DEPARTMENT OF HEALTH & HUMAN SERVICES Food and Drug Administration

MEMORANDUM

To: The Record

From: (b)(5) PhD
Biomedical Engineer, FDA/CDRH/ODE/DCD/PDLB

Date: March 30, 2011

File: **P080006/S002**
Attain Ability Plus Model 4296 Lead

Sponsor: Medtronic, Inc.

Recommendation: Approval

Purpose of Submission

The purpose of this submission is to request approval for the Attain Ability Plus Model 4296 lead. This lead very similar to the Model 4196 lead approved in P080006, but has a thicker lead body, among other changes.

Review Team

Consulting reviews were performed by:

- Animal Testing - (b)(5), MD, CDRH/ODE/DCD/PDLB
- Drug Component - (b)(5), PE, CDRH/ODE/DCD/PDLB
- Drug Component - (b)(5), PhD, CDER/OPS/ONDQA/DPA I
- Clinical - (b)(5), MD, CDRH/ODE/DCD/PDLB
- Post-Approval Study - (b)(5), PhD, CDRH/OSB/DPS/EB)

I reviewed all other sections of the submission: Manufacturing, Mechanical Testing, Biocompatibility, Sterilization, Risk Analysis, and part of the Animal Testing.

Regulatory History

P080006/S2 - Received June 6, 2009

Amendment 001 – Received October 22, 2009 – Draft proposal of the post-approval study (PAS) for the 4296 lead.

Amendment 002 – Received November 2, 2009 – Requests approval for a split suture sleeve for the 4296 lead to be included in the Anchor Sleeve Kit Model 5867AS (master file P030036/S013, approved 28 Apr 09)

Approvable letter – Issued December 3, 2009 with deficiencies related to the PAS

Amendment 003 – Received June 3, 2010 – Requests extension for response to approvable letter (Granted June 25, 2010)

Amendment 004 – Received at the DMC August 12, 2010 – Documents interactive discussion of Post Approval Study (PAS), responds to deficiencies from the December 3, 2009 Approvable letter, and requests approval of 5 additional design and manufacturing changes.

Amendment 005 – Received at the DMC September 13, 2010 – Withdraws 3 of 5 changes requested in Amendment 004 and provides a response to a request for case report forms for the PAS.

PGMP Letter – Issued December 2, 2010

Amendment 006 – Received at the DMC January 13, 2011 – Requests approval of an additional manufacturing change

All supporting review documentation (consulting review memoranda and correspondence) for the original submission, A001 and A002 was transmitted with the lead review memorandum accompanying the Approvable letter dated December 3, 2009. Similarly, supporting review documentation for A003, A004 and A005 was transmitted along with the lead review memorandum accompanying the PGMP letter dated December 2, 2010**. This decision memorandum summarizes the previous review cycles and reviews A006. Only supporting documentation for this round of review are attached.**

Indications for Use

The Attain Ability Plus 4296 steroid eluting, dual electrode, IS-1 transvenous lead has application for chronic pacing and sensing in the left ventricle via the cardiac vein, when used in conjunction with a compatible Medtronic Cardiac Resynchronization Therapy (CRT) system. Extended bipolar pacing is available using this lead in combination with a compatible CRT-D system and RV defibrillation lead or with a compatible CRT-P system and RV pacing lead.

Device Description

The Medtronic Attain Ability Plus Model 4296 is a 5.3 Fr, transvenous, steroid eluting, dual-electrode, polyurethane insulated, single coil, cardiac vein lead with an IS-1 BI connector. It is similar to the Model 4196 lead (P080006, approved April 7, 2009). As with the Model 4196 lead, the Model 4296 lead has two electrodes that are equal in size to allow either of them to be used as cathodes, thus providing two possible unipolar pacing configurations. These two electrodes also allow the possibility of bipolar use. The Model 4296 lead has a compound curve

at the distal end, identical to the Model 4196 lead. The lead is implanted using either a guidewire or a stylet with a Medtronic 5.7 Fr guide catheter. The lead is used with a compatible Medtronic Cardiac Resynchronization Therapy (CRT) system and RV defibrillation lead, or a compatible CRT-P system and RV pacing lead.

Description of Changes

The primary differences between the Model 4196 and Model 4296 leads are (1) the lead body dimension, (2) the absence of strain relief tubing at the distal tubing of the connector sleeve in the Model 4296 lead and (3) a different anchor sleeve used for the thicker lead. These changes were made to improve the handling characteristics of the lead to be similar to the Attain Over-the Wire Lead Model 4194 lead (P010015/S012), a thicker lead. The differences are highlighted in Figure below.

