SUMMARY OF: PMA # P830061/S086

CAPSURE SENSE LEAD, MEDTRONIC

EXECUTIVE SUMMARY/BACKGROUND
The purpose of this submission is to obtain approval for two primary changes to the currently approved CapSure Sense family of leads (P830061/S034, FDA approved July 23, 2002) through this PMA supplement: 1) A design change to remove the (b)(4) trade secret process from the lead tip electrode, while maintaining the primary source of steroid within the same Monolithic Controlled Release Device (MCRD) design, and 2) A manufacturing site change from one internal Medtronic location to another Medtronic location for the manufacture of the MCRD and the related update to proposed for drug related elements of the medical device. These changes are not being made as a result of field issues and are, respectively, to: 1) Improve the product manufacturing efficiency, and 2) Increase the evidence portfolio with regards to state of the art Chemistry, Manufacturing and Controls (CMC) information provided to FDA on Medtronic leads while decreasing potential for manufacturing variability. There were no design or manufacturing changes to the CapSure Sense lead bodies, connectors, intended use, indications for use, contraindications, or distal tip configurations, with exception of the two primary changes described, the removal of (b)(4) trade secret formula and MCRD manufacturing site change.

The firm has proposed to remove the (b)(4) trade secret formula from the tip electrode of the lead. The data provided by the firm appears to demonstrate that the MCRD contains sufficient drug to minimize inflammation around implant site and the (b)(4) trade secret formula almost entirely before inflammation begins. Overall, FDA believes the firm has adequately demonstrated from and engineering a clinical perspective that the lead remains safe and effective without the (b)(4) trade secret formula. The firm has thoroughly evaluated the leads with the proposed removal through the presented non-clinical studies and in-vivo assessment. There were no outstanding concerns related to this change.

The firm has proposed to move the manufacturing site for the MCRD. The change was reviewed by the Office of Compliance and a CDER Chemistry Manufacturing and Controls (CMC) reviewer. I have reviewed the information and concur with the two expert reviewers. OC provided a review of the information as it pertains to the Quality System regulations, 21 CFR 820. OC identified seven deficiencies related to the Manufacturing Site change and processes in the original submission. The OC deficiencies were sent to the firm in a letter dated May 23, 2013. The CMC reviewer identified five deficiencies in the original submission related to the MCRD component testing. An ODE Major Deficiency letter was sent to the firm June 14, 2013.

The firm responded, June 18, 2013, to the OC Deficiency letter with an amendment to the file (P830061/S086/A001). The responses were reviewed by the OC reviewer and were found to be adequate. The reviewer recommended approvable pending a site inspection as this was a (b)(4) trade secret process.
The firm also responded to the ODE Major Deficiency letter with an amendment to the file dated July 19, 2013 (P830061/S086/A002). The CMC reviewer identified three outstanding concerns with the responses to the ODE deficiency letter related to the MCRD component testing. FDA provided the concerns in an email dated August 16, 2013. The firm responded to the interactive review email September 11, 2013 with multiple emails. The CMC reviewer noted that the firm did not adequately address the concerns and requested the firm specifically address the concerns. A follow up email was sent to the firm dated October 1, 2013 to convey this concern. The firm responded with further justification as to why the data submitted in the submission was adequate to support the safety and effectiveness. Internal discussions were held to discuss the firm’s response. Following internal discussions it was determined that based on the data presented by the firm as well as past precedence of P080006/S006 (Attain Ability) the drug specification for the MCRD of [Redacted] was acceptable. However, it is recommended that limited testing based on the FDA analysis. All deficiencies have been resolved and inspection has been completed and found acceptable by the OC. Therefore, I recommend approval of this PMA supplement with a [Redacted].

### DESCRIPTION OF CHANGES/ REASON FOR SUPPLEMENT

A summary of models and sites affected, as well as proposed changes is provided below. Medtronic is proposing changes to the drug containing components of Models 4074, 4574 and 4073 leads.

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<tr>
<th>FDA Reference</th>
<th>Family Name</th>
<th>Model Number</th>
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<tbody>
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**Change #1:**

**Removal of [Redacted] from the lead tip electrode**

**Change #2:**

**Monolithic Controlled Release Device (MCRD) Manufacturing Site Change**

This change (part a) primarily involves moving the manufacturing location of the MCRD from one internal Medtronic location, MECC, to the Medtronic Rice Creek Facility. Within Change 2, a change (part b) occurs. In addition with this change (part c), the development and validation of
INDICATIONS FOR USE
The firm stated the indications for use for the Model 4074, 4574 and 4073 leads are not affected by these changes. Only modifications for consistency across approved Medtronic lead manuals have been made to remove reference to the legacy tined manuals.

