July 5, 2012

Notice

Our file number: 12-111449-690

Re: Guidance Document: Guidance on supporting evidence to be provided for new and amended licence applications for Class III and Class IV medical devices, not including *In Vitro* Diagnostic Devices (IVDDs)

Health Canada is pleased to announce the release of the final version of the *Guidance Document: Guidance on supporting evidence to be provided for new and amended licence applications for Class III and Class IV medical devices, not including In Vitro Diagnostic Devices (IVDDs).* A draft version of this guidance was first released for consultation in 2011. Comments from stakeholders have been considered in producing this final version.

This document is intended to aid manufacturers in the preparation of scientific information to be provided in support of Class III and Class IV non-*in vitro* diagnostic device licence applications and application amendments filed pursuant to the Canadian *Medical Devices Regulations*. An updated guidance on *In Vitro* Diagnostic Devices (IVDDs) will be made at a future date.

Summary Technical Documentation (STED) for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices was developed by the Global Harmonization Task Force (GHTF) and adopted by Health Canada for use in Class III and Class IV premarket device licence applications and licence amendment applications. This guidance is for those manufacturers who choose not to submit a premaket licence application or amendment application for Class III and IV medical device using the STED-based application.

The implementation date is July 4, 2012. Please note that once implemented, failure to file an application in either the format outlined in this guidance or in the STED-based format may result in the rejection of the application at the screening stage if the content cannot be appropriately assessed.

For more information on this guidance document, please contact:

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GUIDANCE DOCUMENT

Guidance on Supporting Evidence to be provided for New and Amended Licence Applications for Class III and Class IV Medical Devices, not including *In Vitro* Diagnostic Devices (IVDDs)

Published by authority of the
Minister of Health

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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 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 : *Ligne directrice sur les données à fournir pour étayer les demandes d'homologation des instruments médicaux de classe III et classe IV et les demandes de modification, à l'exception des instruments de diagnostic in vitro (IDIV)*

FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates, and objectives should be implemented in a manner that is fair, consistent and effective.

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 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 document, 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 guidance documents.

TABLE OF CONTENTS

1 INTRODUCTION

The purpose of this guidance document is to elaborate on the scientific and clinical content to be included in Class III and Class IV (non-IVDD) medical device licence applications and medical device licence amendment applications, in accordance with the medical devices licensing provisions in section 32 of the *Medical Devices Regulations* (Regulations).

All Class III and Class IV medical devices require a review of submitted evidence of safety and effectiveness before their licence applications can be finalized.

The content elaborated upon in this guidance document is to be submitted for review in addition to the general data elements listed in paragraphs 32(1)(a)-(e) of the Regulations, which are required for all medical device licence applications. This guidance document outlines the technical content commonly accepted in support of the safety and effectiveness of a subject device.

1.1 Policy Objectives

To facilitate the submission to Health Canada of scientific and clinical content for medical device licence applications and licence amendment applications for Class III and Class IV medical devices filed pursuant to sections 32 and 34 of the Regulations.

1.2 Policy Statements

This guidance document is to be used in the preparation of Class III and Class IV non-*in vitro* diagnostic devices (non-IVDD) medical device licence applications and licence amendment applications should the manufacturer choose not to use the STED-based application process.

Failure to file an application in either the format outlined in this guidance or in the STED-based format may result in the rejection of the application at the screening stage.

1.3 Scope and Application

This guidance document is intended to aid manufacturers and regulatory correspondants in understanding the content expectations for Class III and IV non-IVDD medical device licence applications or licence amendment applications. This document provides details regarding the scientific and clinical content to be provided in support of applications for Class III and Class IV device licences.

This document does not apply to *in vitro* Diagnostic Devices (IVDDs) or Class II licence applications. The latter are described in the document entitled *Guidance On How to Complete the Application for a New Medical Device Licence,* GD013. An updated guidance on IVDDs will be made available at a future date.

1.4 Background

The *Medical Devices Regulations* stem from 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.

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

2 GUIDANCE FOR IMPLEMENTATION

2.1 Access to Information

Information provided to Health Canada by manufacturers is subject to the provisions of the *Access to Information Act*. Application information containing trade secrets or confidential scientific, technical, commercial or financial information is protected from disclosure by this Act. According to TPD policy, information regarding device licence applications that have been received or are being processed is also considered confidential. Once a licence has been granted, basic information about a device, such as that listed in section 32(1) of the Regulations, is considered public information.

2.2 Format of Application

This section outlines the format for Class III and Class IV non-*in vitro* diagnostic medical devices licence applications and licence amendment applications.

The application's **Table of Contents** should use the headings provided in Tables 1 and 2, with clear references to the corresponding page numbers that contain the relevant information. If no information is available or required under a specific heading, that section of the application should be marked "not applicable" or "not relevant" and justification for the absence of such information should be provided.

The Cover letter is placed within the Additional Class III/IV Premarket Information section for Health Canada's processing needs. The Administrative Information is detached from the Application and/or Amendment prior to being reviewed.

For medical device licence amendment applications, a full device description and the intended use (or indication for use) statement are required in addition to those sections that are relevant to the change. Where information under a specific heading remains unchanged, that section or subsection of the application should be marked "not changed" and cross-reference made to the previously filed application(s) containing that information. The cross-reference should include the Canadian licence number, device name and where possible application ID and manufacturer's name as it appears in the previously filed application.

2.3 Electronic Applications

Health Canada is developing a phased migration plan from the current paper-based application to an electronic-based application for medical devices. To facilitate this transition, applicants are encouraged to submit premarket review documents for Class III and IV medical device licence applications and amendment applications in electronic format, as well as the required paper copy.

Electronic documents should be provided on compact discs (CDs) or digital video discs (DVDs). Please refer to the current Health Canada Notice, *Guidance for Industry: Preparation of a Premarket Review Document in Electronic Format for a Class IV Medical Device Licence Application* (http://www.hc-sc.gc.ca/dhp-mps/md-im/activit/announce-annonce/notice_e-form_classiv_avis-eng.php) for additional details.

The electronic-based application should also include a Letter of Attestation confirming that the content of the electronic application is identical to that of the accompanying paper copy. The Letter of Attestation should be on the manufacturer's letterhead and signed and dated by a senior official of the manufacturer. Applicants should consult the updated notice on the preparation of a premarket review document in electronic format for a sample Letter of Attestation and electronic file requirements.