1. Replacement of Lead Body Tubing

The lead body tubing that spans the 4196 lead from the proximal end of the proximal electrode will be replaced by a lead body tubing of the same 55D polyurethane material with the same inner diameter of 0.034" but with a larger outer diameter of 0.069" (~5.3 Fr). The distal end of the lead body tubing is shaped to transition to the same diameter as the Model 4196 over the most distal 0.160" of the tubing (3.4 Fr).

2. Removal of Strain Relief Tubing

The silicone strain relief tubing in the connector sleeve area of the 4196 lead design is no longer needed and has been removed for the 4296 lead. The new lead body tubing takes the place of this tubing under the connector sleeve and provides a stiffer lead body in this area.

3. Larger Diameter Anchor Sleeve

The anchor sleeve for the Model 4296 lead has larger dimensions than the anchoring sleeve for the Model 4196 lead due to the larger diameter of the lead body tubing. This is the same anchoring sleeve currently used on the Model 4074 lead body (P830061/S034, approved July 23, 2002).

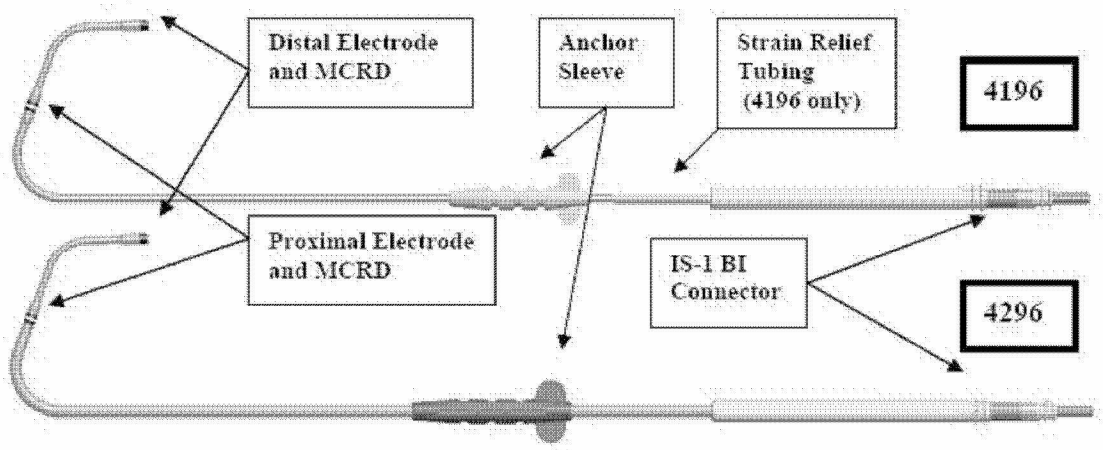

Figure 1. Comparison of Model 4196 and Model 4296 Leads

The sponsor notes that the following characteristics are identical between the 4196 and 4296 leads.

- Compound Curve
- IS-1 BI Connector
- Single coil lead body construction
- Tip Seal
- 5.8mm2 tip electrode
- 5.8mm2 ring electrode
- Polyurethane (b)(4) (outer)
- Soluble Imide Polyimide (Inner) insulation
- Over the guide wire or stylet delivered
- Steroid eluting

The sponsor also notes design similarities between the predecessor Attain Over-the Wire Lead Models 4193 and 4194 and the Model 4196 lead.

LV Lead	Model 4194	Model 4196	Model 4296
Submission Status	P010015/S012 Approved August 20, 2004	P080006 Approved April 7, 2009	N/A
Implant Method	Stylet or guide wire via guide catheter	Stylet or guide wire via guide catheter	Stylet or guide wire via guide catheter
Guide Catheter Size	> 7 French I.D.	> 5.7 French I.D.	> 5.7 French I.D.
Lead Body Design	Coaxial	Single Coil	Single Coil
Lead Body Diameter	6 French	4 French	5.3 French
Lead Body Tubing Insulation (Outer)	Polyurethane (b)(4)	Polyurethane (b)(4)	Polyurethane (b)(4)
Insulation (Inner)	Silicone	SI-PI	SI-PI

Steroid	< 1.0 mg dexamethasone sodium phosphate	Target dose dexamethasone acetate Tip: 160 mg Ring: 72 mg	Target dose dexamethasone acetate Tip: 160 mg Ring: 72 mg
Fixation	Compound Curve	Compound Curve	Compound Curve
Electrode Material	Platinized, platinum alloy	Platinum Iridium alloy with TiN coating	Platinum Iridium alloy with TiN coating
Conductor Material	MP35N Coils	MP35N Ag core coil	MP35N Ag core coil
Cathode(s) Surface Area	5.8 mm^2	5.8 mm^2 (proximal) 5.8 mm^2 (distal)	5.8 mm^2 (proximal) 5.8 mm^2 (distal)
Anode Surface Area	38 mm^2	N/A	N/A
Electrode Spacing	(b)(4) mm (cathode to anode)	(b)(4) mm (cathode to cathode)	(b)(4) mm (cathode to cathode)
Length	20-110 cm	20-110 cm	20-110 cm
Connector	IS-1 BI	IS-1 BI	IS-1 BI

