COMMISSION REGULATION (EU) No 722/2012

of 8 August 2012

concerning particular requirements as regards the requirements laid down in Council Directives 90/385/EEC and 93/42/EEC with respect to active implantable medical devices and medical devices manufactured utilising tissues of animal origin

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Council Directive 90/385/EEC of 20 June 1990 on the approximation of laws of the Member States relating to active implantable medical devices [1], and in particular Article 10c thereof,

Having regard to Council Directive 93/42/EEC of 14 June 1993 concerning medical devices [2], and in particular Article 14b thereof,

Whereas:

(1) Specific rules for medical devices manufactured utilising tissues of animal origin were initially adopted by 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 [3]. This Directive was applicable only to medical devices falling within the scope of Directive 93/42/EEC.

(2) In order to maintain a high level of safety and health protection against the risk of transmitting animal spongiform encephalopathies to patients or other persons via medical devices manufactured utilising non-viable animal tissues or derivatives rendered non-viable, including custom-made devices and devices intended for clinical investigation, it is necessary to update the rules laid down in Directive 2003/32/EC on the basis of the experience with the application of this Directive and to apply them also to active implantable medical devices manufactured utilising tissues of animal origin that fall within the scope of Directive 90/385/EEC.

(3) Taking into account that this measure lays down clear and detailed rules that do not give room for diverging transposition by Member States, a Regulation is the appropriate legal instrument which shall replace Directive 2003/32/EC.

(4) Prior to being placed on the market or put into service, active implantable medical devices and medical devices of class III in accordance with the classification rules set out in Annex IX to Directive 93/42/EEC, whether they originate in the European Union or are imported from third countries, are subject to the conformity assessment procedures laid down in Article 9(1) of Directive 90/385/EEC and in Article 11(1) of Directive 93/42/EEC, respectively. Annex 1 to Directive 90/385/EEC and Annex I to Directive 93/42/EEC, respectively, set out the essential requirements that active implantable medical devices and other medical devices must meet in this regard.

(5) With regard to active implantable medical devices and other medical devices manufactured utilising tissues of animal origin it is necessary to adopt more detailed specifications in relation to the requirements set out in point 6 of Annex 1 to Directive 90/385/EEC and points 8.1 and 8.2 of Annex I to Directive 93/42/EEC. Moreover, it is appropriate to specify certain aspects relating to the risk analysis and risk management in the framework of the conformity assessment procedures referred to in Article 9 of Directive 90/385/EEC and Article 11 of Directive 93/42/EEC, respectively.

(6) Regulation (EC) No 1069/2009 of the European Parliament and of the Council of 21 October 2009 laying down health rules concerning animal by-products not intended for human consumption [4] sets out provisions on the sourcing of materials used in medical devices. It is appropriate to lay down additional provisions on the use of such materials as starting tissue for the manufacture of medical devices.

(7) European and international scientific bodies, such as the European Medicines Agency [5], the European Food Safety Agency [6], the former Scientific Steering Committee [7] and the former Scientific Committee on Medicinal Products and Medical Devices [8], adopted several opinions on specified risk materials and on minimising the risk of transmitting animal spongiform encephalopathy agents which are of relevance to the safety of medical devices.

[1] OJ L 189, 20.7.1990, p. 17.
[2] OJ L 169, 12.7.1993, p. 1.
[3] OJ L 105, 24.4.2003, p. 18.
[4] OJ L 300, 14.11.2009, p. 1.
[5] Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3) (OJ C 73, 5.3.2011, p. 1).
[6] http://www.efsa.europa.eu/en/topics/topic/bse.htm
[7] http://ec.europa.eu/food/fs/bse/scientific_advice08_en.print.html
[8] See http://ec.europa.eu/health/scientific_committees/emerging/opinions/scmpmd/index_en.htm

(8) The Member States should verify that the notified bodies designated to assess the conformity of medical devices manufactured utilising animal tissues have the necessary expertise and up-to-date knowledge to perform this task.

