



MEDICAL IMPLANTS CONTAINING BOVINE MATERIAL

ISSUE

1. The Medicines and Healthcare Products Regulatory Agency (MHRA) has asked the committee to:
 - advise on the BSE risk to humans from medical implants that include bovine material sourced from USA animals.
 - comment on a scheme proposed by a British Standards Institution (BSI) committee to determine whether the BSE risk from a medical device utilising bovine material has been minimised.

BACKGROUND

Regulatory position

2. Bovine material (e.g. pericardium, hide, tendons, blood vessels, collagen and gelatine) is used in a number of medical devices, ranging from orthopaedic footwear to cardiovascular implants. Two EU directives apply to medical devices containing bovine material:
 - the Medical Devices Directive 93/42/EEC deals with medical devices in general terms. It came into force fully in 1998.
 - a supplementary Directive 2003/32/EC deals specifically with transmissible spongiform encephalopathy (TSE) risks in relation to medical devices. It came into force fully on 1 May 2005.
3. The Medical Devices Directive 93/42/EEC provides a framework for the assessment of the safety, health protection and performance characteristics of medical devices¹. It is based on the

¹ Defined as any instrument, apparatus, appliance, material or other article used for humans for the purpose of diagnosis, prevention, treatment or alleviation of disease, or alleviation of, or compensation for an injury or handicap, or investigation, replacement or modification of the

principle that all risks must be eliminated or reduced as much as possible, in line with the state of the art, and that any residual risks must be acceptable when weighed against the benefits to patients. Medical device manufacturers are responsible for meeting the requirements of the Directive. Conformity is assessed and verified by an independent third party (Notified Body) designated by the Competent Authority in a Member State. A Certification of Conformity (CE mark) is provided if the device meets the requirements of the Directive². In the UK, the Competent Authority is the MHRA. There are a number of Notified Bodies.

4. A European Standard BS EN 12442 was adopted in 2000 to support the requirements of the Medical Device Directive 93/42/EEC with respect to viruses and transmissible agents. It provides guidance on risk management and on controls for sourcing, collection and handling of, and inactivation procedures for relevant animal tissues. SEAC commented on a draft of the Standard in 1996 (see paragraph 25 below).
5. Directive 2003/32/EC was introduced to manage risks from medical devices utilising tissues/derivatives originating from animals susceptible to TSEs (e.g. cattle, sheep, goats, deer). From 1 May 2005, statutory consultation and certification has been required for material from TSE-susceptible animals used in a device. This certification supplements the Certification of Conformity required under the terms of Directive 93/42/EEC.
6. The certification involves an assessment of TSE risk by a Notified Body, which should include:
 - pre-clinical and clinical data to support use of the device,
 - an assessment of compliance to relevant standards,
 - a justification for the use of tissues/derivatives from a TSE-susceptible species instead of a non-TSE-susceptible species or a synthetic material,
 - an evaluation of measures to minimise the risk of infection including the source of the materials, veterinary controls,

anatomy or of a physiological process, and which does not achieve its principal intended action on the human body by pharmacological, immunological or metabolic means (adapted from 93/423/EEC).

² The EC Animal By Product Regulation (Regulation EC No 1774/2002) also applies. It indicates that materials used for the manufacture of medical devices should be category 3 material or equivalent (i.e. from animals fit for human consumption).

feeding restrictions, harvesting practices, information on the TSE-related infectivity of the tissue/derivative used, and the effect of processing and methods to eliminate and/or inactivate TSE agents.

7. A summary of the Notified Body's assessment is also circulated to all Competent Authorities in the EU, whose comments must be given due consideration by the Notified Body in reaching a decision on the final certification of the device.
8. Although Directive 2003/32/EC contains some specific technical requirements relating to the assessment, there is a lack of specific guidance on issues such as the acceptability of particular risk estimation models and risk control measures, and the criteria required to justify the use of material from TSE-susceptible animals. Similarly, although compliance with European Standard BS EN 12442 carries the presumption of conformity with the regulations, the standard itself provides no such guidance.

