



Therapeutic Products Directorate
Medical Devices Bureau
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Ottawa, Ontario
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April 8, 2004

To: All Stakeholders

RE: Pre-Market Guidance on Bare Cardiovascular Stents

Please find attached the drafted *Pre-Market Guidance on Bare Cardiovascular Stents*.

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, effective, and meet quality standards.

This guidance document sets out the Therapeutic Product Directorate's guidance for industry on the subject. It is being provided now to assist manufacturers in understanding and complying with the regulatory requirements for bare cardiovascular stents. This guidance document is to be used specifically in the preparation of new bare Cardiovascular Stent device licence applications.

Comments on this draft guidance document should be directed:

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Thank you for providing your comments

Your's sincerely,

Original Signed By:

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Director General

Attachments

DRAFT GUIDANCE FOR INDUSTRY
Pre-Market Guidance on Bare Cardiovascular
Stents

Published by authority of the
Minister of Health

Draft Date	2004/04/08
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FOREWORD

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

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

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

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

TABLE OF CONTENTS

Purpose	1
Scope	1
Definitions	2
Other Helpful Guidance Documents	2
1.0 CLASS III and IV APPLICATIONS	3
1.1 Section 32(3)(f) and 32(4)(i)	3
1.1.1 Preclinical Testing	3
1.1.2 Animal Studies	8
1.2 Clinical Information	12
1.2.1 Introduction	12
1.2.2 Clinical Investigation Objectives	13
1.2.3 Control Group Selection	14
1.2.4 Investigation Variables (including Inclusion/Exclusion criteria) ...	15
1.2.5 Outcome Variables	16
1.2.6 Data Analysis	16
1.2.7 Follow-up	16
1.2.8 Documentation	17
1.3 Process Validation Information	19
2.0 REFERENCES	19

Purpose

This guidance document is intended to assist cardiovascular stent manufacturers and sponsors in preparing a premarket device licence application for Class III or IV bare cardiovascular stents (with or without delivery systems).

Scope

This guidance document is intended to provide a device-specific premarket guidance on the preparation of a device licence application for Class III and Class IV bare cardiovascular stents, including information on core preclinical and clinical testing requirements.

This document does not provide premarket guidance on the specific requirements for a device licence application for drug-eluting (drug-coated) stents or self-expanding stents.

This guidance document does not provide premarket guidance on cardiovascular stents containing biological material. If the stent contains biological material, information on the source is required, and a Class IV application must be completed.

For devices marketed as a stent with stent delivery system, testing in addition to that described in this guidance document may be required in support of the stent delivery system. More information will be required, particularly if this component has not been licensed in Canada as a percutaneous transluminal coronary angioplasty (PTCA) catheter or has not been used in a Canadian licensed stent with stent delivery system.

For Class III and Class IV cardiovascular stents, this device-specific guidance document is to be used in conjunction with the general investigational testing guidance document entitled, *Preparation of an Application for Investigational Testing - Medical Devices V.3* and the general premarket medical device guidance document entitled *Preparation of a Premarket Review Document for Class III and Class IV Device Licence Applications*.

This document is intended to provide guidance. It represents the Department's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind Health Canada or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable regulations.

Definitions

CARDIOVASCULAR STENTS - prostheses which are implanted into diseased blood vessels to maintain luminal integrity and therefore vessel patency.

- Class III cardiovascular stents are implantable devices placed percutaneously to maintain patency in blood vessels other than those in the central cardiovascular system (e.g. trans-jugular intra hepatic porto-systemic shunt, peripheral vessel stents).
- Class IV cardiovascular stents are implantable devices placed percutaneously to maintain patency in blood vessels in the central cardiovascular system (e.g. coronary stents). Class IV cardiovascular stents include all stents containing biological material whether for peripheral or central cardiovascular system use.

CENTRAL CARDIOVASCULAR SYSTEM (as defined in the *Medical Devices Regulations*) - means the heart, pericardium, pulmonary veins, pulmonary arteries, cardiac veins, coronary arteries, common carotid arteries, cerebral arteries, brachiocephalic artery, aorta, inferior and superior vena cava, renal arteries, iliac arteries and femoral arteries. (système cardiovasculaire central)

ADDITIONAL INFORMATION - information provided by the manufacturer in response to a request from the Bureau. Additional information is requested if the Bureau has determined that insufficient information has been provided in support of the safety and effectiveness of a medical device in a licence or licence amendment application.

DEVICE IDENTIFIER - means a unique series of letters or numbers or any combination of these or a bar code that is assigned to a medical device by the manufacturer and that identifies it as different from similar devices.

DEVICE NAME - in respect of a medical device, includes any information necessary for the user to identify the device and to distinguish it from similar devices.