The primary content of the indications will remain the same and are included below:

The Model 4074 implantable, ventricular, transvenous lead has application where implantable ventricular, single-chamber or dual-chamber pacing systems are indicated.

Model – 4073: The lead is intended for pacing in the ventricle.
Model – 4074: The lead is intended for pacing and sensing in the ventricle.
Model – 4574 - The lead is intended for pacing and sensing in the atrium.

DEVICE DESCRIPTION
The CapSure Sense family of leads was approved under P830061/S034 on July 23, 2002. Models 4074/4574 leads are implantable, transvenous, unipolar, steroid eluting, passive fixation pacing leads. Model 4073 is an implantable, transvenous, unipolar, steroid eluting, passive fixation pacing lead. The leads contain a the tip electrode.

The leads are designed to transmit stimuli from the pulse generator to the tissues of the heart and to deliver signals from the heart to the sense amplifier in the pulse generator.

FDA REVIEW

CHANGE #1 – DSP COATING REMOVAL

Non-Clinical Studies, Device Qualification, Verification and Validation
The CapSure Sense leads without will contain identical materials, distal tip design, lead body design, lead level and package specifications, and identical manufacturing processes (with exception of removing the process step) as the currently marketed CapSure Sense leads. Furthermore, the following evaluation has been performed to support this change. Medtronic has evaluated the CapSure Sense Leads through in vitro testing to assure suitability and reliability for the intended use. The major areas of in vitro testing and product assessment include the following categories.

- Bench Testing
- Design Verification Testing Impact assessment
- Packaging Qualification Equivalency
- Biocompatibility Certification Equivalency
- Sterilization Qualification Equivalency
- Shelf Life Assessment Equivalency
- Field Experience of Predecessor leads
- Risk Assessment

Bench Testing
The in-vitro bench testing includes mechanical testing, functional testing, dimensional testing, visual verification and analytical testing. Testing was conducted on CapSure Sense Leads during original design verification testing (DVT) and based on the impact assessment presented in the submission repeat of the original DVT was deemed not required.

LEAD REVIEWER COMMENTS: Based on the of the testing presented above, I agree with the firm’s assessment that the removal of the formula from the tip electrode appears to have to no impact on the testing. Much of the testing identified in the submission is mechanical in nature, or related to the connector. Therefore, it is acceptable to use this previously completed DVT testing, with the exception of the steroid testing. The testing will be reviewed by a clinical reviewer in the next section to determine the clinical benefit of on the tip electrode. The only concern I have is with the overall electrical performance of the lead as it relates to acute and chronic performance. This electrical performance of the lead will be reviewed as a part of the Animal and Clinical studies sections of this memo. There are no other concerns with the bench testing presented as it relates to change #1. Change #2 will be reviewed separately.

Testing
The testing was reviewed by a clinician to determine the clinical benefit of the . The recommendation was provided in a review memo dated May 28, 2013. The testing was conducted to demonstrate that, on average, >95% of analysis, and .

LEAD REVIEWER COMMENTS: The results for leads, demonstrated that the by process of that . The data seems to support the firm’s interpretation that to really impact the lead-tip . FDA considers this data and the justification behind it as strong clinical evidence that removing the is unlikely to measurably affect chronic electrical performance of the lead.

Biocompatibility
Biological evaluations have been performed on the materials that comprise the Model 4073, 4074, and 4574 leads in accordance with ISO 10993-1. The firm states removal or absence of the is not expected to impact the biocompatibility of the lead materials.
**LEAD REVIEWER COMMENTS:** As there are no changes to the materials that comprise the construction of the lead FDA agrees that the removal of the should not impact the biocompatibility of the lead.

**Packaging**
Packaging integrity testing was conducted to verify the effectiveness of the packaging components and to confirm the integrity of the sterile barrier of the product packaging when subjected to stress testing.

**LEAD REVIEWER COMMENTS:** FDA agrees with the firm that that package integrity is not affected by the removal of based on the minimal mass of the being removed. There are no concerns with this section of the review.