2.4 Abbreviations and Acronyms

BGTD	Biologics and Genetic Therapies Directorate
CAS	Chemical Abstract Service
CMDCAS	Canadian Medical Devices Conformity Assessment System
CSA	Canadian Standards Association

CTO	Cells, Tissue and Organs
DoC	Declaration of Conformity
HPFB	Health Products and Foods Branch
HPLC	High Performance Liquid Chromotography
ICH	International Conference on Harmonisation
ISO	International Organization for Standardization
IUPAC	International Union of Pure Applied Chemistry
IVDD	*In Vitro* Diagnostic Device
LAL	Limbus Amebocyte Lysate
MDB	Medical Devices Bureau
MDL	Medical Devices Licence
MSDS	Material Safety Data Sheets
SAL	Sterility Assurance Level
SAP	Special Access Programme
SDS-PAGE	Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis
TPD	Therapeutic Products Directorate
TSE	Transmissible Spongiform Encephalopathies

2.5 Definitions

***In Vitro* Diagnostic Device** is a medical device that is intended to be used *in vitro* for the examination of specimens taken from the body.

Manufacturer means a person who sells a medical device under their own name, or under a trade-mark, design, trade name or other name or mark owned or controlled by the person, and who is responsible for designing, manufacturing, assembling, processing, labelling, packaging, refurbishing or modifying the device, or for assigning to it a purpose, whether those tasks are performed by that person or on their behalf.

Proprietary Information Submissions can be used when firms that manufacture or process the device under contract to the manufacturer elect to submit all or a portion of the manufacturing information applicable to their facility directly to the Medical Device Bureau (MDB) in the form of a Proprietary Information Submission. The manufacturer or device sponsor should inform these firms of the need to provide detailed information on the device. Manufacturers referencing information held in a Proprietary Information Submission 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.

Recall in respect of a medical device that has been sold, means any action taken by the manufacturer, importer or distributor of the device to recall or correct the device, or to notify its owners and users of its defectiveness or potential defectiveness, after becoming aware that the device:
(a) may be hazardous to health;
(b) may fail to conform to any claim made by the manufacturer or importer relating to its effectiveness, benefits, performance characteristics or safety; or,
(c) may not meet the requirements of the *Food and Drugs Act* or the *Medical Devices Regulations.*

Software Validation studies provide objective evidence that the finished device with software is appropriate for its intended use and will be reliable and safe. It ensures that all software requirements have been implemented correctly and completely and are traceable to system requirements.

Software Verification studies provide objective evidence that the design outputs for a phase of the software development lifecycle, meet all of the specified requirements for that phase. They look for consistency, completeness, and correctness of the software and supporting documentation as it is being developed.

3 CLASS III PREMARKET LICENCE APPLICATION CONTENT

An application for a Class III medical device licence must contain the information and documents set out in section 32(3) of the Medical Devices Regulations. Table 1 provides an overview of the format for a Class III medical device application.

Table 1: Table of Contents Format for a Class III Device Premarket Application (non-*in vitro* diagnostic)

SECTION/ SUB-HEADING	MAIN HEADING	APPLICATION LOCATION		
	APPLICATION REQUIREMENTS	**TAB or SECTION**	**PAGES**	**VOLUME**
1.0	**Table of Contents**			
2.0	**Administrative Information**			
2.1	Application Form and Fee Form			
2.2	Quality Management System Certificate			
3.0	**Pre-Submission Correspondance**			
4.0	**Additional Class III Premarket**			

4.1	**Information**			
4.2	Cover Letter			
4.3	Executive Summary			
4.3.1	Device Description			
4.3.2	General Description			
4.3.3	Licence Amendments			
4.4	Drugs			
4.5	Design Philosophy			
4.6	Indications for Use and/or Intended Use and Contraindications			
4.7	Device Labels, Package Labelling and Documentation			
4.7.1	Marketing History			
4.7.2	Canada and International			
5.0	Incident Reports and Recalls			
5.1	**Safety and Effectiveness Studies**			
5.2	Standards			
5.2.1	Preclinical Studies			
5.2.2	Physical and Mechanical Bench Tests			
5.2.3	Software Verification and Validation			
5.2.4	Biocompatibility Tests			
5.2.5	Pyrogenicity			
5.3	Animal Studies			
5.4	Clinical Studies			
5.4.1	Sterilization			
5.4.2	Sterilization Validation			
5.5	Residual Toxicity			
5.6	Packaging			
5.6.1	Shelf Life Validation			
5.6.2	Shelf Life of the Product			
6.0	Shelf Life of the Packaging			
	Bibliography			

(3)1.0 Table of Contents

This section is a placeholder for the Table of Contents for the entire application. The Table of Contents should list all documents included in the application and should follow the structure found in Table 1 above. The last three columns are to be completed by the manufacturer and identify both the section number as well as page numbers. Sections that are not applicable should be clearly denoted "N/A".

(3)2.0 Administrative Information

(3)2.1 Application Form and Fee Form

A completed and signed application form and fee form should be presented in this subsection.

(3)2.2 Quality Management System Certificate

This subsection includes a copy of the quality management system certificate certifying that the quality management system under which the device is designed and manufactured satisfies CAN/CSA ISO 13485:2003, *Medical devices - Quality management systems - Requirements for regulatory purposes*. Health Canada will only accept quality system certificates that have been issued by special third party auditing organizations called Canadian Medical Devices Conformity Assessment System (CMDCAS) recognized registrars.

(3)3.0 Pre-Submission Correspondence

During the product lifecycle, pre-submission correspondence, including teleconference meetings, may be held between Health Canada and the applicant. This subsection is a placeholder for any pre-submission-related information, including the information package that is required to be submitted prior to pre-submission meetings, meeting agenda, presentation slides, final meeting minutes, and any email correspondence related to specific aspects of the application.

(3)4.0 Additional Class III Premarket Information

(3)4.1 Cover Letter

Any information submitted to Health Canada should be accompanied by a cover letter. The cover letter should include the purpose of the application and a brief description of the package being submitted. It may also include information pertaining to Proprietary Information Submission. The cover letter should not contain any detailed scientific information.

(3)4.2 Executive Summary

An Executive Summary of the scientific content being submitted in support of the Class III device licence (or licence amendment) application should be provided and include the device name, its general purpose, as well as a high level summary of key supporting documentation. Every effort should be made to provide introductory text or narratives to help connect the

submitted documents. Any exceptions or unusual circumstance which the manufacturer wishes to highlight, specific to the device or application, should be mentioned in the Executive Summary.

(3)4.3 Device Description

(3)4.3.1 General Description

The name of the device and a detailed description of the device must be provided. Information should explain what the device does and who uses it. If it is part of a system, the relationship of the components in the system should also be described. A labelled pictorial representation of the device in the form of diagrams, photographs or drawings are often helpful.

A brief description of all functional components of the device should be provided including software and its release version, if applicable. Components or accessories that can be sold separately and used with other medical devices, systems or units should be identified. Variants of the device must be identified, as well as the parameter ranges of variants [for example (e.g.), hip implants with varying coatings].

