EU 722/2012 – Animal Tissue Regulations in Effect for Some Medical Devices

Thamizharasan Sampath, Sandhiya Thamizharasan, Krithaksha V., and Prakash Srinivasan Timiri Shanmugam

Abbreviations

EC	European Commission
EEC	European Economic Community
EU	European Union
TSE	Transmissible spongiform encephalopathy
WHO	World Health Organization

Highlights

- The chapter provides information on EU regulation on medical device utilizing animal tissue.
- It also explains the risk of TSE infectious agents and its inactivation methods.

1 Introduction

Modern medical devices incorporate a range of materials into finished products, including animal tissues and other materials of animal origin. The type and quantities of materials of animal origin in medical devices vary. These materials can comprise a major part of the device (e.g., porcine/bovine heart valves, bone substitutes

T. Sampath (✉)
Department of Pharmacology, Maitri College of Dentistry & Research Centre, Anjora, Durg, Chhattisgarh, India

S. Thamizharasan
Maitri College of Dentistry & Research Centre, Anjora, Durg, Chhattisgarh, India

Krithaksha V.
RMKSSS, RMK Group of Institutions, Chennai, Tamil Nadu, India

P. S. Timiri Shanmugam
Global Product Safety & Toxicology, Avanos Medical, Inc., Alpharetta, GA, USA

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for use in orthopedic or dental applications and hemostatic devices), shall be used in the device manufacturing process (e.g., tallow derivatives such as stearates and oleates, fetal calf serum, culture media, enzymes), and can be a product coating/covering or impregnation (e.g., gelatine, collagen, heparin). Although animal materials can provide therapeutic and biocompatibility advantages over non-animal materials, their significant use in medical devices also introduces the risk of disease transmission from animals to humans. Most important concern is the potential transmission of transmissible spongiform encephalopathy (TSE), a devastating disease affecting the brains of susceptible species, including cattle, goats, and sheep, which can be transmitted to humans through contact with TSE-infected animal tissues and materials.

Article 1

(i) 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 utilizing animal tissue which is rendered non-viable or non-viable products derived from animal tissue.
(ii) This Regulation shall apply to animal tissues, as well as their derivatives, originating from bovine, ovine, and caprine species, deer, elk, mink, and cats.
(iii) 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.
(iv) This Regulation shall not apply to any of the following:

- Tallow derivatives, processed under vigorous conditions
- Medical devices 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

The following definitions apply in addition to the definitions set out in Directive 90/385/EEC and Directive 93/42/EEC:

Cell: The smallest organized unit of any living form which is capable of independent existence and of replacement of its own substance in a suitable environment
Tissue: An organization of cells, extracellular constituents, or both
Derivative: A material obtained from animal tissue through one or more treatments, transformations, or steps of processing
Non-viable: Having no potential for metabolism or multiplication
TSE: Transmissible spongiform encephalopathies
TSE infectious agents: Unclassified pathogenic agents which are capable of transmitting TSEs
Reduction, elimination, or removal: A process by which the number of TSE infectious agents is reduced, eliminated, or removed in order to prevent infection or pathogenic reaction
Inactivation: A process by which the ability to cause infection or pathogenic reaction by TSE infectious agents is reduced

Source country: The country or countries in which the animal was born, has been reared, and/or has been slaughtered

Starting materials: Raw materials or any other product of animal origin out of which, or with the help of which, the devices are produced

Article 3

- 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 authorized representative shall carry out the risk analysis and risk management scheme set out in this Regulation.
- For custom-made devices and devices intended for clinical investigation which fall under Article 1(1), the statement of the manufacturer or his authorized 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 this Regulation.

Article 4

- 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.
- 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 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.
- The Member States shall inform the Commission and the other Member States regarding the outcome of the verification.

Article 5

- 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 to this Regulation.
- 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:
  - The manufacturer's risk analysis and risk management process
  - The justification for the use of animal tissues or derivatives, taking into consideration lower-risk tissues or synthetic alternatives
  - The results of elimination and inactivation studies or results of the analysis of relevant literature
  - The manufacturer's control of the sources of raw materials, finished products, production process, testing, and subcontractors

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

- 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.

- 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 summary evaluation report in accordance with this Regulation.
- 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 has been submitted, within 4 weeks from the date on which the notified body informed the coordinating competent authority
  (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

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

- 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.
- 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.

