

July 13, 2001

To: Medical Devices Stakeholders**Subject: Preparation of a Premarket Review Document for Class IV Medical Devices Manufactured from or Incorporating Human Tissue or their Derivative(s) (draft)**

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. These Regulations were published in *Canada Gazette II* on 27 May 1998, and implementation began on 1 July 1998.

This document, entitled *Preparation of a Premarket Review Document for Class IV Medical Devices Manufactured from or Incorporating Human Tissue or their Derivative(s)*, sets out the Programme's guidance for Industry on the subject. It is to be used specifically in the preparation of Class IV medical device licence applications and licence amendment applications, for medical devices described in the *Policy on the Regulation of Medical Devices Manufactured from or Incorporating Viable or Non-Viable Human Tissue or their Derivative(s)*. A separate policy, *Policy on the Regulation of Medical Devices Manufactured from or Incorporating Viable or Non-Viable Animal Tissue or their Derivative(s)*, has been drafted to address animal tissue. These two policies replace the original draft *Policy on the Safety of Medical Devices Manufactured from or Incorporating Animal or Human Tissue or their Derivative(s)* which combined both animal and human tissue.

All medical device licence applications must comply with the licensing provisions in section 32 of the *Medical Devices Regulations*. All Class III and Class IV medical devices will require a scientific and medical review of submitted evidence of safety and effectiveness before their licence applications can be finalized.

For more information on how to prepare a premarket review document for Class III and Class IV device licence applications in general, please consult the following guidance documents and policies: *Preparation of a Premarket Review Document for Class III and IV Medical Device Licence Applications* and the *Management of Applications for Medical Device Licenses and Investigational Testing Authorizations*. The attachment is posted on the TPD's website at:
<http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/guidmd.html>

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Thank you for providing your comments.

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Attachments



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Therapeutic Products Directorate

OUR MISSION: To ensure that the drugs, medical devices, and other therapeutic products available in Canada are safe, effective and of high quality.

Direction des produits thérapeutiques

NOTRE MISSION: Faire en sorte que les médicaments, les matériels médicaux et les autres produits thérapeutiques disponibles au Canada soient sûrs, efficaces et de haute qualité.

DRAFT

Therapeutic Products Directorate
GUIDANCE DOCUMENT

Preparation of a Premarket Review Document for Class IV Devices Manufactured from or Incorporating Human Tissue or their Derivative(s)

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1.0 Introduction

1.1 Purpose

This guidance document is to be used in the preparation of licence applications for medical devices described in the *Policy on the Regulation of Medical Devices Manufactured from or Incorporating Viable or Non-Viable Human Tissue or their Derivative(s)*. Rule 14 of the *Medical Device Regulations* classifies these products as Class IV medical devices. In addition some of these medical devices will be required to meet Sections 66 to 68 of the Regulations regarding implant registration.

All medical device licence applications must comply with the medical devices licensing provisions in section 32 of the *Medical Devices Regulations*. All Class II, III and IV medical devices will be required to meet quality systems requirements. In addition, all Class III and Class IV medical devices require a scientific and medical review of submitted evidence of safety and effectiveness before their licence applications can be finalized.

The evidence to be submitted for review is in addition to the general data elements listed in section 32, subsection (1), paragraphs (a) to (e), which are necessary for all medical device licence applications. A licence application for a Class IV medical device shall contain the information and documents set out in section 32, subsection (4), paragraphs (a) to (p). An amended licence application must contain the relevant information to support the safety and effectiveness of the modified device.

1.2 Background

The *Medical Devices Regulations* (1998) arose from the recommendations of the 1992 report of the Medical Devices Review (Hearn) Committee. The report advocated two principles: (1) The level of scrutiny afforded a device should be dependent upon the hazard that the device presents; and (2) The safety and effectiveness of the device can best be assured through a balance of quality systems requirements, premarket scrutiny and postmarket surveillance.

Approximately two thirds of medical devices in Canada undergo some form of regulatory review before sale. Eighty percent of these devices are Class II, fifteen percent are Class III and the remaining five percent are Class IV.

The technical documentation required for premarket safety and effectiveness assessment is extracted from the complete set of on-site device records, including design input requirements, design output documentation, verification and validation documents and production and process documents.

