DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

Division of Cardiovascular Devices
Pacing, Defibrillator & Leads Branch

Date: 29 March 2011

From: [redacted] Mechanical Engineer, FDA/CDRH/ODE/DCD/PDLB

Subject: P030036/S004
Medtronic, Inc.
SelectSecure Model 3830 Lead

Contact: Mary Plante and Beth Claas

To: The Record

Recommendation: Approval

Executive Summary

The SelectSecure Model 3830 lead is a 4.1F lumenless bipolar lead intended for use to pace and sense in the right atrium or right ventricle. The lead tip is coated with the steroid Beclomethasone Dipropionate (BDP) which may reduce tissue inflammation at implant and reduce acute and chronic pacing capture thresholds. The Model 3830 lead was approved on 3 Aug 2005 with the following Condition of Approval:

> *To further improve your manufacturing specifications, as outlined in our email dated July 12, 2005, you have agreed to work with FDA to address issues related to finished product specifications, test methods per the July 12 email, product release testing, in vivo-in vitro correlations, and the certificate of analysis for the 3830 lead.*

This supplement was originally submitted by Medtronic on 31 Dec 07 to address this condition of approval. Through a series of three amendments to S004, Medtronic and FDA have interactively worked to establish improved methods and specifications for the Model 3830 lead. The improvements and agreements established during this interaction are summarized below and are recommended for approval. Medtronic has committed to continue work on improved methods or design changes which allow the specifications to be further tightened.

Review Team

Engineering: [redacted], FDA/CDRH/ODE/DCD/PDLB
Engineering: [redacted], FDA/CDRH/ODE/DCD/PDLB
Chemistry: [redacted] FDA/CDER/OPS/ONDQA/DNDQA I/BRANCH I
Chemistry: [redacted] Ph.D., FDA/CDER/OPS/ONDQA/DNDQA I/BRANCH I
Pharmacologist: [redacted] Ph.D., FDA/CDER/ OTS/OCP/DCPI

Indications For Use

The Model 3830 lead has application where implantable atrial or ventricular, single-chamber or dual-chamber pacing systems are indicated. The Model 3830 lead is intended for pacing and sensing in the atrium or ventricle.

Device Description

The SelectSecure Model 3830 lead is a device/drug combination product made up of two regulated components: a device (the Model 3830 lead) and a beclomethasone dipropionate (BDP) drug coating on the distal tip. The Model 3830 bipolar pace/sense lead has a lumenless design, a small 4.1 French lead body diameter, and an IS-1 bipolar connector at the proximal end.

Drug Manufacturing, Methods, and Specifications Changes

A large number of drug manufacturing, methods, and specifications changes were introduced in S004 and its three amendments. The changes as reviewed and approved under S004 and its amendments are summarized below:

S004

The original review of S004 was performed by (ODE), (CDER/CMC) and (biopharmaceutics). The supplement contained information to address the original condition of approval for drug coating improvements, and also contained a stability protocol, new regulatory specifications, new finished product analytical methods, analytical methods validation, and analytical methods development information.

CDER provided reviews of S004 for chemistry, manufacturing and controls (CMC) in a memo dated 9 Apr 2008 and for biopharmaceutics in a memo dated 22 Apr 2008. Overall, the supplement was found Not Approvable and a letter was sent on 30 Apr 08. The deficiencies regarded specifications (assay, content uniformity, impurity & degradants, endotoxins), stability testing, Certificates of Analysis (COA), Elution Method, and in-vitro elution test.

S004/A001

Medtronic requested an extension under S004/A001 while they continued development of new methods to improve the 3830 specifications in response to the deficiencies identified in the 30 Apr 08 Not Approvable letter.

The extension was allowed by FDA.

Medtronic/FDA Telcon on 6 Jun 2008 & 4 Aug 2008

Medtronic and FDA held teleconferences on 6 Jun 2008 and 4 Aug 2008 to discuss the deficiencies in the letter dated 30 Apr 2008. Smaller issues were clarified and some agreements were made regarding the future amendment to S004. During the 6 Jun 2008 meeting Medtronic stated that some CDER requirements cannot be met since they were imposed after product development and clinical study. Medtronic and FDA agreed that S004 contained major improvements to reduce process variability and imposed tighter specifications than those provided in the original PMA. Medtronic stated they believed that the proposed improvements met the Conditions of Approval in the 3 Aug 2005 letter. During the 4 Aug 2008 meeting Medtronic and FDA agreed that the next amendment would address deficiencies in the 30 Apr 2008 letter, and propose interim improvements to be approved under S004. Medtronic stated that additional efforts for improved methods or potentially a new drug application process might be necessary to meet CDER's full requirements.

FDA agreed that the S004 proposal held improvements in process variability and specifications but did not agree that they could be considered adequate to meet the Conditions of Approval in the 3 Aug 2005 letter. FDA agreed that A002 could respond to deficiencies and could propose interim improvements for approval, while the firm continued to

develop improved manufacturing methods or potentially a new drug application method.

S004/A002

After use of the extension to continue development of method and process improvements, Medtronic submitted A002 on 1 May 2009 to respond to the deficiencies identified in the Not Approvable letter dated 30 Apr 08. A002 documented the interactive efforts to date, responded to the 30 Apr 08 letter, and also introduced the following new changes: appearance specification update, scale-up of steroid solution, new lab methods, and an alternate analytical laboratory. CDER provided reviews of A002 for chemistry, manufacturing and controls (CMC) in a memo dated 21 Jul 2009 and for biopharmaceutics in a memo dated 4 Aug 2009.

Deficiency 1. As requested, the firm documented that an automated dispenser was approved under P030036/S003.

