



MEMORANDUM

SUMMARY OF:

P950037/S105
P000009/S049
P050023/S053
P070008/S031
Evia HF/HF-T Family of CRT-Ps
Biotronik

BACKGROUND

This PMA Supplement proposes a new family of cardiac resynchronization therapy pacemakers (CRT-Ps) designated as Evia. The Evia CRT-P functions are based on BIOTRONIK's legally marketed Stratos LV I Stratos LV-T CRT-Ps (P070008, dated May 12, 2008). The Evia CRT-Ps are based on the same unified hardware platform as the currently approved Evia single and dual chamber devices (P950037/S72, dated May 7, 2010) with the additional capabilities of biventricular pacing for CRT.

The Evia CRT-Ps contain the same feature set as the legally marketed Evia family of pulse generators (P950037/S72, dated May 7, 2010) and Stratos CRT-Ps. In addition to these core functions, the Evia CRT-Ps will have the following:

- Thoracic Impedance (TI)
- Left ventricular capture control
- Additional Left ventricular (LV) Pacing Configurations
- Home Monitoring data from CRT pacing

In order to utilize the Evia family of CRT-Ps, the current market-released programmer software version (b) (4) has been modified to include the application for programming the Evia family of CRT-Ps as well as implementation of minor changes and bug fixes. The updated programmer software will be identified as (b) (4) and include all of BIOTRONIK's current US legally marketed pulse generators and ICDs.

In **Amendment A001**, the sponsor responded interactively to FDA's request for additional information during review of the original submission.

In **Amendment A002**, the sponsor has responded to the major deficiencies identified during review of the original submission. The sponsor is also proposing an updated version of programmer software which implements minor modifications to existing programmability and is identified as (b) (4) and includes all of Biotronik's current US legally marketed pulse generators, CRT-Ps, ICDs, and CRT-Ds.

INDICATIONS FOR USE

The Indications For Use (IFU) in the original submission is incorrect. The sponsor sent an updated Indications For Use and Contraindications via email. The corrected IFU is listed below.

The Evia HF and Evia HF-T Cardiac Resynchronization Therapy Pacemakers (CRT-Ps) are indicated for patients who have moderate to severe heart failure (NYHA Class III/IV), including left ventricular dysfunction (EF ≤ 35%) and QRS ≥ 120 ms and remain symptomatic despite stable, optimal heart failure drug therapy.

The corrected Contraindications are listed below:

Use of Evia HF and Evia HF-T CRT-Ps are contraindicated for the following patients:

- Unipolar pacing is contraindicated for patients with an implanted cardioverter-defibrillator (ICD) because it may cause unwanted delivery or inhibition of ICD therapy.
- Single chamber atrial pacing is contraindicated for patients with impaired AV nodal conduction.
- Dual chamber and single chamber atrial pacing is contraindicated for patients with chronic refractory atrial tachyarrhythmias.

DEVICE DESCRIPTION

The Evia CRT-Ps contain the same feature set as the legally marketed Evia family of pulse generators (P950037/S72, dated May 7, 2010) and Stratos CRT-Ps.

In addition to these core functions, the Evia CRT-Ps will have the following:

- Thoracic Impedance (TI)
- Left ventricular capture control
- Additional Left ventricular (LV) Pacing Configurations
- Home Monitoring data from CRT pacing

The Home Monitoring models of the Evia CRT family can be utilized with BIOTRONIK's currently approved Home Monitoring Service Center (P950037/S66, dated November 21, 2008; and P950037/S69, dated March 23, 2009). The method of data transmission from the Evia / Entovis HF-T to the patient device remains unchanged as compared to Evia.

The product requirements document (LTH-114-163) for Evia HF / HF-T is provided in Appendix 2 of the original submission.

CHANGES

Hardware

The hardware of the Evia CRT is based on the hardware currently used for the Evia family of pulse generators (P950037/S72, dated May 7, 2010). The header and feedthrough configurations were modified to support three ports and the module was updated to support the CRT device. All other hardware components, such as the titanium housing, epoxy resin header, IS-1 connectors, and batteries are identical to those used in Evia.

The header for Evia CRT is modified to include three ports (LV, RA, RV) and a slightly revised antenna (b) (4) in the (b) (4). The antenna was slightly modified for alignment reasons within the larger header. In addition, the laser etching on the housing will now also reference the third lead port "LV".