1.3 Scope

This guidance document is intended to aid manufacturers and/or device sponsors in organizing the

requirements for a Class IV device licence application or amended licence applications for medical devices referred to in the *Policy on the Regulation of Medical Devices Manufactured from or Incorporating Viable or Non-Viable Human Tissue or their Derivative(s)*. This document provides details regarding the scientific and medical requirements necessary for these licence applications.

This document does not address the issues of quality systems requirements, chargeable review items, significant change amendments, administrative amendments or the general process and procedures of device licensing. These topics are covered in separate guidance documents, available on the Therapeutic Products Programme (TPP) website at www.hc-sc.gc.ca/hpb-dghp/therapeut.

This document does not address medical devices manufactured from or incorporating viable or non-viable animal tissue or their derivatives. A separate guidance document is available to discuss issues related to their safety and effectiveness.

This document does not address items common to all Class III and IV premarket review documents, for additional information on these items please review the guidance document "*Preparation of a Premarket Review Document for Class III and Class IV Device Licence Applications*" (GD008/Rev01-MDB).

1.4 Definitions

1.4.1 Additional Information refers to a written request made under section 35(1) for ADDITIONAL INFORMATION necessary to determine whether a medical device meets the safety and effectiveness requirements for a particular licence application.

1.4.2 Executive Summary provides a contextual background and orientation regarding the device application. For a new device licence application, the executive summary should address the device indications for use, the various technologies employed by the device, and the design rationale. In the case of a device licence amendment application, the executive summary should provide a description of the modifications made to the existing licenced device, and include any changes to the licenced indications for use.

1.4.3 Masterfile refers to a document provided by a subcontractor or manufacturer that contains specific objective evidence, for example material characterization or sterilization processing characteristics. This data is often independent of final device processing and can be referenced by many different device licence applications. If the file has been submitted by someone other than the manufacturer, permission must be granted by the file owner for each licence application using the information contained in the MASTERFILE.

2.0 Procedures

The document *Guidance on How to License a Device* contains detailed information on submitting a device licence application or an amended device licence application to TPP for all Class II, Class III and Class IV devices.

A new licence application for a Class III or a Class IV medical device will contain a premarket review document in addition to the general requirements of section 32(1). Portions of the review submission may reference a MASTERFILE already submitted by the manufacturer or a subcontractor. For complete details, please refer to the document “*Management of Applications for Medical Device Licensing or Investigational Testing Authorization Policy*”.

Under section 35(1) of the *Medical Devices Regulations*, if the information or documentation submitted in respect of the licence application under section 32 is insufficient to determine whether the device meets the safety and effectiveness requirements of sections 10 to 20, then the manufacturer may be requested to submit ADDITIONAL INFORMATION.

In the event of a significant change as defined in the Regulations, an amended licence application is required. This amended device licence application will include the information set out in section 32 that is relevant to the change. It is not necessary to resubmit safety and effectiveness data that has not been affected by the change. This application must be reviewed and accepted before the altered device is offered for sale. Please refer to the “*Guidance Document for Significant Change*”, document number GD001/Rev01-MDB, for further details.

A licence or a licence amendment will be issued if the Minister, after reviewing the information included in the licence application or licence amendment application, determines that a medical device conforms to the safety and effectiveness requirements.

Manufacturers and/or device sponsors with specific questions or concerns are urged to contact the Manager, Device Evaluation Division, Medical Devices Bureau. In addition pre-application consultations are encouraged for devices incorporating novel materials and designs.

3.0 Format of the Class IV Review Document

A licence application for a Class IV medical device manufactured from or incorporating human tissue or their derivatives must contain the information and documentation set out in section 32, subsection (4), paragraphs (a) to (p). These requirements are organized and assigned to nine chapters, as appropriate. These sections or chapters *must* be easily identified in every licence application for a Class IV device.

In the event that some sections are not appropriate for the device in question, a rationale for omitting the information must be provided. Many of the sections, e.g. design philosophy, pre-clinical biocompatibility studies, or mechanical testing may not be applicable for “tissue” devices which do not incorporate any artificial structures.

