To: Medical Devices Stakeholders

Subject: Preparation of a Premarket Review Document for Class III and Class IV Device Licence Applications

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 III and Class IV Device Licence Applications, sets out the Programme’s guidance for Industry on the subject.

This guidance document is to be used in the preparation of Class III and Class IV medical device licence applications and licence amendment applications, in compliance 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, please contact:

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Therapeutic Products Programme

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Programme des produits thérapeutiques

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Preparation of a Premarket Review Document for Class III and Class IV Device Licence Applications

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1.0 Introduction

1.1 Purpose

This guidance document is to be used in the preparation of Class III and Class IV medical device licence applications and medical device licence amendment applications, in compliance with the medical devices 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.

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 III medical device must contain the information and documents set out in section 32, subsection (3), paragraphs (a) to (j). 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. The information will be required in a format applicable to the modified device class.

This guidance document provides assistance in preparing the scientific and medical evidence necessary to support a licence application for Class III and Class IV devices.

1.2 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.

Approximately two thirds of medical devices in Canada will undergo some form of premarket scrutiny before sale. Eighty percent of the devices undergoing scrutiny are Class II and, after January 2001, will be evaluated by a quality systems audit. The other twenty percent will also be subject to a premarket scrutiny of scientific/technical data. Approximately three quarters of this number are Class III and will require review of only the summary of safety and effectiveness information. The remaining quarter of these devices are Class IV, which pose the greatest hazard to the Canadian public, and they will undergo a detailed review of safety and effectiveness information.

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.
1.3 Scope
This guidance document is intended to aid manufacturers and/or device sponsors in organizing the requirements for Class III and Class IV device licence applications or amended licence applications. This document provides details regarding the scientific and medical requirements necessary for Class III and Class IV device licences. This document is applicable to both \textit{in vitro} diagnostic devices (IVDDs) and non-\textit{in vitro} diagnostic medical devices (medical devices). Where differences in the review aspects occur, additional information specific to IVDDs is provided.

This guidance document does not deal with Class II licence applications. They are described in the document entitled \textit{Guidance On How to Complete the Application for a New Medical Device Licence}, GD013.

This document does not address the issues of chargeable review items, significant change amendments, administrative amendments or the general process and procedures of device licensing. These topics will be covered in separate guidance documents, available on the Medical Devices Bureau website.

This document will not supplant planned device-specific guidance documents or requirements outlined in the proposed bulletins to the \textit{Medical Devices Regulations}. A list of available guidance documents is provided in Appendix 1.

Additional guidance documents will be prepared to address issues related to proposed or future mutual recognition agreements as referenced in section 32(5) of the \textit{Medical Devices Regulations}.

1.4 Definitions
\textbf{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.

\textbf{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 \textit{Guidance on How to Complete the Application for a New Medical Device Licence} GD013 contains detailed information on submitting a 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, the manufacturer and/or device sponsor is referred to the guidance document *Guidance on How to Complete the Application for a New Medical Device Licence GD013*.

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 a manufacturer may be requested to submit ADDITIONAL INFORMATION.

In the event of a significant change, 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. Manufacturers are referred to *Guidance for the Interpretation of Significant Change GD001*, 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.

This guidance document provides information for Class III and Class IV devices in general. Manufacturers and/or device sponsors with specific questions or concerns are urged to contact the Manager, Device Evaluation Division, Medical Devices Bureau.

3.0 **Access to Information Act and the Confidentiality of Licence Applications**

Information provided to the Programme by manufacturers and/or device sponsors 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 TPP policy, information regarding device licence applications that have been received or are being processed is also considered confidential. Once a licence is granted, basic information about a device, such as that listed in section 32(1), is considered public information.

4.0 **Presentation of the Review Document**

Manufacturers and/or device sponsors may follow the structure presented in this guidance document when submitting an application for a device licence or device licence amendment. Sections that are not applicable should be clearly indicated.
In certain instances, it may be necessary to follow a special or unique format. In such cases, the concurrence of the Manager, Device Evaluation Division, should be obtained in advance. Information in the document should be recorded in either English or French. Material in a foreign language must be accompanied by an English or French translation. Only one copy of a review document is required.

