File: P080006/S063
Purpose: Drug MCRD Manufacturing & Specification Updates
Applicant: Medtronic, Inc.
Device Name: Attain Ability LV Lead Models 4196, 4296 and 4396

Recommendation: Approval / CTS Code: APPR

SUMMARY MEMO

Brief Submission Purpose/Description:
Medtronic submitted this PMS supplement to request approval for a series of changes for the drug MCRD used with Medtronic Attain Ability models 4196, 4296, and 4396 leads.

Background/History:
Medtronic is introducing a sequence of updates to the manufacturing and specifications of drug MCRD components used on their cardiac pacemaker and defibrillator leads. FDA and Medtronic discussed these updates under Q130431 including a face-to-face meeting on 1 May 2013.

Proposed Changes:
The proposed changes are all related to the manufacturing and specifications of the drug MCRD. The following changes were proposed by Medtronic in S063:

- Implementation of an improved elution test method using a (b)(4) TS/CCI address limitations in the current method. Revised elution specifications are proposed for MCRD and finished lead release and stability testing as a result of the different *in vitro* elution profiles obtained using the improved elution method.
- Transfer of manufacturing for the tip and ring MCRD components from the current (b)(4) TS/CCI, to the Medtronic Cardiac Rhythm Disease Management (CRDM) Rice Creek manufacturing facility. MCRD manufacturing process updates are being incorporated along with the manufacturing site transfer.
- Use of a test vehicle (surrogate) rather than finished leads for tip elution testing associated with finished product release.
- Modification of the annual long term shelf life protocol to address proposed elution testing changes and align storage conditions with (b)(4) TS/CCI conditions (b)(4) TS/CCI A proposal to remove sterility testing from routine annual studies is also included.

Initial Review Summary:

The proposed changes are all related to the manufacturing and specifications of the drug MCRD. As such the principle review of this supplement was performed by CDER reviewers. The initial Chemistry Manufacturing and Controls (CMC) consult was provided on 12 Feb 2014 and is summarized below each proposed change. The initial Biopharmaceutics (Elution) consult was provided on 12 Feb 2014 and is summarized below each proposed change.

- Implementation of an improved elution test method using a (b)(4) TS/CCI to address limitations in the current method. Revised elution specifications are proposed for MCRD and finished lead release and stability testing as a result of the different *in vitro* elution profiles obtained using the improved elution method.

  The CMC reviewer deferred evaluation of this change to the biopharmaceutics reviewer.

  The biopharmaceutics reviewer found that the proposed drug elution method was adequate for quality control and the new elution method was considered largely acceptable; as detailed in her consult memo. The reviewer provided two minor questions to the firm that sent to the firm by email on 2/25/2014 after the first review cycle Principally Interactive (PI) Decision was made. The questions and subsequent resolutions are documented in the next section of this memo.
  MINOR DEFICIENCIES (#1 and #2)

- Transfer of manufacturing for the tip and ring MCRD components from the current (b)(4) TS/CCI to the Medtronic Cardiac Rhythm Disease Management (CRDM) Rice Creek manufacturing facility. MCRD manufacturing process updates are being incorporated along with the manufacturing site transfer.

  The biopharmaceutics reviewer stated that the proposed manufacturing site and process changes do not significantly impact the drug elution performance and are acceptable from the biopharmaceutics perspective.

  The CMC reviewer evaluated the changes, and considered that the new site is already FDA inspected and approved for manufacturing and analytical testing of drug MCRDs for other lead families. The CMC reviewer evaluated the site change, manufacturing process changes, and OQ/PQ testing and results. The firm had followed the advice provided under Q130431. Overall the CMC reviewer found the documentation and evaluation acceptable for the changes in manufacturing site and processes; as detailed in their consult memo.
  ACCEPTABLE.

- Use of a test vehicle (surrogate) rather than finished leads for tip elution testing associated with finished product release.

  The CMC reviewer deferred evaluation of this change to the biopharmaceutics reviewer.

  The biopharmaceutics reviewer found that the tip seal surrogates and finished lead tips exhibited comparable/similar elution profiles and that the use of the test vehicle (surrogate) was acceptable; as detailed in her consult memo. A clarification was requested regarding whether the tip seal surrogate is (b)(4) TS/CCI (b)(4) TS/CCI *. This question was sent to the firm by email on 2/25/2014 after the first review cycle Principally Interactive (PI) Decision was made. The question and subsequent resolution is documented in the next section of this memo.*
  MINOR DEFICIENCY (#3)

- Modification of the annual long term shelf life protocol to address proposed elution testing changes and align storage conditions with (b)(4) TS/CCI conditions (b)(4) TS/CCI. A proposal to remove sterility testing from routine annual studies is also included.

  The biopharmaceutics reviewer had no comments regarding this change and deferred to the CMC reviewer analysis and recommendation.

  The CMC reviewer found the revisions to the annual long term stability program largely acceptable, except for removal of the requirement to perform annual sterility testing, as detailed in her consult memo. A question regarding annual sterility testing was sent to the firm by email on 2/25/2014 after the first review cycle Principally Interactive (PI) Decision was made. The question and subsequent resolution is documented in the next section of this memo.
  MINOR DEFICIENCY (#4)

Initial Review Recommendation: PI (Proceed Interactively)
Under consult to ODE, CDER reviewed Metronic's proposal to update the manufacturing site, processes and specifications as presented in S063. CDER found the documentation and testing largely acceptable to support the changes. Four minor deficiencies/questions were identified by the CDER reviewers. ODE agreed with the questions and concerns. ODE assessed the scope of the questions and in coordination with CDER determined that they can be resolved interactively. A "Proceed Interactively" (PI) recommendation was issued on 2/25/2014 and an automatic notification was sent to Medtronic. The notification was followed by an email from the lead reviewer on 2/25/2014 which listed the 4 questions remaining for S063 and requested that Medtronic provide responses interactively by email.

