
MEDICAL DEVICES : Guidance document

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<p>Guidelines on assessment of medical devices incorporating materials of animal origin with respect to viruses and transmissible agents</p>

These guidelines have been carefully drafted through a process of consultation with various interested parties during which intermediate drafts were circulated and comments were taken up in the document. Therefore this document reflects positions taken in particular by representatives of Competent Authorities and Commission Services, Notified Bodies, Industry and other interested parties in the medical devices sector.

These guidelines are legally not binding. It is recognised that under given circumstances, for example, as a result of scientific developments, an alternative approach may be possible or appropriate to comply with the legal requirements. This guideline document utilizes the word "shall"; in order to claim compliance to this guideline, these elements must be addressed.

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INTRODUCTION

This document has been elaborated to provide guidance to Notified Bodies, manufacturers and interested parties on the assessment of medical devices covered by Active Implantable Medical Device directive and Medical Device directive incorporating materials of animal origin. This principally relates to class III devices and associated conformity assessment procedures shall apply. The use of this document shall also be considered where materials of animal origin are used in manufacturing processes but where the materials are not included in the final device.

NOTE: The manufacture of some devices may use industrial raw materials, which contain small amounts of substances derived from animal tissues (e.g. tallow) through a chemical/physical process, which is likely to destroy the structure of the original molecules. Where such chemicals (e.g. stearates in plastics) are not intended to have any direct effect in relation to the medical function of the device and to be released into the body (see risk analysis), then the application of some of the following guidance may not be relevant. This is justified by the fact that the intensive industrial processing of the substance has removed the original characteristics, which are specific to the animal tissue as well as the risk of transmission of many pathogens.

1. MEETING THE ESSENTIAL REQUIREMENTS – RELEVANT STANDARDS AND OTHER DOCUMENTS.

1.1. Essential Requirements:

Essential requirements 1 - 6 of Directive 93/42/EEC of 14 June 1993 stipulate the requirements for the safety of the device, more specific requirements regarding 'Infection and microbial contamination' are detailed in Essential Requirements 8.1 and 8.2 (see Appendix 1).

The primary principle is to “eliminate or reduce risk as far as possible” and “provide optimal security”; these concepts are paramount during assessment. The application of these primary principles shall also take into account the benefit of the device as well as the generally acknowledged state of the art. It shall be understood that the risk considered in the benefit/risk analysis includes the current epidemiological risk. Furthermore it shall be considered to what extent alternative materials to those of animal origin are available and can be used. Bearing in mind the special risk of TSE (Transmissible Spongiform Encephalopathies), a rationale shall be provided for the use of ruminant origin material.

Where relevant and taking into account the risk analysis and risk management, identified residual risks shall be mentioned (including, where appropriate, the presence of a specific substance of animal origin) in the information provided with the device as required in essential requirements 2 and 13 (see Appendix 1).

1.2. Risk Analysis and Management:

In order to provide optimal security, minimisation of risks shall address all relevant aspects including those in relation to:

- Animals (species – see 2.2 and appendices 2 and 4).
- Sourcing (including geographical origin – see 2.2, 2.3 and appendix 4).
- Nature of starting material used.
- Methods used to remove and/or inactivate viruses or transmissible agents.
- Quantities of animal starting material required to produce one unit of the medical device.
- Quantities of material of animal origin coming into contact with the patients and users
- Route of administration.

These aspects are interrelated and all of them shall be considered during risk analysis. The risk management strategy will be a combination of measures related to some or all of these aspects (see 1.3).

The chosen approach shall be justified in the documentation submitted to a Notified Body and be explicitly addressed in the overall risk analysis and management.

1.3. Harmonised Standards:

Drafts of harmonised standards addressing the use of animal materials (see definition of “animal” in Appendix 2) in medical devices are available:

pr EN 12442 Animal tissues and their derivatives utilised in the manufacture of medical devices -

Part 1: Analysis and management of risk

Part 2: Controls on sourcing, collection and handling

Part 3: Validation of the elimination and/or inactivation of viruses and transmissible agents (see definition of “transmissible agents” in appendix 2).

These documents shall be utilised when performing an assessment of medical devices containing materials of animal origin. Notified Bodies shall apply the principles described in these documents as the basis for their assessment methodology. If a manufacturer chooses to follow a different approach, its relevance and adequacy in achieving an *adequate* level of safety has to be demonstrated.

Other guidance documents and standards are available from national, European and international sources, which may provide useful background information. Currently available documents are detailed in the bibliography.

