SUMMARY MEMO P080006/S073
ATTAIN PERFORMA MODELS 4398 AND4598

EXECUTIVE SUMMARY:

Medtronic has submitted this 180-Day PMA Supplement to request approval for the Attain Performa Model 4398 and 4598 Left Ventricular (LV) Quadripolar Leads. Medtronic's first quadripolar lead, the Attain Performa model 4298 – was approved on August 1, 2014 (P080006/S068). The subject leads are the remaining two leads in the Attain Performa Family. The lead designs are based on the commercially available 4196, 4296 and 4396 Attain Ability leads. These leads contain 4 electrodes designed to function as cathodes or anodes, depending on how the device LV pacing polarity is programmed:

- Electrode LV1, the distal electrode, positioned near the distal tip of the lead
- Electrode LV2, positioned 21 mm proximal to electrode LV1
- Electrode LV3, positioned 1.3 mm proximal to electrode LV2
- Electrode LV4, the proximal electrode, positioned 21 mm proximal to electrode LV3

The lead has application as part of a Medtronic biventricular pacing system. The outer lead body insulation is polyurethane and the conductor wire inner insulation is soluble imide polyimide (SI-PI). (b) (4) [redacted]. The Attain Performa Leads use a silicone tip seal to minimize blood ingress into the lead lumen. The lead is implanted using a guide wire, hybrid guide wire or stylet in conjunction with a Medtronic 5.7 Fr guide catheter. The Attain Performa Model LV Leads contain 4 MCRDs with a total dose of 288ug. The MCRDs are identical to those used on the Attain Ability leads.

To support approval for this lead the firm has submitted the results of their premarket clinical study. Additionally, the firm has submitted in-vitro bench testing, in-vivo animal studies, biocompatibility, manufacturing, and drug component testing.

During the initial review 10 minor deficiencies were noted by the review team. Many of the deficiencies appear to be clarification questions regarding the statistical analysis from the clinical study as well as the proposed post approval study (PAS). There were no concerns noted from the CDER reviewers related to the stability protocol or the requested shelf life. Based on the nature of the concerns and discussions with the firm regarding a response strategy and timeline, the questions were sent to the firm interactively. A teleconference was held with the firm Thursday November 6, 2014 and Friday November 7, 2014 to discuss the proposed responses. All responses to the FDA concerns were received November 14, 2014. All outstanding concerns have been adequately addressed as noted in this memo. Therefore, I recommend approval of the Models 4398 and 4598.

REGULATORY HISTORY:

Multiple discussions between FDA and Medtronic were held under Pre-Submission (b) (4) related to the Attain Performa leads and the clinical investigation. The table below provided (b) (4) .

Submission	Date(s)	Rationale/Purpose of Submission / Meeting	Principle Outcomes
(b) (4)			

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(b) (4)			

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(b) (4)			

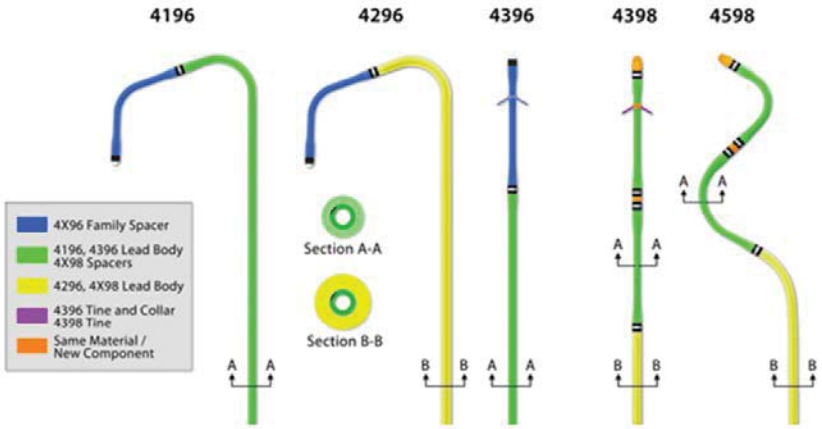
VectorExpress (Pre-Submission (b) (4)
A separate Pre-Submission was initiated in parallel for the LV Automated Test (VectorExpress™ is the market name for this feature, internally this feature has been referred to as QP Easy, and to FDA this feature was called the LV Automated Test) (b) (4) . Following discussions related to VectorExpress FDA agreed with the proposed testing strategies for software, firmware, systems testing, and GLP animal study. With respect to no clinical data being required for approval of the LV Automated Test feature, FDA will not require human clinical data – but FDA did encourage Medtronic to consider some type of "limited confirmation or evaluation of the LV Automated Test feature" in the Quadripolar lead (Attain Performa) clinical study (b) (4) .