Steroid Comparison

The Models 4196 and 4296 share the same exact steroid containing electrode components with the following characteristics:

- The electrodes are coated with titanium nitride (TiN)
- Dexamethasone acetate (DXAC) is contained in the form of two Monolithic Controlled Release Devices (MCRDs).
- The distal tip contains a silicone tip seal/MCRD that allows guide wire passage while minimizing blood ingress into the lead lumen and contains DXAC
- The proximal ring cathode includes an MCRD containing DXAC in a silicone binder.

The sponsor notes that DXAC was used on previous lead models Model 4073 (P830061/S034, approved July 23, 2002) and Model 4076 (P930039/S017, approved February 9, 2004).

Electrical Testing Review

Aspects of electrical testing of the 4296 lead may be found under Mechanical Testing Review and Animal Testing Review.

Mechanical Testing Review

The mechanical testing review was conducted by Dr. (b)(5) as documented in a review memorandum dated June 12, 2009. The sponsor has provided reports documenting the results of bench testing and modeling analysis to support the safety and effectiveness of the 4296 lead from a mechanical performance perspective. The bench testing results are presented in "Model 4296 In Vitro Bench Test Regulatory Summary Report." All sample sizes for *in vitro* testing provide at least 90% conformance to specification with 90% confidence. Samples sizes for given tests range from (b)(4) to (b)(4). The sponsor has performed environmental conditioning and mechanical, electrical, characterization, and packaging testing. The environmental

conditioning included 100% EtO sterilization and thermal shock testing and was performed prior to all subsequent qualification tests. Mechanical testing included Dry Connector Mating Insertion and Withdrawal, Stylet Perforation, Distal Seal Leak Test, Lead Composite Pull Test, Anchoring Sleeve Suture Test, Lead Body Flex Test, Connector Flex Test, Stylet Insertion/Withdrawal, Guide Wire Insertion/Withdrawal, and Composite Torsional Strength. Electrical Testing included DC Resistance, High-Potential Insulation Check, and IS-1 Connector Leakage/Medtronic AC Impedance Test of Unipolar Leads. Characterization testing included Lead Tracking with Guide Wire and Medtronic Delivery System Compatibility and Guide Wire Insertion Tool Compatibility. Package Testing included Temperature Humidity Exposure, Manual Handling Exposure, Vehicle Stacking Exposure, Loose Load Vibration Exposure, Random Vibration Exposure, and Manual Handling Exposure. Test results demonstrate that the Model 4296 lead meets performance requirements.

In addition to this report, the sponsor provides a Fatigue Summary Report in which presents an analysis of the 4296 lead in comparison to the 4196 and 4193 leads, both of which demonstrate good in vivo flex fatigue performance. The sponsor also provides a Corrosion Risk Assessment Report as well as the results of other analyses to address FDA concerns regarding tip stiffness, bending stiffness, and lead handling. All testing and analyses yielded acceptable results, raising no concerns and support the safety and effectiveness of the 4296 lead.

Animal Testing Review

The sponsor conducted a 12 week canine study and reported electrical stability and pathology. The detailed animal testing reviews were performed by Dr. (b)(5) and Dr. (b)(5) and documented in review memoranda dated August 21, 2009 and October 1, 2009, respectively. The electrical stability results (pacing threshold, sensing amplitude, pacing impedance, slew rate and source impedance) did not raise any major concerns, although some interactive review was conducted to clarify some of the reported results. These minor concerns were resolved and the electrical stability results support approval of the 4296 lead.

Dr. (b)(5) 's pathology review did not find any injuries that indicate a major concern, but had questions for the sponsor on findings of nodular proliferation in a vein and coronary sinus (CS), small vein hemorrhages and inflammation of the CS orifice. Dr. (b)(5) 's concerns were conveyed to the sponsor through interactive review. Dr. (b)(5) 's concerns were adequately addressed during the interactive review process and he has no further concerns. I concur with his review. Considering both the electrical stability and pathology information provided, the animal study results are acceptable and support approval of the 4296 lead.

Chemistry Review

The Chemistry, Manufacturing, and Controls (CMC) section of the PMA supplement is located in Volume 4. It includes information on drug substance and drug product, both of which largely referenced the original PMA for the 4196 lead. The CMC section also proposed a method for introducing the 4296 and 4296 leads into the annual stability protocol. These topics were previously discussed under the pre-IDE (b)(4) . A preliminary review of the CMC was performed by (b)(5) based on his familiarity with the chemistry-related issues as lead

reviewer of pre-IDE (b)(4). In review comment dated July 10, 2009, Mr. (b)(5) recommended a more in-depth review by CDER, particularly of the drug stability section.