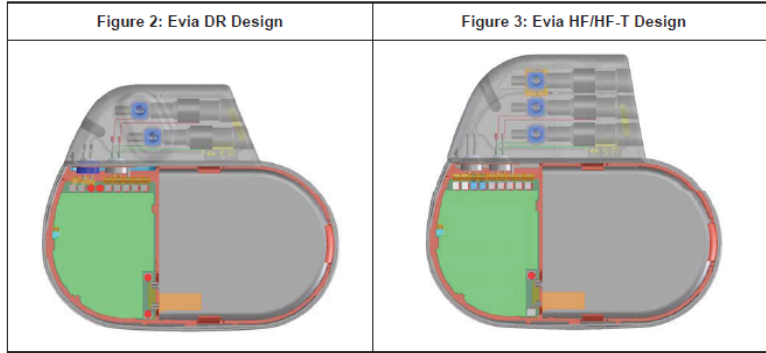
In order to support biventricular (BiV) pacing in backup mode and to increase manufacturing yields, the following ICs were updated in order to support the CRT device:

- Controller IC (CIC)
- Mixed Maple IC (MMIC)

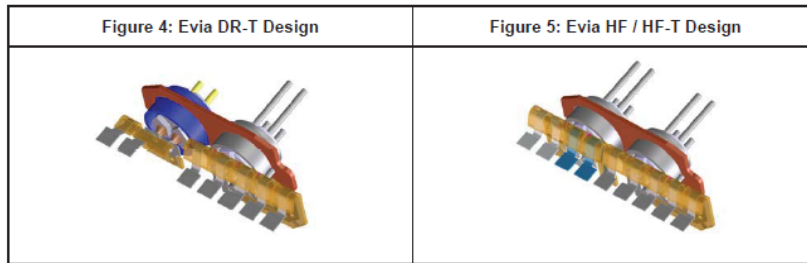
These ICs were approved with the unified platform for Evia through P950037/S72 on May 7, 2010. The ROM mask in the CIC was updated to support CRT pacing in back-up modes and updates to the MMIC were made to improve production yields.

The feedthrough configuration was updated to support the third lead/port. Evia DR-T used (b) (4) (b) (4)

There are no differences in the battery.



Additional (b) (4) to connect the (b) (4) to the (b) (4) for the (b) channel were added to the current Evia devices. Figure 4 shows the current Evia DR-T configuration which includes (b) (4) and Figure 5 shows the new (b) (4) which is connected to the (b) (4). The additional pads to support the (b) (4) are marked in blue.



The current Evia DR-T electronic module was designed to support a CRT device with the additional pads to place the necessary components for a CRT device included in the module. (b) (4)

following figures:

- (b) (4)

In addition, to support of (b) (4) in backup mode and improvement of (b) (4) the ICs (CIC and MMIC) were updated. The batteries utilized in the Evia HF / HF-T devices are a (b) (4) of those currently approved for use with Evia devices and are referenced as (b) (4) batteries.

A technical comparison summary of the Evia HF/HF-T, Evia, and Stratos pulse generators is shown below.

	Evia CRT	Evia	Stratos
Product variants	HF, HF-T	DR, DR-T, SR, SR-T	LV, LV-T
Titanium housing with physiologic shape	Identical		Identical material, different form factor
Epoxy - Header	(b) (4)	Identical material	Identical material
Connector ports	(b) (4)	DR(-T): 2*IS-1 SR(-T): 1*IS-1	LV(-T): 3*IS-1
Feedthroughs	(b) (4)	DR: 2*bipolar DR-T: 1*quadropolar, 1*bipolar SR: 1*bipolar SR-T: 2*bipolar	1*hexapolar 1*bipolar
Communication Coil	Identical		Different Coil
RF Antenna	(b) (4) change to Evia (See 4.2.1)		Different antenna
Electronic Module	Minor enhancements to Evia module (see Section 4.2.5)	FR-4 substrate with Controller IC and Mixed Maple IC	Ceramic substrate with Draco IC, Stratos IC, External RAM, and RF transmitter circuit
Batteries	GB 2596 LiS 3150M	GB 2596 GB 8431 LiS 3150 LiS 3150M	GB 8431 LiS 3150
Firmware	(b) (4)	FW 3.0	LV = FW 3.4.2 LV-T = FW 3.4.4

Firmware

With this PMA Supplement, BIOTRONIK is also introducing (b) (4) firmware for the Evia HF / HF-T family of devices. The firmware, embedded software, of the Evia HF /HF-T devices is stored in the (b) (4) and (b) (4) the updated digital IC “Controller IC (CIC).”