(b) (4) **Attain Performa Clinical Study**
See below for a description of the clinical study.

DEVICE DESCRIPTION:
The Attain Performa Leads (Models 4398 and 4598) are steroid eluting, quadripolar electrode (4-pole), transvenous, over-the-wire (OTW), IS4 compatible, cardiac vein pacing lead with 5.3 French proximal and 3.9 French distal lead body diameters. The outer lead body insulation is polyurethane and the conductor wire inner insulation is soluble imide polyimide (SI-PI). (b) (4) .
The Attain Performa Leads use a silicone tip seal to minimize blood ingress into the lead lumen. The lead is implantable using a guide wire, hybrid guide wire or stylet in conjunction with a Medtronic 5.7 Fr guide catheter.

The Attain Performa Leads contain four electrodes: the first electrode (LV1) is a ring positioned at the distal tip of the lead, the second electrode (LV2) is a ring nominally 21 mm proximal from the tip, the third electrode (LV3) is a ring nominally 1.3 mm proximal from the second electrode, and the fourth electrode (LV4) is a ring nominally located 21 mm

proximal from the third electrode. The Attain Performa Leads use a total of four ring electrode/monolithic controlled release devices (MCRDs), which are identical to the ring electrode / MCRDs for the Attain Ability leads. The design of the Attain Performa Leads are based on the 4196, 4296 and 4396 Attain Ability leads. The Attain Performa Model 4398 lead is straight with tines bonded to the LV1 to LV2 spacer at the distal end to provide fixation, similar to the model 4396 lead. The Attain Performa Model 4598 lead has an S-shaped curve at the distal end. This is the first Medtronic lead with this fixation shape.



The Attain Performa Leads use many of the same components, manufacturing steps, fixation shapes/mechanisms, electrode spacings (21mm), ring electrodes with dexamethasone acetate loaded MCRDs, and SI-PI insulated wire filars as the market approved Attain Ability leads 4196, 4296, and 4396 The Attain Performa Leads use the same lead body tubing from the connector to the most proximal electrode (LV4) as the model 4296. The Attain Performa Leads combine these common attributes with the four pole technology that is available with the ballot approval of the ISO 27186 Four Pole Connector Standard. The figure below depicts the IS4 connector for the Attain Performa Leads compared to the IS-1 connector for the Attain Ability leads.

Models	Connector Configuration
4196/4296/4396 Attain Ability	
4298/4398/4598 Attain Performa	

The table below provides a detailed comparison of the Attain Ability Family of leads to the Attain Performa Model Leads.