Risk reduction methods for medical devices

9. Methods to inactivate TSE agents in the tissues/derivatives used in medical devices are rarely a realistic option as the harsh inactivation methods required tend to destroy the structure of the tissues/derivatives. For many materials, the only practical risk control measure is to use material from sources with a very low/negligible risk of infection with TSE agents.
10. In the case of bovine material, MHRA is of the view that minimisation of risk can be achieved by the use of material from:
 - (i) a closed herd, where controls are in place to prevent the introduction of the BSE agent into an uninfected herd from factors such as the feeding of meat and bone meal (MBM) and the importation of animals with a risk of BSE infection arising from their source³, or
 - (ii) countries/regions with a Geographical BSE Risk (GBR) of I i.e. where the presence of one or more cattle clinically or pre-clinically infected with the BSE agent is highly unlikely (see below).
11. The EC Scientific Steering Committee (SSC) in 2001 considered materials from these sources to be safe for the manufacture of medical devices⁴. The World Health Organisation (WHO) in 2003

³ http://europa.eu.int/comm/food/fs/sc/ssc/out56_en.html

⁴ http://europa.eu.int/comm/food/fs/sc/ssc/out239_en.pdf

reached a similar conclusion⁵. However, apart from advice from SEAC on the use of UK-derived material (see paragraph 26 below), no expert committee opinion is available on which to base the evaluation of BSE risk arising from bovine tissues from other sources.

Geographical BSE Risk

12. GBR is a qualitative indicator of the likelihood of the presence of one or more cattle infected with BSE pre-clinically as well as clinically at a given point in time in a country/region. Where the presence of BSE is confirmed, the GBR gives an indication of the level of infection (see table below). The GBR assessment method was developed by the SSC (2000) and has been applied to countries within the EU and elsewhere⁶. It is based on the assumption that BSE originated in the UK, is only propagated through the recycling of cattle tissues into animal feed and is only transmitted via feed. Thus, for countries other than the UK, the importation of contaminated feed and/or infected animals are the only initial sources of BSE.

Table of Geographical BSE Risk levels

GBR Level	Presence of one or more cattle clinically or pre-clinically infected with the BSE agent in a geographical country/region
I	Highly unlikely
II	Unlikely but not excluded
III ^a	Likely but not confirmed or confirmed at a lower level
IV ^a	Confirmed at a higher level

^a SSC considered the borderline between level III and IV as arbitrary, as no clear scientific justification could be made for this differentiation. As a guide, it adopted a threshold between levels III and IV of an incidence of 100 confirmed BSE cases/million within the cattle population over 24 months of age in a country/region over a 12 month period.

13. The GBR level of a country is based on an assessment of factors that could:

(i) lead to or prevent the introduction of the BSE agent into that country (the external challenge) such as controls on the importation of contaminated feed or infected animals, and,

(ii) help or inhibit its propagation in the country's cattle herd (the stability of the system) such as the structure and dynamics of the cattle population, TSE surveillance systems, culling schemes as well as feeding and rendering practices.

⁵ http://www.who.int/bloodproducts/publications/en/WHO_TSE_2003.pdf

⁶ http://europa.eu.int/comm/food/fs/sc/ssc/out113_en.pdf

14. SSC and now EFSA reassesses GBRs over time. The UK is designated GBR IV.

USA GBR

15. USA was initially assigned GBR II by the SSC in 2000⁷. A reassessment by EFSA in 2004 changed the level to GBR III⁸ (see Annex 1). This was based upon:

(i) the extent of external challenge since 1980. The USA imported cattle and MBM from BSE risk countries, including the UK, during periods of time when a risk of importation of infected animals and contaminated feed existed (see pages 2-8 of the technical annex at Annex 1).

(ii) the stability of USA system to mitigate against the external challenge since 1980. The USA system was considered extremely unstable such that should BSE infectivity have entered the system it would have recycled and amplified quickly (see pages 8-14 of the technical annex at Annex 1).

16. In 2005, BSE was confirmed from a reanalysis of sample collected as part of routine surveillance from a single native USA animal that died in 2004⁹ supporting the change in GBR level.

SEAC CONSIDERATION

Implantable medical devices containing bovine material

17. MHRA recently identified a range of implants (heart valves, heart valve conduits, vascular grafts and pericardial patches) on the UK market that use bovine tissue (mainly pericardium) sourced from an open herd in the USA. The devices were certified by a Spanish Notified Body despite objections being made about the source of the material by the UK and other Member States. The basis for the Spanish certification was that no alternative devices would be available until the manufacturer found another bovine source (i.e. from a closed herd or from a GBR I country). However, since these implants were sourced from an open herd in a GBR III country, MHRA took the view that the TSE-related risk had not been minimised and the products were removed from the UK market.