The (b) (4) firmware version introduced with the Evia HF /HF-T models is (b) (4) in the digital IC “CIC” of the electronic module. The (b) (4) implements the clinical functionality of the device and supports bradycardia therapy, atrial detection, Holter and statistics, Home Monitoring, and ERI.

Additional Device Features

With this PMA Supplement BIOTRONIK is also introducing additional features with the Evia HF / HF-T family of CRT-Ps as compared to Stratos CRT-Ps.

- Closed Loop Stimulation
- Thoracic Impedance
- Additional LV Pacing Polarities
- Left Ventricular Capture Control
- Home Monitoring Data from BIV Pacing
- EasyAV

Detailed discussion of these features listed above is in the Clinical section of this memo.

Evia HF / HF-T incorporate many features which are already approved in BIOTRONIK legally marketed devices. The table below provides a functional comparison overview from the Evia / Entovis CRT-Ps to its predecessors. Evia / Entovis HF include the features from Evia / Entovis devices and combine them with the triple-chamber functionalities of the Stratos and Lumax 500/540 ICD devices.

Function	Evia HF	Evia DR	Stratos LV	Lumax 500/540	Differences
Auto Implant detection	✓	✓			Same as Evia but adapted for triple chamber devices.
Auto-Initialization	✓	✓			Same as Evia but adapted for triple chamber devices.
Remote Follow-Up with IEGM transmission	✓	✓		✓	Same as Evia but adapted for triple chamber devices.
Atrial Threshold Tracking	✓	✓			Same as Evia but adapted for triple chamber devices.
Ventricular Threshold Control	✓ (only at RV stimulation)	✓			Same as Evia but adapted for triple chamber devices.
Ventricular Threshold Tracking	✓ (RV and LV)	✓			Similar to Evia but adapted for triple chamber devices.
Ventricular Threshold Monitoring	✓ (RV and LV)	✓ (RV)		✓ (RV and LV)	Same as Lumax 500/540.
Autosensing	✓	✓		✓	Same as Evia but adapted for triple chamber devices.
Vp Suppression	✓ (only at RV stimulation)	✓			Same as Evia but only available at RV stimulation.
I-Opt: AV-hysteresis to reduce ventricular pacing	✓ (only at RV stimulation)	✓		✓ only for DR model	Same as Lumax 500/540 DR but only at RV stimulation.
V-V Timing	✓		✓	✓	Same as Stratos and Lumax 500/540.
Ventricular Tracking (RV-> LV)	✓		✓	✓	Same as Stratos and Lumax 500/540.
CRT Stimulation during AF	✓		✓	✓	Same as Stratos and Lumax 500/540.
AT prevention	✓	✓	✓		Same as Evia and Stratos.
Lead - Check	✓	✓	✓		Same as Evia and Stratos.
TrendView	✓	✓			Same as Evia but adapted for triple chamber devices.
Auto Follow-up	✓	✓		✓	Same as Evia but adapted for triple chamber devices.
Program Consult and individually saved programs	✓	✓			Same as Evia but adapted for triple chamber devices.
HF Monitor	✓			✓	Same as Lumax 500/540.

Software

With this PMA Supplement BIOTRONIK is proposing a modified version of programmer software, PSW (b) (4), which will be utilized by the (b) (4) (P950037/S89 on April 15, 2011) and the ICS 3000 system (P950037/S35, approved May 18, 2005) to program and interrogate all of BIOTRONIK's current US legally marketed bradycardia pulse generators, ICDs and CRT-Ds. The software PSW (b) (4) is based on the legally marketed PSW (b) (4) programmer software (P950037/S98, approved on September 30, 2011).

The software was updated to implement the following:

- Evia HF / HF-T device models and features
- Bug fixes for global components and applications

The changes to be implemented with the updated programmer software PSW (b) (4), for use with both the (b) (4) and ICS 3000 Implant Control System, include the following:

- The programmer software country list will be applied
- Standard values for IEGM will not be overwritten. Due to product improvement, the previous software version overwrote the standard parameters and the user adjusted values.
- Chinese shall be supported by the global components of the programmer
- (b) (4) PSA will be supported, however the hardware is not available and is the subject of a separate PMA Supplement

The PSW (b) (4) software version was updated to introduce a new (b) (4) application to support the Evia HF /HF-T device models. This updated software implements the following features in the Evia HF / HF-T devices:

- Left ventricular capture control
- Thoracic Impedance (TI)
- Closed loop stimulation (CLS) in a biventricular pacemaker
- Additional left ventricular (LV) Pacing Configurations

