



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian medical device guidelines

Requirements for the assessment of medical devices containing animal material, with particular regard to the minimisation of risks relating to transmitting Transmissible Spongiform Encephalopathies (TSEs)

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TGA Health Safety
Regulation



About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

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DISCLAIMER

This document is provided for guidance only. It should not be relied upon to address every aspect of relevant legislation. Please refer to the *Therapeutic Goods Act, 1989* and the *Therapeutic Goods (Medical Devices) Regulations, 2002* for legislative requirements.

FURTHER INFORMATION

The Medical Devices Information Unit of the Office of Devices, Blood and Tissues of the Therapeutic Goods Administration (TGA) can be contacted by:

Telephone: 1800 141 144
Facsimile: (02) 6232 8299
Email: cab.medical.device.information@health.gov.au
Website: www.tga.gov.au/industry/devices.htm
Mail: PO Box 100
Woden
ACT 2606

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INTRODUCTION

Infectious agents known as prions cause Transmissible Spongiform Encephalopathies (TSEs). In animals, prion diseases include:

- £ Bovine Spongiform Encephalopathy (BSE) in cattle,
- £ Scrapie in sheep and goats,
- £ Chronic Wasting Disease (CWD) in deer and elk (cervid),
- £ Transmissible Mink Encephalopathy (TME) in farmed mink,
- £ Feline Spongiform Encephalopathy (FSE) in domestic cats and captive exotic felines, and
- £ Spongiform Encephalopathy in captive exotic ungulates.

In humans, prion diseases include:

- £ classical Creutzfeldt-Jakob Disease (CJD),
- £ variant CJD (vCJD),
- £ Kuru,
- £ Fatal Familial Insomnia (FFI),
- £ Sporadic Fatal Insomnia (SFI), and
- £ Gerstmann-Sträussler-Scheinker Syndrome (GSS).

vCJD is believed to be caused by the agent responsible for BSE in cattle. The emergence of BSE in the United Kingdom and its spread to other countries within and outside Europe, together with the increasing number of cases of vCJD in humans, have focussed international efforts on minimising the potential for this agent to be transmitted to humans. Moreover, it is generally accepted that the BSE agent may be transmitted from cattle to humans through the consumption of BSE-contaminated food.

This guidance document is one of a series that has been produced to help explain the new regulatory system for medical devices in Australia that commenced on 4 October 2002. The new system has been established by the *Therapeutic Goods Act 1989* as amended by the *Therapeutic Goods Amendment (Medical Devices) Bill 2002* and the *Therapeutic Goods (Medical Devices) Regulations 2002*.

Many other guidance documents are available in this series. The series was developed to assist a wide-ranging audience and additional documents can be included if there is enough demand. A separate guidance document is available describing the series.

Although each guidance document has been developed to provide information about particular aspects of the new medical devices regulatory system in Australia, it is expected that a certain amount of cross-referencing to other documents in the series will be inevitable.

This guidance document applies to:

- € medical devices incorporating tissues, their derivatives or other substances originating from animals for which there is a risk of transmission of TSEs under normal conditions of use, to either the patient or user; and
- € materials derived from tissues, their derivatives or other substances originating from animals for which there is a risk of transmission of TSEs, that are used or come into contact with the medical device during its manufacture.