Performance and technical specifications of the device should be provided.

The materials used in the device should be specified. At a minimum, this will include all materials that would come into direct contact with the user or patient. However, other materials of a significant nature should also be specified. Reference to applicable material standards may be used.

(3)4.3.2 Licence Amendments

If the application is an amendment to a licenced device or is based on a modification of a licensed device, a description of the modifications is required (e.g., changes in design, performance, indications, etc). Comparisons can be used to support the modification only if made to a currently licensed device in Canada. If this method is used, ensure the Canadian medical device licence of the comparator is stated. The comparison of the subject device and the comparator's key specifications can be provided in table format.

(3)4.3.3 Drugs

If the device contains an active pharmaceutical ingredient (API) or drug, a description of the substance, and detailed information concerning this substance should be provided.

This should include its identity and source, the intended reason for its presence and its safety and performance in the intended application. Health Canada policies about the classification of combination products [Policy on Drug/Medical Device Combination Products - Decisions (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/pol/combo_mixte_dec_pol-eng.php) and Drug/Medical Device Combination Products (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/pol/combo_mixte_pol_2006-eng.php)] can be found on the Health Canada website.

(3)4.4 Design Philosophy

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 should be described. A brief description of the underlying science/technology, design concepts, and/or theoretical principles supporting the device's function should be provided, linking them to the claimed indications for use. References and comparisons with appropriate previous versions or generations of the device can be presented with reference to the previous version's Canadian medical device licence number. A tabular format is preferred for comparisons.

(3)4.5 Indications for Use and/or Intended Use and Contraindications

The statement of indications for use and/or intended use for the device as presented in the labelling must be stated. Contraindications for the device are also to be stated as presented in the labelling.

The statement of indications for use should describe the diseases or conditions the device will diagnose, treat, prevent or mitigate, and the clinical condition of the patient under which use is recommended. It may also specify the patient population for which use of the device is indicated.

The statement of intended use should specify the therapeutic or diagnostic function provided by the device and may describe the medical procedure in which the device is to be used and whether the device is intended for single use or multiple uses. It may also specify the medical training the user should have (as recommended by the manufacturer).

The statement of contraindications should specify the clinical conditions of a patient that would make use of the device inadvisable.

This information should be repeated in all licence amendment applications for reference even if the information is unchanged.

(3)4.6 Device Labels, Package Labelling, and Documentation

This subsection should include copies of all labelling, package inserts, product brochures and file cards to be used in connection with the device, as well as copies of information and instructions for use for the practitioner and/or the patient. Labels will be reviewed against the requirements of sections 21, 22 and 23 of the Regulations. While draft labelling may be provided initially in the licence application, final labelling will be required before a licence is issued.

The statements of indications for use and/or intended use must be clearly stated in the device labelling, and will be the official claims against which authorization will be assessed. All expressed or implied claims made elsewhere in the labelling [that is (i.e.), instructions of use, advertising, or promotional material] must be consistent with the official statement.

Labelling materials should include, as appropriate, recommended disposal techniques, the nature of combustion products, the risk of explosion, etc.

Devices sold in non-sterile condition, but intended to be used sterilized, must specify the recommended sterilization process in the labelling.

If the labelling material covers components or devices not currently licensed in Canada this should be indicated in the labelling.

Health Canada has some device-specific labelling guidance documents. These documents should be consulted for additional guidance with regard to device labelling.

Device manuals may be provided on CD instead of hardcopy if they are too large to provide with the application.

(3)4.7 Marketing History

(3)4.7.1 Canada and International

A summary of the marketing history for the subject device is required. The summary should include special access requests made to the Special Access Programme (SAP) and the outcome of these requests. In addition, the manufacturer must provide a list of countries or regions, where the subject device is currently being sold and the total number of units sold by country or region.

Marketing history of a licensed, previous version of the device can sometimes be used in support of safety or effectiveness of the subject device. If this is to be the case, then the name of the comparator, its approval reference number (e.g., MDL) and the number of units sold can be provided.

(3)4.7.2 Incident Reports and Recalls

A summary of reported problems with the device, details of any recalls, and the current status or corrective actions should be provided. The country of the incident or recall should be clearly indicated. Incidents should include any Canadian incidents through SAP or other previous Canadian applications, if known.

If marketing history is presented for a predicate device then the associated recalls, and incident reports for that device should also be summarized here. If the number of incidents are voluminous, please provide a general description by problem types and state the number of reported incidents for each problem type. The description of each type of problem should be clear and any remedial or corrective actions undertaken should be explained.

(3)5.0 Safety and Effectiveness

(3)5.1 Standards

The list of standards applied, in whole or in part, in the design and manufacture of the device should be provided. These standards may be international or national. If full or partial conformity is being claimed to support safety or effectiveness of the device then ensure the full title, version or identifying number, date and responsible agency of each standard are provided. A tabular format may be used.

For standards recognized by Health Canada, the manufacturer may sign a declaration of conformity. Declarations of Conformity (DoC) must be provided on the Health Canada DoC form. Consult the *Guidance Document - Recognition and Use of Standards* under the *Medical Devices Regulations* and its associated updates for important information on this process and its role in medical device licence applications. The DoC form, current list of standards, and associated guidance documents can be obtained on the Health Canada website (http://www.hc-sc.gc.ca/dhp-mps/md-im/standards-normes/index-eng.php).

The use of standards is not compulsory. The manufacturer may choose to demonstrate safety and effectiveness independent of any international or national standard.

(3)5.2 Preclinical Studies

Additional guidance for preclinical testing of some specific medical device classes is available.

Please refer to the Health Canada website for guidance on preclinical testing.

(3)5.2.1 Physical and Mechanical Bench Tests

Physical and/or mechanical bench testing must be conducted to predict the adequacy of a device to function as intended. In addition, testing should address the device's response to physiological stresses, undesirable conditions and forces, long-term use and all known and possible failure modes.

A summary of the purpose, conditions, methods and results for each test presented here is required. The number of units tested, pass and fail criteria and rationales, as well as statistical assessments should be described. The conclusions drawn by the manufacturer are to be provided along with a discussion of the results and conclusions. Justification should be provided for any test failures. A discussion of the testing in relation to safety and effectiveness should be included in the summary, outlining how the selected tests address device-specific issues.

(3)5.2.2 Software Verification and Validation

If a device includes software, a description of that software and its impact on the safety and effectiveness of the device should be provided. In addition, a summary of verification and validation testing and the final results are required, along with the software revision history. This section should clearly provide traceability between system requirements, software risk mitigation and the testing completed. All unresolved anomalies in the release version of the software should be summarized along with a justification for acceptability.

For software validation the testing environment should be specified (e.g., in-house, simulated, clinical, etc.). The version tested must be clearly identified and should match the release version of the software, otherwise justification must be provided.

