COMMISSION DIRECTIVE 2003/32/EC

of 23 April 2003

introducing detailed specifications as regards the requirements laid down in Council Directive 93/42/EEC with respect to medical devices manufactured utilising tissues of animal origin

(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Council Directive 93/42/EEC of 14 June 1993 concerning medical devices [1], as last amended by Directive 2001/104/EC of the European Parliament and of the Council [2], and in particular Article 14(b) thereof,

Whereas:

(1) On 5 March 2001 France adopted a national measure prohibiting the manufacture, placing on the market, distribution, import, export and use of medical devices manufactured from materials of animal origin, where these are used as *dura mater* substitutes.

(2) France justified the measure by the uncertainties that exist with regard to the risk of transmission to humans of animal spongiform encephalopathies from such medical devices, and by the fact that alternatives are available, in the form of synthetic materials or autologous materials taken from the patient.

(3) Other Member States have taken unilateral national measures on other legal bases in relation to the use of certain raw materials originating from animal tissues and presenting specific risks of transmitting animal spongiform encephalopathies.

(4) All those national measures are related to the general protection of public health against the risks of transmitting the animal spongiform encephalopathies via medical devices.

(5) With regard to the sourcing of materials used in medical devices the provisions set out in 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 [3] apply.

(6) In order to improve the level of safety and health protection, it is necessary to further reinforce the protective measures against the overall risk of transmitting animal spongiform encephalopathies via medical devices.

(7) The Scientific Committee on Medicinal Products and Medical Devices has adopted an opinion on the use of Transmissible Spongiform Encephalopathies (TSE) risk materials for the manufacture of implantable medical devices, which recommends that manufacturers of these devices that utilise animal tissues or derivatives be required, as an essential part of the risk management, to fully justify the use of these tissues in the context of the benefits to patients and of the comparison with alternative materials.

(8) The Scientific Steering Committee has adopted several opinions on specified risk materials and on the products derived from ruminant tissues, such as gelatine and collagen, which are of direct relevance to the safety of medical devices.

(9) Medical devices manufactured utilising non-viable animal tissues or derivatives rendered non-viable are Class III devices in accordance with the classification rules set out in Annex IX to Directive 93/42/EEC, except where such devices are intended to come into contact with intact skin only.

(10) Prior to being placed on the market, medical devices, whether they originate in the Community or are imported from third countries, are subject to the conformity assessment procedures laid down in Directive 93/42/EEC.

(11) Annex I to Directive 93/42/EEC sets out the essential requirements that medical devices must meet pursuant to that Directive. Points 8.1 and 8.2 of that Annex set out specific requirements intended to eliminate or reduce as far as possible the risk of infection for the patient, user and third parties due to tissues of animal origin and specifies that the solutions adopted by the manufacturer in the design and construction of the devices must conform to safety principles taking into account the generally acknowledged state of the art.

(12) With regard to medical devices manufactured utilising tissues of animal origin it is necessary to adopt more detailed specifications in relation to the requirements of point 8.2 of Annex I to Directive 93/42/EEC and to specify certain aspects relating to the risk analysis and risk management in the framework of the conformity assessment procedures referred to in Article 11 of that Directive.

[1] OJ L 169, 12.7.1993, p. 1.
[2] OJ L 6, 10.1.2002, p. 50.
[3] OJ L 273, 10.10.2002, p. 1.

(13) Some of the terms used in Directive 93/42/EEC should be further clarified in order to ensure a uniform implementation of this Directive.

(14) It is necessary to provide for an adequate transitional period for medical devices already covered by an EC design-examination certificate or by an EC type examination certificate.

(15) The measures provided for in this Directive are in accordance with the opinion of the Committee on Medical Devices set up by Article 6(2) of Council Directive 90/385/EEC [1],

HAS ADOPTED THIS DIRECTIVE:

Article 1

1. This Directive lays down detailed specifications in relation to risks of transmitting transmissible spongiform encephalophathies (TSE) under normal conditions of use to patients or others, via medical devices manufactured utilising animal tissue which is rendered non-viable or non-viable products derived from animal tissue.

2. The animal tissues covered by this Directive are those originating from bovine, ovine and caprine species, as well as deer, elk, mink and cats.

3. Collagen, gelatin and tallow used for the manufacturing of medical devices, shall meet at least the requirements as fit for human consumption.

4. This Directive does not apply to medical devices referred to in paragraph 1, which are not intended to come into contact with the human body or which are intended to come into contact with intact skin only.

