Health Canada Santé Canada

July 25, 2011

Notice

Our file number: 11-113340-236

Re: Guidance Document: Medical Device Applications for Implantable Cardiac Leads

Health Canada is pleased to announce the release of the final version of the *Guidance Document: Medical Device Applications for Implantable Cardiac Leads.* A draft version of this guidance was first released for consultation in 2009. Comments from stakeholders have been considered in producing this final version.

The guidance is intended to assist manufacturers in preparing device applications for investigational testing, a medical device licence or a licence amendment for implantable cardiac leads filed pursuant to the Canadian *Medical Devices Regulations*. It supplements other guidance documents on general application processes and procedures for Class IV and other medical devices.

The implementation date is October 25, 2011. Once implemented, Health Canada will expect manufacturers to meet the specifications listed in this guidance document.

For more information on this guidance document, please contact:

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Canada

Health Canada Santé Canada

GUIDANCE DOCUMENT

Medical Device Applications for Implantable Cardiac Leads

Published by authority of the
Minister of Health

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Health Products and Food Branch

Canada

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

Également disponible en français sous le titre : **Ligne directrice - Demandes relatives aux sondes cardiaques implantables**

FOREWORD

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

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

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

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

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1.0 INTRODUCTION

1.1 Policy Objective

To clarify the information necessary to satisfy the requirements of the Canadian *Medical Devices Regulations* (Regulations) as they pertain to an application for an investigational testing authorization, a device licence or a licence amendment for implantable cardiac leads in order to facilitate access to these therapeutic products.

1.2 Scope and Application

This guidance document applies to applications for an investigational testing authorization, a device licence or a licence amendment and is intended to be used by manufacturers of permanent endocardial (transvenous) leads with active or passive fixation mechanisms (hereafter referred to as implantable cardiac leads). These are Class IV devices that are usually implanted in the right atrium, right ventricle or cardiac veins (left ventricle) for detection of heart signals and to deliver pacing and defibrillation therapy. The document is not intended to provide guidance for epicardial (myocardial) leads, temporary leads or external (electrocardiography or defibrillator) leads.

The document provides specific guidance for bench testing, biocompatibility, biostability, animal and clinical studies of cardiac leads. It is intended to supplement the guidance available on general application processes and procedures for Class IV and other medical devices (see Bibliography).

Where there are discrepancies between the Regulations and the standards referenced herein, the Regulations apply.

1.3 Background

A number of international standards were consulted in the development of this document and are useful references for manufacturers who are preparing applications for an investigational testing authorization, a device licence, or a licence amendment for implantable cardiac leads. Specifically, manufacturers are referred to ISO 14708-1 and ISO 14708-2 for general guidance on labelling and validation of testing in support of packaging, recommended storage conditions and resistance to damage during transport and handling.

As a guidance, this document represents Health Canada’s current thinking on the information needed to support an application for an investigational testing authorization, a device licence, or a licence amendment for cardiac leads. An alternative approach may be used if such approach satisfies the requirements of the Regulations, and should be discussed with the Medical Devices Bureau prior to filing an application.

1.4 Definitions

Central Cardiovascular System- 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.

Pulse Generator - means an implantable pacemaker, defibrillator or cardioverter/defibrillator. The pulse generator consists of a battery and electronic circuitry controlled by firmware. Particular models in combination with leads can sense the electrical and/or mechanical activity of the heart and delivery therapy in the form of electrical pacing pulses or defibrillation shocks.

Pulse Generator System - consists of the pulse generator, the lead or leads that electrically connect to the pulse generator and the interface between the lead/pulse generator combination and the patient. The system senses heart electrical activity and delivers therapy in the form of low energy pulses or higher energy shocks.

Implantable Cardiac Lead - a device consisting of a lead body containing insulated conductors, electrodes and connectors which carry electrical signals between the pulse generator and electrodes implanted in the heart for the treatment of arrhythmias.