- Home monitoring with data from the LV channel

In addition, the following Brady application was affected:

- Philos II – Ability to support Unicode characters which gives the option to display languages such as Chinese, Russian, or Japanese characters

The changes to be implemented with the updated programmer software PSW (b) (4) which affect the Tachy applications include the following:

- Lumax 300/340 and 500/540: Change of programmer behavior when the wand is applied on a new BIOTRONIK implant while a follow-up session of a current implant is still running: Previously the new implant was automatically interrogated, now the programmer stays in the old implant application without auto-interrogation

In addition to the changes listed above, the following bug fixes were incorporated into the updated programmer software PSW (b) (4)

- Global Functions:
 - ICS 3000 and (b) (4): An issue has been fixed where patient data display in the Implant Module application may be disturbed by (b) (4) data input in the implant application.

In **Amendment A002**, BIOTRONIK proposes an updated programmer software version designated as PSW (b) (4), which implements minor changes and bug fixes for the Evia HF-T devices.

In parallel to the original Evia HF-T submission, BIOTRONIK submitted PSW 1202.U through PMA Supplement P050023/S054 (bundled with P950037/S110, P00009/S050, and P070008/S033). The PMA Supplement was submitted June 29, 2012 and approved on August 8, 2012.

Amendment A002 contains the same software information that was provided in the PMA Supplement for PSW (b) (4) (P050023/S054) which covers the changes from (b) (4) with the addition of the Evia CRT changes for PSW (b) (4). A detailed description of the changes in the updated software version is provided in Section 6 of the submission.

There are no firmware changes included with PSW (b) (4), therefore the (b) (4) information that is presented in Section 3.1 of the submission is still valid for PSW (b) (4).

CLINICAL

A formal review memo from the clinical reviewer was not provided for the original submission. The additional device features were reviewed interactively in a series of meetings. In summary, there were a total of two minor deficiencies in the area of Closed Loop Stimulation and Easy AV which needed to be addressed by the sponsor.

In **Amendment A002**, the sponsor responded to the deficiencies in the area of Closed Loop Stimulation and Easy AV. The responses were reviewed by the clinical reviewer and found acceptable.

RISK ANALYSIS

The sponsor states that during the development process of the Evia CRT-Ps, a thorough risk analysis has been conducted. In the course of the analysis, all possible hazards associated with the design, functionality and use of the devices have been determined. The risks of the so known hazards have been evaluated and classified according to their likelihood and severity. If the risks were determined to be intolerable, adequate measures have been addressed to eliminate or minimize the respective likelihood and/or severity of the hazard. The effectiveness of all risk minimization measures is tested during product verification and validation.

The risk analyses listed in Table 7 of the original submission document all risks associated with the use of the CRT-Ps and an appropriate resolution.

Table 7: Risk Analyses

TITLE	DOCUMENT #	APPENDIX #
Implantable Pulse Generator (General)	(b) (4)	Appendix 3
Programming Device for Implantable Pacemakers, Defibrillators and Monitors including Programmers Software (General)	(b) (4)	Appendix 4

The risk management plan describes the relation between the product requirements, the associated risks, the measures of risk reduction and the proof of the effectiveness of these measures. It documents the different risk analyses and the determination of the remaining residual risk. The verification results which show the effectiveness of the risk reduction measures are listed in the risk management plan. The Risk Management Plan for “Primus CRT Implantable Pulse Generators” (i.e., Evia HF/ HF-T) is (b) (4), and is provided in Appendix 5 of the original submission.

*Review Comment: This information was reviewed and found to be acceptable. For **Amendment A002**, these risk management documents remain unchanged and are still valid for the changes in the updated software version PSW (b) (4)*

HARDWARE VALIDATION AND VERIFICATION TESTING

The sponsor provided a summary of all validation testing for the Evia CRT-Ps in Table 9 of the original submission. Biocompatibility testing was summarized in tests (b) (4). Hardware testing was summarized in tests (b) (4). Firmware testing was summarized in tests (b) (4).

Firmware

The sponsor provided validation test reports and the validation test summary in Table 9 of the original submission (tests (b) (4)). However, there was no information provided about the verification testing that was conducted. The sponsor was asked for this information and included this information in **Amendment A001**. The sponsor provided a summary of the testing conducted and the results for (b) (4) verification.