Other Helpful Guidance Documents

The guidance documents listed below are available on the Therapeutic Products Directorate (TPD) Website at: www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_devices_e.html

- Policy on the Use and Recognition of Standards under the Medical Devices Regulations*
- How to Complete the Application for a New Medical Device Licence*
- Guidance on the Interpretation of Section 28 to 31: Licence Application and Guidance for the Labelling of Medical Devices, Section 21 to 23 of the Medical Devices Regulations*
- Preparation of a Premarket Review Document for Class III and Class IV Device Licence Applications V.2*
- Preparation of an Application for Investigational Testing - Medical Devices V.3*

1.0 CLASS III AND IV APPLICATIONS

Applications for cardiovascular stents must comply with the general requirements for Medical Devices set out in Section 32(1) as well as the specific requirements set out in Section 32(3) for Class III stents or Section 32 (4) for Class IV stents.

1.1 Sections 32(3)(f) and 32(4)(i)

These sections request the preclinical and clinical information that the manufacturer relies on to ensure that the device meets the safety and effectiveness requirements. The relevance and the location of the information within the application or elsewhere should be documented in the introductory summary. Class III and Class IV devices require test summaries and the conclusions drawn from these studies. The Regulations specify detailed summaries for Class IV devices. It is recommended that reports be presented in a scientific format and include sections describing test objectives, methodology, results and the manufacturer's conclusions. Sufficient test data must be provided to enable an independent objective assessment of the results. The results should be stratified in a manner that indicates the range of values for the different models that the sponsor plans to market in Canada. Where appropriate, report results in a statistically meaningful format specifying the number of samples, range of values, mean, standard deviation, p-value and tolerance limits, e.g. 95% confidence limits.

1.1.1 Preclinical Testing:

Preclinical testing includes chemical analyses, physical testing, and mechanical testing, e.g. stress, fatigue, and shelf life studies. Non-human biological testing such as biocompatibility, animal and microbiological testing is also included.

Prior to testing, device samples should be subjected to worst case transport, storage and handling conditions and the maximum number of allowable sterilizations using the sterilization method to be used during production. Known failure modes (risk assessment) should be considered during test selection. Device models chosen for testing should bracket the range of model characteristics to be marketed, e.g. stent diameters and lengths. Include device models expected to have the least desirable test results for the particular characteristic or specification being examined. Test protocols should demonstrate margins of device safety considering the most demanding situations to which the device is likely to be exposed e.g. tortuous vessel pathways, calcified lesions and high blood pressure. Unless justification is provided by the manufacturer for not doing so, testing is conducted on complete sterilized stents or assemblies with stents mounted.

Biocompatibility testing should be conducted in accordance with a recognized standard (e.g. ISO 10993). Refer to the *Policy on the Use and Recognition of Standards under the Medical Devices Regulations*. If the sterilant is toxic or produces toxic residuals (e.g. Ethylene Oxide Residues), test data and methods for establishing that post-process sterilant and/or residuals are within acceptable limits must be presented.

Preclinical animal studies are undertaken in order to support the probability of device safety and effectiveness in humans. Study protocols should follow good laboratory practices guidelines. Animal study conclusions should address the device's interactions with animal fluids and tissues and the functional effectiveness of the device in the experimental animal model(s). The rationale (and limitations) of selecting particular animal models must be discussed.

For regular stents:

1. Specification Conformance Testing: The following testing should be conducted on clean and processed material samples (e.g. metal wire):
 - a. Material Analysis - Applied ASTM or other recognized standards should be reported. Alternatively, tolerance levels (usually elemental) should be determined for stent composition, including impurities, using acceptable analytical methods. In addition, scanning electron microscopy (SEM) testing should be performed on the final stent to detect any evidence of surface contamination, impurities and imperfections on the final device.
 - b. Mechanical Properties - Samples (e.g. whole devices or relevant subassemblies) should be measured for tensile strength and elongation. The requirements of any applicable American Society for Testing and Materials (ASTM) specification should be met.
 - c. Corrosion - Samples should be analyzed for corrosion. Galvanic effects are to be considered if it is likely that the stent will be implanted near stents manufactured with other materials.
2. Stent Integrity - The following testing should be conducted on finished sterilized stents after deployment with the proposed delivery system, except where noted.
 - a. Stent Free-area Percentage and Dimensional Changes - The percentage change in free or open area and decrease in length as a function of stent diameter should be determined and a graphical representation should be submitted.