The following format is recommended, with modifications as required:

Device Licence Application Form
Executive Summary
Table of Contents
1 Background Information
1.1 Device Description
1.2 Design Philosophy
1.3 Marketing History
2 Risk Assessment
3 Quality Plan
4 Device Specific Detailed Information
4.1 Material Specifications
4.2 Manufacturing Process Specifications
4.2.1 Method of Manufacture
4.2.3 Quality Control Activities
4.3 List of Standards
5 Safety and Effectiveness Studies
5.1 Preclinical and Clinical Studies
5.2 Process Validation Studies
5.3 Literature Studies
6 Evidence of Biological Safety
7 Device Label
8 Quality System Requirements
9 Implant Registration Method (if applicable)

3.1 Background Information

3.1.1 Device Description

This section requires a general description of the device, including its principles of operation, and of the materials used in its construction and packaging. Each of the functional components of the device must be described, with labelled pictorial representation of the device in the form of diagrams, photographs or drawings.

Other information necessary to provide a thorough description of the device must be included. For example, for an implant, a description must be provided regarding the anatomical location of the device in the body, including any attachment mechanism for the device. Diagrams, illustrations or photographs of the implant *in situ* should also be supplied.

The materials used in the device and packaging must be specified. Any additional materials in a device derived from any animal source should be identified by tissue type, animal species and country of origin/ residence. Please refer to the draft guidance document *Preparation of a Premarket Review Document for Class IV Devices Manufactured from or Incorporating Animal Tissue or their Derivative(s)*.

If the device contains a medicinal substance or drug, a description of the substance and its

technical specifications must be provided. Details must be provided regarding the regulatory status in Canada of both the drug and its manufacturing facility.

3.1.2 Design Philosophy

This paragraph requests a description of the features that enable the device to be used for the medical conditions and purposes for which it is manufactured, sold or represented by the manufacturer. To satisfy this requirement, a brief description of the design philosophy and performance specifications for the device should be provided, linking them to the declared indications for use. References and comparisons with appropriate previous versions or generations of the device should be presented. A tabular format is recommended for this comparison.

In the event that the use of the device is self-evident to the intended user, the customary or most frequent conditions or uses of the device should be summarised.

This section should include an overview of the purposes and principles of operation for the device and a summary of the method of its use and operation, unless these instructions are not required for the safe, effective use of the device.

The physical aspects of the device, including packaging must be provided. This should include a summary comparison of the design input parameters (operation specifications) with the resultant performance specifications (design output characteristics).

3.1.3 Marketing History

In this paragraph, a summary of the marketing history of the device is requested. This would include a summary of special access requests made to the Programme and the outcome of these requests. In addition, the manufacturer and/or device sponsor must provide a list of countries where the device is currently being sold and the total number of units sold in those countries. A summary of reported problems with the device and details of any recalls in those countries is also required.

3.2 Risk Assessment

Section 32(4)(d) requires a risk assessment, comprised of an analysis and an evaluation of the risks inherent in the use of the device, as well as the risk reduction measures adopted to satisfy safety and effectiveness requirements. For further guidance in this area, please refer to ISO 14971:2000 standard, entitled *Medical Devices - Risk Management*.

A risk analysis should include a complete description and identification of the devices and materials under consideration. A list of possible hazards for these devices must be prepared. An evaluation of the risks as compared with the claimed benefits of the device and steps taken to reduce the risks to acceptable levels must also be provided.

Risk to third parties must also be considered for devices manufactured from or incorporating human tissue or their derivative(s). The manufacturer must identify the individual or organization that carried out the risk analysis. The method of risk analysis must be appropriate for the device and the level of risk involved.

3.3 Quality Plan

The quality plan, as described in ISO 10005, provides a mechanism to tie specific requirements of the product, project or contract to existing quality system procedures. It is not intended to duplicate the device-specific information requested under section 32(4)(f).

A diagram may be used to outline how the specific quality practices, resources and sequence of activities relevant to the device will be met.

3.4 Device-Specific Detailed Information

Section 32(4)(f) and (g) request specific information related to material characterization and manufacturing processes, including quality control activities.

3.4.1 Material Specifications

This part of the application must provide details of material identifications and specifications, including raw materials and components. Information must include complete chemical and physical characterization of all component materials. Most important are the screening and acceptance criteria for materials harvested from human sources.

Information must also be provided regarding the source (country of origin/residence) of the human material, screening criteria, details of storage of materials, and quarantine processes and procedures in place to prevent release of contaminated material. Materials of human origin must be sourced from countries which do not have reported cases of vCJD, and from donors who have not resided in such countries for more than 6 months since 1986.