The Chemistry review was performed by Dr. (b)(5) and documented in memoranda dated August 17 and September 10, 2009. Dr. (b)(5) found the sponsor's drug stability protocol to be acceptable, but noted deficiencies related to (1) the Certificate of Analysis of the Model 4296 lead, (2) details of the Specification of the Finished Product Model 4296 Lead, and (3) clarification of the regulatory sterility method for analysis of the 4296 Lead. These concerns were addressed to the sponsor through interactive review. Dr. (b)(5) found the sponsor's responses to be acceptable.

All issues related to the drug component of the lead have been addressed. The sponsor has proposed a modified drug stability protocol that allows for leads 4196, 4296, and 4396 to be tested on a rotating annual schedule. This annual stability protocol allows for stability data generated for the Model 4196 lead to be applicable to the 4296 lead for expiration dating of the lead. Although the sponsor notes a desire to increase shelf life for the 4296 lead through an annual report, as noted below under Shelf Life, the annual report is not the appropriate mechanism for updating shelf life and this has been conveyed to the sponsor interactively.

Sterilization

The sponsor uses a 100% EtO sterilization process. The process is an overkill sterilization cycle with at least 12 logs of reduction. Lethality testing of Model 4296 was not required because the Model 4296 polyurethane lead provides less of a challenge to sterilization (because it has an open lumen design) than the bipolar, polyurethane, sealed lumen design of the Leads Lethality Process Challenge Device Model control model.

Verification testing required to qualify the sterilization process consisted of EtO, Bioburden and Endotoxin testing. Sterilant residuals data are reported for the 4296 lead and are compliant with the levels stated in the Federal Register (June 23, 1978, Vol. 43, No. 122) and ANSI/AAMI/ISO 10993-7: 1995 Biological Evaluation of Medical Devices – Part 7: Ethylene Oxide Sterilization Residue" and the guidance in AAMI TIR No. 19 (ref. 3.14 and 3.15 respectively). The sterilant residuals are significantly below the stated acceptance criteria. For Bioburden testing, the total average of aerobic and fungal colony forming units (CFUs) must be below the alert level of 300 CFUs/device. For Endotoxin testing, results must be below the alert level of (0.25 EU/ml). Both acceptance criteria were met as reported in the document titled "Sterilization Qualification Report of the Left Heart Lead Model 4296 Manufacture at CRDM Medtronic Villalba P.R. Operations."

The documentation provided is acceptable and there are no concerns related to sterilization.

Biocompatibility

The Model 4296 lead materials that are directly exposed to body tissue and/or fluids have all been used in predecessor Medtronic leads. Compliance with the ISO-10993-1 regarding the

biological effect of the Model 4296 lead materials is achieved by analogy to predecessor devices.

All of the materials used in the Model 4296 lead which have the potential for direct or indirect contact with a patient's body tissues or fluids, are identical to those used in the currently approved Model 4196 lead (P080006, approved 07 April 2009) in formulation, processing, and sterilization, and no other chemicals have been added. The steroid, Dexamethasone acetate, has been used in predicate device, Model 5076. Biocompatibility testing per ISO 10993-1 was not performed on the steroid because it is an active pharmaceutical ingredient. The testing outlined in ISO 10993-1 is not applicable to a biologically active substance.

The sponsor as provided a Biocompatibility Materials Certification (BL0019102) to certify that the materials used in the lead components are equivalent to the materials used in the components of the predicate devices in formulation, processing, sterilization, and no other chemicals have been added. The sponsor also provides a Biological Evaluation Report Summary (R000324) to document the biological evaluation for the 4296 lead.

The biocompatibility information provided in the submission is acceptable.

Packaging

The packaging materials are identical to those already approved for use with Medtronic leads including the Model 4196.

Packaging used for the Model 4296 leads is the Dual Entry Leads Package (DELP III).
The DELP III package consists of a material combination of PETG tray and Tyvek lids coated with Oliver 18B adhesive. More specifically, the primary packaging is composed of a polyethylene teraphthalate glycol (PETG) tray with an adhesive coated spunbound polyolefin lid and a silicone rubber tip protector disc to hold the distal end of the lead in place. This primary packaging is then placed in a paperboard box and shrink-wrapped.

The PETG tray coating used is (b)(4) silicone emulsion. This coating is applied during extrusion, in an aqueous solution with a silicone content of no more than (b)(4). The lid is a (b)(4) material and with an adhesive coating. The paperboard box used consists of white vat non-bending chipboard with box wrap adhesive and a 70# white litho wrap.

