

**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 Formula ) 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 (b)(4) Trade Secret Process 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 process 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 an engineering and 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 (b)(4) Trade Secret process. 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 (b)(4) Trade Secret formula was acceptable. However, it is recommended that (b)(4) Trade Secret formula be limited to (b)(4) Trade Secret formula 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 (b)(4) Trade Secret formula.

**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.

FDA Reference	Family Name	Model Number
P830061	CapSure Sense Lead	4074
	CapSure Sense Lead	4574
	CapSure Sense Lead	4073
	Vitatron Crystalline Lead	ICM09 <sup>1</sup>
	Vitatron Crystalline Lead	ICM09JB8 <sup>1</sup>
	Vitatron Crystalline Lead	ICM09B8 <sup>1</sup>

**Change #1:**  
**Removal of** (b)(4) Trade Secret formula **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) (b)(4) Trade Secret process occurs. In addition with this change (part c), the development and validation of (b)(4) Trade Secret process

(b)(4) Trade Secret process for MCRD components has occurred. Finally with this change (part d), the (b)(4) Trade Secret formula for MCRDs will be (b)(4) Trade Secret formula

### **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 titled 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 (b)(4) Trade Secret formula 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 (b)(4) TS will contain identical materials, distal tip design, lead body design, lead level and package specifications, and identical manufacturing processes (with exception of removing the (b)(4) Trade Secret process 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) (b)(4) Trade Secret process 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 (b)(4) Trade Secret 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 (b)(4) Trade Secret Process testing. The (b)(4) Trade Secret process testing will be reviewed by a clinical reviewer in the next section to determine the clinical benefit of (b)(4) Trade Secret formula 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.*

(b)(4) Trade Secret process Testing

The (b)(4) Trade Secret formula testing was reviewed by a clinician to determine the clinical benefit of the (b)(4) Trade Secret formula. The recommendation was provided in a review memo dated May 28, 2013. The (b)(4) Trade Secret process testing was conducted to demonstrate that (b)(4) Trade Secret process effectiveness. Results from the study demonstrate that, on average, >95% (b)(4) Trade Secret formula of analysis, and (b)(4) Trade Secret formula.

*LEAD REVIEWER COMMENTS: The results for (b)(4) Trade Secret process leads, demonstrated that the (b)(4) Trade Secret formula by process of (b)(4) Trade Secret formula that (b)(4) Trade Secret formula. The data seems to support the firm's interpretation that (b)(4) Trade Secret formula to really impact the lead-tip (b)(4) Trade Secret formula. FDA considers this data and the justification behind it as strong clinical evidence that removing the (b)(4) Trade Secret formula 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 (b)(4) Trade Secret formula 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 (b)(4) Trade Secret formula 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 (b)(4) Trade Secret formula based on the minimal mass of the (b)(4) TS 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 (b)(4) Trade Secret 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. (b)(4) Trade Secret formula testing have been initiated on the modified design (4074 leads (b)(4) Trade Secret formula). Further information in this regard is provided in the (b)(4) Trade Secret Section of the submission.

*LEAD REVIEWER COMMENTS: Since there are no changes to the materials or packaging, from an engineering perspective FDA does not believe that the removal of the (b)(4) Trade Secret formula will have an effect on the approved shelf life of these leads. Further information regarding the (b)(4) Trade Secret formula will be provided in the (b)(4) TS 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 (b)(4) Trade Secret formula 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 (b)(4) Trade Secret formula compared to predecessor leads with (b)(4) Trade Secret formula

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 (b)(4) Trade Secret formula 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 (b)(4) Trade Secret formula 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 (b)(4) Trade Secret formula step.

The manufacturing process flow for the CapSure Sense lead with (b)(4) Trade Secret formula 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 (b)(4) Trade Secret formula. Minor process updates were made with this change, in order to account for the (b)(4) Trade Secret formula. Only the process step which is applicable to (b)(4) Trade Secret formula is removed with this change. All steps are identical with exception to the (b)(4) Trade Secret formula 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 (b)(4) Trade Secret formula 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 (b)(4) Trade Secret formula canine study was to evaluate the electrical performance (b)(4) Trade Secret formula of the CapSure® Sense Family of Leads (Models 4074, 4574, and 4073). The (b)(4) Trade Secret formula Models 4074, 4574, and 4073. Medtronic states that performance of the (b)(4) Trade Secret formula

The study hypothesis was that (b)(4) Trade Secret formula  
1 (b)(4) Trade Secret formula

(b)(4) Trade Secret formula . Medtronic studied (b)(4) Trade Secret formula t options for (b)(4) Trade Secret formula