- b. Stent Uniformity Testing - The uniformity of the expanded stent should be determined by quantitative documentation after expansion in a tube and should be consistent with the labelled expanded diameter.
- c. Radial (hoop) Strength - The change in stent diameter as a function of circumferential pressure should be determined. The pressure at which deformation is no longer completely reversible should be recorded.
- d. Fatigue Testing - An in-depth analysis of the stent's fatigue resistance is required to assure that the arterial/venous implant conditions to which the stent will be subjected will not result in fatigue and corrosion despite millions of cycles of stress. The following data is required:
 - (1) A finite element or other stress analysis that identifies the peak stresses in the stent when subjected to a worst-case physiological load. The amount of residual stress must be determined and accounted for when calculating safety factors. This analysis should demonstrate that fatigue failure of the stent will not occur during the implant life of the stent.
 - (2) Accelerated *in vitro* testing of approximately 10 years equivalent real time should be conducted on a statistically significant sample of stents expanded to their largest intended diameter and dynamically cycled over simulated vessel conditions. A complete description of the test protocol and sample preparation used in this study should be provided.
- e. Stent Recoil - Quantify the amount of elastic recoil (spring-back) for each sized stent and correlate this parameter to the recommended placement (sizing) procedure.
- f. Magnetic Resonance Imaging - Determine whether the stent will cause artifacts with magnetic resonance scans due to distortion of the magnetic field. Literature references may substitute for actual data with adequate justification. Refer to the U.S. FDA draft document entitled, *A Primer on Medical Device Interactions with Magnetic Resonance Imaging Systems*.
- g. Stent Expansion - Determine whether the plastic deformation experienced by the stent in going from its initial to final position could give rise to crack initiation. An examination of expanded stents, using the proposed delivery system, should be performed under an appropriate magnification. In addition, specify the smallest flaw size (length, width and depth) that can be detected by quality control

inspectors on the surface of the stent.

- h. Dimensional Verification - Measure and visually inspect the stent to document that all dimensional specifications do not deviate from the design specifications.
3. Stent Catheter System Testing: Testing is needed to demonstrate that the delivery catheter can safely and reliably deliver the stent to the intended location and that the stent is not adversely affected by the catheter. Unless justification is provided, all testing should be conducted on complete sterilized assemblies with stents mounted. Testing involving the balloon should be conducted after the device has been soaked in a 37°C saline bath.
- a. Maximum Pressure - Conduct this test on balloons/stents of each balloon and length. The test results must show statistically that with 95% confidence, 99.9% of the catheters will not experience balloon, shaft, proximal adaption or proximal/distal seal loss of integrity at or below the maximum recommended pressure (i.e. the pressure required to expand the stent to its labelled diameter).
 - b. Stent Diameter vs. Balloon Inflation Pressure - Conduct this test on balloons/stents of each diameter and plot/graph the stent diameter versus inflation pressure. This graph, or a tabular representation, should be provided in the Instructions for Use and/or the outside package Labelling.
 - c. Bond Strength - Test the bond strength at locations where adhesives or other junction bonding methods are used for bonding between parts of the catheter.
 - d. Diameter and Profile - Determine the diameter of the catheter shaft, profile of the balloons and inflated diameter of the balloons to ensure that the actual diameter matches the labelled diameters. Stent mounting is not required.
 - e. Balloon Deflatability - Show that the balloon can be completely deflated by the recommended procedure following stent expansion when it is in an environment simulating a stenosed vessel. Observe and describe any interference with balloon deflation. In addition, observe and describe any interference in withdrawing the deflated balloon from the deployed stent.

- f. Balloon Inflation and Deflation Time - Show that inflation and deflation of the balloons using the recommended procedure in the Labelling can be accomplished within a specified time.
- g. Catheter Body Maximum Pressure (if applicable) - Determine the maximum pressure that the catheter body can withstand when one of the lumens is used for power injection of contrast media.
- h. Contrast Media Flow Rate (if applicable) - Determine the contrast media flow rate through the inner lumen at or below the maximum recommended injection pressure. Stent mounting is not required.
- i. Pressure Waveform (if applicable) - Determine the natural frequency and damping ratio of the lumen recommended for pressure monitoring. Damping of the pressure waveform must be appropriate and provide accurate measurement; otherwise, the Instructions for Use must clearly state that the catheter is not intended for distal pressure monitoring. Stent mounting is not required.
- j. Tip Pulling and Torquing - Show that the force required to break the joints and/or materials in the distal end of the catheter is sufficiently large to assure the integrity of the tip during pulling, pushing or torquing manoeuvres.
- k. Stent Crimping - If the stent is not provided pre-mounted on the delivery catheter, testing must be conducted to show the functionality of all crimping devices and that the crimping procedure will not damage the stent or catheter.
- l. Crossing Profile - Determine the crossing profile of the stent/delivery system and discuss its clinical acceptability.