There was no additional CDER concern and the response was acceptable.

Deficiency 2. The firm provided updated specifications for assay, content uniformity, impurities and degradants, and endotoxin. The CDER review is summarized for each sub-part below:

a. *CDER agreed that the firm could use interim assay acceptance criteria until an updated or new steroid application process is implemented.*
b. *CDER asked that the tighter content uniformity specification be assigned in a follow-on deficiency.*
c. *CDER asked for tighter assignments of impurity and degradant acceptance criteria in a follow-on deficiency.*
d. *CDER found the response regarding endotoxin testing at release acceptable. CDER requested a tighter specification for residual solvents in a follow-on deficiency.*

Deficiency 3. The firm provided the requested stability testing protocol information.

There was no additional CDER concern and the response was acceptable.

Deficiency 4. The firm provided an updated Certificate of Analysis with the CDER requested format and content.

There was no additional CDER concern and the response was acceptable.

Deficiency 5. The firm provided updated the Elution Rate test method as requested by CDER.

There was no additional CDER concern and the response was acceptable.

Deficiency 6. The firm provided updated in-vitro elution information as requested by CDER.

CDER found that the min/max range at each elution time-point was unacceptably broad based on the batch data submitted. CDER suggested acceptable ranges in a follow-on deficiency.

Evaluation of New Changes Submitted in S004/A002:

a. Revised Appearance Specification.
The CDER reviewer found the revised appearance specification acceptable.

b. Batch Size Scale-up of BDP Dipping Solution

The CDER reviewer found the proposed batch size scale-up acceptable.

c. New Finished Product Analytical Testing Laboratory
CDER reviewed data for updated methods between the approved analytical lab and the new lab. CDER asked for additional comparison data which was provided by Medtronic. Upon review, CDER agreed that the updated methods at the new analytical lab were acceptable. The CDER stated that CDRH Compliance is responsible for evaluation of the new laboratory service supplier. CDRH Compliance determined that FDA does not approved labs but rather expects that the firm's quality system will assess an alternate lab through 21CFR820.50 (purchase controls) and 21.CFR820.80 (Receiving, in-process, and finished device acceptance).

The review of A002 resulted in another Not Approvable letter dated 28 Oct 2009. The remaining issues are sub-parts of the deficiencies summarized above. These issues were resolved in the next amendment detailed below.

S004/A003 & 23 Jul 2010 Response to Deficiency Email

Amendment 003 was submitted on 23 Apr 2010 to address the Not Approvable letter dated 28 Oct 2009. CDER provided reviews of A003 for chemistry, manufacturing and controls (CMC) in a memo dated 22 Jun 2010 and for biopharmaceutics in a memo dated 25 June 2010. Upon CDER review, follow-up deficiencies were sent to the firm by email on 12 Jul 2010. The firm provided responses to the deficiency email on 23 Jul 2010. A summary of the deficiency responses and resolutions is provided below:

Deficiency 1. Medtronic agreed to tighten the content uniformity specification to the level recommended by CDER in the 28 Oct 2009 letter.

There was no additional CDER concern and the response was acceptable.

Deficiency 2. Medtronic agreed to the limits for impurities suggested in the FDA letter dated 28 Oct 2009, other than for epoxy analog.

CDER requested additional information concerning epoxy analog by email on 12 Jul 2010. The firm provided additional information on 23 Jul 2010. CDER reviewed the additional justification in an email dated 28 Jul 2010 and found the overall response acceptable.

Deficiency 3. Medtronic agreed to express the limits for residual solvents as suggested in the FDA letter dated 28 Oct 2009.

There was no additional CDER concern and the response was acceptable.

Deficiency 4. Medtronic did not agree to the in-vitro elution specifications suggested in the FDA letter dated 28 Oct 2009. Medtronic provided a justification to support their own proposed elution specification.

CDER requested additional information by email on 12 Jul 2010. The firm provided additional information on 23 Jul 2010. CDER reviewed the additional justification in an email dated 5 Aug 2010 and agreed to accept the in-vitro elution specifications proposed by the firm in their 23 Jul 2010 response. CDER noted that the improvements do not fully satisfy the original Condition of Approval. The firm agreed to continue to work on manufacturing and controls improvements to fully address the conditions of approval.
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Deficiency 5. Per interactive discussions, Medtronic proposed interim Assay acceptance criteria until new methods, processes, or design is implemented.

There was no additional CDER concern and the response was acceptable. CDER noted that the improvement does not fully satisfy the original Condition of Approval. Medtronic agreed to provide an update on the status and time-line of future work in an amendment to this supplement.

Conclusion

Through a long and interactive process with FDA, Medtronic has developed improvements to the drug application and testing methods and specifications for the SelectSecure Model 3830 lead. While the proposed improvements do not fully satisfy the original condition of approval, the changes provide significant improvements to the controls and specifications on the drug coating compared with what was originally approved. The changes are thus recommended for approval, with the stipulation that they do not satisfy the original condition of approval in the 3 Aug 2005 approval order for SelectSecure Model 3830.

Recommendation

The supplement was recommended for approval on 25 Aug 2010. However, as documented in an email from Office of Compliance dated 23 Aug 2010, the Medtronic manufacturing plant for this PMA is currently on the OAI list. Therefore, an Approvable Pending GMP letter was initially provided on 2 Sep 2010 and later corrected on 18 Oct 2010. The OAI hold order was lifted according to a letter from OC dated 9 March 2011. P030036/S004 is therefore recommended for approval.

[redacted], Lead Reviewer, PDLB Date

[redacted], Chief, PDLB Date