THE MINISTRY OF HEALTH

1796

Pursuant to Article 6, paragraph 3 of the Medical Devices Act (Official Gazette 76/2013), the Minister of Health hereby issues the

ORDINANCE

ON SPECIFIC REQUIREMENTS FOR MEDICAL DEVICES MANUFACTURED UTILISING NON-VIABLE ANIMAL TISSUES

Article 1

(1) This Ordinance lays down specific requirements that must be met by medical devices manufactured utilising non-viable animal tissue or products derived from non-viable animal tissue in relation to risks of transmitting transmissible spongiform encephalopathies (hereinafter: TSE) under normal conditions of use to patients or others users.

2) The provisions of this Ordinance shall apply to animal tissues originating from bovine, ovine and caprine species, as well as 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.

4) The provisions of this Ordinance does not apply to medical devices referred to in paragraph 1 of this Article which are not intended to come into direct contact with the human body or which are intended to come into contact with intact skin only.

Article 2

This Ordinance transposes the following directive into the legal system of the Republic of Croatia:

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) (OJ L 105, 26. 4. 2003).

Article 3

(1) For the purposes of this Ordinance, the following terms shall have the following meanings:

(a) *cell* means the smallest organised unit of any living form which is capable of independent existence and of replacement of its 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 agent* means an unclassified pathogenic entity, prion and bovine spongiform encephalopathies agent and scrapie agent (prion diseases);

(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 medical devices referred to in Article 1, paragraph 1 of this Ordinance are produced.

Article 4

Before lodging an application for a conformity assessment pursuant to Article 31 of the Medical Devices Act (hereinafter: the Act), the manufacturer of medical devices referred to in Article 1, paragraph 1 of this Ordinance shall carry out the risk analysis and the risk management scheme set out in the Annex to this Ordinance, which forms an integral part thereof.

Article 5

(1) The Ministry responsible for health (hereinafter: the Ministry) shall verify that the notified body referred to in Article 38 of the Act has up-to-date knowledge of the medical devices referred to in Article 1, paragraph 1 of this Ordinance in order to assess the conformity of those devices with the provisions of the Act and with the criteria laid down in the Annex to this Ordinance.

(2) If, on the basis of the verification referred to in paragraph 1 of this Article, it is necessary for the Ministry to amend the authorisation of the notified body, the Ministry shall notify the European Commission and the other Member States of the European Union accordingly.

Article 6

(1) Conformity assessment procedures for medical devices referred to in Article 1, paragraph 1 of this Ordinance shall include the evaluation of compliance with the essential requirements for medical devices and the criteria laid down in the Annex to this Ordinance.

(2) The notified body shall evaluate the manufacturer's risk analysis and risk management scheme, and in particular on the basis of:

(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) audits related to sourcing, including third party supplies.

(3) during the evaluation of the risk analysis and risk management in the framework of the conformity assessment procedure, the notified body shall take account of the certificate of the European Pharmacopoeia on the safety of use of the substance with respect to the transmission of TSE (hereinafter: TSE certificate), where applicable.

(4) Except for medical devices using starting materials for which a TSE certificate referred to in paragraph 3 of this Article has been issued, the notified body shall, through the Agency for Medicinal Products and Medical Devices, seek the opinion of the competent authorities of the other Member States of the European Union on their evaluation of and conclusions on the risk analysis and risk management of the tissues or the derivatives intended to be utilised in the medical device as established by the manufacturer. Before issuing a design-examination certificate or a type-examination certificate, the notified body shall take into account any comments received within 12 weeks from the date on which the opinion of the competent authorities of the Member States of the European Union was sought.

Article 7

This Ordinance shall be published in the Official Gazette and shall enter into force on 2 July 2013.

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Zagreb, 26 June 2013

The Minister
Rajko Ostojić,
m. p.

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, paragraph 1 of this Ordinance (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 of this Annex 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 risks associated with those tissues or derivatives, taking into account the intended use and the benefit of the medical device.

The safety of a medical 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 of this Annex, which must be analysed, evaluated and managed. These measures in combination determine the safety of the medical device.

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 (points 1.2.1, 1.2.2 and 1.2.3 of this Annex) taking into account further processing,

– applying a production process to remove or inactivate transmissible agents on controlled sourced tissues or derivatives (point 1.2.4 of this Annex).

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

In performing the risk analysis and risk management strategy, due consideration must be given to opinions of the relevant scientific committees and to the opinion of the Committee for Medicinal Products for Human Use (CHMP), 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 animal species, strains/cultures 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

According to 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 and 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 (Text with EEA relevance), which lay down rules for the

prevention, control and eradication of certain transmissible spongiform encephalopathies, the Geographical BSE risk (hereinafter: 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, preclinically 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	Unlikely
II	Unlikely but not excluded
III	Likely but not confirmed or confirmed, at a lower level
IV	Confirmed, at a higher level

Certain factors influence the GBR associated with the use of raw tissues or derivatives from individual countries. These factors are described in Article 11.5.2, point 1 of the International Animal Health Code of the OIE (Office International des Épizooties).

The Scientific Steering Committee has made an assessment of the GBR of several third countries and Member States, and will continue assessment 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 risks relating to different type of starting tissue. Sourcing of 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 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.

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, as an annex, in the Scientific Steering Committee opinion of 22-23 July 1999 – 'The policy of breeding and genotyping of sheep' and further updated in the opinion of the Committee – TSE

infectivity distributed in ruminant tissues state of knowledge December 2001, adopted on 10 and 11 January 2002.

The classification may be reviewed in the light of new scientific evidence (for example using relevant opinions from the Scientific Committees, the Committee for Medicinal Products for Human Use and European Commission Measures regulating the use of material presenting risks as regards BSE. 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. Livestock

Materials considered as potentially high TSE infective are listed in Regulation (EC) No 999/2001 – The list of specified risk material.

1.2.4. Inactivation or removal of transmissible agents

1.2.4.1. For medical devices which cannot be subject to an inactivation/elimination process, with acceptable degradation, the manufacturer must rely principally on the control of sourcing.

1.2.4.2. If a medical device manufacturer claims that the manufacturing process is able to remove or inactivate transmissible agents, such claims will have to be substantiated by appropriate documentation.

Relevant information from scientific literature can be used to support the stated inactivation/elimination methods, where the specific processes referred to in the literature are comparable to those used for the medical device. This shall 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.

If the literature search fails 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 risk associated with the tissue,

– identification of the relevant types of agents,

– rationale for the choice of the particular combinations of the types of agents,

– 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 approved 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 take into account:

– the quantity of animal tissues or derivatives,

– the contact area: its surface, type (e.g. skin, mucous tissue, brain) and condition (e.g. undamaged or damaged); the type of the tissues or derivatives coming into contact with the patients and/or users, and

– 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 instructions for use, from the highest risk down to the lowest.

1.3. Review of the assessment

The manufacturer must establish and maintain a system 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 applies, 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 medical devices classified into Class III under rule 17 of Annex IX to Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, manufacturers must provide to the notified bodies referred to in Article 5 of this Ordinance all relevant information to allow evaluation of their current risk analysis and risk management strategy. Any new information on TSE risk, collected by the manufacturers and relevant for their medical devices must be sent to the notified body for information.

Any change in the procedures for the control of sourcing, collection, handling and inactivation/elimination 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.