1.1.2 Animal Studies:

A) Testing Objectives

Cardiovascular stents are tested in animals to evaluate performance characteristics after changes in material and design during product development and to demonstrate product safety and effectiveness in support of regulatory applications for investigational testing and/or licensing. Effectiveness indicators for cardiovascular stent animal testing include stent delivery characteristics and early and long-term patency. Device safety is indicated by decreased rate of adverse events such as death, stenosis and thrombosis and the biologic reaction of the vessel to the stent, e.g. evidence of inflammation and incomplete healing. Testing objectives should always be stated in clear hypotheses.

Pharmacokinetic studies, required for drug eluting stents, and biocompatibility testing, described in ISO 10993-1, are not discussed in this section.

B) Animal Model

Medical device testing in animals rarely provides results which are entirely compatible with human risk benefit analysis requirements. Interpretation of the results is often confounded by species differences in physiology and anatomy. Young healthy animals with disease-free arteries are used in this testing as models for senior patients with atherosclerotic cardiovascular arteries and often comorbidities such as dyslipidemias and diabetes. The coronary arteries of farm swine and mini-pigs and the iliac arteries of rabbits are frequent candidates. Testing in rabbit iliac arteries rather than pig coronary arteries could lead to difficulties in interpretation of stent delivery characteristics and to failure to detect adverse events. Early and/or late thrombosis may go undetected due to collateral circulation and arrhythmias, and other cardiac complications could be missed altogether. True safety and effectiveness can only be proven in man (Schwartz et al., 2002).

C) Protocol

Protocol features such as trial duration, number of stents and number of animals implanted depend upon the animal model and outstanding safety/effectiveness issues. For example, a change in stent delivery system may require implantation of a small number of stents with little or no follow-up. Conversely, stents manufactured with novel designs or materials may require large numbers of implanted stents to rule out rare adverse events and six to twelve months of follow-up. The selection of stents should at a minimum bracket the lengths and diameters of the stent model for which investigational testing and/or licensing is being applied. The vessels selected for testing must have diameters similar to those proposed for stent placement in patients. Sponsors should be aware of the risks involved in too carefully limiting the number of animals/stents studied. The majority of stents must remain implanted for a duration commensurate with the objectives of the study, and some stents should be explanted at periodic intervals in order to completely characterize the reendothelialization process. A justification based upon the study objectives must be provided.

Animal Monitoring

The general health of the animals need to be monitored throughout the study. Monitor animal weight, body temperature, complete blood count, infections and survival. Myocardial infarction can be detected by performing electrocardiography at baseline and euthanasia. Necropsy reports should be provided for animals who fail to survive and the relationship to the device, if any, established.

Good laboratory practice guidelines should be considered in the design and implementation of animal testing. The investigator is referred to the U.S. Code of Federal Regulations, 21 CFR 58 - Good Laboratory Practice for Nonclinical Laboratory Studies. Reference the following weblink for guidance:

www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/showCFR.cfm?CFRPart=58

Institutions and accreditations of these institutions where the animal testing is carried out along with the principle investigators and their qualifications, must be documented.

D) Implantation Procedure

Describe thoroughly the implantation procedure. Record medications administered such as antiplatelet agents (e.g. ASA and Plavix), anaesthetics and antibiotics. Describe hematological, biochemical and physiological parameters monitored such as EKG, blood pressure, oxygen, activated clotting time (ACT), complete blood count (CBC) with differential, liver enzymes (ALT, AST) and creatinine (renal function). Comment on the clinical significance of similarities and differences between the medications and methods used in the animal implantation procedure and those to be used for implantation of the subject device into humans.

Provide a clear description of the pre-stenting vessel characteristics (i.e. lumen diameter versus post-stenting and follow-up lumen diameter). Document the exact specifications of the stents used (e.g. unexpanded diameter, length, expanded diameter and inflation pressure). Document the use of multiple stents at one lesion location, if this is part of the protocol.

Describe the catheterization procedure, including the target arteries, route of vascular access, and accessories such as guide wires and guiding catheters. Describe angiography and fluoroscopy procedures used to place stents. Record the balloon to artery ratio, typically about 1.0 but may exceed 1.2 in injury models. Record TIMI (thrombolysis in myocardial infarction) post implantation. Note adverse effects observed during implantation, including stent migration, embolization, balloon rupture, stent thrombosis, dissection, side branch closure and edge effects.

Evaluate the performance of the Stent/Delivery system in the implantation procedure using the following criteria:

1. Performance of Stent/Delivery System

- a. Preparation - the ease by which the device can be prepared for use.
- b. Introduction - the ability of the device to be loaded onto the guidewire or into a guiding catheter.
- c. Pushability - the ability of the system to transmit sufficient, even force proximally allowing for equal and smooth movement distally.
- d. Trackability - the ability of the system to advance distally over a guidewire, following the guidewire tip, along the path of the vessel, including in narrow, tortuous vessels.
- e. Flexibility - the ability of the stent/delivery system to bend in order to accommodate a turn or angle it is required to negotiate and the flexibility of the stent to conform with the vessel after the stent is deployed.
- f. Radiopacity - the visibility of the stent and delivery system under fluoroscopy.
- g. Inspection - a post-evaluation inspection to document any evidence of damage to the delivery system.
- h. Accessories - a description of the performance of all accessories recommended in the labelling such as guiding catheters, hemostasis valves, sheaths, etc.
- i. Investigator Preference - a complete summary of comments made by investigators regarding stent performance.

