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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 **[**[F1]international scientific committees or bodies.**]**

Textual Amendments

F1 Words in Annex 1 s. 1.2 substituted (11.8.2021) by The Medical Devices (Amendment) (EU Exit) Regulations 2021 (S.I. 2021/873), reg. 1(1), **Sch. 2 para. 15(a)**

1.2.1. *Animals as a source of material*

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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 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 [F2]... international scientific committee or body. These opinions are to serve as a reference, in cases where there are conflicting opinions.

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Textual Amendments

F2 Words in Annex 1 s. 1.2.5.2 omitted (11.8.2021) by virtue of The Medical Devices (Amendment) (EU Exit) Regulations 2021 (S.I. 2021/873), reg. 1(1), **Sch. 2 para. 15(b)**

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*

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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. **[**[F3]EVALUATION BY APPROVED BODIES**]**

For the medical devices referred to in Article 1(1), manufacturers must provide to the **[**[F4]approved 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).

Textual Amendments

F4 Words in Annex 1 s. 2 substituted (11.8.2021) by The Medical Devices (Amendment) (EU Exit) Regulations 2021 (S.I. 2021/873), reg. 1(1), **Sch. 2 para. 15(c)(ii)**

2.1. **[**[F5]Information of the Approved 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 **[**[F6]approved body**]** and, where applicable, needs to be approved by the **[**[F6]approved body**]** prior to its implementation.

Textual Amendments

F6 Words in Annex 1 s. 2.1 substituted (11.8.2021) by The Medical Devices (Amendment) (EU Exit) Regulations 2021 (S.I. 2021/873), reg. 1(1), **Sch. 2 para. 15(d)(ii)**

Textual Amendments

F5 Annex 1 s. 2.1 heading substituted (11.8.2021) by The Medical Devices (Amendment) (EU Exit) Regulations 2021 (S.I. 2021/873), reg. 1(1), **Sch. 2 para. 15(d)(i)**

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2.2. **Renewal of certificates**

In the context of its decision regarding the extension for a further period of maximum five years of **[**F7a**]** design-examination certificate or **[**F7a**]** type-examination certificate in accordance with **[**F8regulation 18(3) or regulation 31(3) of the Medical Devices Regulations 2002**]**, respectively, the **[**F9approved body**]** shall review for the purpose of this Regulation at least the following aspects:

Textual Amendments

F7 Word in Annex 1 s. 2.2 substituted (11.8.2021) by The Medical Devices (Amendment) (EU Exit) Regulations 2021 (S.I. 2021/873), reg. 1(1), **Sch. 2 para. 15(e)(i)**

F8 Words in Annex 1 s. 2.2 substituted (11.8.2021) by The Medical Devices (Amendment) (EU Exit) Regulations 2021 (S.I. 2021/873), reg. 1(1), **Sch. 2 para. 15(e)(ii)**

F9 Words in Annex 1 s. 2.2 substituted (11.8.2021) by The Medical Devices (Amendment) (EU Exit) Regulations 2021 (S.I. 2021/873), reg. 1(1), **Sch. 2 para. 15(e)(iii)**

(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 **[**F10an approved body**]** establishes that the overall TSE risk in relation to a medical device is increased, **[**F11this approved body**]** shall follow the procedure set out in Article 5.

Textual Amendments

F10 Words in Annex 1 s. 2.3 substituted (11.8.2021) by The Medical Devices (Amendment) (EU Exit) Regulations 2021 (S.I. 2021/873), reg. 1(1), **Sch. 2 para. 15(f)(i)**

F11 Words in Annex 1 s. 2.3 substituted (11.8.2021) by The Medical Devices (Amendment) (EU Exit) Regulations 2021 (S.I. 2021/873), reg. 1(1), **Sch. 2 para. 15(f)(ii)**

Textual Amendments

F3 Annex 1 Section 2 heading substituted (11.8.2021) by The Medical Devices (Amendment) (EU Exit) Regulations 2021 (S.I. 2021/873), reg. 1(1), **Sch. 2 para. 15(c)(i)**

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

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— 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

[F12Details relating to the submitting approved body]

Textual Amendments

F12 Annex 2 heading substituted (11.8.2021) by The Medical Devices (Amendment) (EU Exit) Regulations 2021 (S.I. 2021/873), reg. 1(1), **Sch. 2 para. 16(a)(i)**

Details relating to the submitting notified body

1. Name of [F13approved body]

Textual Amendments

F13 Words in Annex 2 substituted (11.8.2021) by The Medical Devices (Amendment) (EU Exit) Regulations 2021 (S.I. 2021/873), reg. 1(1), **Sch. 2 para. 16(a)(ii)**

2. [F14Approved body] number

Textual Amendments

F14 Words in Annex 2 substituted (11.8.2021) by The Medical Devices (Amendment) (EU Exit) Regulations 2021 (S.I. 2021/873), reg. 1(1), **Sch. 2 para. 16(a)(iii)**

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. [F15Confirmation that the submitting approved body has been designated by the Secretary of State for the conformity assessment of]

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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

Textual Amendments

F15 Words in Annex 2 substituted (11.8.2021) by The Medical Devices (Amendment) (EU Exit) Regulations 2021 (S.I. 2021/873), reg. 1(1), **Sch. 2 para. 16(a)(iv)**

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:

[F16Approved 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

[F17 Part 3 of the Medical Devices Regulations 2002**]** # **[F18**Part 2 of the Medical Devices Regulations 2002**]**

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Textual Amendments

F17 Words in Annex 2 substituted (11.8.2021) by The Medical Devices (Amendment) (EU Exit) Regulations 2021 (S.I. 2021/873), reg. 1(1), **Sch. 2 para. 16(b)(ii)**

F18 Words in Annex 2 substituted (11.8.2021) by The Medical Devices (Amendment) (EU Exit) Regulations 2021 (S.I. 2021/873), reg. 1(1), **Sch. 2 para. 16(b)(iii)**

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.

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(**1**) OJ L 172, 30.6.2007, p. 84.

Changes to legislation:
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View outstanding changes

Changes and effects yet to be applied to :

- Regulation applied by S.I. 2002/618, reg. 4K(2)(4) (as inserted) by S.I. 2019/791 reg. 3(7) (This amendment not applied to legislation.gov.uk. The affecting text in reg. 3(7) is omitted (31.12.2020 immediately before IP completion day) by virtue of S.I. 2020/1478, reg. 1(3), Sch. 2 para. 9(h))
- Regulation applied by S.I. 2002/618, reg. 4K(3) (as inserted) by S.I. 2019/791 reg. 3(7) (This amendment not applied to legislation.gov.uk. The affecting text in reg. 3(7) is omitted (31.12.2020 immediately before IP completion day) by virtue of S.I. 2020/1478, reg. 1(3), Sch. 2 para. 9(h))
- Regulation revoked by S.I. 2002/618, reg. 4K (as substituted) by S.I. 2021/873 Sch. 1 para. 4