(3)5.2.3 Biocompatibility Tests

Biocompatibility testing characterizes biological responses to materials. If the device comes in contact with the patient then the biocompatibility of all materials which are potentially patient contacting is required. Tests should be conducted on samples from the

final product after all manufacturing and processing has been completed (e.g., sterilization). Deviations from this must be justified. Generic claims from the raw material supplier are generally insufficient.

Summaries should cover the tests conducted, standards applied, test methodology; pass fail criteria chosen with justification, and a summary of the results and conclusions drawn. In general ISO 10993 standards are taken as the gold standards for biocompatibility, use of other standards should be justified and compared against ISO 10993 methods.

If a Declaration of Conformity to ISO 10993 standards is used to support the methodology, a summary of the results as well as the conclusion must also be provided (e.g., cytotoxicity testing found mild toxicity (average score 1) for patient contacting material, therefore device is considered biocompatible for intended use).

MSDS are not sufficient to demonstrate biocompatibility.

(3)5.2.4 Pyrogenicity

When biocompatibility assessment includes systemic toxicity concerns (i.e., acute, subacute or subchronic), pyrogen test data and methods should also be summarized and should cover frequency of testing, number of units tested, methods of testing, any deviations from this testing, and test results. Pyrogenicity testing should be considered in the evaluation of medical devices in accordance with ISO 10993-11.

(3)5.2.5 Animal Studies

Animal studies used to support safety and/or effectiveness in humans should be summarized. These studies should be undertaken using good laboratory practices[1]. The objectives, a summary of the methodology and results, and the manufacturer's conclusions should be covered in the summary. The study conclusion should consider the device's interaction with animal fluids and tissues and the safety and functional effectiveness of the device in the experimental animal model(s). The rationale (and limitations) of selecting the particular animal model should be discussed.

[1] Organisation for Economic Co-operation and Development (OECD) Principles of Good Laboratory Practice and Compliance Monitoring No. 1 (www.OECD.org)

Please refer to section (3)5.2.3 for information regarding biocompatibility testing requiring animal models.

(3)5.3 Clinical Evidence

An evaluation of clinical evidence is necessary to help establish the clinical safety and effectiveness of a medical device for each claimed indication for use. A clinical evaluation considers available, relevant clinical data from published sources, or device-related investigations. It may be necessary to generate additional clinical data to address specific issues for certain medical devices.

If a clinical history has been well established with a given device technology, evidence may be provided in the form of a literature review of relevant publications in the peer-reviewed scientific literature. Reference to devices other than the subject device in support of safety or effectiveness requires a thorough comparison to the subject device design, features and performance capabilities to demonstrate relevance. This may be provided in a table format. Leveraged publications should be referenced but copies only need to be provided if pivotal in supporting safety or effectiveness. Articles listed in Section (3)6.0 are not specific to clinical evidence. Listing all articles only in Section (3)6.0 is acceptable provided there supporting clinical discussion within Section (3)5.3 and appropriate cross-referencing in Section (3)6.0.

Clinical evidence in the form of device-specific clinical investigations conducted in Canada or other countries should be summarized. Summaries should cover the objectives, methodology and results presented in context, clearly and meaningfully. The conclusions on the outcome of the clinical investigations should be preceded by a discussion in context with the published literature. Both statistical and clinical significance should be considered and critically analyzed.

(3)5.4 Sterilization

(3)5.4.1 Sterilization Validation

If the subject device is sold sterile or is to be sterilized, process validation data should include sterility test data, reference to a standardized test method and attestation or evidence of successful validation under real-life conditions under which the product is to be sterilized. Bioburden determination, culture media used, time and temperature of incubation, controls, number of samples examined and frequency of testing should also be presented. A Sterility Assurance Level (SAL) of 10^{-6} is generally required. If a biological indicator was used, its placement needs to be described and rationalized (e.g.,"most difficult to sterilize" location). If a group of devices are to be sterilized together, the worst-case scenario or most difficult to sterilize product should be validated.

An attestation can be used. The manufacturer should also demonstrate that they have a process in place to monitor bioburden levels on a regular basis to confirm that the sterilization method remains valid. Alternatively, a method of parametric release may be proposed and validated. If a process challenge device was used to assess the sterilization process it must be shown to have comparative resistance or a greater challenge to sterilization than the biological indicators placed inside the product/packaging.

If the product is to be re-sterilized by the end user, a description of the recommended sterilization process for the end-user should be provided, and evidence of validation provided. Validation should be for sterility and also to confirm that the process does not compromise integrity or performance of the product. The recommended, validated sterilization method should be stated in the device labelling information.

(3)5.4.2 Residual Toxicity

If the sterilant is toxic or produces toxic residuals, test data and methods for establishing the post-process sterilant and/or residuals are within acceptable limits should be summarized. For Ethylene Oxide residuals, levels should be within the acceptable levels (recommended by the most current published version of ISO 10993-7) in consideration of the body or tissue contact duration of the device. If another sterilization method has been used, a description of how residual toxicity concerns have been addressed should be provided.

(3)5.5 Packaging

Packaging of the device (or its components, if any) should be described including the materials employed. It should be clear what protective characteristics the packaging provides (e.g., maintains sterility, humidity, light sensitivity, transportation protection, etc.).

(3)5.6 Shelf Life Validation

(3)5.6.1 Shelf Life of the Product

If the product is subject to a shelf-life, shelf-life testing should be provided and the claimed shelf-life clearly stated. The method used (e.g. accelerated versus real time) should be provided along with the storage conditions used and the state of the product when tested (e.g. sterilized, production version, prototype, transportation, simulation, etc.). Devices containing materials of unknown stability should have real-time data.

(3)5.6.2 Shelf Life of the Packaging

If the device requires special packaging (e.g., considerations related to sterility, humidity, light sensitivity, pressure or oxidative reaction under irradiation), evidence should be provided that this has been addressed. Likewise, evidence should be provided to demonstrate that the integrity of the device and the internal environment are maintained by the device packaging during handling, transport and storage (i.e., for claimed shelf life). In the case of sterility, ensure that the test methods address both seal integrity and sterility (e.g., bubble test, dye penetration test, etc.).

(3)6.0 Bibliography

To facilitate the review process, the manufacturer should provide a bibliography (i.e., list of references) of all relevant published literature dealing with the use, safety and effectiveness and the indications for use of the subject device in question. If information within the article is being provided as key evidence of safety or effectiveness, a summary of the relevant sections should be provided including data upon which the conclusions are drawn. Copies of the articles should also be provided. Care should be taken to ensure that the references are timely and relevant to the current application. A bibliography may not be necessary if the device or its technology is well known with a long history of use.