2. Angiography

Angiography is performed to determine flow characteristics of the stented vessel immediately following stent deployment and immediately prior to explantation. The angiographic presence of acute thrombus is noted and rated on a scale of 1 to 5. The baseline diameter is measured at implantation and later minimal lumen diameter percent stenosis and TIMI flow are estimated at follow-up.

Acute complications detected with angiography may include stent thrombosis, dissection, intraluminal filling defects, stent migration, balloon rupture, or major side branch closures. Late complications include edge effects and aneurysmal dilations.

E) Pathology/Histology Studies

The protocol should include a provision for explantation of stents and examination of the healing process post implantation at pre-determined times throughout the study. Specimen harvesting procedures and methods of location of stents and assessment of placement (e.g. X-ray), must be documented. Describe procedures for tissue processing, dehydration, embedding, sectioning, staining, methods of viewing (e.g. electron microscopy, light microscopy etc.) and the analytical methods used to process the results. Blinding investigators with respect to study specimen origin and details helps to reduce bias in the results of pathological examinations and interpretation of slides.

a. Pathology

For pathology studies, tissue specimens should be collected at the following locations:

- in the vicinity of the stent,
- in the stented vessel wall immediately in contact with the stent,
- in the vessel wall segments proximal and distal to the stent,
- in the myocardial and epicardial tissue immediately beneath or surrounding the stented vessels; and
- in the myocardium supplied blood passing through the stented coronary arteries and a range of peripheral tissues (e.g. lung, spleen, kidney, liver, lymph, myocardium and carotid artery).

The thoracic cavity of pigs or the abdominal cavity/retroperitoneum of rabbits should be examined for effusion, inflammation, infection, perforation or other problems.

Provide a pathology report including gross findings and microscopic studies involving both conventional and scanning electron microscopic techniques, the presence of infarct, fibrosis, thromboembolus and inflammation.

b. Histology

It is recommended that sections be taken from the entire stent (distal, medial and proximal areas) as well as areas immediately distal and proximal to each stent sampled. Conduct a **detailed** examination of explanted stents and document any occurrences of intravascular trauma induced by stent placement in the vessel of interest. Examine sections containing the stent for presence and type of inflammation, fibrin deposition, thrombus, neointimal formation, endothelial coverage, endothelial maturity and vessel wall injury. Look for strut malapposition and examine the condition of external lamellae for vessel damage such as medial fractures, aneurysm formation, late thrombosis and filling defects. Assess the

vessel wall reaction response to the stent (e.g. presence and location of histiolympocytic infiltrates, macrophages, multinucleated giant cells, granulomatous cells, etc.). Evaluate the expanded vessel for outer diameter enlargement, lumen narrowing, filling defects, patency of side branches, protrusions of the stent into the vessel lumen and medial thinning. Report injury, inflammation, fibrin and other histopathological scores determined for arteries and vessel wall layers (Schwartz et al., 2002).

c. **Histomorphometric Analysis**

Measure the cross-sectional areas (e.g. external elastic lamina [EEL] and internal elastic lamina [IEL]), for each section with digital morphometry. Sample the distal, medial and proximal areas of each stent. Post stent implantation stenosis is evaluated on the basis of differences in intimal area and thickness and lumen area and percent stenosis. Measure the neointimal thickness at each follow-up period throughout the stented length, including at stent/artery junctures.

F) Report

The testing protocol(s), test results and study conclusions must be fully described in order that an independent evaluation of the conclusions can be made. All complications occurring during the procedure and follow-up must be provided.

1.2 Clinical Information

1.2.1 Introduction

In addition to clinical evidence derived from investigational trials, the Bureau considers clinical information from other sources including the following:

Peer-reviewed scientific literature: This includes relevant publications derived from studies conducted in Canada or elsewhere.

Marketing History: The summary should indicate special access requests, a list of countries where the device is currently being sold, the total number of units sold in those countries, reported problems with the device, and details of any recalls. A critical review of published reports and their clinical experience can be helpful in determining complication rates and device failures in clinical uses. It is recognized, however, that reported adverse event rates may underestimate actual rates by one to two orders of magnitude and that there may be large discrepancies between numbers of devices sold and actually implanted.

Registry Data: Registry trials tend to be less controlled than formal clinical trials but can be a source of useful information.

User testimonials: Testimonials are reports in which users describe their experiences with the device.