Article 2

For the purposes of this Directive, the following definitions shall apply in addition to the definitions set out in Directive 93/42/EEC:

(a) 'cell' means the smallest organised unit of any living form which is capable of independent existence and of replacement of its own substance in a suitable environment;

(b) 'tissue' means an organisation of cells and/or extra-cellular constituents;

(c) 'derivative' means a material obtained from an animal tissue by a manufacturing process such as collagen, gelatine, monoclonal antibodies;

(d) 'non-viable' means having no potential for metabolism or multiplication;

(e) 'transmissible agents' means unclassified pathogenic entities, prions and such entities as bovine spongiform encephalophathies agents and scrapie agents;

(f) 'reduction, elimination or removal' means a process by which the number of transmissible agents is reduced, eliminated or removed in order to prevent infection or pathogenic reaction;

(g) 'inactivation' means a process by which the ability to cause infection or pathogenic reaction by transmissible agents is reduced;

(h) 'source country' means the country in which the animal was born, has been reared and/or has been slaughtered;

(i) 'starting materials' means raw materials or any other product of animal origin out of which, or with the help of which, the devices referred to in Article 1(1) are produced.

Article 3

Before lodging an application for a conformity assessment pursuant to Article 11(1) of Directive 93/42/EEC, the manufacturer of medical devices referred to in Article 1(1), shall carry out the risk analysis and the risk management scheme set out in the Annex to this Directive.

Article 4

Member States shall verify that bodies notified under Article 16 of Directive 93/42/EEC have up-to-date knowledge of the medical devices referred to in Article 1(1), in order to assess the conformity of those devices referred to in Article 1(1) with the provisions of Directive 93/42/EEC and with the specifications laid down in the Annex to this Directive.

If, on the basis of that verification, it is necessary for a Member State to amend the tasks of a notified body, that Member State shall notify the Commission and the other Member States accordingly.

Article 5

1. Conformity assessment procedures for medical devices referred to in Article 1(1), shall include the evaluation of their compliance with the essential requirements of Directive 93/42/EEC and the specifications laid down in the Annex to this Directive.

2. Notified bodies shall evaluate the manufacturer's risk analysis and risk management strategy, and in particular:

(a) the information provided by the manufacturer;

(b) the justification for the use of animal tissues or derivatives;

(c) the results of elimination and/or inactivation studies or of literature search;

(d) the manufacturer's control of the sources of raw materials, finished products and subcontractors;

(e) the need to audit matters related to sourcing, including third party supplies.

[1] OJ L 189, 20.7.1990, p. 17.

3. Notified bodies shall, during the evaluation of the risk analysis and risk management in the framework of the conformity assessment procedure, take account of the TSE certificate of suitability issued by the European Directorate for the Quality of Medicines, hereinafter 'TSE certificate', for starting materials, where available.

4. Except for medical devices using starting materials for which a TSE certificate has been issued as referred to in paragraph 3, national bodies shall, through their competent authority, seek the opinion of the competent authorities of the 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 as established by the manufacturer.

Before issuing an EC design-examination certificate or an EC type-examination certificate, the notified bodies shall give due consideration to any comments received within 12 weeks from the date on which the opinion of the national competent authorities was sought.

Article 6

Member States shall take all necessary steps to ensure that medical devices referred to in Article 1(1) are placed on the market and put into service only if they comply with the provisions of Directive 93/42/EEC and the specifications laid down in the Annex to this Directive.

Article 7

1. Holders of EC design-examination certificates or EC type-examination certificates issued before 1 April 2004 for medical devices referred to in Article 1(1) shall apply for a complementary EC design-examination certificate or EC type-examination certificate attesting to compliance with the specifications laid down in the Annex to this Directive.

2. Until 30 September 2004, Member States shall accept the placing on the market and the putting into service of medical devices referred to in Article 1(1) which are covered by an EC design-examination certificate or an EC type-examination certificate issued before 1 April 2004.

Article 8

1. Member States shall adopt and publish before 1 January 2004 the provisions necessary to comply with this Directive. They shall forthwith inform the Commission thereof.

They shall apply those provisions with effect from 1 April 2004.

When Member States adopt those provisions, they shall contain a reference to this Directive or be accompanied by such a reference at the time of their official publication. Member States shall determine how such reference is to be made.

2. Member States shall communicate to the Commission the texts of the provisions of national law which they adopt in the field covered by this Directive.

Article 9

This Directive shall enter into force on the 20th day following that of its publication in the *Official Journal of the European Union*.

Article 10

This Directive is addressed to the Member States.

Done at Brussels, 23 April 2003.