4 CLASS IV PREMARKET LICENCE APPLICATION CONTENT

An application for a Class IV medical device licence must contain the information and documents set out in section 32(4) of the Medical Devices Regulations. Table 2 provides an overview of the format for a Class IV medical device licence application.

Table 2: Table of Contents Format for a Class IV Device Premarket Application (non-*in vitro* diagnostic)

SECTION/ SUB-HEADING	MAIN HEADING	APPLICATION LOCATION		
	APPLICATION REQUIREMENTS	**TAB or SECTION**	**PAGES**	**VOLUME**
1.0	**Table of Contents**			
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(4)1.0 Table of Contents

This section is a placeholder for the Table of Contents for the entire application. The Table of Contents should list all documents included in the application and should follow the structure found in Table 2 above. The last two columns are to be completed by the manufacturer and should identify both the section number as well as page numbers. Sections that are not applicable should be clearly denoted "N/A".

(4)2.0 Administrative Information

(4)2.1 Application Form and Fee Form

A completed and signed application form and fee form should be presented in this subsection.

(4)2.2 Quality Management System Certificate

This subsection should include a copy of the quality management system certificate certifying that the quality management system under which the device is designed and manufactured satisfies CAN/CSA 13485:2003, *Medical devices - Quality management systems - Requirements for regulatory purposes*. Health Canada will only accept quality system certificates that have been issued by special third party auditing organizations called Canadian Medical Devices Conformity Assessment System (CMDCAS) recognized registrars.

(4)3.0 Pre-Submission Correspondence

During the product lifecycle, pre-submission correspondence, including teleconference meetings, may be held between Health Canada and the applicant. This subsection is a placeholder for any pre-submission-related information. This includes the information package that is required to be submitted prior to pre-submission meetings. Examples of documents that are to be placed in this subsection include the meeting agenda, presentation slides, final meeting minutes, and any email correspondence related to specific aspects of the application.

(4)4.0 Additional Class IV Premarket Information

(4)4.1 Cover Letter

Any information submitted to Health Canada should be accompanied by a cover letter. The cover letter should include the purpose of the application and a brief description of the package being submitted. The cover letter should not contain any detailed scientific information.

(4)4.2 Executive Summary

An Executive Summary of the scientific content being submitted in support of the Class IV device licence (or licence amendment) application should be provided and include the device name, its general purpose, as well as a high level summary of key supporting documentation. Every effort should be made to provide introductory text or narratives to help connect the submitted documents. Any exceptions or unusual circumstance which the manufacturer wishes to highlight, specific to the device or application should be mentioned in the Executive Summary.

(4)4.3 Device Description

(4)4.3.1 General Description

The name of the device and a detailed description of the device must be provided. Information should explain what the device does and who uses it. If it is part of a system, the relationship of the components in the system should also be described. A labelled pictorial representation of the device in the form of diagrams, photographs or drawings are often helpful.

A brief description of all functional components of the device should be provided including software and its release version, if applicable. Components or accessories that can be sold separately and used with other medical devices, systems or units should be identified. Variants of the device must be identified, as well as the parameter ranges of variants (e.g., hip implants with varying coatings).

Performance and technical specifications of the device should be provided.

The materials used in the device should be specified. At a minimum, this will include all materials that would come into direct contact with the user or patient. However, other materials of a significant nature should also be specified. Reference to applicable material standards may be used.

(4)4.3.2 Licence Amendments

If the application is an amendment to a licenced device or is based on a modification of a licensed device, a description of the modifications is required (e.g., changes in design, performance, indications, etc). Comparisons can be used to support the modification only if made to a currently licensed device in Canada. If this method is used, ensure the

Canadian medical device licence of the comparator is stated. The comparison of the subject device and the comparator's key specifications can be provided in table format.

(4)4.3.3 Drugs

If the device contains an active pharmaceutical ingredient (API) or drug, a description of the substance, and detailed information concerning this substance should be provided. This should include its identity and source, the intended reason for its presence and its safety and performance in the intended application. Health Canada policies about the classification of combination products [Policy on Drug/Medical Device Combination Products - Decisions (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/pol/combo_mixte_dec_pol-eng.php) and Drug/Medical Device Combination Products (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/pol/combo_mixte_pol_2006-eng.php)] can be found on the Health Canada website.

(4)4.4 Design Philosophy

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 should be described. A brief description of the underlying science/technology, design concepts, and/or theoretical principles supporting the device's function should be provided, linking them to the claimed indications for use. References and comparisons with appropriate previous versions or generations of the device can be presented with reference to the previous version's Canadian medical device licence number. A tabular format is preferred for comparisons.

(4)4.5 Indications for Use and/or Intended Use and Contraindications

The statement of indications for use and/or intended use for the device as presented in the labelling must be stated. Contraindications for the device are also to be stated as presented in the labelling.

The statement of indications for use should describe the diseases or conditions the device will diagnose, treat, prevent or mitigate, ant the clinical condition of the patient under which use is recommended. It may also specify the patient population for which use of the device is indicated.

The statement of intended use should specify the therapeutic or diagnostic function provided by the device and may describe the medical procedure in which the device is to be used and whether the device is intended for single use or multiple uses. It may also specify the medical training the user should have (as recommended by the manufacturer).

The statement of contraindications should specify the clinical conditions of a patient that would make use of the device inadvisable.

This information should be repeated in all licence amendment applications for reference even if the information is unchanged.

(4)4.6 Implant Registration System

This section applies to implants as defined in Schedule 2 of the Regulations:

- heart valve;
- annuloplasty ring;
- active implantable device systems;
- all models of implantable pacemakers and leads;
- all models of implantable defibrillators and leads;
- artificial heart;
- implantable ventricular support system; and
- implantable drug infusion system.

If the subject device requires an implant registration system, the manufacturer must comply with Sections 66-68 of the Regulations. In the submission, the manufacturer is to provide samples of the implant registration cards which meet the requirements outlined in Section 66 of the Regulations.

(4)4.7 Device Labels, Package Labelling, and Documentation

This subsection should include copies of all labelling, package inserts, product brochures and file cards to be used in connection with the device, as well as copies of information and instructions for use for the practitioner and/or the patient. Labels will be reviewed against the requirements of sections 21, 22 and 23 of the Regulations. While draft labelling may be provided initially in the licence application, final labelling will be required before a licence is issued.

The statements of indications for use and/or intended use must be clearly stated in the device labelling, and will be the official claims against which authorization will be assessed. All expressed or implied claims made elsewhere in the labelling (i.e., instructions of use, advertising, or promotional material) must be consistent with the official statement.

Labelling materials should include, as appropriate, recommended disposal techniques, the nature of combustion products, the risk of explosion, etc.

Devices sold in non-sterile condition, but intended to be used sterilized, must specify the recommended sterilization process in the labelling.