2.0 GUIDANCE FOR IMPLEMENTATION

The following information is to be provided in an application for an investigational testing authorization, a device licence, or a licence amendment for implantable cardiac leads.

2.1 Device Description

A general description of the implantable cardiac lead should be provided, including its principles of operation and the materials used in its manufacture, construction and packaging. Include illustrations of the device and its internal components in the form of diagrams, photographs or drawings. Design specifications which distinguish one model from another, electrode configurations (pace/sense and defibrillator), cardiac attachment mechanisms and descriptions of the geometry, dimensions and surface areas of the electrodes should also be included.

2.2 Preclinical Testing

The following sections outline recommended tests to be performed for a new implantable cardiac lead. It is possible that additional testing may be required based on the specific nature of the lead. It is also possible that some testing will not be necessary. It is the responsibility of the manufacturer to determine validation tests appropriate for each device and to formulate a comprehensive testing strategy to ensure that safety and effectiveness objectives are met.

Bench testing should verify that the lead meets acceptable electrical and mechanical specifications and that the performance and integrity of the lead remains acceptable after storage, handling, transport, repeated sterilization and shelf life aging.

i) Biological Effects

Biocompatibility testing should be conducted in accordance with the standard, ISO 10993 "Biological Evaluation of Medical Devices." ISO 10993 is an overall guidance document for the selection of tests enabling evaluation of biological responses relevant to the safety of medical devices and materials (also refer to "Preparation of a Premarket Review Document for Class III and Class IV Device Licence Applications").

Validation testing is required to ensure that parts of the lead in contact with body fluids do not release unacceptable amounts of particulate matter. It is recommended that testing be carried out according to Section 14.2, ISO 14708-1.

ii) Bench Testing

Bench testing should be conducted using acceptable protocols and statistically valid numbers of sterilized components, assemblies, and/or complete devices Test procedures can be documented in the test summaries or cited if carried out according to international standards recognized by Health Canada (see "Recognition and Use of Standards under the *Medical Devices Regulations*"). A rationale for the use of internal protocols and/or other standards should be provided. Protocols should include objectives, the scope of the testing in terms of the range of products to be marketed, test procedures, rationales for test designs, test requirements/acceptance criteria, results and a description of the analyses used to draw conclusions. The testing results should be reported in a statistically meaningful format [for example (e.g.) sample selection, range of values, mean, standard deviation, 95% confidence limits and statistical p-values for comparative studies, etc.]. Test failures and deviations from protocols should be investigated and documented along with corrective activities taken, such as manufacturing changes and quality control measures (where applicable), to assure product safety and effectiveness.

Animal and/or clinical data may be required in addition to bench testing for device licensing where there are reductions in lead diameter, where novel device features or functions are added, or where new indications are introduced, especially when these changes impact the clinical performance of the device.

A) Environmental and Sterilization Testing

Sterilization: Validation testing should be provided that supports the adoption of device sterilization methods that conform with recognized ISO standards.

Conditioning: If it is possible that test outcomes will be affected by sterilization and physiologic conditions, test leads should be conditioned prior to testing by exposure to the maximum number of allowable sterilization cycles and to simulated physiological conditions, e.g. prolonged incubation in a saline bath (9 grams of sodium chloride (NaCl) per litre) at body temperature (37°C).

Storage/Transportation Testing of Lead and Packaging: The lead and lead packaging should be subjected to simulated shipping and storage conditions (thermal challenge, drop testing, stacking in vehicles, loose load vibration and vehicle vibration), and tested for sterility and retention of electrical and mechanical specifications. If damage caused by freezing, for example, is not immediately apparent, then special temperature indicators may be required in the packaging.

Shelf Life of Electrical and Mechanical Specifications: A shelf life study demonstrating retention of the device's electrical and mechanical specifications and the device packaging specifications over the course of the shelf life claimed by the manufacturer on device labels should be provided. The use of accelerated shelf life study techniques may be considered sufficient for common materials and packaging.