For the Commission

Erkki LIIKANEN

Member of the Commission

ANNEX

1. RISK ANALYSIS AND RISK MANAGEMENT

1.1. **Justification for the use of animal tissues or derivatives**

The manufacturer must justify, on the basis of his overall risk analysis and risk management strategy for a specific medical device, the decision to use animal tissues or derivatives, referred to in Article 1, (specifying animal species and tissues) taking into account the expected clinical benefit, potential residual risk and suitable alternatives.

1.2. **Assessment procedure**

In order to ensure a high level of protection for patients or users, the manufacturer of devices utilising animal tissues or derivatives referred to in point 1.1 must implement an appropriate and well documented risk analysis and risk management strategy, to address all relevant relating aspects to TSE. He must identify the hazards associated with those tissues or derivatives, establish documentation on measures taken to minimise the risk of transmission and demonstrate the acceptability of the residual risk associated with the device utilising such tissues or derivatives, taking into account the intended use and the benefit of the device.

The safety of a device, in terms of its potential for passing on a transmissible agent, is dependent on all the factors described in points 1.2.1 to 1.2.7, which must be analysed, evaluated and managed. These measures in combination determine the device safety.

There are two key steps that must be considered.

These are:

— selecting starting materials (tissues or derivatives) considered appropriate regarding their potential contamination with transmissible agents (see 1.2.1, 1.2.2 and 1.2.3) taking into account further processing,

— applying a production process to remove or inactivate transmissible agents on controlled sourced tissues or derivatives (see 1.2.4).

Furthermore, the characteristics of the device and its intended use must be taken into account (see 1.2.5, 1.2.6 and 1.2.7).

In performing the risk analysis and risk management strategy, due consideration must be given to opinions adopted by the relevant scientific committees, and where appropriate to the opinions of the Committee for Proprietary Medicinal Products CPMP, the references of which have been published in the *Official Journal of the European Union*.

1.2.1. *Animals as a source of material*

The TSE risk is related to the source species, strains and nature of the starting tissue. As the accumulation of TSE infectivity occurs over an incubation period of several years, sourcing from young healthy animals is considered to be a factor reducing the risk. Risk animals such as fallen stock, emergency slaughtered and TSE suspected animals must be excluded.

1.2.2. *Geographical sourcing*

Pending the classification of countries according to the BSE status in Regulation (EC) No 999/2001 of the European Parliament and of the Council of 22 May 2001 laying down rules for the prevention, control and eradication of certain transmissible spongiform encephalopathies [1], the Geographical BSE risk (GBR) is used when assessing the risk of the source country. The GBR is a qualitative indicator of the likelihood of the presence of one or more cattle being infected with BSE, pre-clinically as well as clinically, at a given point in time, in a country. Where presence is confirmed, the GBR gives an indication of the level of infection as specified in the table below.

GBR level	Presence of one or more cattle clinically or pre-clinically infected with the BSE agent in a geographical region/country
I	Highly unlikely
II	Unlikely but not excluded
III	Likely but not confirmed or confirmed, at a lower level
IV	Confirmed, at a higher level

[1] OJ L 147, 31.5.2001, p. 1.

Certain factors influence the geographical risk of BSE infection associated with the use of raw tissues or derivatives from individual countries. These factors are defined in Article 2.3.13.2, point 1) of the International Animal Health Code of the OIE (Office International des Épizooties), which is available at web-site www.oie.int/eng/normes/Mcode/A_00067.htm

The Scientific Steering Committee has made an assessment of Geographical BSE Risk (GBR) of several third countries and Member States, and will continue to do so for all the countries, which applied for BSE status categorisation, taking the main OIE factors into account.

1.2.3. *Nature of starting tissue*

The manufacturer must take into account the classification of the hazards relating to different type of starting tissue. Sourcing of animal tissue must be subject to control and individual inspection by a veterinarian and the animal carcass must be certified as fit for human consumption.

The manufacturer must ensure that no risk of cross-contamination occurs at the time of slaughtering.

The manufacturer must not source animal tissue or derivatives classified as potentially high TSE infectivity, unless sourcing of these materials is necessary in exceptional circumstances, taking into account the important benefit for the patient and the absence of an alternative starting tissue.

In addition, the provisions in 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 must be applied.

1.2.3.1. Sheep and goats

A classification of infectivity in tissues for sheep and goats has been established based on actual knowledge on the basis of the titres of transmissible agents in tissues and body fluids from naturally infected sheep and goats with clinical scrapie. A table was presented in the Scientific Steering Committee (SSC) opinion of 22-23 July 1999 on 'The policy of breeding and genotyping of sheep', (as an annex) [1] and further updated in the opinion of the SSC — TSE infectivity distributed in ruminant tissues state of knowledge December 2001 — adopted 10-11 January 2002 [2].