	Attain Ability			Attain Performa		
Design Feature	**Model 4196**	**Model 4296**	**Model 4396**	**Model 4298[6]**	**Model 4398** (subject of this submission)	**Model 4598** (subject of this submission)
Implant Method	Guide wire, Stylet, or hybrid guide wire via Medtronic Delivery System	Same as 4196	Same as 4196	Same as 4196	Same as 4196	Same as 4196
Delivery System Inner Diameter	≥ 5.7 Fr ID	Same as 4196	Same as 4196	Same as 4196	Same as 4196	Same as 4196
Lead body diameter	4 Fr proximal / 3.4 Fr distal	5.3 Fr proximal / 3.4 Fr distal	4 Fr proximal / 3.4 Fr distal	5.3 Fr proximal / 3.9 Fr distal	5.3 Fr proximal / 3.9 Fr distal	5.3 Fr proximal / 3.9 Fr distal
Lead Body Conductor	Single Bifilar Coil (Multiconductor)	Same as 4196	Same as 4196	Single Quadfilar Coil (Multiconductor)	Single Quadfilar Coil (Multiconductor)	Single Quadfilar Coil (Multiconductor)
Conductor Material	Ag core-low Titanium MP35N coil	Same as 4196	Same as 4196	Same as 4196	Same as 4196	Same as 4196
Insulation (Outer/Inner)	Polyurethane 55D SI-PI	Same as 4196	Same as 4196	Same as 4196	Same as 4196	Same as 4196
Polarity	Dual electrode	Same as 4196	Same as 4196	Selectable Quad-electrode	Selectable Quad-electrode	Selectable Quad-electrode
Electrode Material	Pt/Ir/ Pt/Ir alloy with TiN coating	Same as 4196	Same as 4196	Same as 4196	Same as 4196	Same as 4196
Electrode Spacing	21mm	Same as 4196	Same as 4196	21mm / 1.3mm / 21mm	21mm / 1.3mm / 21mm	21mm / 1.3mm / 21mm
Surface Area per electrode (mm^2)	5.8	Same as 4196	Same as 4196	Same as 4196	Same as 4196	Same as 4196

	Attain Ability			Attain Performa		
Design Feature	**Model 4196**	**Model 4296**	**Model 4396**	**Model 4298[6]**	**Model 4398** (subject of this submission)	**Model 4598** (subject of this submission)
Steroid and Dose/ MCRD	Dexamethasone acetate Tip 160ug and Ring 72µg	Same as 4196	Same as 4196	Dexamethasone acetate Each (4) Ring 72µg	Dexamethasone acetate Each (4) Ring 72µg	Dexamethasone acetate Each (4) Ring 72µg
Total Target Dose	232 µg/lead	Same as 4196	Same as 4196	288 µg/lead	288 µg/lead	288 µg/lead
Molded Tip Seal	Silicone (with steroid)	Same as 4196	Same as 4196	Silicone (without steroid)	Silicone (without steroid)	Silicone (without steroid)
Fixation Method	Compound Curve	Same as 4196	Straight with Tines	Same as 4196	Straight with Tines	S-curves
Connector	IS-1	Same as 4196	Same as 4196	IS4	IS4	IS4
Length (cm)	20-110	Same as 4196	Same as 4196	78 and 88 cm	78 and 88 cm	78 and 88 cm

The Attain Performa Leads are part of an implanted cardiac resynchronization therapy / cardioversion-defibrillator (CRT-D) system. The Attain Performa Leads will be packaged with the following accessories that are the same as the Attain Ability:

- Guide wire insertion tool (1)
- Guide wire clip (1)
- Guide wire torque tool (1)
- Radiopaque anchoring sleeve pre-loaded onto the lead
- Extra stylets:
- Gray knob, 0.014 inch diameter (2)
- Purple knob, 0.016 inch diameter (2)
- AccuRead 2.0 analyzer cable interface tools (2) – one pre-loaded onto the lead

INDICATIONS FOR USE

The Attain Performa models 4398 and 4598 steroid-eluting, quadripolar electrode, IS4 transvenous lead are indicated for chronic pacing in the left ventricle via the cardiac vein, when used 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.

SUMMARY OF CLINICAL AND NON-CLINICAL DATA

To support PMA approval, the firm has submitted comprehensive bench testing, comprehensive animal study testing, as well as clinical information for the Attain Performa Quadripolar Leads.

