MEMORANDUM

To: The Record

From: (b)(6)
Biomedical Engineer, FDA/CDRH/ODE/DCD/PDLB

Date: March 30, 2011

File: **P980035/S134 (master)**
Advisa DR A4DR01 Implantable Pulse Generator and Model 9995 Application Software v7.3

P890003/S169
CareLink Monitor Model 2490G, CardioSight® Reader Model 2020A, and Mode12491 DDMA

P980016/S187
Secura™ DR/VR D224DRG / D224VRC, Virtuoso II DR/VR D274DRG / D274VRC and Maximo® II DR/VR D284DRG/D284VRC Implantable Cardioverter Defibrillators (ICDs)

P010031/S150
Consulta™ D224TRK, Concerto II D274TRK, and Maximo II D284TRK ICDs with Cardiac Resynchronization Therapy(CRT-D)

Sponsor: Medtronic, Inc.

Recommendation: Approval

Introduction

The purpose of this submission is to request approval for the Advisa DR A4DR01 Implantable Pulse Generator (IPG) and Model 9995 Application Software v7.1. This IPG combines features from the Adapta (P980035/S043, approved 17 July 2006) and EnRhythm (P980035/S038, approved 28 April 2005) IPGs, and uses software and firmware from the Consulta / Maximo II / Secura CRT-Ds and ICDs (P980016/S114, approved 17 March 2008). No new features or clinical data are introduced in these supplements.

Review Team

Consulting reviews were performed by:

- (b)(6) – Electrical Testing
- (b)(6) – Battery – Electrical

- (b)(6) – Battery- Chemistry
- (b)(6) – Electromagnetic Compatibility Testing
- (b)(6) – Software
- (b)(6) – Animal Testing
- (b)(6) – Clinical
- (b)(6) – Manufacturing (partial)
- (b)(6) – Manufacturing (partial)

Note that the terms Gen2 P2, Gen2 IPG, CRM1 Gen2 P2 or P2 DR appear throughout the submission and in this memo and should be considered synonymous with the Advisa device.

Regulatory History

Original Submission - Received March 6, 2009

Major Deficiency Letter issued – June 17, 2009

A001 - Response to major deficiency letter received July 15, 2009

A002 - Directed Hold requested by manufacturer received September 08, 2009

A003 - Unsolicited major amend; Removal from directed hold received February 16, 2010

A004 - Unsolicited major amend received April 07, 2010

A005 - Unsolicited minor amend received April 28, 2010

Approvable (PGMP) letter issued – May 27, 2010

A006 - Unsolicited minor amend received January 27, 2011

All supporting review documentation (consulting review memoranda and correspondence) for the original submission was transmitted with the lead review memorandum accompanying the Major Deficiency letter dated June 17, 2009. Similarly, supporting review documentation for A001 through A005 was transmitted along with the lead review memorandum accompanying the PGMP letter dated May 27, 2010. This decision memorandum summarizes the previous review cycles and reviews A006. Only supporting documentation for this round of review are attached.

Device Description

The Advisa device is a full featured implantable pulse generator (IPG) for treatment and monitoring of bradycardia and atrial tachyarrhythmia. Pictured in Figure 1, the Advisa IPG combines features of the EnRhythm, Adapta, and Secura IPGs. The Advisa system is comprised of the following:

- IPG Model listed above

- 9995 Software Application version 7.1
- CareLink Programmer Model 2090 (P890003/S080, approved February 18, 2005)
- CareLink Monitor Model 2490G (P890003/S077, approved October 19, 2004)
- InCheck Patient Assistant Model 2696 (P980050/S002, approved February 13, 2001)
- CardioSight Reader Model 2020A (P980050/S002, approved February 13, 2001)
- Commercially available pace/sense leads, and the same commercially available implant support instruments and accessories used with other approved Medtronic products.

Figure 1. Advisa IPG Model A4DR01

Note (per sponsor): "The Advisa DR device features are configured during manufacturing. The flex features were part of the original Consulta / Secura / Maximo II development project, so that new model numbers with different features sets can be created without making any changes to the software and firmware. The Model 9995 Software model select screen includes all of the Gen2 device brand names (i.e. Consulta, Secura, Maximo II, Concerto II, Virtuoso II, Advisa). The changes to the Model 9995 software were made that only affect the Advisa device. However, because the changes made to the Model 9995 software resulted in a version change, this submission includes refer to file letters for the FDA approved Consulta, Secura, Maximo II, Concerto II, and Virtuoso II devices."