(9) The period for scrutiny granted to the competent authorities of the Member States in relation to the notified bodies' summary evaluation report should be shorter for medical devices manufactured using starting material which is certified by the European Directorate for the Quality of Medicines than in cases where uncertified material is used. In both cases, there should be a possibility to shorten the standstill period.

(10) To facilitate the smooth transition to the new requirements it is appropriate to provide for an adequate transitional period allowing for active implantable medical devices already covered by an EC design-examination certificate or by an EC type examination certificate to continue to be placed on the market and put into service.

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

HAS ADOPTED THIS REGULATION:

Article 1

1. This Regulation lays down particular requirements in relation to the placing on the market and/or putting into service of medical devices, including active implantable medical devices, manufactured utilising animal tissue which is rendered non-viable or non-viable products derived from animal tissue.

2. This Regulation shall apply to animal tissues, as well as their derivatives, originating from bovine, ovine and caprine species, deer, elk, mink and cats.

3. Collagen, gelatine and tallow used for the manufacturing of medical devices shall meet at least the requirements as fit for human consumption laid down in Regulation (EC) No 1069/2009.

4. This Regulation shall not apply to any of the following:

(a) Tallow derivatives, processed under conditions at least as vigorous as those laid down in Section 3 of Annex I;

(b) 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 Regulation, the following definitions apply in addition to the definitions set out in Directive 90/385/EEC and 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, extra-cellular constituents or both;

(c) 'derivative' means a material obtained from animal tissue through one or more treatments, transformations or steps of processing;

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

(e) 'TSEs' means all transmissible spongiform encephalopathies as defined in Article 3(1)(a) of Regulation (EC) No 999/2001 of the European Parliament and of the Council [1];

(f) 'TSE infectious agents' means unclassified pathogenic agents which are capable of transmitting TSEs;

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

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

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

(j) '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

1. Before lodging an application for a conformity assessment pursuant to Article 9(1) of Directive 90/385/EEC or Article 11(1) of Directive 93/42/EEC, the manufacturer of medical devices referred to in Article 1(1) of this Regulation or his authorised representative shall carry out the risk analysis and risk management scheme set out in Annex I to this Regulation.

2. For custom-made devices and devices intended for clinical investigation which fall under Article 1(1), the statement of the manufacturer or his authorised representative and the documentation in accordance with Annex 6 to Directive 90/385/EEC or Annex VIII to Directive 93/42/EEC, respectively, shall also address compliance with the particular requirements set out in section 1 of Annex I to this Regulation.

Article 4

1. Member States shall verify that bodies notified under Article 11 of Directive 90/385/EEC or Article 16 of Directive 93/42/EEC have up-to-date knowledge of the medical devices

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

referred to in Article 1(1), in order to assess the conformity of those devices with the provisions of Directive 90/385/EEC or Directive 93/42/EEC, respectively, and with the particular requirements laid down in Annex I to this Regulation. Member States shall regularly verify that those bodies maintain the required up-to-date knowledge and expertise.

Where, 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.

2. The Member States shall inform the Commission and the other Member States regarding the outcome of the verification referred to in the first sentence of paragraph 1 by 28 February 2013.

Article 5

1. Conformity assessment procedures for medical devices referred to in Article 1(1) shall include the evaluation of compliance of the devices with the essential requirements of Directive 90/385/EEC or Directive 93/42/EEC, respectively, and the particular requirements laid down in Annex I to this Regulation.

2. Notified bodies shall assess the documentation submitted by the manufacturer to verify that the benefits of the device outweigh the residual risks. Particular account shall be taken of:

(a) the manufacturer's risk analysis and risk management process;

(b) the justification for the use of animal tissues or derivatives, taking into consideration lower risk tissues or synthetic alternatives;

(c) the results of elimination and inactivation studies or results of the analysis of relevant literature;

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

(e) the need to audit matters related to the sourcing and processing of animal tissues and derivatives, processes to eliminate or inactivate pathogens, including those activities carried out by suppliers.