Further, this document is a guideline for medical devices of animal origin and in particular, the assessment of the risk of transmitting TSEs. It provides guidance on classifying medical devices containing non-viable animal tissues, cells or other substances, or microbial or recombinant tissues, cells or other substances. These requirements are set down in Schedule 2, Part 5, Rule 5.5 and Schedule 1, Part 2, Section 8.2 of the *Therapeutic Goods (Medical Devices) Regulations 2002*, (the Regulations). Clarification of the classification rule 5.5, in Schedule 2, part 5 of the Regulations should assist manufacturers. The difference between those medical devices that are covered by Rule 5.5 and therefore must come to the TGA for conformity assessment under regulation 4.1(2)(a), and those for which the manufacturer may self-assess for TSE risk is described. The self-assessment would be carried out according to the TGA document "*Supplementary Requirements for Therapeutic Goods for Minimising the Risk of Transmitting Transmissible Spongiform Encephalopathies (TSEs)*". The TGA Supplementary TSE document focuses on ingredients of animal (particularly ruminant) origin that are currently classified as Category IV of the European Medicines Evaluation Agency (EMA) Guidance; that is, those ingredients characterised as having no detectable infectivity according to current knowledge of TSE transmission. Category IV ingredients are commonly used in the preparation of therapeutic goods as active substances, excipient substances, raw materials, or as reagents in their production. The document does not apply to these ingredients when used in medical devices that are implantable, injectable or used in the eye. Those devices are subject to conformity assessment procedures.

All Category IV materials must comply with the TGA Supplementary Requirements document whether or not they are covered by Rule 5.5. This document can be downloaded from the Internet address, <http://www.tga.gov.au/industry/tse-supplementary-requirements.htm>.

The TGA document references the European Union "*Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products*" (EMA/410/01 rev 1, 31 May 2001), and its subsequent revisions. This guidance also takes into account the requirements of the draft European Directive on *medical devices incorporating tissues or derivatives originating from animals for which a TSE risk is suspected* (29.07.2002).

In the EMA Note for Guidance, tissues and fluids from implicated animal species are classified into four main categories on the basis of available scientific data on the infectivity in tissues and fluids from naturally infected sheep and goats with clinical scrapie (see the TGA supplementary TSE document). TGA policy requires that therapeutic goods containing ruminant-derived ingredients that have been classified as:

- £ Category I (high infectivity),
- £ Category II (medium infectivity), or
- £ Category III (low infectivity)

tissues or fluids must be sourced from countries free of BSE where possible and are subject to TGA conformity assessment under Regulation 4.1.

It should be noted that the TGA does not exclude wool and wool derivatives or milk derivatives manufactured using enzymes or calf rennet from the requirement for TSE assessment.

DEFINITION OF “ANIMAL”

As in the EMEA document, and for the purposes of TSE assessment only, “animal” shall mean any of the following species:

- £ Bovine
- £ Ovine
- £ Caprine
- £ Deer
- £ Elk
- £ Mink
- £ Cats

It should be noted that this definition of “animal” does not override the definition in the Regulations as “an invertebrate or vertebrate member of the animal kingdom”. The broader definition is used for conformity assessment purposes when identifying those medical devices that fall into Class III.

THE BASIC APPROACH TO MINIMISING RISKS OF TRANSMITTING TSEs

Manufacturers of therapeutic goods containing ingredients identified as animal origin are expected to comply with a number of basic requirements for each of the animal-derived ingredients, according to essential principle 8.2 of Schedule 1 of the Regulations. It should be noted that there might be non-TSE, including virological, safety issues that need to be resolved before the use of biologically derived ingredients in medical devices can be accepted. Because of the risk of transmissible agents, medical devices containing material of animal origin are classified, in general, as Class III by Classification Rule 5.5 of the Regulations.

The risk assessment performed for the medical device concerned must take into account the use of the animal material. Further details on the risk assessment are set out in following sections.

The general objectives of the manufacturer's risk assessment relating to TSE risks are to:

- £ identify the tissue, fluid, species and country of origin of animal-derived ingredients,
- £ assess the method of manufacture of animal raw materials, and
- £ assess the potential for Category IV materials to be contaminated with higher-risk materials

The TGA expects that:

- £ All information on animal-derived ingredients be documented and held by manufacturers, and be accessible to the TGA (in compliance with the *Therapeutic Goods Act* (1989), Part 4-5, Division 1, Section 41FD and Division 2, Section 41FN). These data are crucial should progression of scientific knowledge of TSE transmission require re-evaluation of the safety of certain ingredients in therapeutic goods. Manufacturers are expected to hold details of the tissues/fluids, species, country of origin and method of manufacture, as required in a risk assessment. All documents should be written in or translated into English if the documents are requested by the TGA.
- £ Manufacturers use appropriate ingredients with the lowest potential TSE risk where such alternatives exist. For example, materials of plant origin and materials from animal species that are not known to be naturally susceptible to TSEs.
- £ Raw materials of bovine origin should be sourced from BSE-free or provisionally free countries where possible. (see Chapter 2.3.13 of the International Animal Health Code of the Office International des Epizooties (OIE)). Similarly, as a precautionary approach, materials of cervid origin should not be sourced from areas where chronic wasting disease (CWD) is endemic.