All documents should be legible, and the page size, including tables, should be uniform. The submission should be bound for easy access, for example in a three-ring binder. Each volume must be clearly labelled and numbered both on the spine and on the front cover.

The pagination may be sequential for the entire submission or by volume. In the executive summary and the table of contents, individual sections of text should be identified both by the assigned decimal number and by the correct title. Cross-references should include both volume and page numbers.

### 5.0 Format of a Class III Review Document

A licence application for a Class III medical device must contain the information and documents described in section 32, subsection (3) paragraphs (a) to (j). These requirements are grouped into five general sections. These sections must be easily identifiable in every licence application for a Class III medical device. The following format is suggested:

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<td>5 Quality System Requirements</td>
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This paragraph requires a general description of the device and of the materials used in its construction and packaging, including its principles of operation. Each of the functional components of the device must also be described, with labelled pictorial representation of the device in the form of diagrams, photographs or drawings.

A complete list of all components of the device is required. 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 included, as well as the parameters of the range of variants.

The materials used in the device and packaging must 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 must also be specified.

If the device contains a medicinal substance or drug, a description of the substance and its technical requirements must be provided.

5.1.2 Section 32(3)(b) 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 should be provided, linking them to the claimed indications for use. References and comparisons with appropriate previous versions or generations of the device should be presented. A tabular format is preferred 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 use and operation of the device, unless these instructions are not required for the safe, effective use of the device. Details on the strength of materials and the accuracy, sensitivity and specificity of the device should also be supplied.

The physical aspects of the device, including its packaging, its operational capabilities and the processing of inputs and the resultant outputs, must be identified. This should include a summary comparison of the design input parameters (operation specifications) with the resultant performance specifications for the device (design output characteristics).

5.1.3 Section 32(3)(c) Marketing History
In this paragraph, a summary of the marketing history of the device is requested. The summary must include 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.

5.2 Summary of Safety and Effectiveness Studies.
The requirements of this paragraph depend on the device type. The manufacturer should include sufficient information to establish that the safety and effectiveness requirements in sections 10 to 20 have been fulfilled.

5.2.1 Section 32(3)(d) List of Standards
The manufacturer and/or device sponsor is required by this paragraph to submit a list of standards applied, in whole or in part, in 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.

5.2.2 Section 32(3)(e) Method of Sterilization
In the case of a Class III device sold in a sterile condition, the manufacturer and/or device sponsor is requested to provide a description of the sterilization method used and the packaging used to maintain sterility. This must include the type of sterilization process, the level of sterility assurance and an attestation that the process has been properly validated.

5.2.3 Section 32(3)(f) Summary of Studies
This paragraph requests a summary of all studies that the manufacturer relies on to ensure that the device meets the safety and effectiveness requirements of sections 10 to 20, as well as the conclusions drawn from those studies by the manufacturer. This includes a summary of all preclinical physical testing, such as stress, fatigue, wear and shelf life, all biocompatibility testing and the results of all animal and previous clinical investigations.

For IVDDs, an executive summary, with a conclusion and interpretation section is required of all preclinical studies. This should include, when appropriate, the identification of testing sites and principal investigators involved; population tested; testing algorithm; number of lots tested; test controls; test of record; a summary of results obtained and comparison/agreement analysis between the test of record and the investigational assay; quality calibration (e.g. CO validation); sensitivity and specificity (analytical and/or diagnostic); and statistical analysis (95% CI; ROC, curves, etc.). The technical performance of the device should be summarized, including precision/reproducibility, linearity, carry-over and stability.

Section 20 states that where a medical device consists of or contains software, the software shall be designed to perform as intended by the manufacturer and the performance of the software shall be validated. This requires a summary of studies that includes the software version number, a description of software design and development, functional requirements, specifications, design
safeguards, error checks and controls, and verification and validation, including testing protocols and results.

5.2.4 Section 32(3)(i) Bibliography
To facilitate the review process, the manufacturer and/or device sponsor is requested to provide a bibliography of all published reports dealing with the use, safety and effectiveness of the specific device in question. These references should be supplied in chronological order, with any existing abstracts. The keywords used to generate the list and the source of the list should be specified.