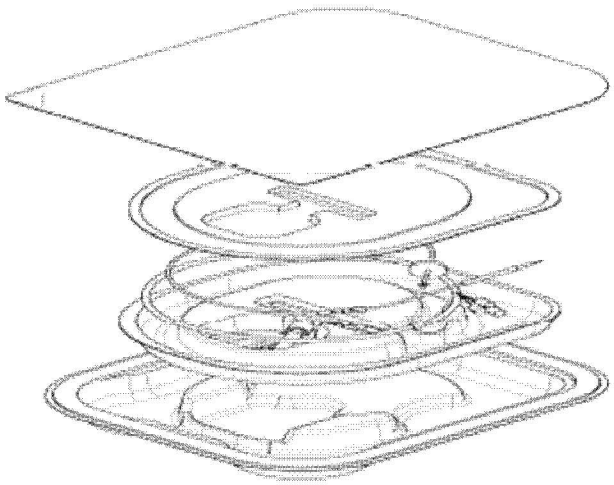

Figure 1: Exploded view of packaging component

Packaging test methods are reviewed in Dr. Kalb's Mechanical Testing Review Memorandum. The Model 4296 Lead will be packaged with the accessories presented in the table below. The accessories may also be packaged individually.

Accessory	Use with Related Models	Quantity	Classification
Guide Wire Loading Tool	Also packaged with market approved the Model 4196 lead	one	Class I, exempt
Guide Wire Torque Tool	Also packaged with market approved 4193, 4194 and 4196 leads	one	Class I, exempt
Guide Wire Clip	Also packaged with market approved 4193, 4194 and 4196 leads	one	Class I, exempt
Stylets	Also packaged with market approved 4193, 4194 and 4196 leads	four	Class II

SHELF LIFE

Medtronic proposes that FDA grant the Model 4296 the same shelf life that the Model 4196 has been granted at the time the Model 4296 lead PMA-S submission is approved and that further shelf life extensions for 4196 will be applicable to Model 4296 and the change will be reported in the Model 4296 annual report. Per informal discussion with Laura Byrd of the PMA staff, it will not be appropriate for Medtronic to report increases in shelf life in the annual report as FDA has not reviewed and approved the testing protocol and it is not provided in this supplement. Future increases to the shelf life should be made through PMA supplements that include both lead models.

Medtronic has provided the following documents: "Model 4296 Two-Year Shelf Life Rationale (BL0019882)" and "Model 4196 Twenty-Four Month Shelf Life Report (BL0019866)." The 4196 lead is currently approved for a 9 month shelf life.

The Model 4296 Two-Year Shelf Life Rationale presents the sponsor's rationale for setting a two-year shelf life for the Lead Model 4296 without conducting additional testing. This report shows that all components listed are similar if not identical in design and materials to the 4196 lead. Although I do not agree that 24 month shelf life should be granted based on the rationale presented, I do agree that separate testing for the 4296 lead is not necessary.

The 4196 Twenty Four Month Shelf Life report indicates that the following procedures/tests were performed: Storage, Thermal Shock, Visual Examination and Shape Check, Guidewire Passage and Guidewire Insertion Tool Compatibility, DC resistance, Intermittence, Dielectric Withstand, Lead Body Fluid Leakage Test, Delivery System Compatibility, Stylet Perforation Test, Connector Insertion/Withdrawal Force, Saline Soak/Electrical Impedance, Composite Torque Test, Composite Tensile Integrity, Composite Tensile Strength, Anchor Sleeve Retention Force, and Pin to Sleeve Tensile Strength. All tests passed with only one anomaly noted for the Composite Tensile Integrity test, which has been adequately justified.

The results presented in the 4196 24 Months Shelf Life Report do not raise any concerns regarding application of the approved 9 month shelf life for the 4196 lead to the 4296 lead. The 24 months shelf life report presented here is not sufficient to give the 4296 lead a 24 month shelf life, as the shelf life depends on both mechanical and drug stability. It is expected that a separate complete review of the 4196 24 Month Shelf Life Report will be conducted when the sponsor submits an application to increase the shelf life from 9 months to 24 months for the 4196 lead.

Risk Analysis

The sponsor provides a Risk Management Report (BL0019893) that outlines the risk management activities for the Model 4296 lead. These activities consist of identification, assessment and mitigation of risk of potential hazards and failure modes associated with the use of the device as intended. For both the hazards and the failure modes, the sponsor assesses the risk by assigning a probability of occurrence (O) ranking and a severity (S) ranking. The failure modes are also assigned a detectability (D) ranking. The risk index for the hazards is determined as the O x S. The risk priority number (RPN) for the failure modes is determined as O x S x D. The risk index or RPN is categorized as Low, As Low As Reasonably Practicable (ALARP), or High. All individual hazards risks and all individual failure mode risks are located in the Low or ALARP regions. None were found in the High regions. Because the initial risk was found to be acceptable, no re-assessment of risk was preformed. There is no unacceptable Overall Residual Risk at this time. The sponsor notes that the risk analysis is in compliance with ISO 14971:2000 (Application of Risk Management to Medical Devices).

