Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation

DATE: May 7, 2010

TO: File

CC: (b)(6) (Consultant Reviewer, Software)
Mitchell Shein (Branch Chief)

FROM: (b)(6) (Lead Reviewer)

SUBJECT: P950037 / S072 / A002 Response to Disapproval
Bundled: P000009 / S035 / A002, P050023 / S024 / A002, and P070008 / S011 / A002
Biotronik – Evia / Entovis Family of Pacemakers

OVERALL RECOMMENDATION

Therefore, based on my review of the submission text, discussions with supporting reviewers, and interactions with the sponsor, **I recommend approval of the submission**.

Signature	*Date*	*Signature*	*Date*
(b)(6)		Mitchell Shein	
Scientific Reviewer		Branch Chief	
(Lead Reviewer)		(Management Oversight)	

PURPOSE OF SUBMISSION

The sponsor would like to introduce a new family of pulse generators (pacemakers) called Evia / Entovis. The submission includes SR, SR-T, DR, and DR-T models, where the "-T" designates a product with the sponsor's Home Monitoring feature. The Evia and Entovis products are identical but will be used to provide price differentiation in the market later, after certain features are locked out. The software will be modified in order to lock out the features, and another PMA supplement will be submitted for this software. This submission is bundled with P000009 / S035, P050023 / S024, and P070008 / S011, because the programmer software used with Evia / Entovis will be used with the company's complete line of products.

DEVICE DESCRIPTION

The following sections are excerpts from the submission. Discussion and proposed deficiencies follow each section of the submission.

Overview of Changes

This PMA Supplement application proposes the introduction of the Evia / Entovis family of pulse generators. The differences between Cylos and Evia / Entovis include an updated electronic circuit, reduction in the number of electronic components (Evia: (b)(4) vs. Cylos: (b)(4), and introduction of updated types of batteries. This family of pulse generators will be marketed under the trade names “Evia” and

"Entovis" even though the devices are identical. The Evia / Entovis pulse generators were initially developed with the engineering project name "Primus." Therefore, all references to "Primus" provided within this PMA Supplement are synonymous with the "Evia / Entovis" family of pulse generators.

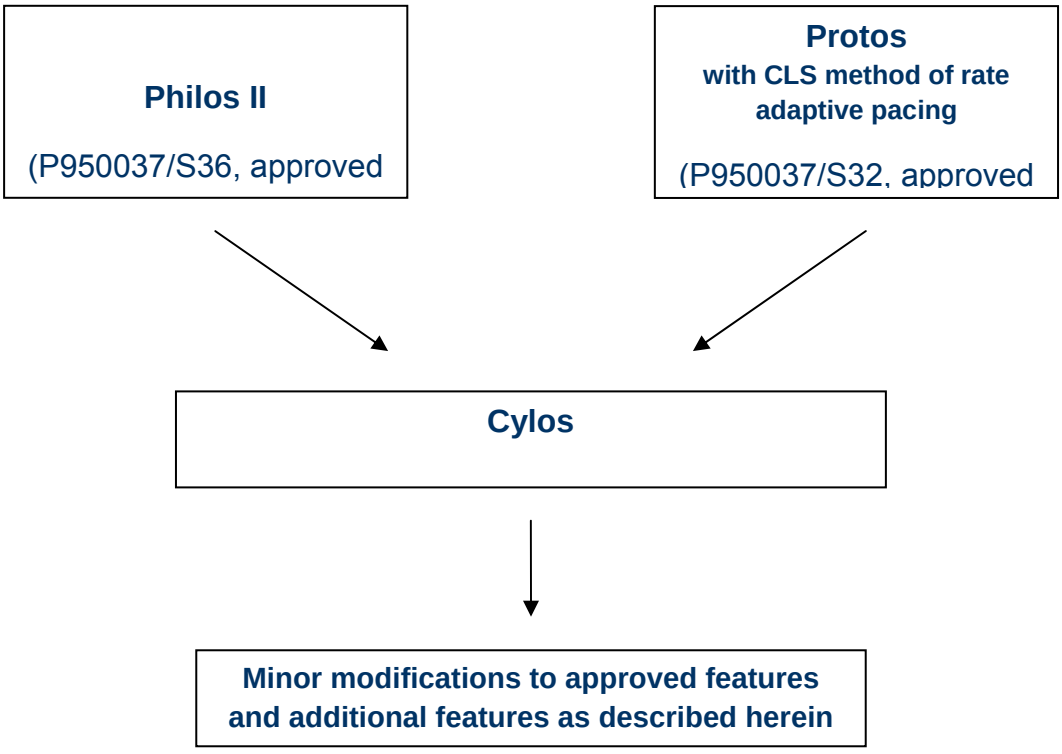
The Evia / Entovis family of pulse generators contains the same feature set as the Cylos family of pulse generators with the addition of the following feature updates:

- Automatic Sensitivity control (ASC)
- Atrial Capture Control
- Vp Suppression (Ventricular pace suppression)
- Modified Auto Initialization (Auto Lead Polarity and Function Activation)
- More automated follow-up

Additionally, the following features are introduced with the new US software version, 901.U:

- "Indication-dependent program recommendation (ProgramConsult®)" and "Store individual programs"
- "Automatic threshold measurement in the atrium" (measured by the ICS 3000 programmer)
- Easy AV® display of the As-Vs Statistics in the AV delay screen

Figure 1 shows the relationship between the Evia / Entovis families of Implantable Pulse Generators and BIOTRONIK's currently approved pulse generators, Cylos, Philos II and Protos.