(b)(4) Trade Secret formula

The reviewer indicated this (b)(4) Trade Secret formula study had (b)(4) Trade Secret formula of the study data. First, the (b)(4) Trade Secret formula of the study (b)(4) Trade Secret formula . Second, review of the electrical report shows that (b)(4) Trade Secret formula .  
verall, 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 (b)(4) Trade Secret formula in the measurements collected. This data is helpful but not strong in supporting the equivalence of (b)(4) Trade Secret formula

*LEAD REVIEWER COMMENTS: Overall, I agree with the reviewer's recommendations that the electrical report shows that much of the data (b)(4) Trade Secret formula the studies. Additionally, I agree that the evidence from the (b)(4) Trade Secret formula is strong enough to (b)(4) Trade Secret formula 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 (b)(4) Trade Secret formula , comparing cohorts (b)(4) Trade Secret formula . 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 (b)(4) Trade Secret formula relative to this discussion:

(b)(4) Trade Secret formula

(b)(4) Trade Secret formula

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 (b)(4) Trade Secret formula which is the key issue under consideration in this file.

This literature review has (b)(4) Trade Secret formula relative to this discussion:

- (b)(4) Trade Secret formula . FDA would not expect a literature review to (b)(4) Trade Secret formula which is the key issue under consideration in this file.

*LEAD REVIEWER COMMENTS: Overall, I agree with the clinicians comments regarding the (b)(4) Trade Secret formula of the performance report and literature review. That being said I also agree the submission provides a sensible and reasonable justification for (b)(4) Trade Secret formula based on evidence collected on the bench showing that (b)(4) Trade Secret formula. 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. (b)(4) Trade Secret formula supporting the change to (b)(4) Trade Secret formula

Lead Technical Manuals in the submission. (b)(4) Trade Secret formula

the use of the (b)(4) Trade Secret formula

Additionally, for ease of review, (b)(4) Trade Secret formula

*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*

(b)(4) Trade Secret formula

1. Clarification and formatting changes to globally align lead package labels across lead families

(b)(4) Trade Secret formula

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

(b)(4) Trade Secret formula

testing was submitted to demonstrate that

(b)(4) Trade Secret formula

production use.

*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*

*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 (P830061/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 (b)(4) Trade Secret formula for the MCRD should be (b)(4) Trade Secret formula. 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 (b)(4) Trade Secret formula. Internal discussions were held to discuss the firm's responses. Following internal discussions it was determined that based on the data presented by the firm as well as (b)(4) Trade Secret formula was acceptable. However, it is recommended that the (b)(4) Trade Secret formula there is no change to the 2 year shelf 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 (b)(4) Trade Secret formula and site change. Drug (b)(4) Trade Secret formula

The CapSure Sense leads were approved by CDRH without a CDER consultative review of the drug component. As a result, (b)(4) Trade Secret formula and the leads have been marketed over the past 10 years (b)(4) Trade Secret formula was provided by the

CDER reviewer in a memo dated May 31, 2013. The reviewer had the following concluding comments:

- The proposed (b)(4) Trade Secret formula are adequate for quality control. Additional recommendations on the (b)(4) Trade Secret formula control standards.
- The manufacturing facility (b)(4) Trade Secret process changes do not significantly impact the (b)(4) Trade Secret formula 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 (b)(4) Trade Secret formula. 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 (b)(4) Trade Secret formula added to any step of the (b)(4) Trade Secret formula. 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 (b)(4) Trade Secret formula and MCRD parts made using the (b)(4) Trade Secret formula was performed on MCRD parts made using both processes to analyze both the (b)(4) Trade Secret formula. I agree with this approach and the analysis appears to show that the (b)(4) Trade Secret formula. There has only been one change to the (b)(4) Trade Secret formula.*

*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 (b)(4) Trade Secret formula. 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 (b)(4) Trade Secret formula

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 (b)(4) Trade Secret formula the MCRDs. There was only one change to the process, (b)(4) Trade Secret formula. This process was evaluated by CDER CMC review above. Overall the risk analysis seems appropriate.*

*The (b)(4) Trade Secret formula 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, (b)(4) Trade Secret formula or Change 2, MCRD manufacturing site changes. There are no further concerns with this section of the review.*

### **CONCLUSION**

#### **Change #1 – (b)(4) Trade Secret formula**

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 (b)(4) Trade Secret formula

. Overall, the firm has adequately demonstrated from an engineering and clinical perspective that the lead remains safe and effective (b)(4) Trade Secret formula. The firm has thoroughly evaluated the leads with the proposed (b)(4) Trade Secret formula 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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