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 of suitability', for starting materials, where available.

Where additional information is necessary to assess the suitability of the starting material for a given medical device, notified bodies may require submission of additional information to allow the evaluation as set out in paragraphs 1 and 2.

4. Before issuing an EC design-examination certificate or an EC type-examination certificate, the notified bodies shall, through their competent authority, hereinafter 'coordinating competent authority', inform the competent authorities of the other Member States and the Commission of their assessment carried out pursuant to paragraph 2 by means of a summary evaluation report in accordance with Annex II to this Regulation.

5. The competent authorities of the Member States may submit comments on the summary evaluation report referred to in paragraph 4 within the following deadlines:

(a) in relation to medical devices using starting materials for which a TSE certificate of suitability as referred to in paragraph 3 has been submitted, within four weeks from the date on which the notified body informed the coordinating competent authority pursuant to paragraph 4;

(b) in relation to medical devices using starting materials for which a TSE certificate of suitability has not been submitted, within 12 weeks from the date on which the notified body informed the coordinating competent authority pursuant to paragraph 4.

The competent authorities of the Member States and the Commission may agree on shortening the time periods set out in points (a) and (b).

6. The notified bodies shall give due consideration to any comments received in accordance with paragraph 5. They shall convey an explanation as regards this consideration, including any due justification not to take account of one or more of the comments received, and their final decisions to the coordinating competent authority, which shall then make these available to the Commission and the competent authorities from which comments were received.

7. The manufacturer shall collect, evaluate and submit to the notified body information regarding changes with regard to the animal tissue or derivatives used for the device or with regard to the TSE risk in relation to the device. Where such information leads to an increase of the overall TSE risk, the provisions of paragraphs 1-6 are applicable.

Article 6

Without prejudice to Article 7(2), Member States shall take all necessary steps to ensure that medical devices referred to in Article 1(1) are placed on the market and/or put into service only if they comply with the provisions of Directive 90/385/EEC or Directive 93/42/EEC, respectively, and the particular requirements laid down in this Regulation.

Article 7

1. Holders of EC design-examination certificates or EC type-examination certificates issued before 29 August 2013 for active implantable medical devices referred to in Article 1(1) shall apply to their notified body for a complementary EC design-examination certificate or EC type-examination certificate attesting compliance with the particular requirements laid down in Annex I to this Regulation.

2. Until 29 August 2014, Member States shall accept the placing on the market and the putting into service of active implantable 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 29 August 2013.

Article 8

Directive 2003/32/EC is repealed with effect from 29 August 2013.

References to the repealed Directive are to be construed as references to this Regulation.

Article 9

This Regulation enters into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

It shall apply from 29 August 2013 except for Article 4 which shall apply from the date of entry into force of this Regulation.

This Regulation is binding in its entirety and directly applicable in all Member States.

Done at Brussels, 8 August 2012.

For the Commission
The President
José Manuel BARROSO

ANNEX I

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, tissues and sourcing) taking into account the clinical benefit, potential residual risk and suitable alternatives (such as lower risk tissues or synthetic alternatives).

1.2. **Process of risk assessment**

In order to ensure a high level of protection for patients and 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 aspects relating to TSE. He must identify the hazards and evaluate the risks 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 TSE infectious agent, is dependent on all the factors described in sections 1.2.1 to 1.2.8, which the manufacturer must analyse, evaluate and manage. These measures in combination determine the device safety.

At a minimum, the manufacturer must consider the following key steps:

(a) selecting starting materials (tissues or derivatives) considered appropriate regarding their potential contamination with TSE infectious agents (see 1.2.1, 1.2.2, 1.2.3 and 1.2.4) taking into account further collection, handling, transport, storage and processing;

(b) applying a production process to remove or inactivate TSE infectious agents on controlled sourced tissues or derivatives (see 1.2.5);

(c) maintaining a system to collect and evaluate production and post-production information regarding changes which may affect the assessment of the suitability of steps referred to in points (a) and (b).