If the labelling material covers components or devices not currently licensed in Canada this should be indicated in the labelling.

Health Canada has some device-specific labelling guidance documents. These documents should be consulted for additional guidance with regard to device labelling.

Device manuals may be provided on CD instead in hardcopy if they are too large to provide with the application.

(4)4.8 Marketing History

(4)4.8.1 Canadian and International

A summary of the marketing history for the subject device is required. The summary should include special access requests made to the Special Access Programme (SAP) and the outcome of these requests. In addition, the manufacturer must provide a list of countries or regions,where the subject device is currently being sold and the total number of units sold by country or region.

Marketing history of a licensed, previous version of the device can sometimes be used in support of safety or effectiveness of the subject device. If this is to be the case, then the name of the comparator, its approval reference number (e.g., MDL) and the number of units sold can be provided.

(4)4.8.2 Incidents Reports and Recalls

A summary of reported problems with the device, details of any recalls, and the current status or corrective actions should be provided. The country of the incident or recall should be clearly indicated. Incidents should include any Canadian incidents through SAP or other previous Canadian applications, if known.

If marketing history is presented for a predicate device then the associated recalls, and incident reports for that device should also be summarized here. If the number of incidents are voluminous, please provide a general description by problem types and state the number of reported incidents for each problem type. The description of each type of problem should be clear and any remedial or corrective actions undertaken should be explained.

(4)4.9 Manufacturing and Quality Control

(4)4.9.1 Material Specifications

Details of material identifications and specifications, including raw materials and components should be provided. Information should include complete chemical and physical characterization of all component materials especially for materials contacting the patient, or when the material chosen is considered critical for the design or function of that component.

If applicable, chemicals should be identified using either the IUPAC (International Union of Pure and Applied Chemistry) or the CAS (Chemical Abstract Service) Registry number. Reference to applicable material standards may also be useful in this description.

Reference may be made to a product's proprietary information submission for this information.

(4)4.9.2 Devices Containing Biological Material or Derivatives

This section is applicable to all medical devices which are manufactured from or incorporate biological material from human, animal or microbial origin. If the only biological materials are heparin or tallow derivatives (e.g., glycerol) this in itself does not change the classification of the device to class IV. Provide a detailed description of the materials, processing, testing, handling, and origin within the Class III application. Additional classification guidance can be sought through the Medical Devices Bureau.

The detailed information expected for each material depends on the type of biological material and the particular risks inherent in that particular material. Some guidance can be found below.

(4)4.9.2.1 Animal Tissue

The following information should be provided, as applicable, relating to animal tissues that are incorporated into the device:

- Tissue type;
- Animal species;
- Certification of country of origin/residence of animal;
- Name and address of the supplier of any animal material;
- Certificate of veterinary inspection;
- Certificate of abattoir inspection;

- Certification that the animal was fit for human consumption;
- Details relating to collecting, handling, storing and transporting of the tissue;
- Discussion of infectious agents/transmissible agents known to infect the source animal.

Evidence should be presented that demonstrates: i) a system is in place for animals and tissue traceability; and ii) quality control processes and procedures are in place to prevent contamination with potential infectious/transmissible agents, including Transmissible Spongiform Encephalopathies (TSEs). Disinfection/decontamination procedures in the event of contamination should also be outlined along with appropriate validation.

Process validation results should be included to substantiate that manufacturing procedures are in place to minimize biological risks in particular, with regard to viruses and other transmissible agents. If claims are made concerning removal/inactivation of TSEs, the details of these studies must be provided. The ICH Q5A which has been adopted by the Therapeutic Products Directorate can be consulted for guidance on viral inactivation validation.

An assessment of other applicable hazards such as those associated with the local host response to the animal material (biocompatibility) including pyrogenic, immunological or toxicological responses should be provided.

(4)4.9.2.2 Human Tissues

Medical devices incorporating tissues of human origin pose a special risk for both patients and health care providers. Reported incidents of pathogen transmission via these types of medical devices have resulted in a heightened awareness of the need for rules governing material selection, harvesting, processing and use.

Medical devices which incorporate viable and non-viable human tissues which have undergone more than minimal manipulation will continue to be regulated under the *Medical Devices Regulations* as Class IV devices. It has been determined that any product that is minimally manipulated cannot be a medical device. A definition of minimally manipulated can be found in the *The Safety of Human Cells, Tissues and Organs for Transplantation Regulations* (CTO Regulations) regulations found at: http://laws.justice.gc.ca/en/SOR-2007-118.

Currently, cryopreserved heart valves and human harvested dura mater are medical devices which incorporate viable and non-viable human tissues which have undergone "minimal manipulation". These products have been regulated as medical devices due to exceptional potential risks. It is the intention to move these to the CTO regulatory regime in the future.

The manufacturing information should include the donor screening and testing procedures (screening assays used must be licensed in Canada), procurement and processing processes, controls placed on the transportation of tissues and their derivatives, 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.

(4)4.9.2.3 Recombinant and Fermentation Products

Recombinant and fermentation products may form part of a medical device. Usually these products on their own are classified as biologicals and regulated by BGTD. Cell lines used in the production of material for medical devices must be 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 ICH guideline on Biotechnology Products adopted by the Health Canada should be consulted for guidance on how this viral validation should be conducted.

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.

(4)4.9.3 Device Specific Quality Plan

The review requirement for a quality plan are not met by the ISO 13485 certificate alone, instead refer to ISO 10005. A quality plan should specify "which processes, procedures and associated resources will be applied by whom and when to meet the requirements of a specific project, product, process or contract…". This information may be provided in an application in the form of a flow chart, process map, document matrix, table or text description. A quality plan specific for the subject device should link device requirements to the processes, resources and projects used by the manufacturer in producing that device.

(4)4.9.4 Manufacturing Process and Quality Control Activities

A description is required of the methods used in, and controls used for, the manufacture, processing, packaging, storage and, where appropriate, the installation of the device. This information may be presented in the form of a flow chart, diagram or text description with each control step clearly indicated. Sufficient detail must be provided to enable the reviewer to judge the appropriateness of the controls in place.

The following activities and specifications may help to ensure that the design output requirements are documented in terms that can be verified against the design input requirements:

A description of the quality control methods used for:

- Raw material;
    - component acceptance;
    - intermediate production steps;
    - the finished device;
- Sampling plans;
- Testing and inspection methods; and
- Related acceptance criteria.

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 stated.

Reference may be made to a product's proprietary information submission for this information.

(4)4.9.5 Process Validation Studies

If process results could not be fully verified during routine production by inspection or testing, the results of process validation studies must be presented. Process validation data should include test data and methods, information on controls, number of samples examined, frequency of testing, and why process validation was used (e.g., routine end product tests have insufficient sensitivity, reliability of a changed process is unknown, etc.). The procedures for monitoring and controlling the process parameters of a validated process should also be fully described. Process validation related to sterilization or shelf life should be captured under separate headings of sterilization or shelf life and need not be included in this section.