5.3 Labelling
5.3.1 Section 32(3)(g) Labelling
Section 32(3)(g) requests a copy of the device label. This will include the product monograph and all advertising brochures intended to be used with the device. Labels will be reviewed with attention to the requirements of sections 21, 22 and 23 of the Medical Devices Regulations.

The Programme has prepared two labelling guidelines, one for IVDDs and the other for medical devices in general. These documents should be consulted for advice with regard to device labelling.

The label of a Class III device sold in non-sterile condition, but intended to be used sterilized, must specify the recommended sterilization process. If resterilization is possible, the method must be described.

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

While draft labelling may be provided initially in the 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 should refer to the guidance documents available on these topics.

5.4 Near-Patient in vitro Diagnostic Devices (if applicable)
5.4.1 Section 32(3)(h) Near-Patient IVDD Studies
Section 32(3)(h) specifies additional information required for a near-patient in vitro diagnostic device. This includes a summary of investigational tests conducted on the device, simulating expected conditions of use. During testing, the device should be operated without assistance by people representative of the intended users, according to the instructions provided in the labelling.
5.5 Quality System Requirements

5.5.1 Section 32(3)(j) Quality System Attestation.

Section 21(3)(j) requests a signed attestation by a senior official of the manufacturing firm that the device is designed and manufactured under an appropriate quality system. This system 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 will not come into force until 1 July 2001.

6.0 Format of a Class IV Review Document (Medical Devices)

A licence application for a Class IV medical device (non-IVDD) must contain the information and documentation set out in section 32, subsection (4), paragraphs (a) to (p). These requirements are organized and assigned to eight chapters. These sections or chapters must be easily identified in every licence application for a Class IV device. The following format is suggested:
## 6.1 Background Information

### 6.1.1 Section 32(4)(a) Device Description

This section requires a general description of the device, including its principles of operation, and 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 of 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. At a minimum, this will include all materials in direct contact with the user or patient. However, other materials of a significant nature must also be specified.
If the device contains a medicinal substance or drug, a description of the substance and its technical requirements must be provided.

6.1.2 Section 32(4)(b) 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 claimed indications for use. References and comparisons with appropriate previous versions or generations of the device should be presented. A tabular format is preferred 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. Details on the strength of materials and the accuracy, sensitivity and specificity of the device should also be supplied.

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

6.1.3 Section 32(4)(c) 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.

6.2 Risk Assessment
6.2.1 Section 32(4)(d) 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, the reader is referred to the current draft of ISO/DIS 14971-1, entitled Medical Devices - Risk Management, Part 1: Application of Risk Analysis.

This first element to be considered is a risk analysis. This will include a complete description and
identification of the devices and accessories 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.

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.

6.3 Quality Plan
6.3.1 Section 32(4)(e) Quality Plan
Section 32(4)(e) requires the manufacturer and/or device sponsor to provide a plan that sets out the specific quality practices, resources and sequence of activities relevant to the device.

The quality plan as described in ISO 10005 provides a mechanism to tie specific requirements of the product, project or contract to existing generic 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 quality system requirements will be met.

6.4 Device-Specific Detailed Information
Section 32(4)(f) and (g) request specific information related to material characterization and manufacturing processes, including quality control activities.

6.4.1 Section 32(4)(f) 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. The chemistry and polydispersity of custom-made polymers or resins must be provided, such as main chain structure, cross-link density and ratio of co-monomers.

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

6.4.2 Section 32(4)(g) 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. This would include production, installation and servicing.

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.

6.4.2.1 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.

6.4.2.2 Quality Control Activities
The quality control activities and specifications should make reference to the acceptance criteria in place for the device. 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 of the quality assurance audit program, record keeping and 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 and reprocessing procedures if applicable.

6.4.3 Section 32(4)(h) List of Standards
The manufacturer and/or device sponsor is required by this paragraph to 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.

6.5 Safety and Effectiveness Studies
Section 32(4)(i) requests 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.

Guidance for preclinical and clinical testing of some medical device classes is available. The list of available documents is presented in Appendix 1.