Although it is the manufacturer's responsibility to perform the risk analysis, sponsors must certify, when submitting an application for inclusion of a medical device into the Australian Register of Therapeutic Goods, that the manufacturer has taken into account the Australian requirements, and that the information on compliance with these requirements will be made available on request.

MEDICAL DEVICES FALLING INTO CLASS III UNDER SCHEDULE 2, PART 5.5 OF THE *THERAPEUTIC GOODS (MEDICAL DEVICES) REGULATIONS (2002)*

The new regulatory regime adopts a classification system to categorise medical devices. The system uses a set of classification rules (see the Guidance Document on the Classification of Medical Devices) based on:

- £ the manufacturer's intended use
- £ the level of risk; and

- £ the degree of invasiveness in the human body.

There are five classes of medical devices:

- £ Class I
- £ Class IIa
- £ Class IIb
- £ Class III
- £ Active Implantable Medical Devices (AIMD)

Classification of medical devices follows a set of rules detailed in Schedule 2 of the Regulations. A specific classification rule has been established for medical devices containing non-viable animal tissues, cells or other substances, or microbial or recombinant tissues, cells or other substances. This classification rule is Rule 5.5.

The rule covers devices in which the animal tissues and their derivatives are used:

- £ as raw and starting materials,
- £ as active substances (such as heparin)
- £ as excipients in the device (such as glycerin), and
- £ reagents used in production (eg bovine serum albumin, enzymes, culture media).

Through the conformity assessment process for these products, sponsors shall provide to the TGA all relevant information that the manufacturer has gathered to allow evaluation of the current risk analysis and risk management strategy. Any new information on the TSE risk, collected by the manufacturer and relevant for their devices shall be sent to the TGA for information.

Additionally, any change to the processes of sourcing, collection, handling and inactivation or elimination that could modify the result of the manufacturer's risk management dossier shall be transmitted to the TGA for approval prior to the implementation of the change.

Classification Rule 5.5 states:

- “1. This clause applies to a medical device if the device contains:
 - (a) tissues, cells or substances of animal origin that have been rendered non-viable, or tissues, cells or substances of microbial or recombinant origin;
or
 - (b) a combination of tissues, cells or substances of the kind described in paragraph (a).

2. The device is classified as Class III, unless:

- (a) the device contains only tissues, cells or substances of animal origin that have been rendered non-viable; and
- (b) the device is intended by the manufacturer to come into contact with intact skin only.

Note A medical device that conforms to the description in paragraphs (2) (a) and (b) is classified as Class I under clause 2.1 of this Schedule.” (*unless a higher classification rule applies: Regulation 3.3(7)*).

Definition: ‘rendered non viable’ refers to tissues and cells that have no inherent capacity for cellular metabolic activity.

As stated earlier, the fuller definition of "animal" used in the Regulations apply to this Rule.

Exceptions to Rule 5.5

1. Rule 5.5, making a device Class III, does not apply to the following tissue or cellular derivatives:
 - £ bovine milk;
 - £ silk;
 - £ beeswax;
 - £ honey
 - £ hair; and
 - £ lanolin

Devices containing these substances will be classified by the manufacturer in accordance with the other applicable rules of Schedule 2 of the *Therapeutic Goods (Medical Devices) Regulations 2002*.