Review Comment: The validation information in the original submission was reviewed and found to be acceptable. Also, the (b) (4) verification testing of the (b) (4) was reviewed and found to be acceptable. It appears the sponsor has completed the appropriate testing successfully. However, the sponsor states that the (b) (4) was updated from (b) (4). The sponsor did not provide any of the software information for the implant device itself. It is unclear what changes have been implemented in the (b) (4) programming, what (b) (4) were performed, and if there are any anomalies. A deficiency has been identified and the sponsor will be asked to provide information congruent with FDA’s guidance document “Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices”. In Amendment A002, the sponsor responded to this deficiency and identified the appropriate Biotronik documents. Some of the documents were not included, but are available upon request. Review of the actual documents was not needed since it appears that Biotronik has appropriately followed FDA’s guidance. There are no further concerns.

Hardware

The sponsor provided validation test reports and the validation test summary in Table 9 of the original submission (tests (b) (4)). However, there was no information provided about the verification testing that was conducted. The sponsor was asked for this information and included this information in **Amendment A001**. The sponsor provided a summary of the (b) (4) Verification, (b) (4) (b) (4), and (b) (4) Verification testing conducted and the results.

Review Comment: The hardware validation information in the original submission was reviewed and found to be acceptable. Also, the (b) (4) testing was reviewed and found to be acceptable. The (b) (4) tests that were conducted are discussed separately below.

EMC/EMI

(b) (4)

(b) (4)

*Review Comment: This information was reviewed informally with the EMC consult. FDA only recognizes AAMI/ANSI PC69. A minor deficiency has been identified and the sponsor will be asked to state that their device conforms to all sections of AAMI/ANSI PC69 as some of the test levels do differ between these standards. If the sponsor did not follow all the requirements of AAMI/ANSI PC69 they will be asked to describe those differences and provide scientific reasoning for doing so. In **Amendment A002**, the sponsor responded to the deficiency by confirming that the Evia HF/HF-T EMC test data provided in **Amendment A001** demonstrates full compliance with AAMI/ANSI PC69. There are no further concerns.*

Software

As described in the (b) (4) of this memo, the sponsor has not provided any software information for the implant device itself in the change from (b) (4). This deficiency was resolved with the additional information submitted in **Amendment A002**.

The sponsor is proposing a (b) (4) which will be utilized by the (b) (4) US legally marketed bradycardia pulse generators, ICDs, and CRT-Ds. The software (b) (4) is based on the legally marketed (b) (4) programmer software.

The software was updated to implement the following:

(b) (4)

The documentation provided by the sponsor was reviewed in accordance to the guidance document, *Content of Premarket Submissions for Software Contained in Medical Devices*, May 11, 2005. The following areas were reviewed:

- Level of Concern
- Software Description
- Device Hazard Analysis
- Software Requirements Specification (SRS)
- Architecture Design Chart
- Software Design Specification (SDS)
- Traceability Analysis
- Software Development Environment Description
- Verification and Validation Documentation
- Revision Level History
- Unresolved Anomalies

Review Comment: This information was reviewed and found to be acceptable.

In **Amendment A002**, BIOTRONIK proposed an updated programmer software version designated as (b) (4) which implements minor changes and bug fixes for the Evia HF-T devices.

In parallel to the original Evia HF-T submission, BIOTRONIK submitted (b) (4) through PMA Supplement P050023/S054 (bundled with P950037/S110, P00009/S050, and P070008/S033). The PMA Supplement was submitted June 29, 2012 and approved on August 8, 2012.

Amendment A002 contains the same software information that was provided in the PMA Supplement for (b) (4) (P050023/S054) which covers the changes from (b) (4) with the addition of the Evia CRT changes for (b) (4). A detailed description of the changes in the updated software version is provided in Section 6 of the submission. At a high level, the (b) (4) software was updated to implement the following along with the changes from (b) (4)

(b) (4)

Biotronik provided software documentation in accordance with the FDA's guidance document, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," dated May 11, 2005.

*Review Comment: In **Amendment A002**, the sponsor has updated the programmer software to (b) (4) (b) (4) were reviewed and there are no concerns with the changes. Also, it appears that Biotronik has appropriately followed FDA's guidance. There are no further concerns.*

LABELING

All labeling for the Evia CRT-Ps is based on the labeling for the Stratos and Evia families.

The technical manuals for the Evia family of CRT-Ps are a revised version of the technical manual for the current legally marketed Evia family of pulse generators with the addition of information on the new features. Appendix 86 of the original submission includes the Evia CRT technical manual. The Entovis CRT-P technical manual was not included in this submission and will be included in the final labeling amendment.