3.4.1.1 Serological Testing

All screening test kits must be listed by name and manufacturer. All test kits must be licensed for use in Canada, or validated by TPP to the safety and effectiveness requirements of the Regulations. For test kits not licensed for use in Canada, information must be provided on the specificity and sensitivity of the assay, including the product monograph. Additional information regarding the validation of unlicensed test kits may be requested.

Donor qualification must include serological testing of a blood specimen from all potential donors. This sample must be tested and found negative for pathogens of concern using screening tests acceptable to MDB, including at least the human immunodeficiency virus, Type 1 and Type 2 (anti-HIV-1 and anti-HIV-2), hepatitis B surface antigen (HBsAg), hepatitis C virus (anti-HCV), HTLV-1/2. Also, testing for syphilis should be done, if tissues retrieved are not stored in a tissue

culture media at 4°C for at least 24 hours.

Donors must also be evaluated for risk factors for, and clinical or physical evidence of neurological and infectious diseases through medical record review and donor history interviews.^{1,2} The licence application must describe the methods for evaluating the possible presence of risk factors for, and clinical or physical evidence of, neurologic or infectious disease. The following information should be considered and reported on. The donor's medical records, autopsy reports or any physical assessment reports (e.g. medical examiner report, police records) should be reviewed to determine donor suitability. These records should be evaluated by an individual who is qualified by profession, education, and training and who is familiar with the intended use of the device.

Interviews must also be performed with one or more individuals who can provide reliable information (e.g., a donor's next of kin, a relative, a member of the donor's household, an individual with an affinity relationship with the donor, or the donor's primary treating physician) concerning the donor's medical history and relevant social behavior. Such an interview should determine whether the donor had signs or symptoms of neurologic disease or engaged in certain activities or behaviors that place a donor at a high risk for HIV or hepatitis infection.

The manufacturer must establish donor selection criteria and develop standardized methods for reviewing medical records and performing interviews. Such procedures should draw upon the appropriate standards of voluntary organizations (e.g., American Association of Tissue Banks, Eye Bank Association of America).

Exclusion criteria based on, but not specifically limited to, the criteria below should be identified:
Regarding neurological screening:

- (1) donors diagnosed with Creutzfeldt-Jakob Disease or a known family history (blood relative) of a person with non-iatrogenic Creutzfeldt-Jakob Disease;
- (2) donors who received injections of human pituitary-derived growth hormone (pit-hGH) or gonadotropin;
- (3) donors who received transplants of dura mater;
- (4) donors diagnosed with any degenerative or demyelinating disease of the CNS (e.g., multiple sclerosis) or other neurologic diseases (e.g., senile dementia, Alzheimer's disease);
- (5) donors who died in a neurological/psychiatric hospital;

Regarding other exclusion criteria:

- (6) donors who meet the exclusion criteria for potential infectious disease as described in the Report on the National Consensus Conference on Safety of Organs and Tissues for Transplantation².

- (7) donors diagnosed with active infections at the time of death, e.g., rheumatic fever, generalized

- septicemia or systemic infection, mycosis, tuberculosis;
- (8) donors diagnosed with diseases of unknown etiology; and
- (9) donors without adequate documentation of medical history;

3.4.1.2 Physical Assessment of Donors

The application must identify standardized donor selection criteria for physically assessing a cadaver in a general autopsy. Exclusion criteria based on clinical evidence of possible infectious or neurologic diseases should include, but not specifically limited to, evidence of:

- (1) physical evidence for risk of sexually transmitted diseases such as genital ulcerative disease, herpes simplex, syphilis;
- (2) physical evidence of anal intercourse including perianal condyloma;
- (3) physical evidence of non-medical percutaneous drug use such as needle tracks;
- (4) disseminated lymphadenopathy;
- (5) oral thrush;
- (6) blue or purple spots consistent with Kaposi's sarcoma;
- (7) needle tracks, including examination of tattoos which may be covering needle tracks;
- (8) unexplained jaundice, hepatomegaly, or icterus; or
- (9) if the body was rejected for routine autopsy due to infectious criteria or if the autopsy was done in an infectious disease control room or under any special precautions and the reasons for these procedures.

3.4.1.3 Materials Expressed from Cells

For medical devices derived from or containing material expressed from 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 product will contain endogenous retroviruses, retroviruses 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 ICH guideline on Biotechnology Products³ should be consulted for guidance on how this viral validation should be conducted.