The documented evidence submitted should include, where applicable, 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. A summary of clinical data stratified according to stent length and diameter is required.

The material in this section describes device specific information requirements in support of investigational testing applications for cardiovascular stents in Canada and is intended to supplement the general information in the following documents:

- *Preparation of an Application for Investigational Testing - Medical Devices V.3;*
- *Guidance for the Submission of Research and Marketing Applications for Interventional Cardiology Devices: PTCA Catheters, Atherectomy Catheters, Lasers, Intravascular Stents (FDA-DCRND-1995).*

1.2.2 Clinical Investigation Objectives

Clinical investigations are intended to resolve clearly defined questions concerning (1) the safety and effectiveness of the device that cannot be satisfactorily resolved using other methods such as bench and animal testing; (2) the indications for use of the device (including conditions for use prescribed, recommended or suggested in the labelling or advertising, or other conditions of use); (3) the probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and (4) the reliability of the device.

Statements of the study purpose should address the generic and/or proprietary name of the device, the objectives of the study, the indications for use (disease to be treated), the treatment schedule, the subjects to be enrolled and the parameters to be measured. Study objectives are focused and clearly stated. Consistent with a research question to be answered, each study objective should be stated statistically as a null or alternative hypothesis or in terms of the claims that the firm seeks to demonstrate and include in the labelling. Since the study must be capable of answering the objective and must be scientifically and medically relevant, it is not sufficient to state that the objective is to determine the device's safety and effectiveness. The specific question will depend upon the criteria for safety and effectiveness, i.e.:

Superiority: Is the investigational device treatment better than other standard treatments;

Equivalence: Is it similar in effectiveness (or at least no worse than a predetermined specific difference) to the standard treatment for the medical device or condition being treated, or;

Non-Inferiority: The protocol is designed to demonstrate that the safety and effectiveness of a device are at least as good as an alternative licensed device or accepted medical practice.

It is recommended that device comparison trials involving stents manufactured with different designs and/or materials consider superiority investigational testing. Stents cited as predicates or used as controls (manufactured by the device sponsor or another manufacturer) must be licensed and have the same specifications as the device models licensed for use in Canada. If information stored in another manufacturer's device files is cited, the device owner's permission is required to access this information.

Broadly stated objectives can lead to the collection of questionable data and should be avoided. More than one objective can be studied during the course of a clinical trial if the objectives are appropriate, if they reflect the goals to be achieved, and if they are similar. All indications and contraindications for use of the device must be consistent with the study objectives and precisely stated. The duration of the study (the followup period typically 6 to 12 months for stents), the number of patients enrolled in the study, and the number of stents to be implanted are required. Statistical justification is required for selection of the number of devices or patients enrolled in the study.

Although standard stents and stent delivery systems are not likely to require feasibility or phased trials, feasibility (pilot or limited) studies may be required to confirm device design and operating specifications, to refine the indications for use and/or hypotheses to be studied or to provide physicians an opportunity to gain experience with the use of the device before initiation of a multicenter trial. These investigations are not separately dealt with in the *Medical Devices Regulations* or guidance documents. Due to small numbers of patients and narrow objectives, the acquisition of sufficient clinical data for licensing purposes may be beyond the scope of these studies. Well defined objectives and statistical justification of numbers of patients are required as with any clinical trial. Consistent well-designed protocols are required, particularly if expansion into a larger multicenter trial is anticipated.

1.2.3 Control Group Selection

The control group should be chosen to be consistent with the study objective(s), medical practice, therapy and ethical considerations for assignment of patients to treatment and control groups. To reduce all potential sources of bias, a randomized concurrent control is recommended. The selection, either randomized concurrent or historical, must be described and justified.

A non-randomized study format could be considered for a stent system that does not contain any significant adjunctive feature that could impact on the safety and effectiveness of standard therapy. If a randomized trial is not included in the study design, it is incumbent upon the sponsor

to provide evidence for why a randomized study design is not appropriate and select an appropriate contemporary control or reference group to be used in the study.

Historical controls are useful when the disease is predictable and consistent, and the influences of baseline characteristics are minimal compared to the treatment effect (i.e. the baseline is well defined and predictable about the course of the disease). The selection of an historical control from published literature, medical records or other databases and registries should ensure consistent use of critical study variables between groups, including study objectives, lesion morphology, inclusion/exclusion criteria, indications for use, baseline characteristics, standard evaluations of outcome variables, and identical definitions of outcome. Furthermore, the historical control group would need to be contemporary (as nearly as possible) with the investigation control. Otherwise, bias would effect the comparison due to differences in assessment methods, definitions of success and other variables. Current patient populations have more multivessel disease and lesions of different characteristics and locations. Technology has improved and patients are being treated adjunctively with other procedures (e.g. improved antiplatelet therapies).