6.5.1 Section 32(4)(i)(i) Preclinical and Clinical Studies
Details must be provided on all biocompatibility tests conducted on 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, the reader is referred to ISO 10993 or the Health Canada publication 94-EHD-109, entitled *Biocompatibility Testing of Device Materials in Canada*.

Complete preclinical physical test data must be provided, as appropriate. The report must include the objectives, methodology, results and manufacturer’s conclusions of 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 effectiveness in humans must be reported. These studies must be undertaken using good laboratory practices. The objectives, methodology, results, analysis and manufacturer’s conclusions 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.

Clinical evidence of 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.

6.5.2 Section 32(4)(i)(ii) 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.

6.5.3 **Section 32(4)(i)(iii) Software Validation Studies (if applicable)**

The correctness of a software product is another critical product characteristic that cannot be fully verified in the finished product. The manufacturer and/or device sponsor must provide evidence that validates the software design and development process. This information should include the results of all verification, validation and testing performed in-house and in a user’s environment prior to final release, for all of the different hardware configurations identified in the labelling, as well as representative data generated from both testing environments.

6.5.4 **Section 32(4)(i)(iv) Literature Studies**

Copies are required of all literature studies that the manufacturer is using to support safety and effectiveness. These will be a subset 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.

6.6 **Devices Containing Biological Material (if applicable)**

6.6.1 **Section 32(4)(j) Additional Information for Devices Containing Biological Material**

In the case of a medical device manufactured from or incorporating animal or human tissue or their derivative, 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. Donor screening concerns must be fully addressed. Methods of harvesting and long-term registries must also be fully described. Process validation results are required to substantiate that manufacturing procedures are in place to minimize biological risks.

6.7 **Device Label**

6.7.1 **Section 32(4)(o) Labelling**

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 Programme has prepared two labelling guidelines, one for IVDDs and the other for medical devices in general. These documents should be consulted for specific advice with regard to device
labelling.

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

6.8 Quality System Requirements
6.8.1 Section 32(4)(p) Quality System Attestation
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 will not come into force until 1 July 2001.

7.0 Format of a Class IV Review Document (IVDDs)
An application for the licensing of a Class IV in vitro diagnostic device (IVDD) must contain the information and documentation set out in section 32, subsection (4) paragraphs (a) to (p). These requirements are organized and assigned to eight sections. These sections or chapters must be easily identified in every licence application of a Class IV IVDD. The following format is suggested:
7.1 Background Information

7.1.1 Section 32(4)(a) Device Description
This section of the Regulations requires a description of the device and of the materials used in construction and packaging. This description should include a descriptive summary of the methodology, biological principles and test procedures, as well as the stage in the progression of the condition for which the test is appropriate. A description of the intended use (what is detected by the assay) and the indications for use (clinical settings appropriate for using an assay) should be
provided, indicating whether the test is qualitative or quantitative, the specific disorder, condition, or risk factor of interest for which the test is intended to detect, define or differentiate (i.e. the analyte to be measured), the type of specimen(s) required (e.g. serum, plasma), and whether the assay is automated.

The function of the IVDD (screening, monitoring, diagnosis, staging or routine test) must be clearly stated. The following definitions may be useful to sponsors to determine the function of their IVDD. A staging test determines the nature or extent of a medical condition; a monitoring test tracks a patient’s progress over time; a diagnostic test identifies a disorder in order to determine whether to start therapy or not; a routine test is one of a battery of tests that may result in a positive test unrelated to the present condition; and a screening test is used to determine whether apparently healthy people who are at sufficient risk of a specific disorder require diagnosis and necessary treatment\(^1\). The population for which the test is appropriate should be identified (e.g. pregnant women).

All components of the test, including antibodies, antigens, PCR primers and buffers, assay controls, substrates used to detect antigen-antibody complexes and test reagents should described. Collection and transport materials provided in the IVDD or recommended for use should also be described. A description should also be given for software elements and dedicated instrumentation used for specimen handling, processing or calculating assay results.

### 7.1.2 Section 32(4)(b) Design Philosophy

This section requires a description of the features that enable the device to be used for the medical conditions, purposes and uses for which it is manufactured, sold or represented by the manufacturer. This would include details on the design philosophy and performance specifications as related to the claimed indications for use. References and comparisons with appropriate previous versions or generations of the device should be presented.