Device characterization of expressed agent(s) and carriers should include such information as: 1) studies of the pharmacokinetics, biodistribution and systemic behaviour of the expressed agent; 2) peptide mapping of the expressed agent and if applicable the carrier; 3) device activity assay *in vivo* (bioassay); 4) full characterization of the peptides present using SDS-PAGE analysis, cation exchange chromatography, 2D-gel electrophoresis, alkaline RP-HPLC; and 5) complete sterilization and stability information.

The viricidal 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. For the hetero hybrid cell lines in which one or more partners are human

or nonhuman primate in origin, tests should be performed in order to detect viruses of human or nonhuman primate origin because viral contamination arising from the cells may pose a particular hazard.

Each working cell bank as a starting cell substrate for therapeutic product production must be tested for adventitious virus either by direct testing or by analysis of cells at the limit of *in vitro* cell age, initiated from the working cell bank.

3.4.1.4 Special Considerations for donors of Human Dura Mater^d **Gross and Histological Examination of Brain**

The application should describe the procedures for performing a full autopsy on each donor's brain. Following fresh examination, the brain should be fixed, sliced, gross examination of the entire brain conducted (including multiple cross sections), and multiple samples of tissue obtained (from different parts of the brain) for histologic examination. This examination should be performed by a qualified neuropathologist after dura mater collection. Potential donors should be excluded when any possible evidence of TSE-related changes is observed during gross and histological examination of the brain.

Archiving of Donor Brain and Dura Mater Tissue

TPP recommends that frozen (at a temperature equal to or less than -70/C) and fixed samples of both donor brain and dura mater tissues should be archived. The donor brain samples should include at least 5 grams of the frontotemporal region. These samples should be retained for 25 years based on the current state-of-scientific knowledge regarding the development of screening tests and our expectation that as the science evolves, screening tests may become available within that time.

While archiving samples of donor brain and dura mater may not immediately increase the assurance of dura mater graft safety, comprehensive collection and storage of such tissues would permit subsequent testing for TSE-induced changes when improved or new test methods become available. In the event that a dura mater-graft recipient becomes ill with CJD, testing of archival donor material might assist in determining whether the dura mater graft was the source of infection.

PrP-RES (Proteinase-Resistant Prion Protein) Testing of Brain Tissue

While reagents for PrP-RES testing are available from certain research laboratories, testing is currently a research/investigational-use tool. Because there is no approved or validated PrP-RES test that is marketed for the screening of CJD in brain tissue, the TPP is not requiring its use at this time. However, when either a validated test becomes available or evaluation of available data demonstrate the utility of PrP-RES testing as an aid in determining that brain and dura mater tissues are not contaminated with CJD, incorporating PrP-RES testing into standard operating procedures will be recommended.

Viral inactivation and CJD disinfection

Careful control of donor selection and dura mater retrieval procedures constitute critical safety practices for processed human dura mater. While histological examination of the brain may detect most infected tissues, it may not identify all CJD-infected grafts. Therefore, treatment of each product with a generally accepted disinfection technique should be performed to provide an additional assurance of device safety. It is recommended that processed human dura mater be treated with 1.0 N sodium hydroxide (NaOH). This recommendation was based on a study in an animal model in which 1.0 N NaOH treatment reduced CJD infectivity. Each application should provide information about the methods for disinfection with NaOH or another procedure that has been validated to significantly reduce CJD infectivity. Such data should also demonstrate that subsequent rinsing steps are sufficient to reduce the concentration of residual NaOH (or other disinfectant) to a non-cytotoxic level and that the processed human dura mater retains its clinical utility.

Reference may be made to a product MASTERFILE for this information.

3.4.2 Manufacturing Process Specifications

The manufacturing process specifications for the device should be provided in the form of a listing of the resources and activities that transform inputs into the desired output. Of particular importance for devices derived from or incorporating human tissues or their derivatives is the screening and acceptance criteria for these materials.

If multiple facilities are involved in the manufacture of a device, the applicable information for each facility must be submitted. If the information is identical for a number of sites, this should be noted.

Firms that manufacture or process the device under contract to the manufacturer and/or device sponsor may elect to submit all or a portion of the manufacturing information applicable to their facility directly to TPP in the form of a MASTERFILE. The manufacturer or device sponsor should inform these firms of the need to provide detailed information on the device.