2. Rule 5.5 does not apply to a medical device that comes into contact with cleaning agents or additives such as softeners, plasticisers and lubricants containing animal, microbial or recombinant derivatives that are used only as an aid to routine manufacture or in the primary packaging.

IMPLICATIONS FOR LODGING APPLICATIONS FOR INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS FOR MEDICAL DEVICES NOT CLASSIFIED AS CLASS III UNDER RULE 5.5

The materials of devices which are not Class III by Rule 5.5, containing tissue derivatives or substances of "animal" origin as defined in the TGA Supplementary TSE document, are required to comply with the EMEA Note for Guidance and TGA Supplementary Requirements using an audit program. It is intended that the Device Electronic Application

Lodgement system (DEAL) will be configured to require identification of these devices at the application stage

A Level 1 Application Audit according to the Guidelines for The Regulation of Medical Devices in Australia “Application Audits” (Document 2) shall apply to devices that contain animal materials and are not classified as Class III by Rule 5.5.

Note: Category IV ruminant materials, such as tallow or tallow derivatives, used in device manufacture exclusively as plasticisers etc, as described in (2) of the exceptions to Rule 5.5 and in the *TGA Supplementary TSE Guideline*, Section 6 Assessment of raw materials of concern, final paragraph, will not be subject to audit.

THE RISK ASSESSMENT PROCESS

Manufacturers shall always justify the use of materials of animal origin and where practicable should use alternative materials, or at least animal material from a non-ruminant source.

Manufacturers are also reminded that medical devices, regardless of Class, must comply with the essential principles of the Regulations, which include requirements for the control of animal materials. In addition, a risk analysis is required for every device, and that risk analysis should take into account the presence of or potential contamination by any animal material and the clinical indication of the device.

As part of the conformity assessment process, the following risk assessment must be undertaken and noted in the “risk assessment” document produced in conjunction with the essential principles checklist.

A report of the evaluation shall be included in the Technical File.

The two key steps that shall be considered are the:

1. selection of appropriate starting materials (species, tissues or derivatives) with regard to their potential for contamination with transmissible agents and taking into account potential mitigation by further processing, and
2. application of a production process to remove or inactivate transmissible agents on controlled sourced tissues or derivatives.

Furthermore, the characteristics of the medical device and its intended use shall be taken into account.

Conditions of purification of the raw material and/or the conditions present in the process of manufacturing the finished device product referred to in Annex A are recognised to be robust and rigorous.

If the assessment carried out indicates that there is potential for a level of transmissible agents to be present in the animal tissues or derivatives, the manufacturer shall extend the risk assessment to consider:

- £ the quantity of animal tissues or derivatives;
- £ the type of animal tissues or derivatives coming into contact with the patient and/or user;
- £ the contact area of the patient and/or user: its surface, type (eg skin, mucosal tissue, brain, etc) and condition (eg healthy or damaged);
- £ how long the device is intended to remain in contact with the patient and/or user, including any bioadsorption and/or bioresorption effects;
- £ the number of medical devices that could be used in a given procedure;
- £ the recommended route of administration for the patient; and
- £ the recommended safe use instructions for the user.

The application of risk assessment and the risk management scheme should be based on Annex B. All Category IV materials should comply with the TGA Supplementary Requirements document, and compliance with that document may be used as a basis for the risk assessment for these materials. The sample TGA questionnaire may provide additional guidance and be a useful adjunct to this process.

ANNEX A

The production procedures referred to below for tallow and tallow derivatives, and bone derived gelatin and collagen may contribute considerably to the reduction of TSE contamination.

Tallow and Tallow Derivatives

- A. Transesterification or hydrolysis at not less than 200°C for not less than 20 minutes under pressure (glycerol, fatty acids and fatty acid production)
- B. Saponification with NaOH 12M (glycerol and soap production)
 - 1. batch process: at not less than 95°C for not less than 3 hours
 - 2. continuous process: at not less than 140°C, under pressure of not less than 8 min, or equivalent

Bone Derived Gelatin and Collagen

Manufacture should be undertaken according to one of the processes outlined in the Report of the Scientific Steering Committee of the European Commission (2003). Updated opinion on the safety of the TSE risks of gelatine derived from ruminant bones or hides, including the report on the current state of knowledge on the TSE infectivity clearance capacity of various gelatine production processes can be found at the Internet address:

http://europa.eu.int/comm/food/fs/sc/ssc/out321_en.pdf.