Attain Performa Quadripolar Leads

- Comprehensive bench testing
  - Risk Assessment
  - Biocompatibility
  - Mechanical/Electrical (DVT)
  - Packaging
  - Sterilization
  - Shelf life
  - Steroid component (CMD & PK)
- Comprehensive animal study testing
  - (b) (4) Chronic Evaluation of Blackwell Quadripolar CRT-D Device and Model 4298 and 4398 Quadripolar Lead
  - (b) (4) Chronic Evaluation of Model 4598 Quadripolar Lead
- Clinical Study

LEAD REVIEWER COMMENTS: The bench testing, animal study testing, and previous testing were all reviewed by expert consultants as documented in individual review memos and summarized in the sections below.

CLINICAL STUDY OVERVIEW

The firm conducted a prospective, non-randomized, multicenter, single-arm, global clinical investigation. The firm has provided appropriate inclusion and exclusion criteria for the study. The clinical study evaluated the safety and efficacy of the Attain Performa Leads independently. The analysis for the primary study objectives were done independently for this lead model. This clinical investigation was conducted in the United States, Canada, Europe, and Australia and may include sites in Asia, the Middle East, Africa, India, and Latin America, or other geographies to support this marketing application.

Sample Sizes (Total 1210 Subjects):

- Lead Model 4298 will consist of 523 subjects.
- Lead Model 4398 will consist of 377 subjects.
- Lead Model 4598 will consist of 310 subjects.

Safety endpoints: Lead complication-free rate at 6 months

- The Attain Performa Model 4298 lead will be considered safe if the probability of subjects free of Attain Performa lead-related complications at 6 months post-implant is greater than 87% (i.e., the one-sided 97.5% lower confidence bound must be greater than 87%).

- The Attain Performa Model 4398 lead will be considered safe if the probability of subjects free of Attain Performa lead-related complications at 6 months post-implant is greater than 87% (i.e., the one-sided 97.5% lower confidence bound must be greater than 87%).

- The safety performance of the Attain Performa Model 4598 lead will be characterized by summarizing the probability of subjects free of Attain Performa lead-relate complications at 6 months post-implant. There is no pass or fail criteria defined for this objective.

Efficacy endpoints:

- The Attain Performa leads will be considered effective if the proportion of subjects with a final programmed LV lead pacing polarity having a pacing capture threshold less than or equal to 2.5 V at 0.5ms pulse width at 6 months post-implant is greater than 80% (i.e., the one-sided 97.5% lower confidence bound must be greater than 80%).

- The Attain Performa leads will be considered effective if the proportion of subjects with a non-programmed LV lead pacing polarity having a pacing capture threshold less than or equal to 4.0 V at 0.5ms pulse width at 6 months post-implant is greater than 81% (i.e., the one-sided 97.5% lower confidence bound must be greater than 81%).

ATTAIN PERFORMA QUADRIPOLAR LEAD (MODELS 4298, 4398, AND 4598) REVIEW

CLINICAL/LABELING REVIEW

The clinical review was documented in a review memo dated 24 October 2014. The clinical trial results show that the Models 4398 and 4598 LV quadripolar leads met their safety and efficacy endpoints. The adverse events (AEs) that did occur were typically dislodgements and extra-cardiac stimulation. Interestingly there were occasional reports of connection issues. There were no serious LV lead AEs due to dissection, perforation, or tamponade. The deaths were reviewed and did not appear to be related to the LV lead. Although there were some missing data for both leads at 6-months, the tipping point analysis was reassuring and did not indicate that the missing data would change the overall results (Refer to statistics review below). Although clinically useful data such as the mean number of available vectors at <2.5V or <3.0V was not provided for these leads (extra-cardiac stimulation thresholds were presented instead) the overall data suggests that most patients had more than one vector available to them. The labeling was also acceptable except for two minor requests to update the final data and use the term "lead dislodgement" which is clearer than "device dislocation."