1.2.4 *Investigation Variables (Including Inclusion/Exclusion Criteria)*

Clinical baseline variables need to be assessed in order to properly select patients for the interventional procedure and to ensure comparability of the patients within the cohort and control group. These variables must be precisely identified and clinically relevant to the specific device and investigation study objectives. Examples are provided below:

A) Baseline variables: Patient demographics (age, sex, etc.), cardiovascular artery disease risk factors, medications, disease (primary and secondary conditions), cardiovascular disease signs and symptoms (e.g. functional stress tests), status of angina and angina class according to the Canadian Cardiovascular Society (CCS) or New York Heart Association (NYHA).

B) Cardiovascular Disease: Patient history and type of prior cardiovascular disease (e.g. myocardial infarction); history and classification of prior interventional treatments for cardiovascular disease and left ventricular ejection fraction.

C) Lesion Characteristics: Single or multivessel, lesion length and location, percent stenosis, absolute dimensions (in mm), type of vessel involved (i.e. native coronary saphenous graft, internal mammary artery graft), lesion morphology (i.e. focal, tubular or diffuse, calcific or non-calcific, eccentric or concentric, thrombus, ulceration), and a description of the lesion history (i.e. *de novo* or number of prior restenoses etc.).

1.2.5 *Outcome Variables*

Clinically relevant endpoints (i.e. outcome variables, and the appropriate times to measure them)

need to be identified. These should include clinically relevant assessments for vessel patency and restenosis (e.g. percent stenosis or TIMI flow classification (consult ACC/AHA Guidance)).

Restenosis is the specific late-term failure of an acutely successful interventional cardiology procedure. Restenosis is the narrowing of a successfully dilated vessel segment resulting in regionally under-perfused myocardium. Although restenosis is a continuous process, current definitions treat it as a dichotomous event, i.e. it either does or does not occur. To standardize comparisons, the manufacturer is encouraged to use the Emory definition of restenosis (i.e. restenosis $\geq 50\%$ reduction in lesion diameter when compared to the reference luminal diameter).

Definitions and methods of analysis for each potential complication (major or minor) must be provided. Major complications are assessed and reported regardless of whether the complication is related to the investigational device, another device or the procedure itself. Major complications include myocardial infarction (MI), emergency coronary artery bypass graft (CABG), surgery, emergent repeat in hospital intervention or bail out stenting and death. The data should be presented both on a per patient and a per complication basis.

1.2.6 Data Analysis

Statistical methods for the analysis of data generated during the study need to be described. Sponsors are encouraged to consult the services of a statistician in order to identify the best approach for the particular experimental design. The use of 95% confidence intervals, rather than point estimates, to summarize data (e.g. late restenosis rates) is strongly encouraged.

The number of subjects to be enrolled in a clinical trial should be based on statistical calculations at a pre-defined level of statistical significance consistent with the study objectives and to ensure that an adequate number of patients will complete the protocol. The statistical procedure and calculation formula used to determine the number of patients (both treatment and control) needed to meet the objective(s) of the study are required. The variables approximated in the calculation should be justified in a discussion including relevant background information from similar trials.

Kaplan-Meier survival analysis or other appropriate statistical methods for stent-related adverse events should be provided.

1.2.7 Follow-up

Instructions to the investigators must clearly state that data must be collected and recorded on the case report forms (CRF's) immediately after the procedure and at predetermined intervals postoperatively. Patient followup after hospital discharge typically consists of repeat angiography at 6 months for all patients of the initially successful population supporting the indication(s) for use. Results from recent randomized clinical trials indicate that followup at 1 year may be necessary to

fully evaluate new interventional cardiology devices and certain applications (e.g. peripheral arteries). Sponsors are advised to continue following patients past the 6-month interval in the event that 1 year followup data is required. Intravascular Ultrasound (IVUS) can be useful for trials involving coronary stents but it is recognized that this technology is not universally available.

Any patients not evaluated by angiography at 6 months must be evaluated using other acceptable methods, such as stress tests, need for subsequent target vessel revascularization, and clinical history. If non-invasive evaluation is chosen, the sponsor must justify its use and relevance in the assessment of vessel patency. Problems associated with non-invasive followup tend to make this methodology unreliable as a sole determinant of restenosis in treated vessels.

In addition to procedures used to ensure accountability of all patients that have been enrolled in the study and at all followup intervals, procedures for dealing with any patient who discontinues participation in the study need to be described. Statements such as “lost-to-followup” are not sufficient and every effort must be made to account for all such patients. Patients should be followed for a predetermined period of time, including pre-hospital discharge, 6 weeks, 6 months, and yearly thereafter (until the device receives marketing approval) or until an event such as repeat intervention (e.g. CABG or death occurs). An angiographic followup rate of less than 80% is not recommended due to the selection bias introduced by not accounting for the confounding influences of the patients lost to continued monitoring. In all cases where patients do not receive angiographic followup, the reason for failure to obtain it should be well documented. Analyses should demonstrate that there was no investigator selection bias adversely affecting angiographic followup.