⁷ http://europa.eu.int/comm/food/fs/sc/ssc/out137_en.pdf

⁸ http://www.efsa.eu.int/science/tse_assessments/gbr_assessments/573_en.html

⁹ http://www.aphis.usda.gov/lpa/issues/bse/epi-updates/bse_final_epidemiology_report.pdf

18. The products will not be re-introduced on the UK market until suitable alternatives are available. However, the devices can be used in the UK on humanitarian grounds on a named patient basis where no alternative treatment is available.
19. It is likely that in the past (prior to 1 May 2005 when the additional certification under the terms of Directive 2003/32/EC was required) that several thousand devices incorporating material from the same and similar sources were implanted into patients in the UK.

BSE infectivity of bovine heart tissues

20. Few studies have examined the presence/absence of BSE infectivity in bovine heart or pericardium (no studies have reported the presence/absence of PrP^{Sc} in these tissues). SSC reviewed data on the distribution of BSE infectivity in cattle (mostly data from the VLA pathogenesis experiment) in 2002¹⁰. It reported that no infectivity, as assessed by mouse bioassay, was detected in the heart of confirmed cases of BSE or in the heart, pericardium, mitral valve or aorta from cattle after 18 and 32 months following oral exposure to BSE. WHO (2003) classified bovine heart/pericardium as tissues with no detected infectivity based on similar (the same) data¹¹.
21. In a more recent report¹², no infectivity was found in the heart from a single animal with clinical BSE using a mouse bioassay utilising a transgenic mouse line expressing the bovine prion protein gene (bioassay of the pericardium was not conducted¹³). This bioassay is reported to be approximately 10 000 times more sensitive than conventional mouse bioassay and approximately 10 times more sensitive than cattle bioassay.

BSI committee scheme

22. The lack of specific guidance on risk assessment and control measures in relation to use of material from TSE-susceptible animals in medical devices has led to discrepancies in implementation of the legislation (such as the situation described above). A revision of the European standard BS EN 12442 is under development and MHRA is pressing for this to facilitate more

¹⁰ http://europa.eu.int/comm/food/fs/sc/ssc/out296_en.pdf

¹¹ http://www.who.int/bloodproducts/publications/en/WHO_TSE_2003.pdf

¹² Buschmann & Groschup (2005) Highly bovine spongiform encephalopathy-sensitive transgenic mice confirm the essential restriction of infectivity to the nervous system in clinically diseased cattle. *J. Infect. Diseases* 192, 934-942.

¹³ Buschmann. Personal communication.

consistent decisions to be made about the TSE risks associated with medical devices.

23. A risk evaluation scheme incorporating an assessment of whether the BSE risk has been minimised has been developed by the BSI standards committee (see Annex 2) for discussions to revise the standard. It aims to facilitate the application of more consistent judgements about the acceptability of BSE risk arising from medical devices that include material from TSE-susceptible animals. The BSI committee proposes that where the BSE risk has not been minimised in line with specified criteria, the risk may only be judged acceptable when balanced by exceptional benefit and feasibility considerations. Even when the risk is minimised, it would be necessary (as with Directive 2003/32/EC) to demonstrate a clinical benefit that cannot be achieved by other means.

PREVIOUS SEAC ADVICE ON BOVINE MATERIAL IN MEDICAL DEVICES

24. At SEAC 9 (1991), the committee considered the use of bovine material in non-food products (pharmaceuticals, medical devices and cosmetics). The committee agreed that the human risk from BSE would likely reside in the bovine tissues most likely to contain the infective agent and where parenteral exposure could occur.
25. At SEAC 36 (1996), the committee considered a draft of the European Standard BS EN 12442. The draft stated that use of bovine tissues should take into account factors including the BSE status of the country and herd of origin, the feeding history of the herd, the age of the cattle used and the extent of inactivation of the agent by processing. The committee suggested that the Standard cover all TSEs.
26. At SEAC 42 (1997), the committee considered a report prepared by the Medical Devices Agency (now part of the MHRA) on the geographical sources of materials of bovine origin in medical devices. The committee noted that all bovine products used in medical devices were sourced from outside the UK. It was content that UK raw materials were not used in these products.

ADVICE SOUGHT FROM THE COMMITTEE

27. The committee is asked:

(i) to consider to what extent the TSE risk in relation to medical implants utilising bovine pericardium¹⁴, and medical devices in general utilising bovine material, that is sourced from the USA is influenced by the following factors:

- the likelihood that the BSE agent is present in the tissue used, if it is taken from infected cattle;
- the likelihood cattle in the USA are infected with BSE now and were infected with BSE in the past (see Annex 1), in particular whether sourcing from open herds in the USA represents a significant risk now or from any particular time in the past;
- implantation, rather than ingestion, of infectious material;
- any other significant factors?