Furthermore, the manufacturer must take into account the characteristics of the device and its intended use (see 1.2.6, 1.2.7 and 1.2.8).

In performing the risk analysis and risk management strategy, the manufacturer must give due consideration to the relevant published opinions adopted by the relevant European or international scientific committees or bodies, such as the Scientific Steering Committee (SSC), the European Food Safety Agency (EFSA), the European Medicines Agency (EMA), the World Organisation for Animal Health (OIE) and the World Health Organisation (WHO).

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 as a source of material.

1.2.2. *Geographical sourcing*

When assessing the risk of the source country, Commission Decision 2007/453/EC of 29 June 2007 establishing the BSE status of Member States or third countries or regions thereof according to their BSE risk [1] is to be taken into account.

1.2.3. *Nature of starting tissue*

The manufacturer must take into account the classification of the risks relating to different types of starting tissue as defined in the WHO Guidelines on Tissue Infectivity Distribution in Transmissible Spongiform

[1] OJ L 172, 30.6.2007, p. 84.

Encephalopathies (2006), as amended. Sourcing of animal tissue must be performed in such a manner as to maintain control over the traceability and integrity of source tissue. Where appropriate, the animals shall be subjected to veterinary ante- and post-mortem inspection.

In addition, Regulation (EC) No 1069/2009 applies.

Without prejudice to the provision in the following paragraph, only category 3 material in accordance with Article 10 of Regulation (EC) No 1069/2009 shall be used.

The manufacturer must not source animal tissue or derivatives classified as potentially high TSE infective, 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.

For bovine, ovine and caprine animals, the list of specified risk material (SRM) laid down in Annex V to Regulation (EC) No 999/2001 is to be considered as being potentially of high TSE infectivity.

1.2.4. *Slaughtering and processing controls to prevent cross contamination*

The manufacturer must ensure that the risk of cross-contamination during slaughtering, collection, processing, handling, storage and transport is minimised.

1.2.5. *Inactivation or removal of TSE infectious agents*

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

1.2.5.2. For other devices, if claims are made by the manufacturer for the ability of manufacturing processes to remove or inactivate TSE infectious agents, these must be substantiated by appropriate documentation.

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

If the literature search fails to substantiate the claims, the manufacturer must set up a specific inactivation or elimination study, as appropriate, on a scientific basis and the following need to be considered:

(a) the identified hazard associated with the tissue;

(b) identification of the relevant model agents;

(c) rationale for the choice of the particular combinations of model agents;

(d) identification of step and/or stage chosen to eliminate or inactivate the TSE infectious agents;

(e) documentation of the parameters for any TSE inactivation or elimination validation study;

(f) calculation of the reduction factors.

The manufacturer must apply appropriate documented procedures to ensure that the validated processing parameters are applied during routine manufacture.

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

1.2.6. *Quantities of animal 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. The manufacturer must assess whether the production process has the potential to concentrate levels of TSE infectious agents present in the animal starting tissues or derivatives.

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

The manufacturer must consider:

(a) the maximum quantity of animal tissues or derivatives coming into contact with the patient or user when using a single medical device;

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

(c) the type of the tissues or derivatives coming into contact with the patients or users;

(d) the period of time the device is intended to remain in contact with the body (including bioresorption effect); and

(e) the number of medical devices that could be used in a given procedure or, if possible, over the lifetime of a patient or user.

1.2.8. *Route of administration*

In the risk assessment, the manufacturer must take into account the route of administration as indicated in the product information.

1.3. **Review of the risk assessment**

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

(a) previously unrecognised hazards are identified;

(b) the estimated risk arising from a hazard has changed or is no longer acceptable;

(c) the original assessment is otherwise invalidated.