**Sterilization**
Sterilization validation testing was conducted to verify all products are sterilized to a minimum sterility assurance level (SAL) of $10^{-6}$. Ethylene Oxide (ETO) sterilization cycling completed during the original DVT testing.

**LEAD REVIEWER COMMENTS:** As this change only removes the from the tip electrode, FDA does not believe there will be an impact on the sterility of the lead. There are no further concerns with this section of the review.

**Shelf Life**
Medtronic holds two years of finished lead stability data representing multiple lead configurations, including the CapSure Sense family. Testing have been initiated on the modified design (4074 leads ). Further information in this regard is provided in the Section of the submission.

**LEAD REVIEWER COMMENTS:** Since there are no changes to the materials or packaging, from and engineering perspective FDA does not believe that the removal of the will have an effect on the approved shelf life of these leads. Further information regarding the will be provided in the review of this memo for both changes.

**Field Experience of Predecessor leads**
Please refer to the clinical studies portion of this memo for a review of this information.

**Risk Assessment**
Medtronic conducted a detailed risk analysis on safety hazards associated with the CapSure Sense leads in compliance with ISO 14971. Hazardous scenarios associated with lead design and manufacturing processes were analyzed.

The focus of the risk management process for the CapSure Sense Family of leads for this change was to identify and analyze the risks associated with from the lead compared to the currently approved CapSure Sense leads. It was determined that there are
no new attributes for the CapSure Sense Family of leads without compared to predecessor leads with.

The risk assessment activities focused on evaluating potential new/unique safety risks associated with the following:

- Design implementation and system reliability
- Manufacturing

**LEAD REVIEWER COMMENTS:** Overall, FDA agrees with the firm’s Risk Assessment from an engineering perspective. FDA believes that removal of the  does not increase the risk as it relates to design and manufacturing. The clinical reviewer will provide their expert assessment as the removal of the  related to the risk to the patients. Please refer to the clinical studies section of this review memo for further discussion.

**Manufacturing**
The manufacturing site information that was approved for the CapSure Sense lead family remains unchanged with exception of the removal of the  step.

The manufacturing process flow for the CapSure Sense lead with  is similar to the manufacturing process flow of existing CapSure Sense leads. The submitted manufacturing process flow diagram provides a high-level overview of the manufacturing process flow for the CapSure Sense leads with and without . Minor process updates were made with this change, in order to account for the . Only the process step which is applicable to  is removed with this change. All steps are identical with exception to the  step, which is eliminated.

**LEAD REVIEWER COMMENTS:** This section discusses the manufacturing changes related to Change #1 only. The manufacturing site change for the MCRD (Change #2) will be discussed in a separate section. FDA agrees that the only change to the manufacture process flow was the removal of the  step. No other changes were made to the approved process flow. Appropriate changes were also made to the manufacturing work instructions for the removal of this step. There are no further concerns with this section of the review.

**Animal Studies**
The animal study review was conducted by and expert veterinary reviewer in a review memo dated May 22, 2013. The purpose of this  canine study was to evaluate the electrical performance of the CapSure® Sense Family of Leads (Models 4074, 4574, and 4073). The Medtronic states that performance of the  The study hypothesis was that
The reviewer indicated this study had no safety signals emerged.

The animal study was also reviewed by a clinician in a review memo dated May 28, 2013. The clinician indicated the firm found no evidence that the measurements collected. This data is helpful but not strong in supporting the equivalence of

**LEAD REVIEWER COMMENTS:** Overall, I agree with the reviewer’s recommendations that the electrical report shows that much of the data from the studies. Additionally, I agree that the evidence is strong enough to a meaningful way. There are no further concerns with the animal studies section of this review memo.

**Clinical Studies**

The clinical review was conducted by an expert clinician in the branch in a review memo dated May 28, 2013. As indicated in pre-IDE discussions clinical data was not necessary to support the lead with provision of proven equivalent performance of both the electrical data in canines and equivalent, comparing cohorts. Therefore the clinical review focused on field data, a literature review, and a risk assessment.

The product performance report (PPR) was reviewed. Product performance reports have relative to this discussion:
FDA has previously expressed large scale concerns that PPR include a minor proportion of total performance concerns since they this reporting would not include failures for which leads were not returned. Also, leads are rarely returned no matter their performance, since lead extraction is usually not indicated or safe to perform unless specific clinical indications warrant.