The sponsor provides their Hazard Analysis and Failure Mode and Effects Analysis for these leads. In these documents, hazards/failure modes and their causes and effects are identified, risk is assessed, and risk control measures are listed. I have reviewed these and they appear appropriate. The risk management activities conducted by the sponsor appear acceptable and I have no concerns.

Clinical Review

Dr. (b)(5) provided the clinical review for this submission as documented in a memorandum dated August 28, 2009. His review covered the following areas:

Applicability of 4196 Lead Clinical Data to the 4296 Lead

Dr. (b)(5) reviewed the summary of Pre-IDE meetings on the subject of whether clinical data would be required for the 4296 lead, as well as the final investigational protocol and results from the IDE study for the 4196 lead. Dr. (b)(5)' review confirmed his belief that the 4196 study results do provide applicable safety and effectiveness support because the differences between the two leads would not be expected to alter safety and effectiveness and because minor differences in performance between the two leads are unlikely to be characterized in a reasonably sized trial.

Lead Handling Study

The FDA requested a lead handling study for the 4296 lead that appears on pages 2-297 through 2-301 of Volume 2 of the PMA submission. In this animal study, (b)(4) physicians ranked the 4196, 4296, and 4194 leads in terms of trackability, pushability, torqueability, and steerability. Dr. (b)(5) notes that this study adequately addresses FDA's request for a modest handling study to help implanting physicians understand lead differences to rationally choose among the various models. He also notes that the results suggest that the 4296 lead is received about as well as prior models, if not better, although the study is too small to draw conclusions.

Proposed Labeling

Dr. (b)(5) reviewed the Technical Manual, Patient Identification Card, and Website Card. He noted that all were acceptable and supportive of approval.

Post-Approval Study

Dr. (b)(5) provides comment regarding the sponsor's proposal for no collection of post-market data for the 4296 lead beyond the sponsor's System Longevity Study (SLS). The sponsor argues that a post-approval study (PAS) is unnecessary because FDA deemed that pre-market data from 4196 could serve as a reasonable surrogate for the 4296 lead and the 4196 lead will be studied extensively post-approval. However, Dr. (b)(5) argues that although chronic data from the 4196 lead will apply for the 4296 lead, there may be small differences that could affect long-term performance. He suggests that some formal collection of high quality data is warranted. Dr. (b)(5)' recommendation prompted additional discussion which is presented below under "Post-Approval Study."

Overall, Dr. (b)(5) recommends approval of the 4296 lead with no deficiencies, from a clinical perspective. I concur with his recommendation.

Manufacturing Review

The following aspects of Model 4296 lead manufacturing are the same as the approved 4196 lead: manufacturing facility, major equipment, general assembly process, incoming part

inspections, tensile tests, electrical testing, final lead assembly and inspection processes, final pagkaging inspection, documentation verification and inspection processes, and component traceability activities.

The sponsor notes that manufacturing and analytical method changes have been implemented on the Model 4196 production line that will be in place for the Model 4296 lead. The Model 4196 and 4296 leads are manufactured on the same production line and utilize the same manufacturing process steps. The sponsor notes that the manufacturing and analytical method changes are appropriate for reporting in the annual report. I have reviewed these changes and they do not raise any concerns and do not appear to affect safety or effectiveness.

The sponsor also notes that several changes were requested by FDA during PMA review of the model 4196 lead and that these will also be implemented for the 4296 lead. These are:

- Add sub-method numbers to Method IM1200 of the Dexamethasone Acetate-Anhydrous specification (M925604A)
- Decrease the paddle speed for the elution test specification from 100 rpm to 50 rpm
- Define "RF" in Method IM1193, Determination of Identity, Assay and Content Uniformity of Dexamethasone Acetate in MCRD Tip & Ring and In-Process Samples of Medtronic Model 4196/4296/4396 Lead

I have no concerns with the implementation of these changes for the 4296 lead.

One manufacturing process, the (b)(4) , is specific to the 4296 lead and has been qualified. The sponsor notes that this process uses the same equipment, same process parameters, and the same method. Only the lead body tubing component is different due to the difference in outer lead body tubing diameter in the Model 4296. Due to the tubing diameter difference, this (b)(4) was separately validated. This is acceptable appropriate. All other processes are identical to those for the 4196 lead.