The firm responded to the two clinical/labeling concerns stating that at the time of the PMA-S analyses, the clinical study was ongoing; therefore, the disposition of patients who have not yet reached their 6 month follow-up visit is presented as such. This approach is consistent with the clinical study summary for the Attain Performa Model 4298 lead (P080006/S068, approved August 1, 2014). Additionally, the firm has agreed to make the requested change of the term device dislocation. I believe the response is acceptable as the labeling captures the data that was used to support this PMA. I asked the firm to review data collected after the submission of the PMA in order to identify any additional adverse events that could be used to inform the labeling. A discussion was held with the firm Friday November 7, 2014, where it was determined that no additional information was needed for the labeling. There are no further concerns with this section of the review.

STATISTICAL REVIEW

The statistical review was documented in a review memo dated 31 October 2014. This PMA supplement included separate clinical reports on Model 4398 and Model 4598 leads. It appears that the primary safety and effectiveness objectives have been met. (b) (4)

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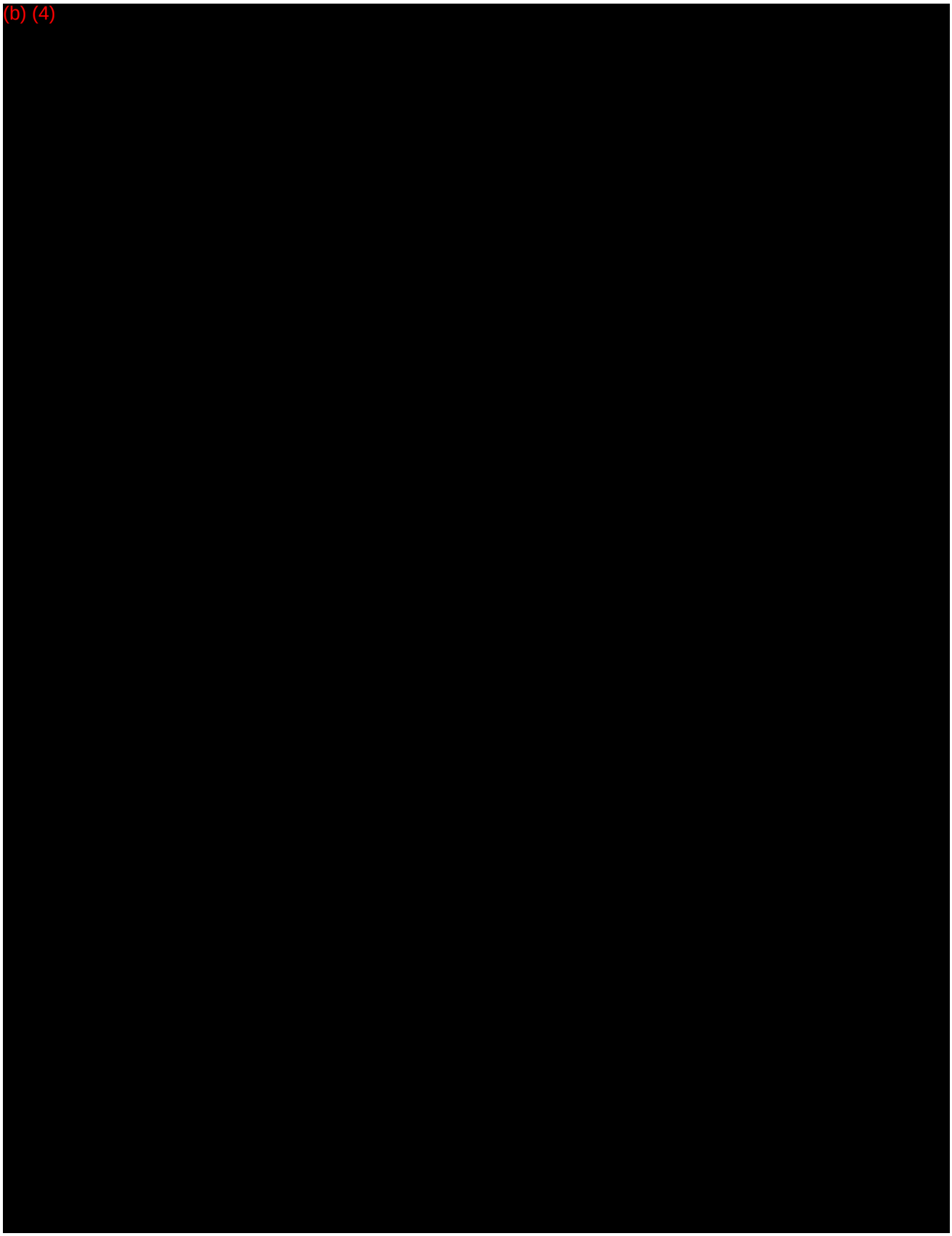

