Health Canada Santé Canada

Therapeutic Products Directorate
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July 12, 2004

To: Medical Devices Stakeholders

Subject: Guidance Document on the Regulation of Medical Devices Manufactured from or Incorporating Viable or Non-Viable Animal Tissue or their Derivative(s)

The *Medical Devices Regulations* set out the requirements governing the sale, importation and advertisement of medical devices. The goal of the Regulations is to ensure that medical devices distributed in Canada are safe and effective and meet quality standards.

The attached document, entitled *Guidance Document on the Regulation of Medical Devices Manufactured from or Incorporating Viable or Non-Viable Animal Tissue or their Derivative(s)* outlines the regulatory safety requirements for Class IV medical devices that are manufactured from or contain animal tissue, in compliance with the licensing provisions in section 32 (4) (j) of the *Medical Devices Regulations.* It was originally posted for comment period from July 13, 2001 to September 1, 2001. The document has been revised according to comments received with the major changes being:

- an indication that ovine or caprine derived material in medical devices must be from a scrapie free country;
- an Appendix (A) which provides a checklist of requirements for new devices and amendments.

Comments regarding this document should be directed by to:

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Thank you for providing your comments.

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Health Canada Santé Canada

GUIDANCE FOR INDUSTRY

Guidance Document on the Regulation of Medical Devices Manufactured from or Incorporating Viable or Non-Viable Animal Tissue or their Derivative(s)

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Health Products and Food Branch

Canada

Our mission is to help the people of Canada maintain and improve their health. *Health Canada*	The Health Products and Food Branch's mandate is to take an integrated approach to the management of the risks and benefits to health related to health products and food by: • Minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and, • Promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health. *Health Products and Food Branch*

Également disponible en français sous le titre **:** Lignes directrices sur la réglementation des instruments médicaux fabriqués à partir de tissus animaux viables ou non viables ou de leurs dérivés ou contenant de tels tissus ou dérivés

FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with the policies and governing statutes and regulations. They also serve to provide review and compliance guidance to staff, thereby ensuring that mandates are implemented in a fair, consistent and effective manner.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document ***may be*** acceptable provided they are supported by adequate scientific justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this guidance, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidances.

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1 INTRODUCTION

1.1 Purpose

The purpose of this guidance document is to provide interpretation on the application of the *Food and Drugs Act* and the *Medical Devices Regulations* for Class IV medical devices manufactured from or incorporating viable and non-viable animal tissue or their derivative(s). The document describes the minimum criteria that must be satisfied in order to substantiate the biological safety of these devices with respect to the non-human animal material used in the manufacturing of the device.

1.2 Definitions

XENOGRAFT - The live cells, tissues, and organs used in xenotransplant procedures.

XENO-HARVESTED - Material obtained from an animal species other than *Homo sapiens*.

XENOTRANSPLANTATION - The use of live cells, tissues, or organs from a nonhuman animal source transplanted, infused or implanted into a human or used for ex vivo contact with human body fluids, cells, tissues or organs that are subsequently transplanted, infused or implanted into a human recipient. Excluded are live cells tissues or organs from a nonhuman animal source that due to modification, manipulation or combination with other components fall under the definition of a medical device.

MEDICAL DEVICE - any article, instrument, apparatus or contrivance, including any component , part or accessory thereof, manufactured, sold or represented for use in:

a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals;

b) restoring, correcting or modifying a body function or the body structure of a human beings or animals;

c) the diagnosis of pregnancy in a human beings or animals; or

d) the care of human beings or animals during pregnancy and at and after birth of the offspring, including the care of the offspring,

and includes a contraceptive device, but does not include a drug.

DERIVATIVES - Material obtained from an animal tissue by a manufacturing process.

1.3 Background

Medical devices incorporating tissues of animal origin pose a special risk for both patients and health care providers due to the potential for pathogen transmission from non-human animals to humans. To ensure that this doesn't occur, control measures are needed regarding animal material sourcing, selection, harvesting, processing and use.

While there are concerns with regard to all infective agents, there is particular concern with regard to the abnormal prion protein agents which are generally believed to be responsible for the transmission of Transmissible Spongiform Encephalopathies (TSEs). Examples of TSEs are, Creutzfeldt-Jakob disease (CJD) and kuru in humans, scrapie in sheep and goats, chronic wasting disease (CWD) in deer and elk and bovine spongiform encephalopathy (BSE) in cattle. Abnormal prion proteins are known to resist complete inactivation by most traditional treatments that remove infectivity of conventional infective agents and thus recommended inactivation procedures involve harsh chemical treatment such as treatment with 2N sodium hydroxide for one hour[1]. The seriousness of these diseases is compounded by the fact that currently there are no live animal or human tests, no approved treatments and no vaccines for these diseases available[1].