B) Lead Connector Testing

Leads are connected to pulse generators or defibrillators by lead connectors or adaptors. It is recommended that connectors intended to join leads to implantable pulse generators or defibrillators comply with Health Canada's currently recognized standards ISO 5841-3 (IS-1 Connectors), ISO 11318 (DF-1 Connectors), and ISO 27186 (IS-4 and DF-4 Connectors). Equivalent validation testing is required in support of adaptors. Testing should encompass requirements for insertion and withdrawal forces, electrical isolation, current carrying capacity of defibrillator lead connectors and deformation due to set screws.

C) Electrical Testing

Finished product samples or appropriate assemblies should be selected for testing. It is recommended that specimens be preconditioned by subjecting them to conditions simulating the physiological environment (e.g., by soaking in a preconditioning saline bath at 37°C for 10 days).

Insulation Integrity and Tensile Force Test: Insulation integrity and tensile force testing verifies that the leads are capable of withstanding tensile forces occurring after implantation, without fracture of any conductors or joints or breaching of any functional electrical insulation. Testing should be carried out in accordance with the methods and test flex fixtures described and illustrated in Section 23.3, ISO 14708-2.

Electrical Continuity: The electrical continuity of each conduction path should be verified by determining that the DC resistance meets design specifications.

Magnetic resonance image (MRI) and Electromagnetic Interference (EMI) Compatibility: Where claims are made regarding MRI or EMI compatibility or conditional use (e.g., with MRI or diathermy), this should be specified in the labelling and test data should be provided to support these claims.

Lead Electrical Characteristics: Validation testing should be provided to demonstrate that values for the lead conductor resistance, pacing impedance and sensing impedance, measured in accordance with the methods described in Section 6.2 of ISO 14708-2, are within the ranges of values stated by the manufacturer in the documentation accompanying the lead.

Polarization Characterization Test: Where claims are made regarding lead polarization, data from bench testing should be provided to support these claims. Where lead tip design incorporates a novel design feature (such as a new surface coating), data should be provided that compare polarization characteristics to licensed models. Testing should use fully assembled leads for a range of pulse scenarios (varying amplitudes and durations).

D) Mechanical Testing

Dimensional Testing: The dimensional characteristics of the sterilized final product should meet the manufacturer's product dimensional specifications (including overall shape where this is the primary means of fixation).

Composite Lead Tensile Strength: The manufacturer should verify that the overall tensile strength of the completed lead meets specifications (lower 95% confidence bound). Although it is recognized that distal components may require less tensile strength than proximal components, a five Newton load (5 N) is often used as a minimum benchmark for acceptability. Leads should be soaked in saline at 37°C for 10 days prior to testing to reproduce any influence that body fluids might have on the lead joints and materials after implantation. For more complex leads with multiple connectors (e.g. a defibrillator lead with a trifurcation boot) it may be necessary to subject distal and proximal components of the lead to separate pull tests to validate the strength of each bond, joint, etc, in the lead. Acceptance may be based upon the absence of separation and breakage in crimp and weld joints which can be verified by visual examination and mechanical and electrical testing. The lead should meet specifications and should not exhibit permanent elongation greater than 5%.

Torsional Strength Test: The manufacturer should provide test data demonstrating that an appropriate number of turns or magnitude of torque in both clockwise and counterclockwise directions with tip fixed can be applied to the lead without inducing any mechanical or electrical failure. The test data should describe the acceptance criteria and provide clinical justification for the criteria used.

Fatigue Strength and Flex Life Test of Conductor and Conductor-Connector Assembly: The fatigue test validates the lead's ability to withstand post-implantation flexural stresses without conductor fracture. Test procedures are designed to evaluate unique uniform flexible lead segments and the lead segments joined to the connectors. Prior to testing, the leads or lead components are preconditioned as fully assembled and shipped product. Testing should be carried out using the methods and test flex fixtures described and illustrated in Section 23.5, ISO 14708-2.

Note that the accelerated tests referenced above are designed to simulate conductor fatigue and not insulation fatigue. *In vivo* testing may be required to support the stability of new insulation materials.