(b) (4)
actually attempted on that subject.

(b) (4)
(b) (4) . The statistical reviewer indicated that the responses were acceptable. There are no further statistical concerns.

ANIMAL STUDY REVIEW

The animal studies submitted to support this PMA/s were identical to those submitted under the Original IDE (b) (4) I have chosen to include the review memos from the IDE as a part of this PMA review without requesting an additional consult review. The animal study review was documented in a review memo for (b) (4) The review included three GLP studies: two chronic (26 week) studies of the Attain Performa Quadripolar Leads and one study of the automatic PCT measurement function of the Viva CRT-D.

The two chronic leads studies related to this submission were:

- (b) (4): Chronic Evaluation of Blackwell Quadripolar CRT-D Device and Model 4298 and 4398 Quadripolar Lead
- (b) (4): Chronic Evaluation of Model 4598 Quadripolar Lead

All concerns noted during the review of the Original IDE were adequately addressed. No new or additional data pertaining to the animal studies was submitted to support this PMA. The animal studies presented supported the initiation of the clinical trial and provide additional information to support a reasonable assurance of safety and effectiveness of these lead models. There are no further concerns with this section of the review.

ENGINEERING REVIEW

The engineering review was documented in a review memo dated 03 November 2014. The review memo covered the Mechanical/ Electrical bench testing for the Attain Performa Leads. It was noted that much of the testing that was submitted to support this PMA/s was identical to that submitted for the Original IDE (b) (4) and the Model 4298 PMA/s (P080006/S068-Approved August 1, 2014). All of the testing submitted was re-reviewed and found to be acceptable. The review included the interactive discussions that were held during the review of the Original IDE in his consult memo. The firm had provided responses to concerns related to stylet perforation, simulated implant handling, and an analysis of abrasion following flex fatigue testing. All concerns were adequately addressed by the sponsor interactively during the review of the IDE. There were no new questions or concerns identified for the provided bench testing.

STERILIZATION, PACKAGING, SHELF LIFE, AND MANUFACTURING REVIEW

The sterilization, packaging, shelf life, and manufacturing review was documented in a review memo dated November 3, 2014. The review assessed the information and testing provided and found the firm provided information and testing that was appropriate and

acceptable to support this PMA/s. The majority of the information provided was identical that submitted for the Attain Performa Model 4298 LV lead, approved August 1, 2014.

All manufacturing changes post DVT provided by the firm have been reviewed and found acceptable as there appeared to be no impact to the DVT units. The firm also provided a listing of previously reported annual reportable changes and previously submitted changes (30Day Notices and Real-Time Supplements). There were no new previously-reported Annual Reportable changes applicable to the Attain Performa model 4398 and 4598 leads

There were no noted changes to the sterilization process as the firm was adopting this lead family into their already existing process. This process has already been approved for the Model 4298. The firm provided and adequate process challenge device and the process appear to be capable of sterilizing these new lead models. The review of the shelf life information was only from an engineering perspective. The review also covered the package testing and mechanical performance information provided by the firm. There were no concerns with the package testing or mechanical performance. The reviewer deferred the drug stability portion of the review to the CDER reviewer. Please refer to the drug component reviews below for any shelf life concerns due to drug stability.