The following standards address the essential requirements 8.1 and 8.2:

1.3.1 pr EN 12442-1: Animal tissues and their derivatives utilised in the manufacture of medical devices - Part 1: Analysis and management of risk (see appendix 2)

This standard provides requirements and guidance on:

- Definitions: *Transmissible agents has been defined in prEN 12442-1. This term is equivalent to “Transferable agents” used in section 8.2 of Annex 1 of Directive 93/42/EEC. Several definitions including “animal”, “tissue”, “cell”, “derivative”, “transmissible agents” are provided in prEN 12442-1. The definitions provided complement those in Directive 93/42/EEC.*
- Risk analysis: by providing additional requirements and guidance to EN 1441,
- Risk management: Risk management shall be implemented by taking into account separately the risks related to viruses and transmissible agents. After having defined the characteristics of the product, the medical device manufacturer shall comply with the relevant requirements of Part 2 and Part 3 of prEN 12442 cumulatively. The manufacturer shall document his rationale and justification for any requirements considered not to be relevant (see 2.2).

NOTE 1: For medical devices which cannot withstand an inactivation process, without undergoing unacceptable degradation, medical device manufacturers may rely principally on Part 2 of prEN 12442 in order to meet the requirements of this Part.

NOTE 2: When the animal species is such that manufacturers cannot fully meet the requirements of Part 2 of prEN 12442, they should demonstrate a level of inactivation of viruses and transmissible agents in a validated manufacturing process, as required in Part 3 of prEN 12442, in order to meet the requirements of this Part of prEN 12442

This part of the standard also provides a specific guidance on risk analysis and risk management for transmissible agents.

1.3.2 pr EN 12442-2: Animal tissues and their derivatives utilised in the manufacture of medical devices - Part 2: Controls on sourcing, collection and handling (see appendices 2 and 4)

This standard provides requirements and guidance on:

- Quality system for the collection (including traceability),
- Requirements or guidance on the veterinarian surveillance of the animals and the slaughter,
- Requirements or guidance to avoid further cross-contamination during dissection, storage and transport.

This part of the standard also provides a specific Annex for additional requirements relating to bovine sourced materials.

1.3.3 pr EN 12442-3: Animal tissues and their derivatives utilised in the manufacture of medical devices - Part 3: Validation of the elimination and/or inactivation of viruses and transmissible agents (see appendix 3).

This standard provides requirements and guidance on:

- Quality system for the inactivation/elimination studies,
- Requirements or guidance to assess that inactivation/elimination studies' parameters are equivalent to those of the manufacturing process,
- Requirements or guidance to design and perform inactivation/elimination studies,
- Requirements or guidance on the role of literature search.

1.4. Additional relevant Decisions and Opinions:

Particular attention is drawn to the Decisions taken at Community level in relation to the restriction of use of defined material from animal origin for the manufacture of medical devices.

The concept of level of infectivity in relation to the nature of tissues, and the concept of incidence are currently in evolution. In bibliography, the latest available versions of such concepts at the moment of issuance of the present document are referenced.

The manufacturer of medical devices shall not involve the use of “high infectivity” tissues¹ taking also into account the origin of the animal and other relevant parameters (see bibliography), unless the use of such tissues may under exceptional circumstances be justified, taking into account the benefit for the patient and the absence of adequate therapeutic alternative.

The Scientific Steering Committee² has adopted an opinion on the safety of gelatine dated 26-27 March 1998 (see bibliography).

The Scientific Steering Committee has also adopted an opinion on the safety of tallow derived from ruminant tissues, dated 26-27 March 1998 (see bibliography).

The Scientific Steering Committee has also adopted an opinion on BSE risk, dated 26-27 March 1998 (see bibliography).

The Scientific Steering Committee has also adopted an opinion on the definition of BSE risk for specified geographical areas, dated 23 January 1998 (see bibliography).

The Scientific Committee on Medicinal Products and Medical Devices has also adopted an opinion on the equivalency of alternative products to intestines of

¹ The definition of such tissues is provided in World Health Organization report as Category I.

² The web site of the Scientific Committees can be consulted: <http://europa.eu.int/comm/dg24> (choose icons “Consumer health protection” “Scientific Committees”).

animal origin for use as surgical sutures, dated 16 September 1998 (see bibliography).

The manufacturer shall duly take into account the aforementioned opinions of the Scientific Committee and follow further developments in this area.

2. DOCUMENTATION REQUIREMENTS

2.1 Manufacturers' documentation

Examples of documentation are laid down in prEN 12442-1, prEN 12442-2 and prEN 12442-3.