1.2.8 Documentation

For required documentation, the manufacturer is encouraged to consult the following guidance document: *Application for Investigational Testing - Medical Devices V.3*.

A) Case Report Form: Examples of all patient report forms (e.g. baseline or pre-procedure, operative, and all followup evaluations) which are consistent with the study protocol and the patient informed consent form are required. These forms must be completed by each investigator for each patient entered in the study and at each followup evaluation.

B) Baseline Forms: Baseline and or pre-procedure forms should include the dates of evaluation, patient identification, pre-treatment symptoms, CCS functional class, results of tests performed on the patient and all previous therapies. Space must be provided to record all baseline assessments in an objective and definitive manner. These types of assessments will facilitate comparisons to postprocedure results.

C) Operative Reports: The operative report forms must include adequate space to record information on device performance and the lesion being treated. The report form should include, for

example, the model, diameter and length of each stent and each guidewire used during the procedure. For stents mounted on balloons, balloon inflation pressure, balloon diameter, balloon inflation duration, and the number of inflation cycles need to be recorded. Records of device failures and the total time the patient undergoes fluoroscopy should be obtained. The form must also provide space to record information about the lesion being treated, including the location and characteristics of the lesion(s), the degree of stenosis (lumen diameter and percent stenosis), success or failure of the procedure according to predetermined criteria, complications, medications required, and any other pertinent data. In addition, all problems encountered with each of the devices used and a description of all subsequent therapies must be recorded in order to appropriately assess the device's association to the cause of a complication. Finally, information should be recorded about the intent to treat specific lesions and actual lesions that were actually attempted and completed.

D) Postprocedure Report: This form must provide adequate space to record measurements of the study variables, as predetermined in the study protocol, including restenosis assessment based on objective measurements (e.g. caliper measurement, computer assisted or digital subtraction angiography) and on the use of blinded core laboratory analysis, angina status based on CCS classification scores, exercise functional test and electrocardiography.

E) Institutions and Investigators: Institutional Review Board (IRB) approval is required for enrolment into the studies. Qualified investigators selected for the study must sign an undertaking to follow the study protocol and provide curriculum vitae to verify personal qualifications for participating in the study. Certification of the operator's ability to use the device through sponsor training may be required. Total numbers of institutions and investigators are based upon the number of patients required to test the statistical hypotheses implicitly or explicitly stated in the objectives of the study. Estimates are made assuming equal distributions of patients among all sites (treatment and control) and on the anticipated accrual rate per institution.

F) Previous Studies (Subsection 81(f)(i)): The results of any previous research, testing and studies conducted with the device must be provided. These results provide a background to the investigational testing authorization application.

G) Alternate Treatments (Subsection 81(f)(ii)): A description of currently available alternate treatments should be presented. This may include the methods currently used to diagnose or treat the medical conditions that are relevant to the current investigational testing authorization request.

H) Precautions (Subsection 81(f)(iii)): All known information respecting any cautions, warnings, contraindications and possible adverse effects associated with the use of the device must be presented.

1.3 Process Validation Information

Refer to the guidance document entitled *Preparation of a Premarket Review Document for Class*

III and Class IV Device Licence Applications V.2 for details on Process Validation Studies. The following information on Packaging and Shelf life validation is not included in the general guidance above and should be taken into consideration:

Packaging validation must include a description of the device packaging and the shipping container. Indicate any tests performed to demonstrate that the device is protected from alteration or damage during storage and shipping. Provide protocol and reports for the testing procedures used to indicate whether the packaging materials have been challenged to ensure that they are microbially retentive, and that the seal(s) maintain sterility.

Shelf life validation for cardiovascular stents must be provided. Determination of the shelf life involves assessing the barrier properties of the packaging to assure sterility. In addition, stents (as well as the delivery systems, if applicable) must be tested to assure that storage and shipping conditions do not alter the safety and effectiveness of the device. Justifiable accelerated shelf life validation results can be used at the time of submitting the application however, the manufacturer should simultaneously carry out real time shelf life validation tests and provide data to the Medical Devices Bureau when available.

2.0 REFERENCES

1. Schwartz et al. (2002) Drug-eluting stents in preclinical studies. Recommended evaluation from a consensus group. *Circulation*. 106:1867-1873.
2. FDA-CDRH (1995) Guidance for the submission of research and marketing applications for interventional cardiology devices: PTCA catheters, atherectomy catheters, lasers and interventional stents. Draft copy available at FDA web site.