The classification may be reviewed in the light of new scientific evidence (for example using relevant opinions from the Scientific Committees, the Committee for Proprietary Medicinal Products CPMP and Commission Measures regulating the use of material presenting risks as regards TSE). A review of the references to relevant documents/opinions will be published in the *Official Journal of the European Union* and will be listed after a Commission Decision has been taken.

1.2.3.2. Cattle

The list of specified risk material (SRM) laid down in Regulation (EC) No 999/2001 shall be considered as potentially high TSE infective.

1.2.4. *Inactivation or removal of transmissible agents*

1.2.4.1. For devices which cannot withstand an inactivation/elimination process without undergoing unacceptable degradation, the manufacturer must rely principally on the control of sourcing.

1.2.4.2. For other devices, if claims are made by the manufacturer for the ability of manufacturing processes to remove or inactivate transmissible agents, these will have to be substantiated by appropriate documentation.

Relevant information from an appropriate scientific literature search and analysis can be used to support inactivation/elimination factors, where the specific processes referred to the literature are comparable to those used for the device. This search and analysis should also cover the available scientific opinions that may have been adopted by a EU Scientific Committee. These opinions shall serve as a reference, in cases where there are conflicting opinions.

When the literature search failed to substantiate the claims, the manufacturer must set up a specific inactivation and/or elimination study on a scientific basis and the following need to be considered:

— the identified hazard associated with the tissue,

— identification of the relevant model agents,

— rationale for the choice of the particular combinations of model agents,

[1] Available on the website of the Commission http://europa.eu.int/comm/food/fs/sc/ssc/outcome_en.html.
[2] Available on the website of the Commission http://europa.eu.int/comm/food/fs/sc/ssc/outcome_en.html.

— identification of stage chosen to eliminate and/or inactivate the transmissible agents,

— calculation of the reduction factors.

A final report must identify manufacturing parameters and limits that are critical to the effectiveness of the inactivation or elimination process.

Appropriate documented procedures must be applied to ensure that the validated processing parameters are applied during routine manufacture.

1.2.5. *Quantities of animal starting tissues or derivatives required to produce one unit of the medical device*

The manufacturer must evaluate the quantity of raw tissues or derivatives of animal origin required to produce a single unit of the medical device. Where a purification process is involved, the manufacturer must assess whether it may have the potential to concentrate levels of transmissible agents present in the animal starting tissues or derivatives.

1.2.6. *Tissues or derivatives of animal origin coming into contact with the patients and users*

The manufacturer must consider:

(i) the quantity of animal tissues or derivatives;

(ii) the contact area: its surface, type (e.g. skin, mucous tissue, brain) and condition (e.g. healthy or damaged);

(iii) the type of the tissues or derivatives coming into contact with the patients and/or users; and

(iv) how long the device is intended to remain in contact with the body (including bioresorption effect).

The number of medical devices that could be used in a given procedure shall be taken into account.

1.2.7. *Route of administration*

The manufacturer must take into account the route of administration recommended in the product information, from the highest risk down to the lowest.

1.3. **Review of the assessment**

The manufacturer must establish and maintain a systematic procedure to review information gained about their medical device or similar devices in the post-production phase. The information must be evaluated for possible relevance to safety, especially:

(a) if previously unrecognised hazards are detected;

(b) if the estimated risk arising from a hazard is no longer acceptable;

(c) if the original assessment is otherwise invalidated.

If any of the above apply, the results of the evaluation shall be fed back as an input to the risk management process.

In the light of this new information, a review of the appropriate risk management measures for the device must be considered (including rationale for choosing an animal tissue or derivative). If there is a potential that the residual risk or its acceptability has changed, the impact on previously implemented risk control measures must be re-evaluated and justified.

The results of this evaluation must be documented.

2. EVALUATION OF CLASS III MEDICAL DEVICES BY NOTIFIED BODIES

For devices falling into Class III under rule 17 [1] of Annex IX to Directive 93/42/EEC, manufacturers must provide to the notified bodies referred to in Article 4 of this Directive all relevant information to allow evaluation of their current risk analysis and risk management strategy. Any new information on TSE risk, collected by the manufacturer and relevant for their devices must be sent to the notified body for information.

Any change in relation to processes of sourcing, collection, handling and inactivation/elimination and that could modify the result of the manufacturer's risk management dossier must be transmitted to the notified body for the purpose of an additional approval prior to its implementation.

[1] All medical devices utilising animal tissue or derivatives rendered non-viable except devices intended to come into contact with intact skin only.