilitating verification of the Notified Body's evaluation of the manufacturer's risk management activities (see section 6.1). 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) (see section 5.2).

1.3 - 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.

2.0 – Scope

2.1 - Commission Directive 2003/32/EC is applicable to medical devices which utilise tissue from bovine, ovine and caprine species, or deer, elk, mink or cats rendered non-viable or non-viable products derived from such tissue. 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), an aid to the manufacturing stages of production (e.g. fetal calf serum, bovine serum albumin, enzymes, culture media) or they may be used for channelling, processing or storing blood, body liquids, cells, or tissues, liquids or gases for subsequent infusion, administration or introduction into the body.

2.2 - 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. *In-vitro* diagnostic medical devices and products such as leather orthopaedic footwear, are excluded from this Directive. Nonetheless the application of a risk management scheme by the manufacturer is appropriate under all circumstances.

[1] The Commission intends to place a list of the Notified Bodies verified for this subject on its website.

2.3 - The provisions of the Animal By Product Regulation[2] are relevant to medical devices within the scope of Commission Directive 2003/32/EC. The import, export, transit, and trade of raw and starting materials intended for medical device manufacture must therefore comply with this Regulation. A Commission guidance document[3] confirms that the Regulation is applicable to intermediate products but it is not applicable to finished medical devices[4]. As defined in the Regulation, materials used for the manufacture of medical devices shall be category 3 material or equivalent, i.e. from animals fit for human consumption (however see 2.4).

2.4 Tallow derivatives (e.g. stearates) are used, for example, as a plasticiser or mould releasing agent in the production of some medical devices (e.g. blood bags). Tallow used as the starting material for the manufacture of tallow derivatives shall be Category 3 material or equivalent, as defined by Regulation No 1774/2002, as amended. Tallow derivatives manufactured from tallow by rigorous processes have been subject to specific consideration[5]. Materials manufactured under conditions at least as vigorous as those in Annex 1 (below) should be considered compliant with the regulatory expectations of this Commission Directive. Whilst these are considered excluded from this Directive, the requirements of Directive 93/42/EEC and the application of a risk management scheme by the manufacturer is still relevant. Other tallow derivatives produced using other manufacturing conditions should demonstrate compliance with this Commission Directive.

2.5 The specific reference in this document to “cell culture media” is applicable to both Working Cell Banks and Master Cell Banks. The principles and practices on this specific subject by the medicinal sector should be adapted for the purposes of the medical device sector. (References:Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products, adopted by CPMP/CVMP, EMEA/410/01 rev2 – October 2003; O.J.E.C. 28.01.2004. Position paper on re-establishment of working seeds and working cell banks using TSE compliant materials. EMEA/22314/02 10 September 2002).

2.6 The management by Member States of the applications for the safety and quality of clinical investigations of medical devices utilising material of TSE susceptible species is the responsibility of the Competent Authority where the application is submitted. The Competent Authority should take into account the principles of the Annex in Commission Directive 2003/32/EC.

3.0 - Purpose

3.1 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.

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[2] Regulation (EC) No 1774/2002 of the European Parliament and of the Council laying down health rules concerning animal by-products not intended for human consumption (OJ L 273, 10.10.2002, p.1), last amended by Commission Regulation 92/2005.

[3] http://europa.eu.int/comm/food/food/biosafety/animalbyproducts/guidance_faq_en.pdf

[4] Quote from above-mentioned Commission Guidance: *The Animal By Product Regulation only applies to cosmetics, medicinal products (pharmaceuticals) and medical devices (including laboratory reagents) as far as the source and starting materials of animal origin that are used in the manufacture of such products are concerned. It requires that such starting materials must derive from "Category 3 materials" i.e. materials from animals fit for human consumption following veterinary checks. When such starting materials are to be imported into the EU, they must meet the minimum conditions set out in the Regulation, ensuring their safety vis-à-vis animal and public health. There were similar provisions in the animal waste Directive 90/667/EEC and the Balai Directive 92/118/EC (Annex I, Chapters 7 and 10), which have now been repealed by the Animal By Products Regulation.*

[5] Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 Rev. 2 - October 2003) adopted by the Committee for Proprietary Medicinal Products (CPMP) and by the Committee for Veterinary Medicinal products (CVMP)
Official Journal C 024 , 28/01/2004 P. 0006 - 0019

4.0 - Evaluation by the Notified Body

4.1 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 benefit/risk 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.