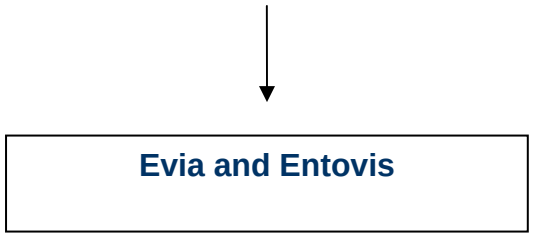


Figure 1: History of BIOTRONIK Pulse Generators

BIOTRONIK obtained FDA approval of the Philos II family of rate-adaptive cardiac pulse generators on March 31, 2004 under PMA Supplement P950037/S36. The Protos family of pulse generators was originally approved through P950037/S28 on December 6, 2002. The Cylos family of rate-adaptive cardiac pulse generators was originally approved through P950037/S41 on December 21, 2005.

The Evia / Entovis families of Implantable Pulse Generators are available in four different variants: DR, DR-T, SR and SR-T with the T variants having BIOTRONIK's Home Monitoring functionality. The Evia / Entovis DR, Evia / Entovis DR-T, Evia / Entovis SR, and Evia / Entovis SR-T are detailed in the drawings that are included in Appendix 1, Appendix 2, Appendix 3, and Appendix 4, respectively. The Evia / Entovis family of pulse generators are identical; however, they will be marketed under different trade names. Consequently, Evia will be used throughout this submission to describe both the Evia and Entovis devices.

Evia utilizes the (b)(4) substrate for the printed circuit boards, which is also currently approved in BIOTRONIK's Philos (P950037/S51, dated August 31, 2007) and Philos II (P950037/S65, dated November 6, 2008) pulse generators. All patient contact materials used to manufacture the Evia pulse generators are identical to those utilized in the currently approved Cylos family in formulation, processing, and sterilization, and no other chemicals have been added (e.g., plasticizers, fillers, and color additives, cleaning agents, mold release agents, etc.). There are no changes in any tissue/blood contact materials for the Evia pulse generators compared to the currently marketed Cylos pulse generators. Furthermore, the shelf life of 18 months for Evia is identical to that for the Cylos family of pulse generators.

The current legally marketed programmer software version, 802.U/2 (P950037/S67, dated March 31, 2009), has been modified to include the application for programming the Evia family of pulse generators. The updated ICS 3000 programmer software will be identified as 901.U.

Similar to the Cylos family of pulse generators, the Evia family of implantable pulse generators utilizes IS-1 lead connectors and there are no new requirements in terms of lead compatibility. Evia uses the bi-directional Home Monitoring patient device, CardioMessenger II-S (TLine) approved under P050023/S16, dated December 11, 2008.

The Evia family of implantable pulse generators includes the Closed Loop Stimulation (CLS) method of rate adaptive pacing utilizes patient-specific impedance measurements to determine the pacing rate. CLS was approved by the FDA for Cylos pulse generators under P950037/S41, dated December 21, 2005. CLS is implemented in the Evia family of pulse generators in an identical manner as compared to the Cylos family.

Discussion

The proposed changes and descriptive comparison to previous devices and supporting data were reviewed. There were some questions regarding the changes, which the sponsor was able to resolve with information provided in amendments to the submission.

Detailed Device Description

The Evia family of pulse generators contains the same feature set as the legally marketed Cylos family of pulse generators (P950037/S41, dated December 21, 2005).

In addition to these core functions, the Evia pulse generators will have the following:

- Automatic operation for:
  - Sensing (Auto Sensing for atrial and ventricular channel)
  - Atrial Capture Control (and – already existing - Ventricular Capture Control)
  - Follow Up (programmer based automatic features to ease Follow-ups)
  - Ventricular Pace Suppression (Vp Suppression)
- Bi-directional Home Monitoring with periodic IEGM transmission
- Additional functionality with the ICS 3000
  - New graphical user interface (GUI) with ICS 3000
  - Data transfer to data manager capabilities
  - EasyAV® (assistance with setting of AV delay)
  - ProgramConsult® (assistance with device programming)
  - TrendView® (expanded diagnostics)

The features from Cylos that are not implemented in the Evia family are:

- 2:1 Lock-In Protection
- NIPS (Non-Invasive Programmed Stimulation)

The Home Monitoring models of the Evia / Entovis families of Implantable Pulse Generators (Evia / Entovis DR-T and Evia / Entovis SR-T) 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 DR-T/SR-T to the patient device remains unchanged as compared to the Cylos DR-T.

The main hardware components are based on the hardware used for the Cylos family of pulse generators. As the predecessors, the Evia devices contain embedded software (firmware) and the (b)(4) firmware version is (b)(4).

Evia pulse generators are capable of storing up to 20 IEGM snapshots, which is identical to the Cylos family of pulse generators. Additionally, the sensor for accelerometer-based activity is identical to that used in the Cylos family.

The housing and header used for the Evia family of pulse generators are identical in materials and manufacturing processes to what is used in the Cylos pulse generators, and are made of titanium and epoxy resin, respectively. **Table 1** shows a size comparison of the Evia and Cylos pulse generators.

Table 1: Evia and Cylos Size Comparison

Model	Evia DR	Cylos DR	Evia DR-T	Cylos DR-T
Volume	11 cc	12 cc	12 cc	14 cc

Mass	26 g	28 g	25 g	31 g
Dimensions	6.5 x 43 x 53 mm	6.4 x 42 x 57 mm	6.5 x 45 x 53 mm	6.4 x 50 x 57 mm

The Evia longevity is as specified in the technical manual, which is provided in **Appendix 124**. A technical comparison summary of the Evia and Cylos pulse generators is shown in **Table 2**.