Manufacturers and/or device sponsors referencing information held in a MASTERFILE submitted by another company must obtain permission from the owner of the file each time the file is accessed. The letter of permission should indicate the extent of information to be considered for each application.

3.4.2.1 Method of Manufacture

A complete description is required of the methods used in, and the facilities and controls used for, the manufacture, processing, packaging, storage and, where appropriate, the installation of the device. Sufficient detail must be provided to enable a person generally familiar with quality systems to judge the appropriateness of the controls in place.

3.4.2.2 Quality Control Activities

The quality control activities are operational techniques and activities that are used to fulfil requirements for device quality. These activities and specifications ensure that the design output requirements are documented in terms that can be verified against the design input requirements.

To satisfy this requirement, manufacturers and/or device sponsors should provide a description of the quality control methods used for raw material and component acceptance, intermediate production steps and the acceptance criteria for the finished device. Sampling plans, testing and inspection methods and related acceptance criteria should be provided.

A summary should be provided regarding record keeping and the traceability of all components from raw materials to finished product, including procedures to ensure correct labelling.

A summary of segregation, identification and storage procedures for untested or unacceptable items should also be provided, including details of the disposal procedures of these items. Details must also be provided regarding how the manufacturing facilities and equipment will be treated in the event that an unacceptable or contaminated lot has been accepted or produced.

3.4.3 List of Standards

The manufacturer and/or device sponsor must submit a list of standards applied, in whole or in part during the design and manufacture of the device. These standards may be international or national. In addition, the manufacturer should indicate if the device complies with the policies, guidelines or voluntary standards of a recognized authority in terms of material, design or performance. The full title, version or identifying number, date and responsible agency of each standard must be provided in a tabular format.

3.5 Safety and Effectiveness Studies

Section 32(4)(i) of the Regulations requires the submission of details of any studies that the manufacturer relies on to ensure that the device meets the safety and effectiveness requirements. These studies must be organized into the following four subsections and reported as appropriate. An introductory summary should accompany each study presented.

3.5.1 Preclinical and Clinical Studies

Details must be provided on all biocompatibility tests conducted for all non-human derived materials used in the device. At a minimum, tests must be conducted on samples from the finished, sterilized device. All materials that are significantly different must be characterized. Information describing the tests, the results and the analyses of data must be presented. For further information on biocompatibility testing, please refer to the ISO 10993 series of standards or the Health Canada publication 94-EHD-109, entitled *Biocompatibility Testing of Device Materials in Canada*. For some devices derived from biotechnology products the International Committee on Harmonization (ICH) documents on genotoxicity, carcinogenicity and mutagenesis should also be consulted.

Complete preclinical physical test data must be provided, as appropriate. The report must include the objectives, methodology, results, analysis of the results and a summary of the conclusions reached by the manufacturer, for all physical studies of the device and its components. Physical testing must be conducted to predict the adequacy of device response to physiological stresses, undesirable conditions and forces, long-term use and all known and possible failure modes.

Preclinical animal studies used to support the probability of safety and effectiveness in humans must be reported. These studies must be undertaken using good laboratory practices. The objectives, methodology, results, analysis of the results and the conclusions reached by the manufacturer must be presented. The study conclusion should address the device's interaction with animal fluids and tissues and the functional effectiveness of the device in the experimental animal model(s). The rationale (and limitations) of selecting the particular animal model should be discussed.

For some products, where there is a limited availability of donor tissue it may not be appropriate to carry out animal testing.

Clinical evidence of safety and effectiveness may comprise device-related investigations conducted in Canada or other countries. It may be derived from relevant publications in the peer-reviewed scientific literature. The documented evidence submitted should include the objectives, methodology and results presented in context, clearly and meaningfully. The conclusions on the outcome of the clinical studies should be preceded by a discussion in context with the published literature.

3.5.2 Process Validation Studies

The results of all process validation studies must be presented. When the results of a particular process cannot be verified by subsequent observation, that process must be validated to obtain objective evidence. This applies to sterilization processes as well.

The procedures for monitoring and controlling the process parameters of a validated process must be fully described. For example, the type of process, details of the equipment and process parameters employed in sterilization must be specified. Process validation data must include sterility test data and methods, culture media, time and temperature of incubation, controls, number of samples examined and frequency of testing. Pyrogen test data and methods are required, including frequency of testing, number of units tested, methods of testing, data from test results or a substantial rationale for not conducting this kind of testing. Toxicity test methods and data must be described. If the sterilant is toxic or produces toxic residuals, test data and methods for establishing that post-process sterilant and/or residuals are within acceptable limits must be presented.