- FDA would not expect product performance reports to which is the key issue under consideration in this file.

This literature review has relative to this discussion:

- which is the key issue under consideration in this file.

**LEAD REVIEWER COMMENTS:** Overall, I agree with the clinicians comments regarding the quality of the performance report and literature review. That being said I also agree the submission provides a sensible and reasonable justification for based on evidence collected on the bench showing that The justification and bench data are sufficient alone to support the change. No other concerns arise in this review and I agree with the reviewer’s approval recommendation for this change.

**Labeling**

The labeling review was conducted by me and the clinical reviewer. The clinical reviewer provided a review of the proposed labeling changes in a review memo dated May 28, 2013. supporting the change to Lead Technical Manuals in the submission.

Additionally, for ease of review, 

**LEAD REVIEWER COMMENTS:** FDA agrees that all changes proposed are acceptable. The changes were very simple in nature and did not add any inappropriate claims or misleading information. There are no further concerns with the proposed labeling. Following the initial review of the labeling the firm has indicated via email dated August 7, 2013 that they have made minor changes to the package labeling. In discussions with the firm I agreed that these minor changes could be included in the scope of this review
1. Clarification and formatting changes to globally align lead package labels across lead families.

The proposed changes to the labeling have been reviewed and FDA agrees that they are minor in nature as well as the appropriate target dose for the drug has been correctly added. There are no further concerns with the labeling.

Change #2 – MCRD Manufacturing Site Change

Non-Clinical Studies

LEAD REVIEWER COMMENTS: The MCRD Process Qualification was reviewed by myself and the Office of Compliance (OC). Based on our review of the qualification seems to be incomplete. This validation procedure does not contain or refer to production use. Additionally, the validation procedure should for data collection and analysis are used. The firm should address the previous statements before it can be determined if the consistently produces MCRDs that meet all predetermined specifications. Deficiencies were sent to the firm in a letter dated May 23, 2013 from OC. The firm responded to the OC deficiency letter with an amendment (PS30061/S086/A001) to the original submission. OC reviewed the responses to the letter in a memo dated July 17, 2013. The reviewer indicated that all of the OC concerns have been adequately addressed. The reviewer recommended approval pending inspection because . The site inspection was completed by OC and documented in a review memo dated February 10, 2014.

Chemistry Manufacturing Controls (CMC)
The MCRD Analytical Test Comparison Report in the submission included the following analyses: Appearance, Elution, Content Uniformity, Assay, and Degradation Products.

CDER CMC was consulted to review the manufacturing site change for the MCRD which included and new automated mixing process and tightening of the drug specifications. The review was provided in a review memo dated June 10, 2013. From CMC perspective, moving the manufacturing site of the steroid-containing components from Medtronic Energy and Component Center (MECC) to Medtronic Cardiac Rhythm Disease Management (CRDM) is acceptable. However, there were some issues related to
LEAD REVIEWER COMMENTS: Overall, I agree with the CDER reviewer’s comments. While the recommendation is that the site change information is adequate, I believe there are outstanding major concerns with the information presented. This submission centers on the change in the MCRD manufacturing site and therefore I believe a major deficiency letter should be sent to the firm to address these concerns. An ODE major deficiency letter was sent to the firm June 14, 2013 to address noted concerns.

The firm submitted an amendment (A002) to the original submission to address the CDER CMC concerns related to the MCRD drug specification. Most of the responses were justifications for why the data that was submitted in the original submission was sufficient while also providing clarifications. The response indicated that Medtronic received approval through P080006/S006 (Approved October 4, 2012) to release Attain Ability (4196) leads based on assay results from the MCRD with a similar analysis and similar results.

The responses were reviewed by CDER CMC in a review memo dated August 14, 2013. The reviewer noted outstanding concerns with the responses submitted by the firm. The reviewer believed that due to [Redacted] for the MCRD should be [Redacted]. The firm responded to the CDER concerns in an email dated September 11, 2013. The firm again provided justifications for why the submitted data was sufficient with relation to the testing of the MCRD. The firm also provided a copy of the requested 4074 MCRD installation process. The responses and justifications were reviewed by CDER CMC in a review memo dated September 26, 2013. The reviewer again had concerns with the responses. After discussions with the CDER review team, they felt the analysis was not satisfactory and that the [Redacted] was acceptable. However, it is recommended that the [Redacted] life of the finished lead. All deficiencies have been resolved except the final review of the inspection from OC.