Table 2: Technical Comparison

	Evia / Entovis	**Cylos**
Product variants	DR, DR-T, SR, SR-T	DR, DR-T, VR
Titanium housing with physiologic shape	identical	
Epoxy - Header	identical	
Connector ports	DR(-T): 2*IS-1 SR(-T): 1*IS-1	
Circuit	Hybrid electronics with (b)(4) chip	
Technology	(b)(4) Substrate[1]	(b)(4) -Substrate
Pulse form	Biphasic, asymmetric	
Current limiting	(b)(4)	
Cut-off voltage		
Output capacitor		
Input impedance		
DC protection[2]		
Batteries	GB 8431	
	LiS 3150	
	GB 2596 LiS 3150M as described below	GB 8431 LiS 3150

Additional Battery Models

The Evia family utilizes four types of batteries which are manufactured by Greatbatch and Litronik. The GB 2596 and LiS 3150M batteries are new battery models that will be implemented in Evia DR-T and Evia SR-T devices. These batteries will offer higher current and voltage to support Home Monitoring IEGM transmissions. **Table 3** shows the characteristics of each type of battery.

Table 3: Evia / Entovis Battery Characteristics

Manufacturer	**GREATBATCH, INC. Clarence, NY14031, USA**		**LITRONIK GmbH 01796Pirna, Germany**	
Battery Type	GB8431	GB2596	LiS 3150	LiS 3150M
System	LiJ	Ag/SVO/CFx QMR®	LiJ	LiMn02

[1] FR4 has been approved in Philos (P950037/S51, dated 8-31-2007) and Philos II (P950037/S65, dated 11-6-2008)
[2] Calculated values provided by manufacturer

Model	DR, SR	DR-T, SR-T	DR, SR	DR-T, SR-T
Battery voltage at BOS	2.8 V	3.0 V	2.8 V	3.1 V
Open-circuit voltage	2.8 V	3.0 V	2.8 V	3.1 V
Nominal capacity	1.3 Ah	1.3 Ah	1.3 Ah	1.2 Ah
Useable capacity until EOS (at Standard Program: 3V/0.4ms, 60ppm; 500Ω)	1.2 Ah	1.1 Ah	1.2 Ah	1.0 Ah

As a result of the different battery types, the programmer screen will display the battery information in a new way. Voltage, current, and battery impedance will not be displayed on the screen in order to avoid confusion due to the different battery dependent values. The only energy indicator on the programmer is the fuel gauge on the follow-up screen together with the calculated time to ERI as shown in **Figure 2**. The fuel gauge is independent of the current programmed parameters; it is directly related to the remaining usable battery capacity.

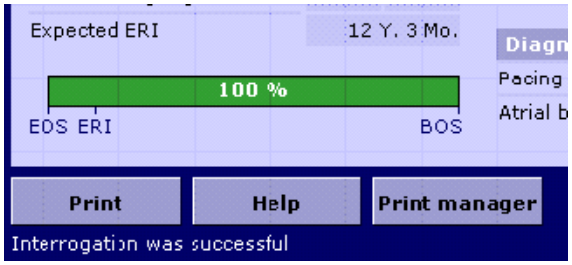


Figure 2: Battery Indicators on the Programmer Screen

Discussion

The proposed changes to the battery and longevity related features and supporting data were reviewed. There were some questions regarding these changes, which the sponsor was able to resolve with information provided in amendments to the submission.

Automatic Sensitivity Control (ASC)

During an atrial or ventricular tachycardia, the sensing thresholds can decrease to significantly lower values that are prone to undersensing in case of fixed sensing settings. Autosensing helps to correctly detect AF episodes when the signal amplitude is significantly decreased. Consequently, the implementation of autosensing functionality in pacemakers is common in the CRM industry. The autosensing functionality used in Evia is functionally equivalent to the same feature utilized in the BIOTRONIK Lumax 500 / 540 ICDs (P050023/S11, dated November 4, 2008) and several previous BIOTRONIK ICDs.

The electrograms measured at the tip of the leads are converted to digital signals in the analog-to-digital converter. The digital signals are then filtered with (b)(4) band pass. After filtering, the signals are tested against the actual sensing threshold. If two consecutive samples of the electrogram have higher amplitude than the threshold, then a sense count is generated. The following figure illustrates the sensing circuit.

The above described functionality is the same for fixed threshold sensing and automatic sensitivity (ASC). In case of the fixed sensitivity, the physician programs the sensing threshold. In case of the ASC algorithm, the device measures automatically the peak amplitude of a sensed event and adapts the sensing threshold accordingly as illustrated in **Figure 3**.

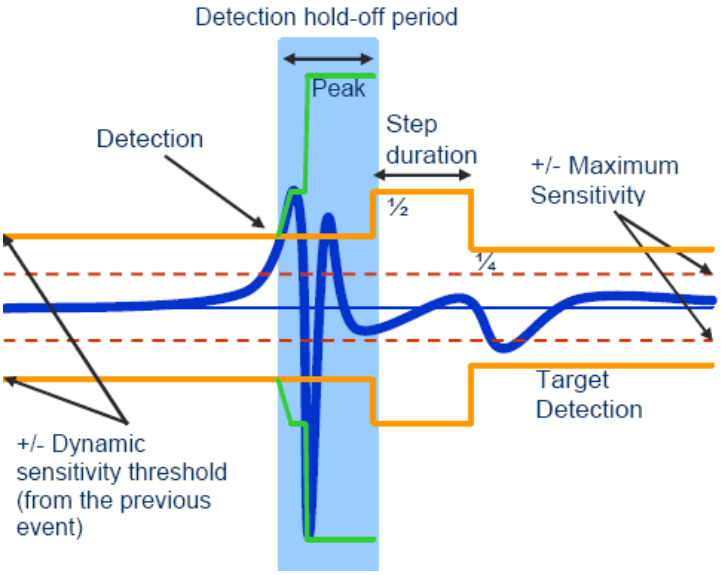


Figure 3: Automatic Sensitivity Control (ASC)

After each sense detection (electrogram is above actual threshold for 2 consecutive samples), the ASC begins the detection hold-off period of 121 ms in the ventricle (101 ms in the atrium) and detects within the first 80 ms of this interval the highest amplitude of the peak. After this initial period, the sensing threshold is first set to 50% of the measured peak amplitude. After the step duration of 125 ms, the threshold is set to 25% of the peak amplitude (82 ms in the atrium) but never below the minimum threshold of 2.0 mV in the ventricle (atrium: 0.2 mV bipolar and 0.5V unipolar). This functionality unburdens the physicians from manual programming of the sensing threshold, the ASC detects signals with varying and small amplitudes, and the threshold is set to a 1:4 signal-to-noise ratio to eliminate unwanted detection of noise.