### 7.1.3 Section 32(4)(c) Marketing History

This section requires a summary of how the device is marketed outside Canada. The summary should include a list of countries where the device has been sold, the number of units sold globally, and a summary of reported problems and/or recalls of the device in these countries.

### 7.2 Risk Assessment

#### 7.2.1 Section 32(4)(d) Risk Assessment

This section requests an analysis of all risks inherent in the use of the IVDD and the solutions adopted to satisfy the safety and effectiveness requirements of sections 10 to 20 of the Regulations.

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The first element to be considered is a risk analysis describing and identifying the devices and accessories under consideration. Guidance on the risk analysis procedure for IVDDs is found in the Draft International Standard ISO/DIS 14971-1, entitled *Medical Devices - Risk Management, Part 1: Application of Risk Analysis*. More specific information can be found in Annex A of that document.

A list of possible hazards for these devices must be prepared. Indirect risks from IVDDs may result from device-associated hazards, such as instability, which lead to erroneous results, or from user-related hazards, such as infectious reagents. The evaluation of these risks against the claimed benefits of the device and the method used to reduce risk to acceptable levels must be described.

The individual or organization that carries out the risk analysis must be clearly identified. The technique used to analyze risk must be specified, to ensure that it is appropriate for the device and the risk involved.

### 7.3 Quality Plan
#### 7.3.1 Section 32(4)(e) Quality Plan
Section 32(4)(e) requests a plan that sets out the quality practices, resources and sequence of activities relevant to the device. This quality plan would outline the design and process control (except sterilization) and material characterization. The plan may be presented as a narrative or in the form of a flow diagram as shown in ISO 10005.

### 7.4 Device-Specific Detailed Information
Section 32(g)(f) and (g) request detailed information related to material specifications and manufacturing processes, including quality control activities.

#### 7.4.1 Section 32(4)(f) Material Specifications
This part of the application must include complete details of material specifications, including raw materials. All components of the IVDD should be listed and chemically and biologically characterized, including antibodies, antigens, assay controls, substrates used to detect antigen-antibody complexes, and test reagents. Appropriate references should be cited.

If synthetic peptides are used, the peptide sequence should be supplied. If components are of biological origin or recombinant, the manufacturer and/or sponsor must indicate the source and provide details on production. These details would include the strain of the virus, the cell line for cultivation of the virus, sequences of relevant nucleic acids and amino acids, etc., used in the manufacturing process of viral lysate, purified proteins, recombinant and synthetic proteins, primers, probes, etc.

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

#### 7.4.2 Section 32(4)(g) Manufacturing Process Specifications
The manufacturing process specifications for the device should be provided in the form of a list of
resources and activities that transform inputs into the desired output. This includes production, installation and servicing of the device.

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 and/or device sponsor should inform these contractors of the need to supply detailed information on the device.

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

7.4.2.1 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, 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.

7.4.2.2 Quality Control Activities
The critical processes that directly affect the quality of the device must be identified. These include all processes that cannot be verified by subsequent inspection or testing, for example, viral clearance.

To satisfy this requirement, manufacturers and/or device sponsors should provide a description of quality control methods used for raw material and component acceptance, intermediate production steps and acceptance criteria for the finished device. Sampling plans and testing, inspection methods and relevant acceptance criteria should be provided. In addition, detailed information on the quality assurance procedures, including specifications and acceptance criteria for reagents, raw materials, labels, packaging materials, controls, intermediate and finished products should be provided. When applicable, sterilization process details should be included. Any testing panels used should be described. If a lot release program exists, if should be described, along with data from three lots.

This section should also contain a flow chart of the manufacturing process for the IVDD, indicating all quality control steps. All production methods should be described and relevant literature references given.
7.4.3 Section 32(4)(h) List of Standards
The manufacturer and/or device sponsor is required to 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 and performance. The full title, version or identifying number and date and responsible agency of the standard must be provided in a tabular format.