The manufacturing information provided by the sponsor for the 4296 lead appears appropriate. Almost all aspects of manufacturing are the same as those approved for the 4196 lead. It appears that any changes to the manufacturing process will be appropriately reported in an annual report. The process specific to the 4296 lead has been reviewed and does not raise any safety or effectiveness concerns. I have no concerns regarding the manufacturing of the 4296 lead.

Post-Approval Study

In the original submission, the sponsor noted that they believe that a post-approval study (PAS) is not required for the 4296 lead due to the similarities between it and the 4196 lead and because the performance of the 4196 lead is already being evaluated in a separate PAS. The sponsor proposed to monitor the chronic performance of the 4296 lead through the 4196 lead PAS and through Medtronic's System Longevity Study (SLS).

The review team did not agree with this approach. While we agree that the data provided for the 4196 lead is supportive of approval of the 4296 lead, chronic performance data for the 4196

lead is not yet available and can not be assumed to be favorable. Therefore, collection of separate data in a PAS for the 4296 lead assures collection of chronic performance data for the 4296 lead, should enrollment in the 4196 study be low for any reason. Moreover, should a problem arise with the 4196 lead, availability of separate data for the 4296 lead allows for discernment of whether the problem applies to the 4296 lead. Therefore, the sponsor was asked to develop a PAS.

Medtronic submitted a draft protocol for a PAS as Amendment 001 to this submission. (b)(5) (b)(5) and Dr. (b)(5) led the initial review of the PAS from the ODE and OSB perspectives, respectively in review comment dated November 25, 2009 and November 9, 2009. Several deficiencies were noted and were conveyed to the sponsor in the approvable letter dated December 3, 2009. The most significant deficiency regards the sponsor's plan for an interim analysis that would potentially allow limiting enrollment and pooling data between the 4196 and 4296 leads. Dr. (b)(5) 's concern is that the failure modes between the two leads may be different and that it will not be possible to discern these failure modes if the data are pooled. Mr. (b)(5) also noted that if an issue arises after one year (the time point for the interim analysis), which may be the case for a lead fracture, for example, the study will be underpowered for such issues. Other deficiencies were more minor in nature. Amendment 004 provided a response to these deficiencies and reflected substantial interactive review that was conducted prior to submission of Amendment 004. Amendment 005 included the electronic Case Report Forms that were requested by FDA in the Approvable letter. All deficiencies were satisfactorily addressed through Amendments 004 and 005. The following summarizes the PAS:

The sponsor agrees to conduct a nonrandomized, multi-site, world-wide study of implanted commercially available Model 4296 leads. The primary objective of the study is to evaluate the chronic performance of the Model 4296 lead. The hypothesis is to demonstrate that the Model 4296 lead-related complication-free rate is greater than 92.5% at five years post-implant. The complication free rate will be estimated based on clinical adverse events including: failure to capture, failure to sense/under-sensing, threshold rise, over-sensing, abnormal pacing impedance, lead insulation breach, lead conductor fracture, extra-cardiac stimulation, cardiac perforation, lead dislodgement, and structural lead failure. The secondary objectives are descriptive in nature and are intended to gain additional information about the Model 4196 lead. They consist of summarizing all lead related adverse events, characterizing any changes in electrode programming, characterizing fractures with and without loss of function, e.g. another conductor used, and summarizing bipolar electrical performance at 1 year. The subjects of study are patients who are enrolled into the SLS and meet the inclusion criteria but do not meet any of the exclusion criteria. In both the 4196 and 4296 PAS protocols, the enrollment window is ≤ (b)(4) days post implant. The sample size of 4296 lead is (b)(4), assuming (b)(4) % attrition per year, which is to satisfy primary objective analysis requirement and to provide reliable estimates on individual failure mode rates for the general population. An interim analysis will be conducted to test the hypothesis that the Model 4296 LV lead related complication-free survival probabilities at (b)(4) years post implant are similar to the Model 4196 leads. If there is evidence that the chronic performance of the Model 4296 lead is not equal to or better than the Model 4196 lead, study

enrollment requirements will increase to (b)(4) for the Model 4296 lead. Subjects will be followed from their enrollment date, and at (b)(4) month intervals through (b)(4) years post-implant.

Other Review Comments

Tip Position and Contact Pressure Assessment

The determination letter sent to the sponsor on December 24, 2008 for (b)(4) listed seven items for establishing the effectiveness of the Model 4296 left ventricular lead. All of these items have been addressed above with the exception of a Tip Position and Contact Pressure Assessment. Specifically, the sponsor was asked to address (1) whether the wider lead body of the Model 4296 lead affects the final placement location of the distal tip electrode within the coronary vessel compared to the Model 4196 and Model 4194 leads and (2) whether the wider lead body of the Model 4296 lead affects the distal tip orientation, electrode contact point, or contact pressure against the vessel wall compared to the Model 4196 and Model 4194 leads. The responses to these questions were provided during review of (b)(4) and repeated in the subject supplement to P080006.