After paced events, the sensing threshold is initially set to 2.5 mV (1 mV in the atrium), which corresponds to the default sensitivity values using fixed sensitivity settings. The detection hold-off period after a pace (see Figure 3) is doubled to 200 ms in the ventricle to avoid in-channel detection of the pacing artifact. After a paced event, the first step is with 250 ms (164 ms in the atrium) twice as long as after a sensed event to avoid T-wave over-sensing. Environmental noise is declared if sense events occur within the noise interval of 50 ms.

Discussion

The proposed changes to the sensing behavior and supporting data were reviewed. There were some questions regarding the changes, which the sponsor was able to resolve with information provided in amendments to the submission.

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Auto Initialization

BIOTRONIK's Auto Initialization feature continuously monitors the lead connector port in order to detect when a pacing lead has been connected to the pulse generator at implantation as well as the polarity of

the lead. The Evia family of pulse generators incorporates a slightly modified version of this feature, which was originally approved with Philos II and Cylos families of pulse generators (P950037/S36, dated March 31, 2004 and P950037/S41, dated December 21, 2005, respectively).

Auto Initialization consists of four phases, starting with lead detection. In order to detect a lead, the Evia pulse generator delivers a ping in both the ventricle and the atrium at low amplitude (instead of pacing unipolar as in the previously approved devices). Upon successful detection, the Evia pulse generator automatically determines the polarity of the lead detected and initiates pacing, followed by a 10-minute confirmation phase. After the confirmation phase has been successfully completed and lead detection is confirmed, Evia initiates several features, including Mode Switching, PMT Management, Active Capture Control's ATM mode, data collection for CLS, and Statistics, which is identical to the implementation of this feature in the Cylos family. If the device is programmed prior to being implanted, the device will remain in the confirmation phase until a lead is detected and confirmed, at which point, all features will be activated.

Automatic Follow-Up

Evia offers updated features to allow a more automatic follow-up by the physician. All standard Follow-Up tests can be carried out automatically and the measured test values will be displayed at the initial interrogation on the follow-up screen. The following test results will be displayed on the follow-up page after interrogation:

- Battery/lead status
- Atrial sensing measurements
- Ventricular sensing measurements
- Auto atrial threshold test results
- Auto ventricular threshold test results

The maximum duration for the automatic follow-up will not exceed 120 seconds. If an automatic test fails to complete, the user will be notified. Manual follow-up will continue to be supported by the device. Additionally, an automatic test summary will be provided which displays the test results at a glance.

PVARP Timing

Evia also adopts the PVARP-timing approach. This timing approach is also implemented in the Stratos LV (P070008, dated May 12, 2008); however, a simplified version is included within Evia pulse generators. The nomenclature of the timing parameters will change slightly as compared to the Stratos LV devices.

The pacing is checked in the atrium by automatic adaptation of the atrial refractory period to avoid pacemaker-induced tachycardia. The automatic PVARP function checks the automatic post-atrial refractory period.

Automatic PVARP

After a PMT termination, the PVARP and PVARP(ext.) gets automatically increased by 50ms. The limit is the VA-Criterion + 50ms. After 7 days without PMTs, Auto PVARP reduces the PVARP and PVARP(ext.) by 50 ms as shown in **Figure 6**.

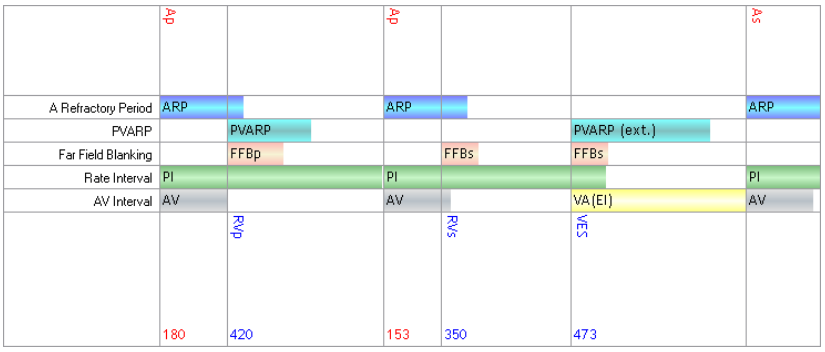

Figure 6: Automatic PVARP

Sub Threshold Lead Impedance Measurement

Automatic lead impedance measurement is an established feature in general pacemaker therapy. In current BIOTRONIK pacemakers, lead impedance is measured every 90 min by delivering a maximum of four triggered paces at 4.8 volts. Using these triggered paces the pacemaker can measure the lead impedance even in phases of sensing. In some rare cases the paces of 4.8V, especially when the pacemaker is programmed to unipolar pacing, lead to muscle stimulation felt by the patient so that the measurement algorithm had to be turned off. Additionally, in 24 hour Holter recordings, the paces are recorded and make the interpretation of the ECG difficult especially when the physician is not familiar with BIOTRONIK's lead impedance measurement technique.

To avoid paces at such a high voltage, Evia utilized a lead impedance measurement which is independent from sensing and pacing phases. The difference is that the implemented measurement uses low energy sub threshold pulses for lead impedance measurements, so that the lead integrity testing is not detectable by the patients and does not appear on the ECG.