In the cases set out in points (a), (b) or (c), the manufacturer shall feed back the results of the evaluation 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 BY NOTIFIED BODIES

For the medical devices referred to in Article 1(1), manufacturers must provide to the notified bodies referred to in Article 4 all relevant information to allow evaluation of their risk analysis and risk management strategy in accordance with Article 5(2).

2.1. **Information of the Notified Body regarding changes and new information**

Any change in relation to processes of sourcing, collection, handling, processing and inactivation or elimination and any new information on TSE risk collected by the manufacturer and relevant for the medical device that could modify the result of the manufacturer's risk assessment must be transmitted to the notified body and, where applicable, needs to be approved by the notified body prior to its implementation.

2.2. **Renewal of certificates**

In the context of its decision regarding the extension for a further period of maximum five years of an EC design-examination certificate or an EC type-examination certificate in accordance with Article 9(8) of Directive 90/385/EEC or Article 11(11) of Directive 93/42/EEC, respectively, the notified body shall review for the purpose of this Regulation at least the following aspects:

(a) updated justification for the use of animal tissue or derivative, including a comparison with lower risk tissues or synthetic alternatives;

(b) updated risk analysis;

(c) updated clinical evaluation;

(d) updated test data and/or rationales, for example in relation to the current harmonised standards;

(e) identification of any changes made since the issue of the original certificate (or last renewal) that could impact the TSE risk;

(f) evidence that the design dossier remains state of the art in relation to TSE risks.

2.3. **Increase of the overall TSE risk**

Where on the basis of information submitted in accordance with section 2.1 or 2.2 a notified body establishes that the overall TSE risk in relation to a medical device is increased, this notified body shall follow the procedure set out in Article 5.

3. RIGOROUS PROCESSES FOR TALLOW DERIVATIVES AS REFERRED TO IN ARTICLE 1, PARAGRAPH 4, OF THIS REGULATION

— 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.

ANNEX II

Summary Evaluation Report in accordance with Article 5(4) of Regulation (EU) No 722/2012

Details relating to the submitting notified body

1. Name of notified body	2. Notified body number	3. Country
4. Sent by	5. Contact person	6. Telephone
7. Fax	8. E-mail	9. Client reference (name of manufacturer and, if applicable, of authorised representative)

10. Confirmation that, in accordance with Article 11 of Directive 90/385/EEC and Article 16 of Directive 93/42/EEC, respectively, and Article 4 of Regulation (EU) No 722/2012, the submitting notified body has been designated by its competent authority for the conformity assessment of

☐ active implantable medical devices manufactured utilising tissues of animal origin subject to Regulation (EU) No 722/2012,

☐ medical devices manufactured utilising tissues of animal origin subject to Regulation (EU) No 722/2012

Data relating to the (active implantable) medical device

11. (a) ☐ Active implantable medical device ☐ Other medical device

11. (b) Product description and composition

12. Information on intended use

13. Starting material

13. (a) EDQM certificate available ☐ YES ☐ NO

(If the EDQM certificate is available, it must be submitted with this summary evaluation report.)

13. (b) Information regarding

— the nature of the starting tissue(s):

— animal species(s):

— geographical source(s):

14. A description of the key elements adopted to minimise the risk of infection:

15. An 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:

16. 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 estimate, the evaluation of alternative materials and the expected clinical benefit:

17. The approach to the auditing of source establishments and suppliers for the animal material used by the device manufacturer:

Notified Body Statement

18. Conclusion of this assessment:

Based on the evaluation of data and the assessment process it is our preliminary decision that the application meets the requirements of conformity with

☐ Council Directive 90/385/EEC ☐ Council Directive 93/42/EEC

and Regulation (EU) No 722/2012.

Date of submission

19. This report was sent on ..... to the Coordinating Competent Authority of ..... to inform the Competent Authorities of the other Member States and the Commission and to seek their comments, if any.