(4)4.9.6 Sterilization

(4)4.9.6.1 Sterilization Validation

If the device is sold sterile or is to be sterilized, process validation data should include sterility test data, reference to a standardized test method, and attestation or evidence of successful validation under real-life conditions under which the product is to be sterilized. Bioburden determination, culture media used, time and temperature of incubation, controls, number of samples examined and frequency of testing should also be presented. A Sterility Assurance Level (SAL) of 10^{-6} is generally required.

If a biological indicator was used, its placement needs to be described and rationalized (e.g., most difficult to sterilize location). If a group of devices are to be sterilized together, the worst-case scenario or most difficult to sterilize product should be validated. Attestation of validation may be used. The manufacturer should also demonstrate that they have a process in place to monitor bioburden levels on a regular basis to confirm that the sterilization method remains valid. Alternatively, a method of parametric release may be proposed and validated. If a process challenge device was used to assess the sterilization process it must be shown to have comparative resistance or a greater challenge to sterilization than the biological indicators placed inside the product/packaging.

If the product is to be re-sterilized by the end-user, a description of the recommended sterilization process for the end-user should be provided, and evidence of validation provided. Validation should be for sterility and also to

confirm that the process does not compromise integrity or performance of the product. The recommended, validated sterilization method should be stated in the device labelling information.

(4)4.9.6.2 Residual Toxicity

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 should be presented. For Ethylene Oxide residuals, levels should be within the acceptable levels recommended by the most current published version of ISO 10993-7, taking into consideration the body or tissue contact duration of the device. If another sterilization method has been used, a description of how residual toxicity concerns have been addressed should be provided.

(4)4.9.7 Packaging

Packaging of the device (or its components, if any) should be described including the materials employed. It should be clear what protective characteristics the packaging provides (e.g., maintains sterility, humidity, light sensitivity, transportation protection, etc.).

(4)4.9.8 Shelf Life Validation

(4)4.9.8.1 Shelf Life Validation of the Product

If the product is subject to a shelf-life, shelf-life testing should be provided and the claimed shelf-life clearly stated. The method used (e.g. accelerated versus real time) should be provided along with the storage conditions used and the state of the product when tested (e.g. sterilized, production version, prototype, transportation, simulation, etc.). Devices containing materials of unknown stability should have real-time data.

(4)4.9.8.2 Shelf Life Validation of the Packaging

If the device requires special packaging (e.g., considerations related to sterility, humidity, light sensitivity, pressure or oxidative reaction under irradiation), evidence should be provided that this has been addressed. Likewise, evidence should be provided to demonstrate that the integrity of the device and the internal environment can be maintained by the device packaging during handling, transport and storage (i.e., for claimed shelf life). In the case of sterility, ensure

that the test methods address both seal integrity and sterility (e.g., bubble test, dye penetration test, etc.).

(4)5.0 Safety and Effectiveness

(4)5.1 Standards

The list of standards applied, in whole or in part, in the design and manufacture of the device should be provided. These standards may be international or national. If full or partial conformity is being claimed to support safety or effectiveness of the device then ensure the full title, version or identifying number, date and responsible agency of each standard must be provided. A tabular format may be used.

For standards recognized by Health Canada, the manufacturer may sign a declaration of conformity. Declarations of conformity (DoC) must be provided on the Health Canada DoC form. Consult the *Guidance Document - Recognition and Use of Standards* under the *Medical Devices Regulations* and its associated updates for important information on this process and its role in medical device licence applications. The DoC form, current list of standards, and associated guidance documents can be obtained from the Health Canada website (http://www.hc-sc.gc.ca/dhp-mps/index-eng.php).

The use of standards is not compulsory. The manufacturer may chose to demonstrate safety and effectiveness independent of any international or national standards.

(4)5.2 Preclinical Studies

(4)5.2.1 Physical and Mechanical Bench Testing

Physical testing should be conducted to predict the adequacy of device to function as intended. In addition, testing should address the device's response to physiological stresses, undesirable conditions and forces, long-term use and all known and possible failure modes.

Complete physical or mechanical bench test data should be provided. Reports should cover the objectives, methodology, results and manufacturer's conclusions of all physical studies of the device and its components. Justification of any unexpected test failures should be provided. Acceptance criteria along with a rationale for this criteria should be included along with the results of testing (pass/fail criteria should clearly be defined based on methods from an internationally recognized standard or a method that has been validated and provided to Health Canada for review).

(4)5.2.2 Software Verification and Validation

If a device includes software, a description of that software and its impact of the safety and effectiveness of the device should be provided. In addition, a summary of verification and validation testing and the final results are required, along with the software revision history. This section should clearly provide traceability between system requirements, software risk mitigation and the testing completed. All unresolved anomalies in the release version of the software should be summarized along with a justification for acceptability.

For software validation the testing environment should be specified (e.g., in-house, simulated, clinical, etc.). The version tested must be clearly identified and should match the release version of the software, otherwise justification must be provided.

(4)5.2.3 Biocompatibility Studies

Biocompatibility testing characterizes the biological response to the material. If the device comes in contact with the patient then the biocompatibility of all materials which are potentially patient contacting is required. Tests should be conducted on samples from the final product after all manufacturing and processing has been completed (e.g., sterilization). Deviations from this should be justified; generic claims from the raw material supplier are generally insufficient.

Reports describing the tests, the results and the analyses of data should be presented. For each test, the predefined acceptance criteria and the results should be clearly provided (e.g., tabular form). In general, ISO 10993 standards are taken as the gold standards for biocompatibility. If testing was not conducted from a currently recognized standard, the validated alternative method should be provided along with a justification for its use (e.g., devices incorporating nanotechnology). Any deviations from a standard method should also be specified.

(4)5.2.4 Pyrogenicity

When biocompatibility assessment includes systemic toxicity concerns (i.e., acute, subacute or subchronic), pyrogen test data and methods should also be summarized and should cover frequency of testing, number of units tested, methods of testing, any deviations from this testing, and test results. Pyrogenicity testing should be considered in the evaluation of medical devices in accordance with ISO 10993-11.

(4)5.2.5 Animal Studies

Animal studies used to support safety and/or effectiveness in humans should be presented. These studies should be undertaken using good laboratory practices.[2] The objectives, methodology, results, analysis and manufacturer's conclusions should be covered by reports submitted. The study conclusion should address the device's interaction with animal fluids and tissues and the functional effectiveness or safety of the device in the experimental animal model(s). The rationale (and limitations) of selecting the particular animal model should be discussed.