Biopharmaceutics
CDER Biopharmaceutics was consulted to review the [Redacted] and site change. Drug [Redacted] and the leads have been marketed over the past 10 years [Redacted] was provided by the
CDER reviewer in a memo dated May 31, 2013. The reviewer had the following concluding comments:

- The proposed [trade secret] are adequate for quality control. Additional recommendations on the control standards.
- The manufacturing facility changes do not significantly impact the performance.

Additionally, the reviewer had two recommendations for the sponsor. As indicated in the memo from the reviewer the CDER comments are general advice comments and not major deficiencies.

LEAD REVIEWER COMMENTS: I agree with the CDER expert’s recommendation and it appears there are no further concerns with the [trade secret]. The CDER general advice comments in the reviewer’s memo will be sent to the firm via email.

Biocompatibility Evaluation
This evaluation was to demonstrate patient biological safety of the proposed manufacturing process/site changes. There were no changes added to any step of the [trade secret]. A Clinical History of Use is provided as well as an analysis of Historical Biological Safety Test Data.

LEAD REVIEWER COMMENTS: In order to demonstrate and MCRD parts made using the was performed on MCRD parts made using both processes to analyze both the . I agree with this approach and the analysis appears to show that the There has only been one change to the . That being said I agree that previously cited biological evaluation safety testing and clinical history of use contained in the BioEvaluation Report are considered applicable to support the biological safety of the [trade secret]. The biological evaluation report combined with the clinical history appears to demonstrate the proposed manufacturing site change for the MCRD do not significantly impact the biocompatibility of the MCRD.

GMP/Quality Systems
Change #2, MCRD Manufacturing Site Change was reviewed by the Office of Compliance (OC) in a review memo dated May 21, 2013. Since the change was to the combination (drug) component of the lead, MCRD, the change was classified by OC as a manufacturing site change. The MCRD is being treated [trade secret]
OC provided a review of the information as it pertains to the Quality System regulations, 21 CFR 820. OC identified seven deficiencies related to the Manufacturing Site change and processes. The deficiencies were sent to the firm in a letter dated May 23, 2013. The firm responded to the OC deficiency letter with an amendment to the original submission (P830061/S086/A001). OC reviewed the responses to the letter in a memo dated July 17, 2013. The reviewer indicated that all of the OC concerns have been adequately addressed. The reviewer recommended approval pending inspection because this is a combination product site change request. The site inspection was completed by OC and documented in a review memo dated February 10, 2014.

**Risk Management**

A Risk Assessment of this change was conducted to document any impact of the design and manufacturing changes to the CapSure Sense lead family and to identify whether any new hazards or risks are introduced to the lead accessories.

**LEAD REVIEWER COMMENTS:** Overall there were the MCRDs. There was only one change to the process, evaluated by CDER CMC review above. Overall the risk analysis seems appropriate.

The and site change described in this review memo were evaluated against and appropriate hazard scenarios. The firm has established a risk estimate (Green, Yellow, Red) and severity level (Major, Moderate, Minor). Based upon the risk assessment activities performed described in the submission, the incremental residual risk profile of the CapSure Sense leads is appears acceptable and has not increased based on the Change 1, or Change 2, MCRD manufacturing site changes. There are no further concerns with this section of the review.

**CONCLUSION**

**Change #1**

The firm has proposed to remove the from the tip electrode of the lead. The data provided by the firm appears to demonstrate that the . Overall, the firm has adequately demonstrated from an engineering and clinical perspective that the lead remains safe and effective. The firm has thoroughly evaluated the leads with the proposed changes through the presented non-clinical studies and in-vivo assessment. There were no outstanding concerns related to this change.

**Change #2 – MCR) Manufacturing Site Change**

The firm has proposed to move the manufacturing site for the MCRD. The change was reviewed by the Office of Compliance and a CDER Chemistry Manufacturing and Controls (CMC) reviewer. I have reviewed the information and concur with the two expert reviewers. OC provided a review of the information as it pertains to the Quality
System regulations, 21 CFR 820. OC identified seven deficiencies related to the Manufacturing Site change and processes in the original submission. The OC deficiencies were sent to the firm in a letter dated May 23, 2013. The CMC reviewer identified five deficiencies in the original submission related to the MCRD component testing. An ODE Major Deficiency letter was sent to the firm June 14, 2013.

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