Sub threshold biphasic current pulses (30 µs, 100 µA) are delivered to determine the impedance for each polarity (unipolar, bipolar) for each implanted lead every 30 seconds independent of pacing and sensing functionality. The current pulses are synchronized with the ventricular activity (even for measurements in the atrium) and delivered within 100 ms after the ventricular event. The pulse energy is very low (20 mV to 150 mV) so that it is not expected to be visible on the ECG. To avoid the possibility of detection of far field senses the pulses are delivered in the far field blanking period of the pacemaker.

As long as these measured impedance values remain within a valid impedance range (150 - 2000 Ohm), the leads are considered to be functional. If the measured impedance value is outside of the specified range, two additional measurements are performed within the next two timing cycles in order to confirm the initial measurement. After 3 consecutive measured values outside of the specified range a lead failure is declared. Evia DR-T and SR-T can transmit this information on a daily basis to the physician via Home Monitoring.

Automatic Lead Check

Evia also incorporates the automatic lead check (ALC) feature from the currently approved Philos pulse generator. ALC is by default enabled and not user-programmable.

Lead impedance is measured for each used polarity for each lead:

- One measurement per cardiac cycle
- Sequence: A_{bi}, A_{uni}, V_{bi}, V_{uni}
- Sequence repeated every 30s

An event triggered measurement occurs:

- 100 ms after RVs or RVp in dual-chamber and ventricular-only modes
- 100 ms after As or Ap in atrial-only modes

ALC works every 30 seconds and bipolar lead failure is declared after 3 consecutive measurements are out of range. Unipolar lead failure is detected also after 3 cycles. After 60 minutes, a confirmation measurement is performed to determine whether there was unipolar lead failure.

Programmer Software

The Evia software application was built into the ICS 3000 programmer to support the Evia implants. The software consists of two main components: the embedded software of the implant and the programmer software. The embedded software is stored in the ROM and RAM of the CIC. The RAM-firmware used in all Evia variants is firmware (b)(4) The RAM firmware controls the clinical functionality of the Evia which includes bradycardia therapy, atrial detection, ventricular therapy sequences, holter and statistics, and Home Monitoring features.

The software application for the Evia has been added to the 802.U/2 programmer software versions that are currently being distributed to create the following software for BIOTRONIK's programming systems:

- 901.U – Software for use with ICS 3000 programming system (P950037/S35, dated May 18, 2005)

The following sections describe changes to existing features that have been implemented in the 901.U version of programmer software.

Home Monitoring Modes

With the Cylos application, Home Monitoring can only be activated when a dual chamber mode is programmed. With the programmer software version presented in this PMA Supplement, the pacing modes in which it is possible to activate Home Monitoring have been expanded to include CLS and single chamber modes. **Table 5** provides a list of all Evia DR-T and Evia SR-T pacing modes in which the Home Monitoring functions are available.

Table 5: Home Monitoring Modes

Implant Type	Pacing Mode	Standard
DR-T	• DDD-CLS, VVI-CLS • DDDR, DDIR, DVIR, DOOR, VDDR, VDIR, VVIR, VVTR, VOOR, AAIR, AATR, AOOR • DDD, DDT, DDI, DVI, DOO, VDD, VDI, VVI, VVT, VOO, AAI, AAT, AOO, OFF	DDDR
SR-T	• VVI-CLS • VVIR, VOOR • AATR*, AATR*, AOOR* • VVI, VVT, VOO • AAI*, AAT*, AOO* *availability depends on the programmer software	VVIR
Note: Home Monitoring is possible in all pacing modes		

New Graphical User Interface with ICS 3000

A new graphical user interface (GUI) for the ICS 3000 programmer has been implemented with the 901.U programmer software. The GUI has a more intuitive design, including the implementation of globally defined control concepts (e.g. links) and a visualization of parameters. The GUI is similar to what is approved for use in BIOTRONIK Lumax 500 / 540 ICDs (P050023/S11, dated November 4, 2008).

EasyAV

Statistical data are helpful for diagnosis and patient-specific programming of the devices, and quick, intuitive access to the diagnostic data is not always given. In order to assist with quick intuitive programming of the AV timing, the diagnostic data stored in the pacemaker can now be displayed in the AV delay screen (as shown in **Figure 7**). The light blue bars show the As-Vs or Ap-Vs distribution respectively. The median value of the AV conduction is shown by a small horizontal bar.

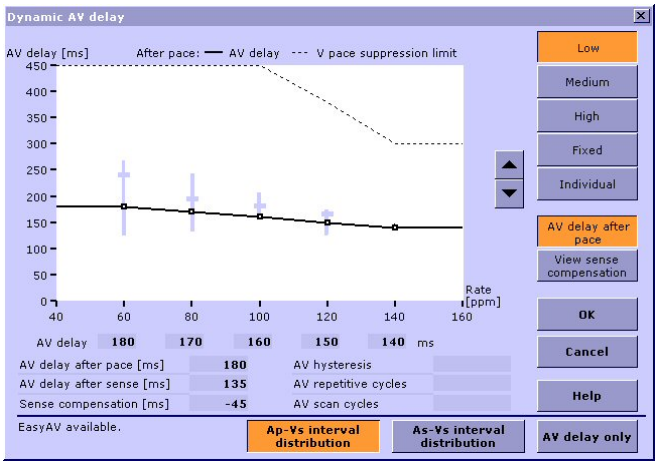

Figure 7: EasyAV®

ProgramConsult

To increase automation during follow-up procedures, the programmer software offers new characteristics in an attempt to increase efficiencies. The project name is "Indication-dependent program recommendation" and the market name is ProgramConsult®. These patient-condition programs modify the preset parameters with respect to the pacing indication by ECG-recordings. Depending on the condition, each program includes specific functions (e.g. rate-adaptive mode in the case of chronotropic incompetence) tailoring parameter settings to the special needs of the patient. The ProgramConsult® includes switching on and off of certain functions which are relevant to the corresponding indication.