Principally Interactive (PI) Review Summary:

A total of 4 questions were generated by CDER consultants during the first round of review of this supplement and were sent to the firm by email on 2/25/2014. Medtronic responded to Questions 1, 2 and 3 by email on 2/28/2014. Medtronic responded to Question 4 by email on 3/20/2014. The CDER CMC reviewer provided an assessment of these responses in a review memo received by email on 3/26/2013. The CDER Biopharmaceutics reviewer provided an assessment of these responses received by email on 4/29/2013. The PI questions are copied below followed by a summary of the CDER review and recommendations. My review of the response to question 4 is provided below as the response regarded packaging and sterilization which is reviewed by ODE.

Proceed Interactively (PI) Questions and Review

1. Although your elution method development and validation studies provide a reasonable assurance of the newly proposed elution method' suitability, the studies are incomplete. As part of your continuous improvement efforts, we recommend that you more closely evaluate the ability of the method to detect meaningful manufacturing or process changes that could impact drug elution performance. These studies are a useful and important part of overall elution method validation.

   Medtronic acknowledged FDA's recommendation and agreed that they will continue to evaluate performance of the method and conduct additional assessments as appropriate per their quality system. The Biopharmaceutics reviewer considered the response and found it acceptable per an email dated 3-29-2014 and subsequent review memo dated 5-13-2014.
   ACCEPTABLE RESPONSE

2. The proposed drug elution acceptance criteria are acceptable as part of the quality control specifications for the Attain Ability leads family, models 4196, 4296 and 4396, with the exception of the proposed last sampling time point for the finished lead tip seal; we recommend that (b)(4) TS/C hours be used as the last sampling time point, instead of the proposed (b)(4) TS/C hours.

   Medtronic agreed to shorten the final elution time point from (b)(4) TS/CCI *hours for* (b)(4) TS/CCI *elution criteria for Attain family leads and stated that identical acceptance criteria would apply for finished product release using the proposed test vehicle (tip seal surrogate). The Biopharmaceutics reviewer considered the response and found it acceptable per an email dated 3-29-2014 and subsequent review memo dated 5-13-2014.*
   ACCEPTABLE RESPONSE

3. Confirm that the elution testing on the Tip Seal Surrogates is performed on sterilized products, and provide a cross sectional drawing of the Tip Seal Surrogate (to clarify whether it is empty inside or not).

   Medtronic stated that the tip seal surrogate (b)(4) TS/CCI *for analytical testing, with drawings provided. While a small amount* (b)(4) TS/CCI *there was no impact to the*

comparative results with the tip seal surrogate. In the response Medtronic stated that the tip seal surrogate is (b)(4) TS/CCI *. Extensive evaluation demonstrated that nominal and up to 4x sterilization had no impact on assay, degradation product, or elution characteristics for Attain Ability leads. The Biopharmaceutics reviewer considered the response and found it acceptable per an email dated 3-29-2014 and subsequent review memo dated 5-13-2014.*
ACCEPTABLE RESPONSE

4. You propose to remove sterility testing from the annual batch long-term stability studies. This is not acceptable. Per FDA's "Guidance for Industry – Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products" (February 2008), package integrity testing may be used in lieu of sterility testing. However, this is a "replacement of the sterility test with an appropriate container and closure system test in the stability written testing program (referred to in this guidance as the stability protocol")." Therefore, you can retain your current sterility test (b)(4) TS/CCI in your annual stability studies or you can develop a package integrity test that will replace the sterility test for evaluation at the appropriate time points during the stability studies (i.e., at least annually and at expiry). If you choose to develop a new package integrity test, provide the analytical procedure, the validation report, and the revised annual stability protocol replacing the sterility test with the new package integrity test.

   Per the option in the question above, Medtronic provided documentation of their package integrity testing and assurance program to justify removal of the annual sterility testing requirement. Medtronic submitted documentation of their packaging integrity testing, and a revised Annual Stability Protocol for the Attain family of leads which included package integrity testing (b)(4) TS/CCI *in lieu of* (b)(4) TS/CCI *sterility testing. The CMC reviewer considered the response and found it acceptable from a CMC perspective per an email consult dated 3-26-2014. The CDER reviewer deferred review of the packaging integrity testing to CDRH. I reviewed the packaging integrity testing information provided by Medtronic on 3/20/2014. This information had been previously reviewed and approved for the same container (sterile barrier blister packages) under a number of Medtronic PMA submissions and found acceptable. I reviewed the information provided and agree that the packaging integrity testing methods are appropriate, and that annual testing will provide assurance that the sterile barrier is maintained over the shelf life of the Attain Ability product.*
   ACCEPTABLE RESPONSE

Recommendation: Approval (APPR)

All changes in the PMA supplement have been reviewed by CDER and CDRH, and have been found acceptable following completion of an initial review cycle followed by resolution of 4 questions during a Principally Interactive (PI) review process. There are no further concerns or questions and the supplement is recommended for approval CTS Code APPR.