Note that the fatigue testing referenced above may not sufficiently represent worst-case fatigue scenarios. Fatigue testing that approximates flexural stresses on lead segments at critical anatomic zones (e.g. pocket, subclavian, lead tip, etc) during implantation and 10-year simulated life (e.g., 400 million cycles) may be required for new leads with little to no clinical history or leads with reduced diameters, new functions, or new indications.

Corrosion Resistance: The manufacturer should demonstrate that corrosion resistance of conductors and electrode materials meet device specifications. There should also be evidence provided that confirms adequate resistance to crevice and pitting corrosion for lead connector contacts. A rationale for the test method used should be provided. Validation should also address concerns with regard to corrosion caused by current leakage and current pulsing. It is recognized that sustained (long-term) direct currents from implanted electrodes may cause electrode corrosion.

Leak Test and Insulation Integrity (Pressure) Test: For leads that are sealed at the distal end, the manufacturer should verify that the lead is leak-proof after conditioning the lead by immersion in saline at 37°C under physiological pressure for a minimum period of 10 days. Where some leakage is permitted, testing should demonstrate that device function and accessory compatibility (such as use of guidewire or stylet in the lumen) is not compromised. A rationale for the test method selected and test acceptance criteria should be provided.

Lead Tip Pressure and Stiffness Test: Data should be provided to demonstrate that the lead tip pressure against the heart or vessel walls is within acceptable clinical limits. The maximum pressure that the lead tip can exert should be determined.

Lead Deliverability: The deliverability of the lead should be verified through simulation testing using representative anatomic models. Device deliverability may be sufficiently demonstrated through animal studies.

Accessory Compatibility Test: Test data should be provided to ensure that the amount of force required to insert and withdraw stylets and/or guidewires that aid in lead placement meets the manufacturer's specifications. Additionally, a stylet should not damage the lead body after multiple insertions simulations, when using a worst-case lead configuration. It is recommended that the manufacturer also verify that the lead passes through its introducer without bond delamination or insulation damage.

Anchoring (Suture) Sleeve Performance Test: Ensure that the anchoring sleeves, provided premounted or as accessories, securely attach the lead when used according to the instructions for use. Sleeves should move freely on the lead body until secured, should provide adequate retention when secured, and should not damage the lead after securing the lead to tissue.

Devices With Active Fixation Design: Test data should be provided to demonstrate that the active fixation feature can be extended and retracted an adequate number of times when exposed to anticipated clinical usage. The number of revolutions required to extend and retract a helix should be tested to ensure it meets the design specifications. The manufacturer should examine the response of the system to over-torquing (e.g. rotating two to three times the number of terminal pin rotations). The integrity of the helix seal should also be validated.

E) Drug Eluting Leads

A drug eluting component may be placed at the distal tip of the lead or on an electrode to reduce post-implantation local inflammatory reactions in order to reduce peak pacing thresholds and increase pulse generator battery life. The following information should be provided for drug eluting leads:

Drug Identification and Quantification: Identify the drug substances and provide the brand or trade names of their corresponding drug products, and Drug Identification Numbers (DIN). Alternatively, provide the name and address of the drug substance supplier (DMF number) and drug product manufacturer, as well as an attestation that the drug substance complies with a Schedule B pharmacopeial standard or monograph. Provide supporting data indicating the maximum quantity of the active ingredient that could be provided with the lead.

***In Vitro* Elution Test:** Distal subassemblies containing the drug eluting component should be immersed in an appropriate physiologic, or non-physiologic, solution and analyzed at periodic intervals. The amount of drug eluted over time should be quantified and reported.

Shelf Life Test/Drug Stability: Using aged leads, the manufacturer should verify that the drug composition and quantity will remain stable over the device's intended shelf life.

Drug Matrix Swelling: Drug matrix and housing materials should be tested for the degree of swelling over time. The housing material, if different from the insulation material, should be examined for biocompatibility and evidence of degradation.