If the user chooses a specific programming recommendation, the new settings will be displayed as an edited program and the modified parameters appear in blue. The user can check the recommendations, make modifications where necessary, and then transmit this program as a permanent program to the implanted device.

ProgramConsult® provides clinicians with an easy solution for programming by providing programming suggestions for frequent pacemaker patient conditions and having the capability to store individual programming for future usage (can store up to three individual parameter sets for future programming). This feature is part of the ICS parameter section and can be programmed easily by selecting the patient's pacemaker condition. This feature provides a chart of the individual program sets as well as the indication relevant programs at one click. The advantages of using this feature include the following:

- Fast and convenient programming of multiple parameters with one click

- Predefined customized program sets according to established pacemaker indication
- Program selection from clinical point-of-view
- Patient individual program adaptation is always possible

Discussion

The feature descriptions were reviewed. FDA requested some clarifications about the operation of the program consult feature. The sponsor was able to address our concerns in an amendment. FDA did not have concerns about any of the other features described above.

Storage of Individual Programs

Any individually composed program can be saved during follow-up on the programmer. This program is not exclusive to one particular device, but can also be transferred to other pacemakers of the same type. It is possible to store up to three individual programs. By offering a way to transfer individual settings to another pacemaker without any reprogramming, storage of individual parameters saves time, increases the efficiency of a follow-up, and ensures that all of the parameters are included.

Both ProgramConsult® and "Storage of individual programs" are not device based algorithms; therefore interaction with device algorithms is not expected.

TrendView

This diagnostic feature provides a quick overview of the follow-up page and shows the atrial and ventricular pacing ratio and lead integrity as shown below in **Figure 8**.

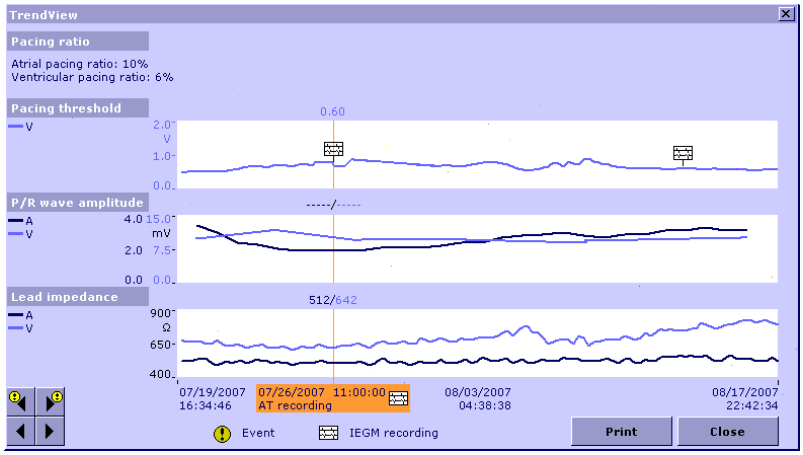

Figure 8: TrendView®

With this diagnostic, the following is possible:

- Use of database from current statistics
- Trends can be shown that are up to 240 days long, afterwards overwriting the oldest data (FIFO)
- Atrial and Ventricular threshold trend available only if Capture Control is enabled
- Cursor keys for 'Step-by-Step' or for 'Event-to-Event' navigation
- Direct navigation to IEGM recordings of special events via cursor link possible

Enhanced Data Transfer to Data Manager

This feature allows the automatic storage of ECG and IEGM for different tests at P-/R-wave measurement and at automatic atrial threshold test (~7 sec. at the end of the test).

Home Monitoring

Home Monitoring is BIOTRONIK's remote communication system, which allows specific BIOTRONIK implantable devices to automatically transmit diagnostic patient data from the device to the physician at any time. The system utilizes wireless and landline communications technology to provide the physician with continuous patient monitoring and trend analysis information between regular office follow-up visits. This type of diagnostic information is also available in the physician's office when the pulse generator is interrogated using BIOTRONIK's programming and monitoring system, the ICS 3000 (P950037/S35, dated May 18, 2005).

Home Monitoring communications are achieved through a series of four distinct data transmission steps between the following components:

Pulse Generator (Evia DR-T, Evia SR-T, Entovis DR-T, Entovis SR-T) – **Subject of this PMA Supplement**

Patient Device (CardioMessenger II and CardioMessenger II-S) – **Unchanged**

BIOTRONIK Service Center – **Modified** (as described below)

Cardio Report (Fax, Internet, Email, SMS) - **Unchanged**

Home Monitoring Service Center 3 (HMSC3), which receives data from all BIOTRONIK implantable devices with Home Monitoring functionality and transfers the formatted information to the physician, was updated to incorporate the Evia family of pulse generators and is designated as Version 3.5.1. This pulse generator plug-in is the same format as the plug-ins for current legally marketed Home Monitoring pulse generators. However, there will be a low cost Home Monitoring mode available only for the Evia pulse generators. This low cost mode is available through the CardioMessenger II-S (TLine) devices, which were approved with P050023/S16, dated December 11, 2008.

This new mode is designed to reduce transmission costs and therefore open up the Home Monitoring Service to a wider range of patients. Daily (periodic) messages can be stored up to 14 days in the CardioMessenger II-S (TLine) and then sent as one package to the Service Center. All event messages with data that are potentially critical are sent in the currently used schedules. In order to distinguish between these two types of messages, the messages from the implant will use an additional bit to indicate the type of message.