(4)5.3 Clinical Evidence

An evaluation of clinical evidence is necessary to help establish the clinical safety and effectiveness of a medical device for each claimed indication for use. A clinical evaluation considers available, relevant clinical data from published sources, or device-related investigations. It may be necessary to generate additional clinical data to address specific issues for certain medical devices.

If a clinical history has been well established with a given device technology, evidence may be provided in the form of a literature review of relevant publications in the peer-reviewed scientific literature. Reference to devices other than the subject device in support of safety or effectiveness requires a thurough comparison to the subject device design, features and performance capabilities to demonstrate relevance. This may be provided in a table format. Leveraged publications should be referenced but copies only need to be provided if pivotal in supporting safety or effectiveness. Articles listed in Section (4)6.0 are not specific to clinical evidence. Listing all articles only in Section (4)6.0 is acceptable provided there is supporting clinical discussion within Section (4)5.3 and appropriate cross-referencing in Section (4)6.0.

Clinical evidence in the form of device-specific clinical investigations conducted in Canada or other countries should be provided. Reports should cover the objectives, methodology and results presented clearly and meaningfully with context. The conclusions on the outcome of the clinical investigations should be preceded by a discussion within the context of the published literature. Both statistical and clinical significance should be considered and critically analyzed.

[2] Organisation for Economic Co-operation and Development (OECD) Principles of Good Laboratory Practice and Compliance Monitoring No. 1 (www.OECD.org)

Additional guidance for clinical testing of some specific medical device classes is available. The list of available documents is located on the Health Canada website under Medical Devices Guidance Documents (http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/index-eng.php).

(4)6.0 Literature Studies and Bibliography

To facilitate the review process, the manufacturer should provide a bibliography (i.e list of references) of all relevant published literature dealing with the use, safety and effectiveness and the indications for use of the subject device. If information within the article is being provided as key evidence of safety or effectiveness, a summary of the relevant sections should be provided including data upon which the conclusions are drawn. Copies of these pivotal articles should also be provided. Care should be taken to ensure that the references are timely and relevant to the current application. A bibliography may not be necessary if the device or its technology is well known with a long history of use.

(4)7.0 Risk Assessment

A risk assessment should be based on 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. The manufacturer should identify the individual or organization that carried out the risk analysis and it should be conducted on the version of the device under review.

The information provided should include a description and identification of the devices and accessories under consideration in a risk assessment. Design aspects should be evaluated. The method of risk analysis must be appropriate for the device and the level of risk involved. A brief description of the technique used to perform the risk assessment, definitions of risk and any standards used in this process should be stated. A list of critical hazards should be provided, which includes how the risks associated with these hazards have been evaluated and what risk reduction measures have been taken. An evaluation of the risks as compared with the claimed benefits of the device and steps taken to reduce the risks to acceptable levels should also be presented.

If the application is for an amendment or modification of a previously licenced class IV device (in Canada), then the risk assessment information should focus on new and/or modified risks and mitigation.

It is recommended that the current version of ISO 14971-1, entitled *Medical Devices - Application of Risk Management to Medical Devices*, be consulted.

5.0 PRESENTATION OF APPLICATIONS

This section describes the physical specifications for paper applications. A paper application will serve as the official copy until such time as Health Canada is prepared to accept applications solely in electronic format. Only one copy of an application is required. Manufacturers and/or device sponsors should follow the format outlined below.

5.1 Organization and Identification of Application Volumes

Paper applications should be bound for easy access to information. Three-ring binders of four inches or less should be used for all application volumes. The Administrative Information may be submitted by being placed in a separate docket or plastic document protector within the application however avoid putting any other sections within plastic document protectors. Each binder should be identified with the device name, manufacturer's name, and licence number (if applicable). Each binder should be sequentially numbered, starting with Volume 1. Also to be specified on the binder label are the volume number out of the total number of volumes, the section(s) contained within the volume, and the date of the application (month, day and year).

Below is an example of a binder label.

Device Name: "ABC"
Manufacturer's Name: "XYZ"
Licence Number: "12345"
Volume: 1 of 3
Sections: 1-6
Submission Date: January 01, 2010

The above information should appear on the spine as well as on the front cover of the binder.

5.2 Organization and Identification of Information within Applications

Information within an application should be organized into a series of sections and subsections. The Table of Contents provide an overview of the structure that applicants are expected to follow for Class III and Class IV premarket medical device licence applications, respectively. In the Table of Contents, sections and subsections should be identified both by the assigned decimal number and heading. The pagination may be sequential for the entire application, by volume or by section and report/supporting documentation.

The Cover letter is placed within the Additional Class III/IV Premarket Information section for Health Canada's processing needs. The Administrative Information is detached from the Application and/or Amendment prior to being reviewed.

If cross-references are made within an application, both the volume and page numbers should be clearly identified. Acronyms or abbreviations should be defined the first time they are used in each volume. Alternately, an abbreviation/acronym key may be provided at the beginning of each volume. Tabs should be used to identify the start of new sections and appendices.

5.3 Language

Information in an application should be recorded in either English or French. Any material in a language other than English or French must be accompanied by an English or French translation.

5.4 Margins and Font

Text, tables and figures should be prepared using margins that allow the document to be printed on 8.5 x 11 inch paper. The left-hand margin should be sufficiently large such that information is not obscured by the method of binding. The font for narrative text and text within tables and figures should be of a style and size that can be easily read, even after photocopying. Times New Roman, 12-point font is recommended for narrative text.

6.0 BIBLIOGRAPHY

Device Specific Premarket Guidance Documents:

Device Licence Applications for Ultrasound Diagnostic Systems and Transducers
(http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/ultrasound_ultrasons-eng.php)

Guidance Document on the Regulation of Medical Devices Manufactured From or Incorporating Viable or Non-Viable Animal Tissue or their Derivative(s)
(http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/anim_tiss-eng.php)

Pre-Market Guidance on Bare Cardiovascular Stents
(http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/stents_nues-eng.php)

Preparation of a Premarket Review Document for Breast Implant and Tissue Expander Device Licence Applications
(http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/breast_impl_mammaires-eng.php)

Guidance Document - Medical Device Applications for Implantable Cardiac Leads
(http://www.hc-sc.gc.ca/dhp-mps/consultation/md-im/consult-draft_ebauche_cardi_lead_sondes-eng.php)

Additional Premarket Guidance Documents:

For up to date listings of Health Canada Guidance Documents related to medical devices refer to the Health Canada website (http://hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/index-eng.php).

Guidance for the Labelling of Medical Devices under Section 21 to 23 of the Medical Devices Regulations, Appendices for Labelling: Soft Contact Lenses and Menstrual Tampons (http://hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/labl_etiq_dv10-eng.php)