BIOCOMPATILITY REVIEW

The biocompatibility documentation for the Attain Performa models 4398 and 4598 Left Ventricular leads is identical to that which was submitted and approved as part of the Attain Performa model 4298 Left Ventricular lead submission (P080006/S068, approved August 1, 2014). I have included the consult review memos for the Model 4298 for completeness.

DRUG COMPONENT REVIEWS (Chemistry Manufacturing and Controls and Elution)

The drug component Chemistry Manufacturing and Controls (CMC) review was performed by a CDER reviewer. The review is documented in a review memo dated 23 October 2014. The CMC information provided for the two new Attain Performa lead models (4398 and 4598) was found to be acceptable. Most of the data referred to the previous submission (P080006/S068) for the first Attain Performa lead model (4298). The new models (4398 and 4598) of the Attain Performa family of leads can be granted the same expiration date of 2 years as the Attain Performa Model 4298 Lead and the Attain Ability family of leads (when stored at controlled room temperature). There were no additional concerns.

The drug component Biopharmaceutics review was performed by a CDER reviewer and documented in a review memo dated 23 October 2014. The reviewer indicated the proposed drug elution method, using (b) (4) is adequate for the quality control testing of Attain Performa model 4398 and 4598 MCRD components and finished leads. The following additional recommendation on the method is provided to support the firm's continued efforts to improve their quality control standards:

"As part of your continuous improvement efforts, we recommend that you more closely evaluate the ability of the drug elution method to detect meaningful manufacturing or process changes that could impact drug elution performance."

The following proposed drug elution acceptance criteria for the MCRD components and finished leads are acceptable as part of the quality control of the Attain Performa lead models 4398 and 4598.

Time (hours)	%LC Released
(b) (4)	

The elution test and acceptance criteria will follow the stage testing as outlined in USP <724>. There were no additional concerns.

POST APPROVAL STUDY REVIEW

The proposed PAS was reviewed and documented in a review memo dated 13 June 2014. Overall, the PAS appeared to be complete and contain all the required elements with one minor concern. In the section "C.1.3: Sample Size Requirements for Primary Objective", the proposed a minimum enrollment of 1,778 Attain Performa leads, which is expected to result in approximately 1,050 leads followed for 5-years. The proposal did not include a plan for poolability analysis. This is needed to verify the data from each lead model can be combined for analysis. The study protocol should be revised to include a poolability analysis plan. This concern was sent to the firm interactively. The review of the initial response raised a couple of questions. The firm was asked via email to address the following:

1. Please add a column to Table 1 for studied enrollment that is counted with attrition in 5 years.
2. Please change "Anticipated enrollment" to "Minimum enrollment"
3. FDA would like to have information on lead safety performance, such as dislodgement rate or perforation rate, by lead model accounted for in the PAS
4. Please provide clinical distribution for Attain Ability Model 4196, 4296, and 4396
5. A formal poolabilty analysis would be ideal. However, the proposal is acceptable if you can provide more details on the stratified analysis
6. Although the lower bound of the below 92.5% for Model 4398 is a concern, we understand the sample size may be limited because of the distribution of this model. We do want to make sure the minimum enrollment is achieved and the poolability analysis is evaluated.

The firm provided the requested updates via email and an updated version of the protocol. The PAS reviewer indicated in a memo dated December 2, 2014 that the responses were acceptable. There are no further concerns.

CONCLUSION AND RECOMMENDATION:

Recommendation: Approval

During the initial review (b) (4) minor deficiencies were noted by the review team. Many of the deficiencies appear to be clarification questions regarding the statistical analysis from the clinical study as well as the proposed PAS. There were no concerns noted from the CDER reviewers related to the stability protocol or the requested shelf life. Based on the nature of the concerns and discussions with the firm regarding a response strategy and timeline, the questions were sent to the firm interactively. A teleconference was held with the firm Thursday November 6, 2014 and Friday November 7, 2014 to discuss the proposed responses. All responses to the FDA concerns were received November 14, 2014. All outstanding concerns have been adequately addressed as noted in this memo. Therefore, I recommend approval of the Models 4398 and 4598.