Data transmission from the implant is performed on a daily basis with the trend message. Depending on the transmitter used, these data are passed on immediately or, if the data is normal, it is collected for up to 2 weeks. If certain events occur in the patient's heart or in the implant itself, an event message is sent. Additionally, patients can send a patient message by applying the magnet. Test messages can be initiated using the programmer.

Home Monitoring data transmitted from Evia contain important information including, among others, the following:

- Ongoing atrial and ventricular arrhythmia
- Parameters relevant to leads in the atrium and ventricle: thresholds, sensing amplitudes, impedances, and polarity
- Current statistics on bradycardia therapy and physiologic data (e.g. patient activity)
- Individually adjustable remote interrogation messages which enhance the standard message with additional information relevant for follow-up

- IEGM online HD® with up to 3 channels in high definition with markers for RA and RV, which each include a sequence of rhythm programmed setting (native) and sequences with encouraged sensing and encouraged pacing
- Sending of the IEGM recordings with the remote interrogation messages
- Test message, triggered by the programmer, to immediately check the Home Monitoring function including notification of the physician

Compared to the existing Home Monitoring, Evia / Entovis will have additional features. Evia / Entovis will incorporate the following additional Home Monitoring functionalities:

- Home Monitoring periodic IEGM – These are IEGMs in the mentioned IEGM online HD® resolution. The idea of the Evia pacemaker is the support of remote device interrogation; therefore, the IEGM contains sequences of native, encouraged sensing and encouraged pacing according to the medical guidelines for electrocardiograms for pacemaker follow-up. To fulfill international standards, a complete dataset including programmed parameters, actual measurements and the periodic IEGM will be transmitted.
- Atrial Arrhythmia Management – To aid the management of atrial arrhythmias, the device will generate highly specific information about atrial arrhythmias to enable early detection.

Discussion

The Home Monitoring feature descriptions were reviewed. There were some questions regarding these features, which the sponsor was able to resolve with information provided in the amendment.

General Discussion

In general, the descriptions provided by the sponsor were sometimes very general, and it was not clear how the features proposed in the Evia / Entovis platform compare to the company's previous devices. For example, in the section for PVARP timing, the sponsor states, "This timing approach is also implemented in the Stratos LV (P070008, dated May 12, 2008); however, a simplified version is included within Evia pulse generators." However, no explanation is provided to explain how the algorithm has been simplified. As another example, the submission includes an explanation of the Automatic PVARP feature. However, the implementation of PVARP in the Evia platform is not compared to the implementation of PVARP in other Biotronik products. Therefore, the sponsor should provide more details about several new or modified features and also provide a more detailed comparison to previous Biotronik products. This deficiency applies to the following features: Automatic Follow-Up, PVARP Timing, and Automatic PVARP.

However, the sponsor was able to address these question in subsequent amendments to the submission.

INDICATIONS FOR USE

There were no changes to the indications for use, which are provided below. The sponsor stated, "The Indications for Use and Contraindications for the Evia and Entovis families of pulse generators are identical to those currently approved for the market released Cylos pulse generators (P950037/S41, dated December 21, 2005)."

Rate-adaptive pacing with the Evia pulse generators is indicated for patients exhibiting chronotropic incompetence and who would benefit from increased pacing rates concurrent with physical activity.

Generally accepted indications for long-term cardiac pacing include, but are not limited to: sick sinus syndrome (i.e. bradycardia-tachycardia syndrome, sinus arrest, sinus bradycardia), sino-atrial (SA) block, second- and third- degree AV block, and carotid sinus syndrome.

Patients who demonstrate hemodynamic benefit through maintenance of AV synchrony should be considered for one of the dual chamber or atrial pacing modes. Dual chamber modes are specifically indicated for treatment of conduction disorders that require both restoration of rate and AV synchrony such as AV nodal disease, diminished cardiac output or congestive heart failure associated with conduction disturbances, and tachyarrhythmias that are suppressed by chronic pacing.

Discussion

I have no concerns regarding this section.

HARDWARE TESTING

The sponsor submitted a number of appendices (Appendix 9 through Appendix 50) in the original submission as well as additional details in two subsequent amendments.

Discussion

The test plans and results were reviewed. There were some questions regarding this testing, which the sponsor was able to resolve with information provided in the amendments.

SOFTWARE VERIFICATION AND VALIDATION

The documentation provided within the subject includes verification and validation testing, revision level history, risk analysis, remaining anomalies, and software specifications. The documentation provided indicates that the modifications were developed and evaluated in terms of an ongoing software development system. Twelve anomalies are noted: Biotronik evaluated the risk to determine that the anomalies present no concern. The proposed modification present only minor changes to existing SW: No concern is presented by the proposed modifications in terms of software. The following discusses changes of note:

- Section 9.1.1 Test Documentation – All test documentation has been generated using a common test report form (VER). Each test result details the test procedure performed, equipment used, specification(s) followed, Pass/Fail criteria, and the actual test results. Particularly, the effectiveness of risk mitigations as required by the risk analyses has been tested during the entire composition process. Those test results were summarized in the Risk Management Plan document (RMP). All validation testing for the Evia / Entovis and programmer software version 901.U have been successfully completed as summarized in Table 9 and Table 10 respectively.

- Section 9.1.2 Known Software Anomalies – During the validation process, minor deviations in the firmware and programmer software as compared to the specifications were found. The risks of each known anomaly were assessed and classified into either an acceptable or a negligible range. The remaining residual risks, resulting from the known specification deviations, do not exceed the ALARP risk region. The effectiveness and the performance of the software as well as the respective implants are not negatively influenced by the listed anomalies. The behavior is acceptable for the respective software. A list of all known software anomalies for the Evia application is provided in Appendix 126.

- Section 9.1.3 Regression Testing: – Since the Evia programmer software application was written as modified code as described in Section 8, regression tests have only been performed during the verification / validation phase to demonstrate that necessary bug fixes did not impair previously obtained test results. All implant applications are completely independent of each other during run time; therefore, the introduction of the Evia / Entovis application did not require any further regression testing on implant applications other than Evia.