2.2 Documentation provided to the Notified Body by manufacturers

Documentation provided to the Notified Body by manufacturers shall enable the Notified Body to assess conformance with the requirements of the directives in relation to the utilization of animal material.

The result of the risk analysis report³, including a rationale on the use of animal origin material, shall be submitted to the Notified Body (e.g. see directive 93/42/EEC, annex II point 3.2.c and 4.2 or annex III point 3 as appropriate).

The following documentation shall also be provided, depending on the nature of the material used:

- Information from the risk analysis report on the origin of animal material used (animal species, animal age, animal feeding, nature of tissue, quantity...)
- Statement on the presence of animal materials in the finished device and/or utilised during manufacture.
- Certificates or other documents establishing the origin of the animals,
- Certificates or documents to demonstrate conformance with veterinary inspection criteria and the nature of this inspection.
- Documentation related to the slaughtering of animals, and contractual arrangements with the abattoir.
- Documentation and work instructions relating to the collection, transport and storage of the material.
- Documentation relating to controls performed on raw materials and/or final product.
- Detailed documentation describing the inactivation/elimination process and validation of this inactivation/elimination process.
- Manufacturers audit and review of sub-contractors.

Where it is not possible to provide a part of this documentation, a justification shall be given with reference to the risk analysis.

³ The risk analysis report is described in prEN 12442-1, clause 4.9.

2.3 Specific guidance for Notified Bodies

All information contained in section 1 of the present document is relevant for Notified Bodies activities.

Essential Requirements 8.2 requires Notified Bodies to retain information on the geographical origin of the animals. The concept of geographical origin includes place of birth, rearing and slaughtering. Special consideration shall be given to the feeding practices for transmissible agent's susceptible species. The depth of information required shall be commensurate with the risk of the material and the reliance on sourcing as a means of risk management.

Notified Bodies are not required to hold all batch specific information, which shall be available from the manufacturer on request. Nevertheless, the Notified Body shall be aware of how this information is kept by the manufacturer.

The manufacturer shall inform the Notified Body of changes in the geographical origin of animals, the incidence of BSE in a source country, sourcing, processing and use of animal materials.

3. CONDUCT OF CONFORMITY ASSESSMENT

The Notified Body shall review the documentation (see 2.2) as part of the assessment process (e.g. see directive 93/42/EEC).

The processes involved in sourcing control and handling and inactivation of relevant animal materials are to be considered as “special processes”. Any substantial change of the quality assurance system in relation to special processes shall be notified to the Notified Body for the purpose of an additional approval prior to its implementation.

Notified Bodies shall pay particular attention to verification of manufacturer's control of raw materials, finished products and subcontractors. Notified Bodies shall consider and document the need to audit matters relating to sourcing including subcontractors.

4. NOTIFIED BODY'S SPECIFIC PROCEDURES AND EXPERTISE

4.1 Notified Bodies internal procedures

Notified Body shall establish and implement internal policy and procedures for assessing medical devices manufactured from materials of animal origin.

4.2 Expertise

The Notified Body shall possess relevant knowledge in order to:

- Identify the potential hazards and estimate the associated risks arising from the use of animal materials for the manufacture of medical devices,
- Evaluate the manufacturer's risk analysis and risk management strategy,

- Evaluate information provided by the manufacturer including information referred to in section 2.2,
- Interpret the results of any elimination and/or inactivation study and/or literature search.

This knowledge shall reside within the Notified Body, which may be supplemented by external experts. Such external experts shall have a sufficient in depth and up to date knowledge in the field concerned.

The Notified Body shall maintain awareness of legislation relevant to a particular application and of the incidence of animal disease in sourced countries.