An outbreak of BSE in cattle began in the United Kingdom in 1986 and has since spread to many European countries. It is now assumed due to strong scientific evidence that vCJD, the human form of BSE that was first recognised in the UK in 1996, is caused by the BSE agent and that the illness is thought to arise primarily through the consumption of meat products derived from BSE-infected cattle[1]. Ruminant species are the only route of transmission of BSE to humans[1]. Although there is no evidence of the transmission of BSE to humans through the use of medical devices, it is important to minimize the potential for the BSE agent to be transmitted by medical devices by minimizing the risks of exposure of these agents in the manufacture and use of medical devices.

1.4 Scope

This guidance document is applicable to all medical devices which are manufactured from or incorporate animal tissue or their derivatives. The requirements in this document are for new device licence applications and for investigational testing applications. Tissues or derivatives from all animal species, excluding human beings [for example (e.g.) bovine, ovine, porcine, avian, fish, insects etc.] are included. As defined in the *Medical Devices Regulations*, a medical device does not include any device that is intended for use in relation to animals. This guidance document is applicable to medical devices incorporating animal materials that have been processed, combined with non-tissue components, or that may have a systemic effect on the body. This includes wax, coral, collagen, gelatin, silk, hyaluronic acid and material obtained from animal cell lines.

In vitro diagnostic devices are excluded from this guidance document. Also excluded, through Rule 14 (2) of the *Medical Devices Regulations*, are devices intended to come into contact with intact skin only. Devices that are manufactured from human tissues or their derivatives are excluded from this document. Xenografts are not included in this guidance although animal sourced live cells, tissues or organs that have been modified, manipulated or combined with other components and fall under the definition of a medical device are included.

Medical devices manufactured from or incorporating non-viable or viable animal or human tissue or their derivatives are classified as Class IV devices, according to Rule 14 of the Classification Rules for Medical Devices in Schedule 1 to the *Medical Device Regulations*. As such, these devices must satisfy the requirements of a Class IV medical device outlined in the *Medical Devices Regulations* and guidance document *Preparation of a Premarket Review Document for Class III and Class IV Device Licence Applications*. Section 32(4)(j) of the *Medical Devices Regulations* requires, for Class IV devices, the submission of detailed information substantiating the adequacy of the measures taken with regard to risks associated with transmissible agents. This guidance document describes the additional safety requirements that the Therapeutic Products Directorate (TPD) will use to determine compliance of devices manufactured from or incorporating non-viable or viable animal tissues or their derivatives.

2 ADDITIONAL REQUIREMENTS FOR XENO-HARVESTED MATERIAL

2.1 General

All materials in a device derived from any animal source must be identified by tissue type, animal species and country of origin/residence. Some examples of materials are: porcine heart valves, porcine collagen corneal shields, porcine blood vessels used in vascular grafts, porcine collagen used in wound dressings, and hyaluronic acid from rooster combs used in viscoelastic fluids. This also includes devices exposed to materials of animal origin during manufacture (e.g. porcine trypsin used in artificial skin.).

A risk assessment must be provided to address the risks associated with the animal material contained in the device, including a risk analysis which identifies and estimates the risks and a risk evaluation which determines the acceptability of the risks. ISO Standard 14971[2] and EN 12442 (Parts 1, 2 and 3)[3] may be consulted for guidance. Refer to Appendix A for a list of information which must be submitted for a new device licence application and for an amendment resulting from a change in the geographical source or animal source of the material or the abattoirs used, all of which are significant changes. The significant change amendment document entitled “Guidance for the Interpretation of Significant Change a Medical Device" may be consulted for determining the principles of a significant change to a medical device and it is available on the Health Canada website.

2.2 Ruminant Sourced

2.2.1 Bovine Sourced

All materials in a device which are derived from a bovine source must be identified. Examples are: bovine pericardium in heart valves, bovine viscera in gut sutures, bovine bone in dental implants, and bovine collagen in lacrimal plugs. These also include devices which are exposed to materials of bovine origin during manufacture (e.g. human or animal cells grown in media containing fetal calf serum, tissue culture cells exposed to bovine trypsin).

The risk of potential infectivity of BSE is being addressed primarily by selective sourcing. All bovine material must be sourced from a country considered by Canada to be BSE free using criteria established by the Canadian Food Inspection Agency (CFIA)[3]. BSE status must be verified by consulting Appendix A of the CFIA's Canadian BSE Import Policies[3].

2.2.2 Ovine and Caprine Sourced

Devices derived from ovine (sheep) or caprine (goat) materials must, at this time, be sourced from CFIA designated BSE free countries as sheep and goats have been shown to be experimentally infected with BSE[1]. In addition, this material must be sourced from a country that is free of scrapie.

2.2.3 Other species

If tissues or derivatives from other ruminant species are used in the manufacture of medical devices, any potential risks should be addressed in the risk assessment. Documentation must be provided that feed that is or contains protein that originated from a mammal other than a porcine or an equine (excluding milk, blood, gelatin, rendered animal fat or their products) is not fed to ruminants[4,5].