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/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

- 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 this Regulation.
- 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. This Regulation enters into force on the 20th 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.

2 Risk Analysis and Risk Management

2.1 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).

2.2 Process of Risk Assessment

In order to ensure a high level of protection for patients and users, the manufacturer of devices utilizing animal tissues or derivatives must implement an appropriate and well-documented risk analysis and risk management strategy, to address all relevant aspects relating to TSE. The manufacturer must identify the hazards and evaluate the risks associated with those tissues or derivatives, establish documentation on measures taken to minimize the risk of transmission, and demonstrate the acceptability of the residual risk associated with the device utilizing 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 below to which the manufacturer

must analyze, evaluate, and manage. These measures in combination determine the device safety.

The manufacturer must consider the following key steps:

- Selecting starting materials (tissues or derivatives) considered appropriate regarding their potential contamination with TSE infectious agents taking into account further collection, handling, transport, storage, and processing.
- Applying a production process to remove or inactivate TSE infectious agents on controlled sourced tissues or derivatives.
- Maintaining a system to collect and evaluate production and post-production information regarding changes which may affect the assessment of the suitability.

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 Organization (WHO).

2.3 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.

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 is to be taken into account.

2.4 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 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 postmortem 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.

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 minimized.

2.5 Inactivation or Removal of TSE Infectious Agents

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

- The identified hazard associated with the tissue
- Identification of the relevant model agents
- Rationale for the choice of the particular combinations of model agents
- Identification of step and/or stage chosen to eliminate or inactivate the TSE infectious agents
- Documentation of the parameters for any TSE inactivation or elimination validation study
- 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.

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.

Tissues or Derivatives of Animal Origin Coming into Contact with the Patients and Users The manufacturer must consider:

- The maximum quantity of animal tissues or derivatives coming into contact with the patient or user when using a single medical device
- The contact area: its surface, type (e.g., skin, mucous tissue, brain), and condition (e.g., healthy or damaged)
- The type of the tissues or derivatives coming into contact with the patients or users
- -The period of time 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 or, if possible, over the lifetime of a patient or user

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

2.6 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:

- Previously unrecognized hazards are identified.
- The estimated risk arising from a hazard has changed or is no longer acceptable.
- The original assessment is otherwise invalidated.

In the cases set out in the above points, 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.

3 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).

3.1 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, need to be approved by the notified body prior to its implementation.

3.2 Renewal of Certificates

In the context of its decision regarding the extension for a further period of maximum 5 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 in the following aspects:

- Updated justification for the use of animal tissue or derivative, including a comparison with lower-risk tissues or synthetic alternatives
- Updated risk analysis
- Updated clinical evaluation
- Updated test data and/or rationales, for example, in relation to the current harmonized standards
- Identification of any changes made since the issue of the original certificate (or last renewal) that could impact the TSE risk
- Evidence that the design dossier remains state of the art in relation to TSE risks

Increase of the Overall TSE Risk Where on the basis of information submitted in accordance with Sects. 3.1 or 3.2 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.

3.3 Rigorous Processes for Tallow Derivatives

- Trans-esterification or hydrolysis at not less than 200 °C for not less than 20 min 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 h
- Continuous process: at not less than 140 °C, under pressure for not less than 8 min or equivalent
- Distillation at 200 °C

3.4 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 the 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 the manufacturer and, if applicable, of authorized 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 utilizing tissues of animal origin subject to Regulation (EU) No 722/2012
    ○ Medical devices manufactured utilizing tissues of animal origin subject to Regulation (EU) No 722/2012

Data relating to the (active implantable) medical devices:

11. (a) ○ Active implantable medical devices ○ other medical devices

    (b) Product description and composition

12. Information on intended use
13. Starting material

(a) EDQM certificate available ○ Yes ○ No
(if the EDQM certificate is available, it must be submitted with this summary evaluation report)
(b) Information regarding

– The nature of the starting tissue(s)
– Animal species(s)
– Geographical source(s)

14. A description of key the elements adopted to minimize 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 and 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 decisions that the application meets the requirements of conformity with:
○ Council Directive 90/385/EEC and Regulation (EU) No 722/2012
○ Council Directive 93/42/EEC

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.

Reference

1. EU – 722/2012, Commission Regulation 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, 09.08.2012, Official journal of European Union, 212:3–12.