3.5.3 Literature Studies

Copies are required of all literature studies that the manufacturer is using to support safety and effectiveness. This includes all articles and studies specifically referenced in the application. These will be a selection of the bibliography of references supplied in response to section 32(4)(n).

General bibliographic references should be device-specific and supplied in chronological order. Care should be taken to ensure that the references are timely and relevant to the current application.

3.6 Evidence of Biological Safety

For medical devices manufactured from or incorporating human tissue or their derivatives, detailed information must be provided substantiating the adequacy of the measures taken with regard to the risks associated with transmissible agents. This will include viral clearance results for known hazards.

The manufacturer should describe fully the donor screening and testing procedures, procurement and processing processes. Controls placed on the transportation of tissues and excipients, and the method of tracking employed. Infection control procedures must also be fully described and take into consideration the potential infectivity of the materials involved

The information provided and the control necessary depend upon the type of tissue involved and the extent of subsequent processing. The manufacturer is required to justify the processes and procedures employed.

3.7 Device Label Section

The manufacturer and/or device sponsor is requested to submit the packaging and labelling specifications for the product, including actual labelling materials. Labelling will be reviewed with attention to the requirements of sections 21, 22 and 23 of the *Medical Devices Regulations*.

The device label of a Class IV device sold in non-sterile condition, but intended to be used sterile, must include the appropriate details related to the recommended sterilization process. Similar information must be provided for re-sterilization of the device.

The licence application should include copies of all labelling, package inserts, product brochures and file cards to be used in connection with the device and copies of information and instructions for use given to practitioners and/or patients. Labelling materials should include, as appropriate, the recommended disposal techniques, nature of combustion products, explosion risk, etc. While draft labelling can be provided with a device licence application, final labelling will be required before a licence is issued. Subsequent changes to labelling materials may be either an administrative amendment or a significant change amendment. For additional information, the manufacturer and/or device sponsor is referred to the guidance documents available on these

topics.

3.8 Quality System Requirements

Section 32(4)(p) requires an attestation signed by a senior official of the manufacturing firm that the device is designed and manufactured under an appropriate quality system. The quality system in question must satisfy the Canadian Standards Association criteria in CAN/CSA - ISO 13485-98, entitled *Medical Devices - Particular Requirements for the Application of ISO 9001*, as amended from time to time. This attestation must be based on the results of an audit by an organization that performs quality system audits.

This paragraph of the Regulations has not been implemented at this time. Please refer to our website for additional information regarding the quality systems requirements, or contact the Head, Quality Systems at (613) 954-0385.

4.0 Implant Registration

Some medical devices of human origin have been listed on the Schedule 2 of the *Medical Device Regulations*, including human dura mater and wound coverings containing human cells. These devices are subject to Sections 66 to 68 of the Regulations with regard to implant registration.

These regulatory provisions were intended to facilitate the tracking of certain high risk implanted medical devices so that recipients of these products could be notified of pertinent post-implant information.

Sections 66 and 67 describe one method of implant registration acceptable to the programme using two registration cards, one provided to the patient and the second returned to the manufacturer by the health care facility involved in the use of the implant.

Pursuant to Section 68 a manufacturer may apply in writing for authorization to use an alternate method of implant registration. Authorization will be provided in writing by the Minister if the method is adequate to achieve the purpose set out in paragraph 66(1)(c) of the Regulations.

Details of the proposed method of implant registration must be provided in the licence application, including copies of all cards and instruction materials for the health care facility and patient.

5.0 References

- 1) Guidance for Industry: Screening and Testing of Donors of Human Tissue Intended for Transplantation. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. July 1997.
- 2) Report on the National Consensus Conference on Safety of Organs and Tissues for

Transplantation. Health Canada, Therapeutic Products Programme. October 1995.

3) Q5A ICH Harmonised Tripartite Guideline. Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin.

4) Guidance for the Preparation of Premarket Notification Application for Processed Human Dura Mater. Food and Drug Administration, Center for Devices and Radiological Health. July 1999.

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

Canadian General Standard on Safety of Organs and Tissues for Transplantation (draft) September 1996.