BIOTRONIK has reformatted the technical manuals and has pulled out the (b) (4). This information will be included in a (b) (4) document which is provided in Appendix 87 of the original submission.

In the clinical review of **Amendment A002**, the clinical reviewer found an issue with (b) (4). His review noted that there was an inappropriate reference.

Review Comment: This issue was discussed with FDA management and agreement was made that FDA would accept the (b) (4) was previously approved in PMA-s P050023/S001 and the sponsor is not claiming any predictive benefits.

BIOCOMPATIBILITY

All of the materials in contact with the human body or fluids used to construct the Evia CRT-Ps remain unchanged from the currently market-released Evia pulse generators (P950037/S72, dated May 10, 2010) and have been used extensively in US market released BIOTRONIK products. Table 6 of the submission presents the external (body/fluid contact) materials used in Evia CRT-Ps. These materials are used with BIOTRONIK's market-released Evia family of pulse generators (P950037/S72, dated May 10, 2010) in which material biocompatibility has been reviewed and approved for distribution in the United States. The biocompatibility of these materials has been proven according to international standard EN ISO 10993-1: 2009.

Review Comment: This information was reviewed and found to be acceptable.

PACKAGING/STERILIZATION

The packaging controls and materials used with the Evia family of CRT-Ps are identical to the market released Evia family of pulse generators (P950037/S72, dated May 7, 2010).

The CRT-P is shipped in a box, equipped with a quality control seal and product information label. The label contains the model specifications, technical data, serial number, expiration date and sterilization and storage information.

The Evia and the corresponding accessories have been sealed in a container (b) (4) (b) (4). The recommended storage temperature range of the packaging is -10° to 45° C.

The Evia family of CRT-Ps, as with all BIOTRONIK pulse generators and CRT-Ps, are sterilized with (b) (4) (b) (4) to achieve a sterility assurance level (SAL) of 1x10-6. (b) (4) (b) (4) (b) (4) (b) (4)

Evia family of CRT-Ps, as well as all other BIOTRONIK pulse generators, CRT-Ps, leads and accessories, are sealed within a (b) (4)

(b) (4)

Review Comment: This information was reviewed and found to be acceptable.

SHELF LIFE

The shelf life for the Evia CRT-Ps is (b) (4), which is the same for Evia (P950037/S72, dated May 7, 2010) and Stratos (P070008, dated May 12, 2008). BIOTRONIK assigns an 18-month expiration date, "Use Before Date" (UBD), to the Evia CRT in order to assure the required longevity after the shelf life is expired. The shelf life starts when the battery is connected during the manufacturing process and ends on the last day of the 18th month after this connection. The recommended storage temperature range of the packaging is -10°C to 45° C.

(b) (4)

Review Comment: This information was reviewed and found to be acceptable.

MANUFACTURING

All manufacturing and quality control procedures, including packaging and sterilization of the Evia HF-T family of CRT-Ps, are performed per specifications at the following facilities:

(b) (4)

(b) (4)

(b) (4)

The Evia family of CRT-Ps and programmer software (b) (4) are designed, validated, and manufactured according to standard procedures utilized by BIOTRONIK, which follow US FDA regulations including the Quality System Regulation (21 CFR 820).

Review Comment: This information was reviewed and found to be acceptable.

SUMMARY OF INTERACTIONS

Original:

- Mar 22, 2012: Corrected Indications and Contraindications from Biotronik (included in original review memo)
- May 15, 2012: Email request for additional information (part of **Amendment A001**)
- May 18, 2012: Email response from Biotronik with partial information (part of **Amendment A001**)
- May 22, 2012: Email response from Biotronik with remaining information (part of **Amendment A001**)

Amendment A002:

- Sep 10, 2012: Telephone discussion with Biotronik to discuss concerns about labeling
- Sep 14, 2012: Email response from Biotronik regarding labeling issue
- Sep 18, 2012: Additional question to Biotronik regarding labeling issue
- Sep 18, 2012: Response to additional question from Biotronik

CONCLUSION/RECOMMENDATION

The sponsor responses to the identified deficiencies have been found to be acceptable. Also, the additional software change has been found acceptable. The (b) (4) issue has been adequately resolved. This issue was discussed with FDA management and agreement was made that FDA would accept the proposed labeling as it was (b) (4), previously approved, and the sponsor is not claiming any predictive benefits. The sponsor has shown that the Evia HF-T is safe and effective at this time.

I recommend that the sponsor receive an **APPROVAL** letter.