NOTE: Where new drugs that do not have substantial past clinical experience are introduced into a cardiac lead, additional requirements may apply. In this case, please contact the Medical Devices Bureau of TPD for clarification on the applicable requirements.

iii) Animal Studies

Preclinical animal studies, performed using Good Laboratory Practices, are recommended to provide supporting evidence of the safety and effectiveness of the implantable lead in humans. These studies are intended to verify the handling characteristics, structural integrity, electrical performance (pacing threshold, sensing threshold, and/or defibrillation threshold), mechanical performance and biocompatibility and biostability of the fully assembled lead. Sufficient numbers of leads should be implanted into animals to draw clear conclusions. Electrical data should confirm satisfactory lead position, attachment and performance. Any specific testing required to verify novel device features should also be performed. Device failures that are detected during testing should be fully discussed. The discussion should include corrective activities.

Although the canine model is frequently used to evaluate pacemaker leads, the choice of animal models is the responsibility of the manufacturer. The appropriateness of animal models chosen should be explained and justified. The lead should be studied at implantation and at appropriate time intervals therafter. Leads with new insulation materials or new designs may require follow-up periods of six months or longer. The following validation testing is recommended:

Lead Handling Characterization: The manufacturer should report lead handling characteristics, procedural success and user observations with regard to the implantation procedure in animals.

Sensing Performance: The P-Wave amplitudes for atrial electrodes and R-Wave amplitudes for ventricular leads should be measured following implant and at appropriate intervals. The manufacturer should report pulse generator settings for sensing thresholds. The signal obtained with the lead should not exhibit under- or over-sensing and the signal should be sufficiently stable over prolonged periods of time.

Pacing Lead Impedances: Pacing lead impedances should be measured.

Pacing Performance: Pacing capture (stimulation) thresholds represent the smallest electrical stimulus required to consistently produce cardiac depolarization. It is recommended that threshold values for atrial leads and ventricular leads should be determined at implantation and at appropriate intervals following implantation.

Defibrillation Performance: The defibrillation threshold in joules [J] and impedance in ohms should be measured if the device is designed for cardioversion or defibrillation. The defibrillation threshold (DFT) is the lowest energy value resulting in successful defibrillation. For ventricular leads, this is usually carried out after VF induction using a step-down method starting with a high energy shock, e.g. 30 J, and decreasing by increments, e.g. 5 J, until defibrillation failure.

The testing should be repeated for each shock configuration. Where all possible shock configurations are not assessed, provide a justification as to why no additional testing is required.

Attachment Stability: Lead structural integrity and positional stability (resistance to dislodgement) and handling should be assessed by radiography at the time of implantation and in cases of presumptive lead dislodgement. Testing should be performed to ensure that lead functions (sensing, pacing, etc.) and positional stability are not affected by high voltage defibrillation shocks. If a novel fixation feature is present, evidence should be provided that demonstrates that lead extraction is possible when required (e.g., for histology at 60-90 days after implantation).

Biostability: Long-term studies may be required to assess the durability of new insulation and other materials. Leads should be excised and examined for biostability and structural integrity indicators including insulation degradation, bond failure and abrasion. Analytical techniques such as scanning electron microscopy (SEM), infrared spectroscopy and stress-strain analysis should be used to document the biostability of the insulation material. Evidence of any bioinstability must be fully discussed.

Pathology and Histology: Biocompatibility should be documented via necroscopy and histopathology analysis. Explanted hearts and leads should be excised, examined for lesions or trauma, and preserved for histopathology. Infections should be assessed by

culturing and identifying pathogens. A final report should include a summary of autopsy and histology findings for all animals used during the testing as well as the pre-operative condition of each animal and the surgical techniques used.

Drug Eluting Leads: In the case of a new drug or new drug carrier, the drug eluting components should be tested to characterize the effects on lead performance over time. Appropriate leads, licensed in Canada, should be used as controls in studies to establish comparative threshold and sensing, comparative battery longevity and comparative fibrous tissue encapsulation for new the drug eluting lead tips.