(ii) to comment on the BSI committee proposal for the evaluation of the BSE-risk from bovine material used in medical devices (see Annex 2) and to consider:

- whether the BSE risk associated with a medical implant utilising bovine material is minimised by sourcing material from a closed herd or GBR I country, irrespective of the infectivity of the tissue or the manufacturing methods used;
- whether the BSE risk associated with a medical device contacting only intact skin is negligible even if the bovine material is sourced from a GBR IV country, irrespective of the infectivity of the tissue or the manufacturing methods used;
- the extent to which additional control measures (e.g. controlled harvesting and/or prion reduction processes) would minimise the BSE risk for implants incorporating bovine material sourced from open herds in GBR II and III countries?

¹⁴ SEAC's consideration of the risks from use of these materials in implantable devices may be used by the CJD Incidents Panel when considering cases where such devices have been implanted.



Scientific report of the European Food Safety Authority on the assessment of the Geographical BSE Risk (GBR) of the United States of America (USA) including

- **report**
- **technical annex**

These documents can also be found at:

http://www.efsa.eu.int/science/tse_assessments/gbr_assessments/573_en.html



British Standards Institution committee proposal for the determination that BSE risk from bovine material used in medical devices is minimised

UK comment on risk evaluation (new Clause 4.5 of ISO 22442-1) [Animal tissues and their derivatives utilised in the manufacture of medical devices – Part 1: Analysis and management of risk]

4.5. Risk Evaluation

4.5.1 General

Clauses 5, 6 and 7 of ISO 14971 apply. [This refers to requirements for risk evaluation, risk control and evaluation of overall residual risk acceptability, in the international standard on risk management for medical devices]

4.5.2 Evaluation of TSE Risk

For materials sourced from species that are susceptible to TSE, risk control measures shall be reviewed and the overall TSE risk estimated and assessed in relation to the medical benefits of the intended use and the feasibility of other treatment or supply options. Figure 1 identifies the risk control measures that can be applicable to a particular product and indicates circumstances that may be judged to correspond to minimal BSE risk. The TSE risk may be judged acceptable if the BSE risk has been minimised in accordance with Figure 1 and the medical benefit arising from the intended use of the device cannot feasibly be achieved by other means. Where the BSE risk has not been minimised, the TSE risk may only be judged acceptable when balanced by exceptional benefit and feasibility considerations. The rationale for the judgement that the TSE risk is acceptable shall be documented in the risk management file.

Figure 1 (Normative): Circumstances leading to minimisation of BSE risk
(see attached flowchart)

Notes to Figure 1:

This flowchart can be used to determine whether the circumstances of sourcing, processing and use of a particular device that incorporates bovine material minimise the BSE risk.

The infectivity of a starting tissue can be determined by reference to a literature survey (see D.3.4).

The risk relating to geographical sourcing can be determined by reference to a literature survey (see D.3.3). The terminology used in the flowchart is that used by the Scientific Steering Committee of the European Union and corresponds to circumstances where the presence of infection with the BSE-agent in a country has been determined as follows: GBR I: highly unlikely; GBR II: unlikely but not excluded; GBR III: likely but not confirmed or confirmed at a lower level; GBR IV: confirmed at a higher level.

A prion reduction process can be any process which, although not formally validated or assured by the manufacturer, is known, by reference to a literature survey, to substantially eliminate or inactivate prions.

A validated prion inactivation process is one which includes a prion elimination or inactivation step that complies with relevant parts of Clause 6 of ISO 22442-3. [This clause (Elimination and/or inactivation study of viruses and transmissible agents) requires that such studies must substantiate the effectiveness of manufacturing steps and that validation data for the elimination/inactivation of transmissible agents must be provided to support sterilization processes. There are also requirements for protocols, study conduct and data interpretation.]

Controlled harvesting comprises a process that complies with Clauses 6, 7, 8, A.5 and A.6 of ISO 22442-2. [These clauses contain requirements for collection, handling, storage and transport of material, including the need for control of procedures by the manufacturer, prevention of cross-contamination, environmental control and justification of the method of stunning.] This is in addition to the routine veterinary surveillance and abattoir certification required to ensure fitness for human consumption.

Figure 1 (Normative): Circumstances leading to minimisation of BSE risk