For countries that are free or provisionally free of BSE, both acid and alkali treatments are acceptable. The Scientific Steering Committee report outlines gelatin manufacturing methods and the recommendations for use of these processes are in line with recommendations from the EMEA.

Use of a stringent manufacturing process does not preclude the requirement to source from low risk countries.

ANNEX B

RISK ANALYSIS AND RISK MANAGEMENT

Introduction

The manufacturer shall justify, on the basis of their overall risk analysis and risk management strategy for a specific medical device, the decision to use animal tissues or derivatives from any of the following species:

- £ Bovine
- £ Ovine
- £ Caprine
- £ Deer
- £ Elk
- £ Mink
- £ Cats

The justification should take into account the expected clinical benefit, potential residual risk and suitable alternatives.

Assessment procedure

To ensure a high level of protection for patients or users, the manufacturer of devices incorporating animal tissues or derivatives shall implement an appropriate and well documented risk analysis and risk management plan to address all relevant aspects relating to TSE agents. The manufacturer shall identify the hazards 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 incorporating such 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 factors described, which shall be analysed, evaluated and managed. These measures in combination determine the device safety. The factors are:

- £ animals as a source of material;
- £ source country;
- £ nature of the starting tissue;
- £ inactivation or removal of transmissible agents;
- £ quantities of animal starting tissues or derivatives required to produce one unit of the medical device;
- £ tissues or derivatives of animal origin coming into contact with the patients and users; and
- £ route of administration.

The two key steps that shall be considered are:

- £ selecting starting materials (tissues or derivatives) considered appropriate for their potential contamination with transmissible agents, taking into account further processing. Refer to the following sections:
 - Animals as a source of material,
 - Source country, and
 - The nature of the starting tissue,
- £ applying a production process to remove or inactivate transmissible agents on controlled sourced tissues or derivatives (see the following section , Inactivation or removal of transmissible agents)

Furthermore, the characteristics of the medical device and its intended use shall be taken into account. Refer to the following sections:

- £ Quantities of animal starting tissues or derivatives required to produce one unit of the medical device
- £ Tissues or derivatives of animal origin coming into contact with the patients and users
- £ Route of administration

In performing the risk analysis and developing risk management strategies, due consideration should be given to opinions adopted by the relevant scientific committees, and where appropriate to the opinions of the Committee for Proprietary Medicinal Products (CPMP), the references of which have been published in the Official Journal of the European Community.

Animals as a source of material

The TSE risk is dependent on 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. For this reason, the TGA specifies that only healthy animals may be used as source material.

Risk animals such as fallen stock, emergency slaughtered and TSE suspected animals should be excluded.

Source country

The TGA is developing an Australian system of country classification. In the interim, the Geographical BSE risk (GBR) categorisation may be used, as below. It should be noted however that the TGA does not accept material sourced from "high risk" or GBR category IV countries.

The GBR categorisation is used when assessing the risk of the source country, pending the classification of countries according to the BSE status in 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.

The GBR categorisation 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 time, in a country. Where presence is confirmed, the GBR categorisation gives an indication of the level of infection as specified in the table below.

Table 1 – Geographical BSE Risk Categorisation

GBR Category Level	Presence of one or more cattle clinically or pre-clinically infected with the BSE agent in a geographical region/country
I	Highly 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 geographical risk of BSE infection associated with the use of raw tissues or derivatives from individual countries. These factors are defined in chapter 2.3.13 of the International Animal Health Code of the O.I.E. (Office International des Epizooties), which is available at web-site, www.oie.int/eng/normes/mcode/a_00068.htm.