2.3 Porcine Sourced

Where porcine sources are used in the production of medical devices, the products must be validated for the removal or inactivation of any potential zoonotic infectious agents that have been identified in pigs, including those that are known to infect human cells *in vivo* or *in vitro*, by inactivation/removal studies or through other valid scientific evidence, including scientific literature reports to support specific processing.

2.4 Expressed from Cells

For medical devices derived from or containing material expressed from animal cells, information must be provided which verifies that the Cell Line has been fully characterized and tested for the absence of undesirable viruses which may be infectious and/or pathogenic for humans.

It is recognized that some cell lines, especially those from rodents, used for the manufacture of products will contain endogenous retroviruses, retrovirus particles or retrovirus-like particles. In this case, the capacity of the manufacturing process to remove and/or inactivate these retroviruses from the product should be demonstrated. The International Conference on Harmonisation (ICH) guideline on Biotechnology Products[6] adopted by the Therapeutic Products Directorate of Health Canada, should be consulted for guidance on how this viral validation should be conducted.

The virucidal capabilities of the processing steps must be validated. This would include extensive screening for both endogenous and nonendogenous viral contamination which should be performed on the master cell bank. Each working cell bank as a starting cell substrate for therapeutic product production must be tested for adventitious virus using either direct testing or analysis of cells at the limit of *in vitro* cell age, initiated from the working cell bank.

A complete characterization of the expressed material(s) and carrier should be provided including such information as:

1) full physical/chemical/biochemical characterization of the peptides/proteins using analysis including mapping of the expressed peptide/protein and/or the carrier if applicable, SDS-PAGE, cation exchange chromatography, 2D-gel electrophoresis and HPLC;

2) device activity bioassays *in vivo* and *in vitro;*

3) studies of the pharmacokinetics, biodistribution and systemic effects of the expressed agent; and;

4) complete sterilization and stability information.

3 FUTURE CONSIDERATIONS

Canada is committed to keeping current with validated scientific developments in the areas relating to the biological safety of materials of animal origin. The questions of biological safety are international and dependent upon many factors. The BSE status of countries is not static and

is determined by the CFIA[5]. This guidance document reflects the current state of knowledge and is founded on the recognition that incidence levels of infectious agents are not synonymous with risk.

4 REFERENCES

1) Health Canada TSE Science Team, Table of TSE Assumptions, Sept. 2001.

2) ISO 14971:2000(E), Medical Devices - Application of risk management to medical devices. First edition 2000-12-15.

3) EN 12442-1:2000 Animal tissues and their derivatives used in the manufacture of medical devices - Part 1: Analysis and management of risk.
EN 12442-2:2000 Animal tissues and their derivatives used in the manufacture of medical devices- Part 2: Controls on sourcing, collection and handling.
EN 12442-3:2000 Animal tissues and their derivatives used in the manufacture of medical devices- Part 3: Validation of the elimination and/or inactivation of viruses and transmissible agents.

4) Canadian Health of Animals Regulations (C.R.C., c. 296) Health of Animals Act Part XIV Sections 162-170.

5) Canadian BSE Import Policies. Canadian Food Inspection Agency, Animal Health and Production Division. Revised March 2, 2001.

6) International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH)/Therapeutic Products Programme Guidance, Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin, ICH Topic Q5A. January 5, 2001.

At the time of issuance of this document, the existence of the following Draft Document is acknowledged:

Proposed Canadian Standard for Xenotransplantation. Draft #14. July 1999.

Appendix A

Biological Safety Requirements for medical devices manufactured from or incorporating viable or non-viable animal tissues or their derivatives

A) Requirements for a New Device

1. Tissue type
2. Animal species
3. Certification of country of origin/ residence of animal
4. Name and address of the supplier of any animal material
5. Certificate of veterinary inspection
6. Certificate of abattoir Inspection
7. Certification that the animal was fit for human consumption
8. Risk assessment including:

- Details of collecting, handling, storage and transport of materials.

- Evidence of a system in place for animals and tissue traceability.

- Quality control processes and procedures in place to prevent contamination with potential infectious/transmissible agents including TSEs and disinfection/decontamination procedures in the event of contamination.

- Details of processes used for inactivation or removal of infectious/transmissible agents* and demonstration of the absence of infectious agents such as bacteria, fungi, yeast, mycoplasma, viruses. This must include viral validation studies (in exceptional cases, literature studies may be accepted solely, as proof of viral inactivation/removal, but a justification and rationale must be provided by the manufacturer along with a copy of all literature reports cited). Special consideration should be given to infectious agents/transmissible agents known to infect the source animal.

- Assessment of other applicable hazards such as those associated with the local host response to the animal material including pyrogenic, immunological or toxicological responses.

* Validation studies for the removal/inactivation of TSEs are not currently required as they are difficult to interpret. However, if claims are made concerning removal/inactivation of TSEs the details of these studies must be provided.

B) Requirements for an amendment for change of geographical or animal source of material

1. Certification of abattoir inspection (if a new abattoir is being used)
2. Validation that the new material does not affect the performance of the device

C) Change of Abattoir

1. Certification of abattoir inspection
2. Certification of veterinary inspection