4.2 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 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[6], feeding restrictions, harvesting practices, significant processing stages, elimination and/or inactivation studies, or of literature searches;
- whether or not the product complies with relevant horizontal and product standards[7];
- confirmation that any collagen, gelatin or tallow used meets the requirements "fit for human consumption" [8];
- any evaluation and certification of the suitability of raw materials by the European Directorate for the Quality of Medicines (EDQM).

4.3 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 with the TSE-relevant parts of Council 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:

[6] Essential Requirements laid down in Annex I, § 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.

[7] EN ISO 14971, Medical devices - the application of risk management to medical devices and EN 22442, Medical Devices utilizing animal tissues and their derivatives , Parts 1, 2 & 3, are considered to be relevant.

[8] 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 from raw material fit for human consumption and using a recognised processing method, see Regulation (EC) 1774/2002, as amended.

- a product description, including information on intended use and composition. This should include information on the nature of the starting tissue [9], the species and geographical origin[10];

- 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 [11] estimate which takes into account the evaluation of alternative materials [12] and the expected clinical benefit [13] ;

- 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.

4.4 Where there are EDQM TSE Certificate(s) of Suitability for the starting material(s) the Notified Body shall document the complete audit trail leading to the decision for the complementary certification. The evaluation process of the medical device by the Notified Body should document and verify the indents of Section 4.3, except the first two.

4.5 The device manufacturer has the responsibility to verify the validity of the EDQM certificate underlying a medical device design examination certificate at least on an annual basis, e.g. by verifying with the supplier of the TSE material and on the EDQM website. This validity will be verified by the responsible Notified Body during the on-going regulatory audits of the medical device manufacturer.

5.0 - Verification by the Competent Authorities

5.1 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

[9] 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).

[10] Commission Regulation (EC) N° 722/2007 of 25th June 2007, amending Regulation 999/2001, replaced the four category GBR assessment procedure with a system of three country categories according to their BSE risk based on the international OIE Standards. Commission Decision N°2007/453/EC of 29 June 2007 establishes the BSE status of different Member States or third countries according to their BSE risk. Relevant parties in the device sector are expected to apply this information from the date of entry into force.

[11] 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.

[12] Such as similar materials of animal origin not susceptible to TSE or other synthetic alternatives that achieve the desired product characteristics and intended purpose.

[13] The justification should identify the specific advantages expected and include an analysis of the supporting data. For instance the device may provide an improvement in the treatment or prevention of a disease or injury, it may eliminate or reduce an existing treatment so limiting the potential for certain adverse effects, or it may provide beneficial treatment in a specific group of patients within the population.

judgements [14] have been made;

5.2 If the medical device utilises only EDQM certified starting materials, the Notified Body is not required to approach its National Competent Authority for an opinion of the Competent Authorities of the other Member States (see section 4.4). However, an exchange of information between the concerned parties (Notified Body and National Competent Authority) may be foreseen in the interest of gaining increased experience in relation to medical devices utilising EDQM certified materials [15].

5.3 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.

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

6.0 - Coordinating Competent Authority

6.1 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 [16].

6.2 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.

6.3 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.

6.4 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.

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

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[14] The verification of the review process by the Notified Body, the presentation of the summary data, the adoption of key principles for minimising the risk of TSE and the relevance of the risk factors to the risk assessment form the basis of a sound judgement which builds confidence in the safety of the product.

[15] This is outside of the certification process as detailed in the Directive.

[16] This Report (circa 3-5 pages) should be in English and is to be sent by e-mail between all the relevant parties.

6.6 The Coordinating Competent Authority should inform the other Member States on the final decision by the Notified Body on the certification of the product (e.g. confirmation the certificate was issued or refused by the Notified Body).

7.0 - Review of the opinions from the Competent Authorities

7.1 The Notified Body is required to give due consideration to any comments received through their National Competent Authority.