The Scientific Steering Committee has made an assessment of GBR categorisation of several third world countries and Member States, and will continue to do so for others, taking the OIE factors into account.

Nature of starting tissue

The manufacturer shall take into account the classification of the hazards relating to different types of starting tissue. Sourcing of animal tissue shall be subject to control and individual inspection by a veterinarian and the animal carcass shall be certified as fit for human consumption.

The manufacturer shall ensure that no risk of cross-contamination occurs at the time of slaughtering.

The manufacturer shall not source animal tissue or derivatives classified as having potentially high TSE infectivity, 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.

Sheep and Goats

A classification of infectivity in tissues for sheep and goats has been established based on knowledge of the titres of transmissible agents in tissues and body fluids from naturally infected sheep and goats with clinical scrapie. A table was presented in the Scientific Steering Committee (SSC) opinion of 22-23 July 1999 on “*The policy of breeding and genotyping of sheep*”, as an annex. It can be downloaded from the Internet address,

http://europa.eu.int/comm/food/fs/sc/ssc/outcome_en.html. This has been updated in the opinion of the SSC – “*TSE infectivity distributed in ruminant tissues state of knowledge December 2001*” and was adopted 10-11 January 2002. This report can be downloaded from the same Internet website.

The classification may be reviewed in the light of new scientific evidence. For example, using relevant opinions from the Scientific Committees, the Committee for Proprietary Medicinal Products (CPMP) and Commission Measures regulating the use of material presenting TSE risks. A review of the references to relevant documents and opinions will be published in the Official Journal of the European Community and will be listed after a Commission decision has been taken.

Cattle

The list of specified risk material (SRM) laid down in Regulation (EC) No 999/2001 shall be considered as potentially highly TSE infective.

Inactivation or removal of transmissible agents

For medical devices that cannot withstand an inactivation or elimination process without undergoing unacceptable degradation, the manufacturer shall rely principally on the control of sourcing.

For other devices, if claims are made by the manufacturer about the ability of manufacturing processes to remove or inactivate transmissible agents, these will have to be substantiated by appropriate documentation.

Relevant information from an appropriate scientific literature search and analysis can be used to support inactivation or elimination factors, where the specific processes referred to in the literature are comparable to those used for the medical device. This search and analysis should also cover the available scientific opinions that may have been adopted by a EU Scientific Committee. In cases where there are conflicting opinions, these opinions shall serve as a reference,.

When a literature search fails to substantiate the claims, the manufacturer shall set up a specific scientific inactivation and/or elimination study. 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 stage chosen to eliminate and/or inactivate the transmissible agents; and
- € calculation of the reduction factors.

A final report shall identify the manufacturing parameters and limits that are critical to the effectiveness of the inactivation and/or elimination process.

Appropriate documented procedures shall be applied to ensure that the validated processing parameters are applied during routine manufacture.

Quantities of animal starting tissues or derivatives required to produce one unit of the medical device

The manufacturer shall 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 shall assess whether it may have the potential to concentrate levels of transmissible 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 shall consider:

- £ the quantity of animal tissues or derivatives;
- £ the contact area: its surface, type (eg skin, mucous tissue, brain, etc) and condition (eg healthy 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 any bioadsorption and/or bioresorption effects).

The number of medical devices that could be used in a given procedure shall be also taken into account.

Route of administration

The manufacturer shall take into account the route of administration recommended in the product information, from contact with the central nervous system, being the highest risk, down to application to undamaged skin, the lowest risk.

Review of the assessment

The manufacturer shall establish and maintain a systematic procedure to review information gained about their medical device or similar devices in the post-production phase. The information shall be evaluated for possible relevance to safety, especially:

- £ if previously unrecognised hazards are detected;
- £ if the estimated risk arising from a hazard is no longer acceptable;
- £ if the original assessment becomes invalid.

If any of the above apply, 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 medical device shall be considered (including the 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 any previously implemented risk control measures shall be re-evaluated and justified.

The results of this evaluation shall be documented.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia

Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605

www.tga.gov.au