- Section 9.1.4 Evia Validation Testing: The Evia family of pulse generators has been subjected to thorough validation testing according to the change description as summarized in Table 9. The Evia pulse generators have passed all in vitro laboratory validation tests, and all test reports may be found in the referenced appendices. Each test report details the testing performed, equipment used, specification(s) followed and the actual test results.

Discussion

The software documentation was. There were no questions regarding the documentation in the original submission. However, there were questions regarding the software changes to lock-out various features identified as being problematic by FDA. The sponsor was able to address these concerns in a subsequent amendment.

BIOCOMPATIBILITY

I personally reviewed the relevant portions of the submission. The sponsor's text is provided below.

> *All of the materials in contact with the human body or fluids used to construct the Evia family of pulse generators remain unchanged from the currently market-released Cylos family (P950037/S41, dated December 21, 2005) and have been used extensively in US market released BIOTRONIK products.* ***Table 6*** *presents the external (body/fluid contact) materials used in Evia. These materials are used with BIOTRONIK's market-released Cylos family of pulse generators (P950037/S41, dated December 21, 2005) 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: 2003.*

Table 6: Evia Materials of Construction

PART	MATERIAL
IS-1 Connector Ports	Titanium
Sealing plugs	Silicone ((b)(4) (b)(4)
Header	(b)((b)(4) Epoxy Resin (b)(4) (b)(4) Hardener (b)(4) (b)(4)
Housing (can)	Titanium ((b)(4) (b)(4)
Set Screw	Titanium

Discussion

I have no concerns regarding this section.

CLINICAL

(b)(6) performed a complete assessment of the clinical impact of the changes proposed by the company. I also personally reviewed the submission for all of the changes with a potential clinical impact. (b)(6) expressed several concerns regarding the proposed changes. His primary concerns have were incorporated into the discussion and proposed deficiencies outlined in the Device Description section of this memo. (b)(6) is familiar with the clinical data used to support the performance of Medtronic's Managed Ventricular Pacing and Atrial Capture Management features. These features are similar to the Ventricular Pacing Suppression and Atrial Capture Control features proposed by the sponsor of this submission. (b)(6) provided the clinical study summaries for the studies Medtronic completed to support the performance of these features.

The sponsor was able to address our concerns regarding these new features by locking-out these features.

STATISTICAL

This section is not applicable to this submission.

ANIMAL TESTING

This section is not applicable to this submission. The original submission did not include any animal data.

PACKAGING, STERILIZATION, AND SHELF-LIFE

I personally reviewed the relevant portions of the submission. The sponsor's text is provided below.

> *The packaging controls and materials used with the Evia family of pulse generators are identical to the market released Cylos family of pulse generators (P950037/S41, dated December 21, 2005).*
>
> *The pulse generator 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. Appendix 125 contains labeling intended for these devices.*
>
> *The Evia and the corresponding accessories have been sealed in a container gas-sterilized with ethylene oxide. The recommended storage temperature range of the packaging is –10° to 45° C.*
>
> *The Evia family of pulse generators, as with all BIOTRONIK pulse generators, are sterilized with Ethylene Oxide (EtO) gas to achieve a sterility assurance level (SAL) of $1x10^{-6}$. Sterilization is performed in a (b)(4) automatic sterilizer[.] The environmental controls, sterilization process, and sterility assurance procedures for Evia are identical to those used for other BIOTRONIK market-released pulse generators.*
>
> *Evia family of pulse generators, as well as all other BIOTRONIK pulse generators, leads and accessories, are sealed within a double sterile blister package consisting of (b)(4) (b)(4). The blister packs are sealed with Tyvek® covering (Perfecseal). The Tyvek® pores are permeable to sterilization gas and water vapor, but are impermeable to bacteria. These sterile packaging materials fulfill the requirements of a non-toxic reaction with the enclosed products, as well as compatibility with the ethylene oxide sterilization process. Package validation testing with Evia was successful and met specifications. No sterilization product validation tests were conducted for the Evia pulse generators as the test results from Cylos are also valid for Evia. Cylos sterilization validation is valid for Evia because:*
>
> - *The sterilization equipment and sterilization process are identical for these pulse generators.*

- *All materials used in the Evia and Cylos pulse generators are identical and the pacemaker size is comparable.*
- *The packaging material is the same for all pacemakers.*

Discussion

I have no concerns regarding this section.

LABELING

I personally reviewed the relevant portions of the submission. The sponsor's text is provided below.

All labeling for the Evia / Entovis families of Implantable Pulse Generators is based on the labeling for the Cylos family.

TECHNICAL MANUAL

The technical manuals for the Evia / Entovis families of Implantable Pulse Generators are a revised version of the technical manual for the current legally marketed Cylos family of pulse generators with the addition of information on the new features. Appendix 124 includes the Evia technical manual. The Entovis technical manual will be included in the final labeling amendment.

OTHER LABELING

Appendix 125 provides the following proposed labeling for the Evia / Entovis families of Implantable Pulse Generators, which are processed and applied and/or inserted with the pulse generators prior to device distribution:

- *Outer Box Label*
- *Medical Device Registration Form (MDRF)*
- *Medical Device Registration Labels (MDRL)*
- *Patient Temporary Identification Cards*
- *Return Envelope*
- *Quality Assurance Box Seal*
- *Gas Sterilization Label (applied by Manufacturer)*
- *Software CD-ROM Label*
- *Out of Service Form*
- *Brady Patient Manual*
- *Warranty*

Discussion

The labeling was reviewed. There were some questions regarding the labeling, which the sponsor was able to resolve with information provided in the amendments.

POST-MARKET REQUIREMENTS

This section is not applicable to this submission.