5. BIBLIOGRAPHY

- Council Directive 93/42/EEC of 14 June 1993 concerning medical devices (Official Journal of European Communities No. L 169/L)
- Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices (Official Journal of European Communities No. L 189/17)
- pr EN 12442-1 : Animal tissues and their derivatives utilized in the manufacture of medical devices - Part 1 : Analysis and management of risk.
- pr EN 12442-2 : Animal tissues and their derivatives utilized in the manufacture of medical devices - Part 2 : Controls on sourcing, collection and handling.
- pr EN 12442-3 : Animal tissues and their derivatives utilized in the manufacture of medical devices - Part 3 : Validating of the elimination and/or inactivation of viruses and transmissible agents.
- European guideline CPMP/BWP/268/95, FINAL version 2 «Note for guidance on virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses.
- Notification on the marketing authorization and registration of drugs, Measures to avert risks associated with drugs, stage II, of March 28, 1996 of the Bundesinstitut für Arzneimittel, Germany (BfArM).
- Guidelines for minimizing the risk of transmission of agents causing spongiform encephalopathies via medicinal products - III/3298/91 - EN FINAL.
- Note for Guidance for minimising the risk of transmitting animal Spongiform Encephalopathy Agents via medicinal products - EMEA - CPMP/BWP/877/96 - draft of October 1997
- Commission decision 98/256/EC, Official Journal no. L113, 15.4.1998, p. 32
- Opinion of the Scientific Steering Committee on the safety of meat and bone meal from mammalian animals naturally or experimentally susceptible to transmissible spongiform encephalopathies (March 1998).
- Listing of Specified Risk Materials: a scheme for assessing relative risks to man.
- Opinion on BSE risk adopted by the Scientific Steering Committee at its plenary meeting of 26-27 March 1998, following a public consultation on the preliminary opinion adopted on 19-20 February 1998.
- Opinion on the Safety of Gelatine adopted at the Scientific Steering Committee at its plenary meeting of 26-27 March 1998 following a public consultation on the preliminary opinion adopted on 19-20 February 1998 (Version updated on 3.04.1998) – Background
- Opinion on the Safety of tallow derived from ruminant tissues – Background

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- Opinion & report on the equivalency of alternative products to intestines of animal origin for use as surgical sutures adopted by the Scientific Committee on Medicinal Products and Medical Devices on 16 September 1998.
- Opinion of the Scientific Steering Committee on defining the BSE risk for specified geographical areas – 23 January 1998

APPENDIX 1

Essential Requirements Of Directive 93/42/Eec Relating To Infection And Microbial Contamination



- 8.1. The devices and manufacturing processes must be designed in such a way as to eliminate or reduce as far as possible the risk of infection to the patient, user and third parties. The design must allow easy handling and, where necessary, minimize contamination of the device by the patient or vice versa during use.
- 8.2. Tissues of animal origin must originate from animals that have been subjected to veterinary controls and surveillance adapted to the intended use of the tissues.

Notified Bodies shall retain information on the geographical origin of the animals.

Processing, preservation, testing and handling of tissues, cells and substances of animal origin must be carried out so as to provide optimal security. In particular safety with regard to viruses and other transferable agents must be addressed by implementation of validated methods of elimination or viral inactivation in the course of the manufacturing process.

Essential requirements of Directive 93/42/EEC relating to labelling:

2. ... - inform users of the residual risks due to any shortcomings of the protection measures adopted.
- 13.3.k any warnings and/or precautions to take
- 13.6.e where appropriate, information to avoid certain risks in connection with implantation of the device

APPENDIX 2

Definitions and requirements for sourcing from Pren 12442-1 + pren 12442-2 (extracts)

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Definition of “animal” from pr EN 12442-1:

All vertebrates including fish, amphibians, reptiles, birds and mammals, excluding humans (Homo sapiens).

Definition of “Transmissible agents” from pr EN 12442-1:

Unclassified pathogenic entities, prions and similar entities.

Note: e.g. BSE agent, scrapie agent.

Requirements on sourcing from pr EN 12442-2:

6 Sourcing of animal materials: Inspection, certification and traceability

6.1 Sourcing of animal material shall where technically practicable be subject to control and individual inspection by a veterinarian. There will however be some source species where this is not possible (e.g. fish). If individual animals cannot be inspected, the justification for this shall be documented and a relevant sampling plan provided. To minimize the potential risk of the causative agents of spongiform encephalopathies in medical devices the requirements of normative Annex A shall be applied to relevant animal species.

6.2 Material of animal origin intended for utilization in medical devices shall have originated from animals confirmed by a veterinarian as being fit for human consumption. For species not usually consumed by humans a status equivalent to “fit for human consumption” is required. Records to demonstrate conformance with veterinary inspection criteria at the abattoir, certificate details and source shall be available.

NOTE: Animals should be subject to ante-mortem veterinary inspection. Prior to certification, a post-mortem inspection should be performed immediately after slaughter and should include:

- a) visual inspection;
- b) palpation of specified organs;
- c) incision of organs and lymph nodes;
- d) investigation of anomalies, for example inconsistency, colour, and smell;
- e) if necessary laboratory tests.

6.4 Depending on the source species of the tissues used, the perceived risk from pathogens, and the ability to obtain appropriate assurances, it may be necessary to specify the origin of the animals (such as place of birth; country, region or farm of rearing; and place of slaughter) and to obtain additional assurances on their state of health and system of management (see Part 1 of EN 12442). (For bovine species, see Annex A).