With regard to the first question, the sponsor indicated that the distal tip of the 4296 lead would be placed at a position intermediate to positioning obtained with the 4196 and 4194 leads and that the 4296 lead has a trackability force in between that obtained with the 4196 and 4194 leads. The review team for (b)(4) and I believe that the data provided supported the reason for the change (improved control with a thicker lead body) and that the rationale and test data were adequate to support that the 4296 lead could be placed in a position that would result in acceptable electrical performance comparable with 4196 and 4194. With regard to the second question, the sponsor provided a finite element analysis demonstrating similar lead contact locations and pressures between the 4196 and 4296 leads. The sponsor also pointed to a canine study pathology analysis that specifically examined the interaction between the electrodes and the vein. I have informally discussed this analysis with Dr. (b)(5) and he noted that he had no concerns regarding the contact orientations and pressures that may be experienced by the coronary vasculature with the use of the 4296 lead. Based on my review of the response, as well as the tip stiffness, bending stiffness, and in-vitro characterization reported in the Mechanical Testing sections of the submission, I concur with Dr. (b)(5) and expect the performance of the lead to be acceptable.

Review of Amendment 002 - Inclusion of the 4296 Lead in the Model 5867AS Anchor Sleeve Kit

The sponsor submitted Amendment 002 to allow the inclusion of the 4296 Lead model in the Model 5867AS Anchor Sleeve Kit. This Kit contains slit suture sleeves of various inner diameters that are compatible with specific leads. One of the suture sleeves in the kit also compatible with the 4296 lead, and the sponsor has submitted this Amendment to allow the Model 5867AS Kit labeling to be modified to include the 4296 lead. Mr. (b)(5) reviewed this amendment and his review comment is documented in correspondence dated November 25, 2009. He found the data submitted to support inclusion of the 4296 Lead in the Model 5867AS Anchor Sleeve Kit to be acceptable for approval. As the 5867 Anchor Sleeve Kit spans several PMAs, those PMAs will be updated to reflect the labeling inclusion of the 4296 lead model through their respective annual reports.

Review of Changes in Amendments 004, 005, and 006

The following 5 changes were proposed in Amendment 004:

- (b)(4)
- **Sterile Blister Packages** approved under Real-Time Review for 4196 and several other devices
- **Ethylene Oxide Sterilization Gas Concentration Change** approved under 30-Day notice for several other devices
- (b)(4)
- (b)(4)

As it is not typically appropriate for new changes to be submitted after the device has been found to be approvable, the sponsor was advised to withdraw these changes from the Amendment. The sponsor withdrew three of the changes in Amendment 005 ((b)(4) (b)(4) (b)(4)), requesting that the remaining two changes be reviewed with the present submission as these are supplier changes or CRDM manufacturing system-wide changes for which no alternate exists. After discussion with (b)(5) (b)(5) of the PMA staff, it was determined that although it is typically unacceptable for additional changes to be reviewed after an approvable letter is issued, it is reasonable to make an exception in this case as we agree that it would be burdensome for both FDA and the sponsor to conduct reviews on these changes for which we have no concerns and readily approve for the 4296 lead. One additional change was resubmitted in Amendment 006 ((b)(4)) with the same rationale.

(b)(5), the original reviewer for the Sterile Blister Package Change that was reviewed under Real-Time Review (master file P980035/S145) was consulted and he noted no concerns with approving this change for the model 4296 lead. (b)(5) and (b)(5) of the Office of Compliance were consulted regarding the Ethylene Oxide Sterilization Gas Concentration Change and the Implementation of FACTORYworks Software at MPROC Change, which were approved under P980006/S001 and P080006/S009, respectively. They noted no concerns with approving these changes for the model 4296 lead. Mr. (b)(5) note regarding the latter change is attached (Attachment A). These three changes are acceptable for approval for the 4296 lead.

Conclusion and Recommendation

This submission was found to be approvable after submission of A002, and later found to be approvable pending resolution of QSR issues (PGMP) after review of A005. While on hold, the sponsor submitted A006, which was found to be acceptable by the Office of

Compliance/DOEB/CREBD as noted above. A memorandum from (b)(5) dated March 9, 2011 (Attachment B) indicates that issues related to QSR non-compliance have been resolved and that the hold status for this PMA is lifted. Therefore, this supplement may now be approved.

Based on the information provided in this submission and associated amendments, consulting reviews, and interactive review with the sponsor, I recommend approval of this supplement.

(b)(5) Lead Reviewer Date

Mitchell Shein, Branch Chief Date
FDA/CDRH/ODE/DCD/PDLB