2.3 Clinical Studies

Safety and effectiveness questions associated with minor amendments to currently licensed implantable leads can frequently be resolved with preclinical testing alone. A requirement for clinical testing could arise for new leads with little or no clinical history or leads with new designs, components, functions, or new indications for use. For example, high voltage defibrillation leads remaining unchanged except for modifications to the lead connector may require a post-market clinical study, whereas changes to lead design that result in new therapeutic capabilities may require premarket clinical studies.

Requirements for testing are determined on a case-by-case basis, and the manufacturer is encouraged to contact the Medical Devices Bureau of TPD for advice on how best to proceed in marginal situations.

Clinical Safety and Effectiveness Requirements: Clinical effectiveness indicators include implantation success, voltage stimulation thresholds, sensing characteristics and pacing impedances. Defibrillation thresholds and lead impedances should be measured if the device is designed for cardioversion or defibrillation. Several years of patient follow-up data might be required to assess the biostability of a new lead. Clinical safety indicators include adverse events and complications associated with conductor failure, extracardiac stimulation, insulation failure, low or high pacing impedance, loss of capture, sensing problems (loss, over-sensing or under-sensing), lead dislodgement, perforation and other lead-related adverse events, including death. Appropriate evaluation methods should be used to establish the safety and effectiveness of drug-eluting leads by assessing the role of the drug in improving lead electrical performance.

2.4 Investigational Testing

To obtain an investigational testing authorization for a device, manufacturers are referred to the guidance document entitled Preparation of an Application for Investigational Testing - Medical Devices. Other useful information in this regard can be obtained in the following:

- ISO 14155 Clinical investigation of medical devices for human subjects - Good clinical practice

2.5 Device Labelling

In addition to device labelling, provide copies of implant registration cards in conformance with the applicable sections 66 - 68 of the Regulations.

2.6 Contacting the Medical Devices Bureau of TPD

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3.0 BIBLIOGRAPHY

Preparation of a Premarket Review Document for Class III and Class IV Device Licence Applications V.2

Guidance on How to Complete the Application for a New Medical Device Licence

Guidance for the Interpretation of Section 28 to 31: Licence Application Type

Guidance for the Labelling of Medical Devices under Section 21 to 23 of the *Medical Devices Regulations*

Preparation of an Application for Investigational Testing - Medical Devices

Guidance for the Interpretation of Significant Change of a Medical Device

Recognition and Use of Standards under the *Medical Devices Regulations*

The documents listed above are available on the Therapeutic Products Directorate (TPD) website at: http://www.hc-sc.gc.ca/dhp-mps/md-im/applic-demande/guide-ld/index-eng.php#guidance_devices

International Standards Related to Implantable Cardiac Leads:

EN 45502-2-1	Active implantable medical devices Part 2-1: Particular Requirements for Active Implantable Medical Devices Intended to Treat Bradyarrhythmia (Cardiac Pacemakers)
EN 45502-2-2	Active Implantable Medical Devices Part 2-2: Particular Requirements for Active Implantable Medical Devices Intended to Treat Tachyarrhythmia (Includes Implantable Defibrillators)
ISO 14708-1	Implants for Surgery - Active Implantable Medical Devices - Part 1: General Requirements for Safety, Marking and for Information to be Provided by the Manufacturer
ISO 14708-2	Implants for Surgery - Active Implantable Medical Devices - Part 2: Cardiac Pacemakers
ISO 5841-3	Implants for Surgery - Cardiac Pacemakers - Part 3: Low-Profile Connectors (IS-1) for Implantable Pacemakers
ISO 11318	Cardiac Defibrillators - Connector Assembly DF-1 for Implantable Defibrillators - Dimensional and Test Requirements
ISO 27186	Active Implantable Medical Devices - Four-Pole Connector System for Implantable Cardiac Rhythm Management Devices - Dimensional and Test Requirements
ISO 10993	Biological Evaluation of Medical Devices
FDA Guideline	Guidance for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions, November 1, 2000.