7.5 Safety and Effectiveness Studies
Section 32(4)(i) requests detailed information on any preclinical, clinical, process validation, software validation and literature studies relied upon by the manufacturer to ensure that the IVDD is safe and effective. This information would include summaries and conclusions drawn from tests and a bibliography of all published reports dealing with the use, safety and effectiveness of the IVDD. An introductory summary should accompany each study presented.

The performance data requested should be able to establish the safety and effectiveness of the device for all claimed specimen type(s). Studies must be performed to establish performance for each claimed indication for use, and prospectively collected samples/specimens should be included for every study and for each indicated use.

All testing protocols should be provided along with raw-line data, analyses, conclusions and a summary of results, including explanations of discrepant results. The statistical methods and reasons for choosing them must be presented. Details of the studies conducted to determine performance values must be presented, including the testing algorithm, the population tested, the type of samples used, the site of the studies and principal investigators and a description of any panels used. Also necessary is information of where applicable results are expressed as the number initially reactive and repeat reactive, agreement with the test of record (percentage) confirmation results of assays, and when appropriate, discrepant results and how they have been resolved. Pictures, rather than photocopies, of blots, gels, etc., should be supplied. A copy of the laboratory evaluation report signed and dated by the principal investigator must be provided for all studies conducted on behalf of the applicant. All appropriate references should be provided.

If two or more test procedures are possible for the assay, (e.g., automated/manual, different incubation modes/temperatures/times), performance values for the different methods should be included.

The following section describes in detail some of the most common performance characteristics that need to be validated. This is not an exhaustive list.

7.5.1 Section 32(4)(i)(i) Preclinical and Clinical Studies
7.5.1.1 Sensitivity/Specificity
The analytical sensitivity of the assay, which is the smallest detectable amount of the analyte in
question, should be determined, when applicable. Data must be presented to show how this value was obtained, for instance, through end-point dilution analysis.

The sensitivity (proportion of known, confirmed positive samples that test positive in the assay) and specificity (proportion of negative samples that test negative with the assay) must be determined and expressed as a percentage, with 95 percent confidence intervals (CI), to establish “disease present” and “disease absent,” respectively.

Evidence of sensitivity must include studies with well-characterized, confirmed positive samples, with sero-conversion panels, with low antibody titer samples, and with samples representative of the different clades or strains of the agent.

Complete reports of prospective studies, conducted with samples representative of the specific population, under conditions similar to the conditions of use, must be submitted in support of the sensitivity and specificity of the IVDD. These could include, for example, prospective studies conducted in a donor population, that could be blood donors or cadaveric samples, or in populations prevalent with a specific clade or strain of the agent. For diagnostic applications, samples should be tested from populations with a high risk of infection with the organism in question, with relevant concurrent disease or with conditions that predispose them to such infection.

7.5.1.2 Validation of Cutoff
The manufacturer must describe, using laboratory data, and explain the rationale for determining the assay cutoff (CO) value (distinction between positivity and negativity). The statistical method used to determine the CO and the receiver-operating characteristic (ROC) analysis of CO and other graphical representations should be provided, as appropriate.

7.5.1.3 Interference
Potentially cross-reacting or interfering substances encountered in specific specimen types or medical conditions unrelated to the test condition should be evaluated. For example, if the antigen in the device is a recombinant, or if the antisera in the device were produced using a recombinant as the immunogen, then sera that contain antibodies against the organism in which the vector was introduced and the recombinant produced should be tested in order to ascertain that there is no cross-reactivity with the organism.

The manufacturer must verify that recommended specimen storage conditions are compatible with the assay. For example: Can the specimen be frozen and thawed one or more times without affecting the qualitative detection of the analyte? The possibility of either false positivity or false negativity due to storage conditions of the specimens should be evaluated. If the use of plasma is claimed, a study with each anticoagulant (EDTA, Na-citrate, heparin, etc.) must be performed to show that the anticoagulant does not interfere with the assay.
7.5.1.4 Reproducibility
To establish the amount of agreement between results of samples tested in different laboratories, intra-assay and inter-assay variations and inter-laboratory variations must be determined using samples that represent the full range of expected analyte concentrations in the target population. The standard deviation and percent of coefficient of variation should be given for each sample or panel member for intra-lot, inter-lot and inter-laboratory. All panels used must be fully described.