NOTE: When official information systems are in place, animals should be individually traceable, where the results of the risk analysis indicate that this is necessary.

APPENDIX 3

Requirements On Literature Search From Pr En 12442-3

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5 Literature search

5.1 Conduct of the literature search

A literature search shall be performed as specified in Annex A, to identify and analyse data on the elimination and/or inactivation of viruses and transmissible agents (see C.2).

5.2 Application of literature search output

Technical information from the literature search shall be used in optimising the design of an inactivation and/or elimination study.

Any extrapolation based on the inactivation of viruses and transmissible agents shall be justified and documented.

Intrinsic variability of materials of animal origin utilised in medical devices and of manufacturing processes can lead to misinterpretation of the validity of published data and shall be taken into account.

5.3 Viruses

The manufacturer shall demonstrate whether the literature search provides an indication of which inactivation and/or elimination steps are likely to be effective and is a prerequisite to performing a viral inactivation study. In exceptional cases, if a manufacturer chooses not to perform a study this shall be justified and documented.

5.4 Transmissible agents

The manufacturer shall demonstrate whether the literature search provides an indication of which methods are likely to be effective in the elimination and/or inactivation of transmissible agents. In particular it shall be demonstrated that the specific materials of animal origin and the specific processes referred to in the literature are comparable to those used for the medical devices concerned. Where the materials or processes are not comparable, an inactivation study shall be performed.

If the available information does not support the elimination and/or inactivation of transmissible agents, then an alternative risk management strategy shall be implemented (see EN 12442-1).

APPENDIX 4

Requirements And Guidance On Bse/Tse Risks In Pr En 12442-2

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Annex A of prEN 12442-2 stipulates

Additional requirements relating to the application of Part 2 of EN 12442 for bovine sourced materials

NOTE 1: Taking into account the current state of science and technology, similar principles to those discussed in this annex should also be applicable to other transmissible spongiform encephalopathies in animals.

NOTE 2: The agent that causes BSE presents a hazard to humans. Experimentally it has been shown that sheep and goats are susceptible to the BSE agent via the oral route. The risk from the hazard of BSE will vary with the incidence of BSE in cattle, which will depend on the measures taken by government competent authorities to prevent, control or eradicate the disease. Determination of incidence of disease depends on the extent and quality of surveillance measures. The best guarantees can be given when the results of effective surveillance show that neither BSE nor scrapie exists in a country, region, herd or flock.

A.1 General aspects

Assurance on BSE incidence shall be verified using the latest information from OIE (Office International des Epizooties, Paris) and FAO (Food and Agricultural Organization, Rome), taking into account the most recent information from relevant government competent authorities. The manufacturer shall assess the incidence and trend using at least the last 3 years' data and preferably the last 5 years' data.

NOTE: The aim is to source all tissues from countries which present little or no risk. It is acknowledged that this may not always be achievable. The highest risk will be represented by high risk tissues (e.g. brain, spinal cord and eye) derived from countries of high incidence. Whether or not a risk is unacceptably high will depend on the use to which the tissue is put. Risk analysis and risk management are addressed in Part 1 of EN 12442.

The use of tissues of bovine origin shall take into account the following factors:

- a) the BSE status of the country, the herd(s) or origin of the animals and the breeding history (maternal line) (see also Annex A.2);

NOTE: Factors involved in the BSE status of a country include:

- i) the incidence of disease in the country,
- ii) whether or not there is compulsory notification of disease (official veterinary surveillance),
- iii) whether there is compulsory clinical and laboratory verification of suspected cases.

- b) the age of the donor animals; and the nature of tissues used (see Annex E of Part 1 of EN 12442);

NOTE: As clinical BSE has not been diagnosed in young animals (less than 20 months), sourcing from animals particularly under 6 months of age gives an additional level of safety.

- c) whether or not the tissues will be pooled or derived from single animals, and
d) feeding history (A.3).

A higher level of risk shall be assumed if a collected tissue cannot comply with the above criteria.

pr EN 12 442-2 is defining a “low risk herd”

Low risk herd (“closed herd”): a herd in which for at least the previous six years:

- a) there has been documented veterinary monitoring;
- b) there has been no case of BSE;
- c) there has been no feeding of mammalian-derived protein;
- d) there is a fully documented breeding history;
- e) each animal is traceable, and
- f) genetic material has been introduced only from herds with the same BSE-free status.

NOTE: Attention is drawn to possible future regulatory definition of this term

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