7.2 For uniformity and consistency the principle activities by which the Notified Body should review the opinions received from their Coordinating Competent Authority are to :

- collate all correspondence from their Coordinating Competent Authority;
- identify all the opinions raised, which may be in different formats;
- document their response, or corrective actions, to each point;
- add additional information from manufacturers data file where necessary;
- decide if they disagree with or deviate from any of the opinions from any Member State[17];
- consult with their device Competent Authority, if this was the case[18];
- record their final decision on the complementary certification of the product;
- notify the manufacturer and the National Competent Authority of this decision.

7.3 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.

8.0 - Significant changes

8.1 Information related to any changes to the sourcing, collection and handling or inactivation / elimination that may modify the result of the manufacturers risk assessment dossier must be transmitted to the Notified Body for the purposes of an additional approval prior to its implementation (e.g. the use of a different abattoir for the primary raw material, a reclassification of BSE status of the country). These ongoing activities are to be performed by the Manufacturer and the Notified Body. Any new information on TSE risk collected by the manufacturer, and relevant for their devices, must be sent to their Notified Body.

8.2 Any product involving a significant change that is assessed by the Notified Body, after consultation with their Competent Authority, as increasing the overall TSE risk will be regarded as a new product needing a renewed consultation procedure that references the previous consultation.

9.0 - Renewal of TSE Certificates

9.1 At the renewal of the Certificate[19] the Notified Body shall perform a reassessment to verify its conformity with the requirements of the relevant Directives (i.e. Council Directive 93/42/EEC and Commission Directive 2003/32/EC). In the updated design dossier, there should be information on:

[17] Where a Member State stated there was no mention of a relevant standard in the SER or there was no review of the clinical data to support the performance of the product, and the Notified Body can demonstrate it was contained in the manufacturers submission/file, it should not be viewed as a disagreement.

[18] 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.

- the updated risk analysis;
- the updated clinical evaluation;
- the test data and/or rationales in relation to applicable new harmonized standards;
- the evidence on the file to be "state of art" in relation to TSE risks, scientific knowledge, a reclassification of BSE status of the country etc.
- the justification for the use of animal tissue or derivative in the medical device (including comparison with alternatives).

9.2 The Notified Body needs to verify if aspects of the updated design dossier should be regarded as a significant increase in risk. If that is the case, the consultation process as described for significant changes will need to be followed, including the pre-evaluation on the increase of the TSE risk (see section 8.0).

10.0 - Medical device with ancillary medicinal substance utilising material from TSE species

10.1 The combination of a medical device with an ancillary medicinal substance (i.e. utilising material from a TSE species) is within the scope of the Medical Devices Directive and the TSE Directive. The Notified Body should perform their review according to the existing procedures, including liaison with the relevant medicinal authorities in relation to the consultation for the medicinal component. The consultation procedure in MEDDEV 2.1/3 should be followed. Thereafter the Notified Body should proceed with the consultation procedure (see section 4.3). For medical devices incorporating pharmaceutical substances utilising non-EDQM CEP TSE certified materials the notified bodies and competent authorities should take account that the drug regulatory body would have covered the safety and quality of the medicinal substance, including TSE issues.

10.2 This regulatory approach provides confidence in the safety of the final product as there are aspects of the TSE Directive (e.g. evaluation of alternative materials, justification rationale) which are not covered by the existing procedures alone.

11.0 - "Discoveries"

11.1 This relates to where a manufacturer of an existing medical device has verified their product to be outside the scope of Directive 2003/32/EC but is then informed by a third party the product, or its components, utilises material of TSE susceptible species. The manufacturer should explain the full details of the "discovery" and seek advice from their Notified Body[20]. Before the start of any assessment process the Notified Body and its Competent Authority shall define the full regulatory process for these special circumstances. The Competent Authority should keep the other Member States informed of their activities.

[19] Conformity assessments are typically valid for five years and may be renewed on application (Article 11, MDD).
[20] Where applicable, this may involve the manufacturer's Competent Authority.

ANNEX 1

Examples of Rigorous Processes for Tallow Derivatives are :

- Trans-esterification or hydrolysis at not less than 200°C for not less than 20 minutes under pressure (glycerol, fatty acids and fatty acid esters production),

- Saponification with NaOH 12 M (glycerol and soap production)

  - Batch process: at not less than 95°C for not less than 3 hours
  - Continuous process: at not less than 140°C, under pressure for not less than 8 minutes or equivalent,

- Distillation at 200°C.