7.5.1.5 Stability
Real-time stability data must be provided on testing of at least three different manufactured lots at various time intervals at the recommended storage temperature. This must be done to substantiate the recommended shelf life of the unopened IVDD, the opened IVDD, reagents, controls etc. under recommended storage conditions. The stability protocol should also be described.

Testing should be included to show that the IVDD is stable under variable shipping conditions, such as extreme cold or heat. If the IVDDs are shipped under special conditions (e.g. in dry ice) and there is evidence that they are not exposed to temperatures outside the recommended range, studies at the higher temperature are not required.

7.5.2 Section 32(4)(i)(ii) 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 is applicable to the inactivation of infectious organisms in IVDD controls and the production of monoclonals.

7.5.3 Section 32(4)(i)(iii) Software Validation Studies (if applicable)
The correctness of a software product is another critical product characteristic that cannot be fully verified in the finished product. The manufacturer and/or device sponsor must provide evidence validating the software design and development process. This information should include the results of all verification, validation and testing performed in-house and in a user environment prior to final release, for all of the different hardware configurations identified in the labelling, as well as representative data generated from both testing environments.

7.5.4 Section 32(4)(i)(iv) Literature Studies
Copies of all literature studies that the manufacturer is using to support safety and effectiveness are required. These studies will be a subset of the bibliography of references supplied in response to section 32(4)(n).

Appropriate peer-reviewed literature references related to the technology of the device should be submitted. General bibliographic references should be device specific and supplied in chronological order. Care must be taken to ensure that the references are timely and relevant to the current application.
7.5.5 Other Studies
Any other preclinical or clinical studies used to establish the safety and effectiveness of the device should be presented. These could include, where appropriate, prozone studies or robustness studies pertaining to the IVDD.

7.6 Additional information for Near-Patient IVDDs (if applicable)
7.6.1 Section 32(4)(k) Near-Patient IVDD Studies
Section 32 (4)(k) specifies additional information required for a near patient in vitro diagnostic device, detailed information on an investigational test conducted on the device by individuals representative of intended users, simulating expected conditions of use. Apart from laboratory evaluations of the performance of the assay, a consumer field evaluation would also be required to determine the device’s performance when used without assistance by the intended users, following instructions provided in the labelling. To conduct these studies in Canada, a request for authorization for sale for investigational testing is required, as per Part 3 of the Medical Devices Regulations.

Section 32 (4)(m) requests an introductory summary of the above information to aid in the review process.

7.7 Device Label
7.7.1 Section 32(4)(o) Labelling
Section 32 (4)(o) requests a copy of the device label. All draft labels must be supplied. Labelling includes main device labels (immediate container labels), outer package labels, package inserts, reagent labels and product brochures.

Final labelling will be required before a licence is issued. Subsequent changes to labelling materials may be accomplished through 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 and the requirements of sections 21, 22 and 23 of the Medical Devices Regulations.

7.8 Quality System Requirements
7.8.1 Section 32(4)(p) Quality System Attestation
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 must satisfy the Canadian Standards Association criteria 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. In addition to the above attestation, a copy of the quality system audit certificate is requested. This section of the Regulations will come into force 1 July 2001.
Appendix 1 - Device Specific Guidance Documents

Supplemental information is provided in a number of device class specific guidance documents. These documents are available upon request, please fax your request to:

Liaison and Information Control Officer  
Device Evaluation Division  
Medical Devices Bureau  
2934 Baseline Road, Tower B  
Address Locator: 3403A  
Ottawa, Ontario K1A 0K9

Telephone: (613) 957-1909  
Facsimile: (613) 957-1596  
Email: DED_Manager@hc-sc.gc.ca

Currently, the following documents are available. Additional documents are being prepared and this list will be updated in subsequent versions of this document.

1) Automatic Implantable Cardioverter Defibrillators  
2) Endosseous Dental Implants  
3) Breast Implants and Tissue Expanders  
4) HIV Test Kits  
5) Intraocular Lenses  
6) Implantable Cardiac Leads  
7) Implantable Cardiac Pacemakers and Programmers