The major Advisa components are identical or similar to those used in other previously approved Medtronic IPGs and consist of the following:

Component / Subassembly	**Change from EnRhythm/Adapta**
Connector module	Same as EnRythm
Activity sensor	Same as EnRhythm
Filter Feedthrough (FT)/ FT capacitor	Similar to Adapta (The value of the capacitor will be unique to Advisa.)
Battery	Same as EnRhythm
Electronic Module Assembly (EMA/hybrid)	Updated as described in "Detailed Description of Changes" section – Volume 1
Telemetry B Antenna	Similar construction to EnRhythm but slightly smaller

The software for Advisa is similar to the commercially available Consulta / Maximo II / Secura software. The firmware for Advisa is the FDA approved Consulta / Maximo II / Secura firmware.

Indications for Use

The indications for use for the Advisa A4DR01 IPG are given below in italicized text. These indications are identical to those approved for the EnRhythm (P150DR) IPG (P980035/S038, approved 28 April 2005) and Adapta IPGs (P980035/S043, approved 17 July 2006), with the exception of the item denoted by (*) which is identical to Adapta only, and those items denoted by (**), which are identical to EnRhythm only.

The Advisa DR system is indicated for the following:

- *Rate adaptive pacing in patients who may benefit from increased pacing rates concurrent with increases in activity*
- *Accepted patient conditions warranting chronic cardiac pacing include:*
    - *Symptomatic paroxysmal or permanent second- or third-degree AV block*
    - *Symptomatic bilateral bundle branch block*
    - *Symptomatic paroxysmal or transient sinus node dysfunctions with or without associated AV conduction disorders*
    - *Bradycardia-tachycardia syndrome to prevent symptomatic bradycardia or some forms of symptomatic tachyarrhythmias*
    - *Vasovagal syndromes or hypersensitive carotid sinus syndromes**

The device is also indicated for dual chamber and atrial tracking modes in patients who may benefit from maintenance of AV synchrony. Dual chamber modes are specifically indicated for treatment of conduction disorders that require restoration of both rate and AV synchrony, which include:

- *Various degrees of AV block to maintain the atrial contribution to cardiac output*
- *VVI intolerance (for example, pacemaker syndrome) in the presence of persistent sinus rhythm*

*Antitachycardia pacing (ATP) is indicated for termination of atrial tachyarrhythmias in bradycardia patients with one or more of the above pacing indications.***

*Atrial rhythm management features such as Atrial Rate Stabilization (ARS), Atrial Preference Pacing (APP), and Post Mode Switch Overdrive Pacing (PMOP) are indicated for the suppression of atrial tachyarrhythmias in bradycardia patients with atrial septal lead placement and one or more of the above pacing indications.***

Description of Changes

The following sections describe the changes proposed in this supplement. Review of the changes follows in a later section. The sponsor notes that the Advisa device has changes to device features, hardware, and software/firmware.

Feature Modifications

The sponsor notes that no new features have been introduced in the Advisa device, and provides the following summary of key device features, all of which are available in the previously approved EnRhythm IPG (P980035/S038), Adapta IPG (P980035/S043), and/or Secura implantable cardioverter defibrillator (ICD) (P980016/S114). In many cases, these features were modified for the Advisa device.

Feature	**EnRhythm IPG**	**Adapta IPG**	**Advisa DR IPG** ***Subject of this submission***	**Secura ICD**
Tachyarrhythmia Functionality				
Atrial Arrhythmia Detection	X		X	X
Atrial Therapies and Rhythm Management	X	Only APP and PMOP	X	X
PR Logic plus Sinus Tach Rule	X		X	X
Bradycardia Functionality				
Unipolar pacing polarity		X	X	
Rate Adaptive AV	X	X	X	X
Ventricular Rate Stabilization (VRS)	X		X	X
Premature Ventricular Contraction (PVC) Response	X	X	X	X
Pacemaker Mediated Tachycardia (PMT)	X	X	X	X
Ventricular Safety Pacing (VSP)	X	X	X	X
ModeSwitch	X	X	X	X
Non-Competitive Atrial Pacing (NCAP)	X	X	X	X
Sleep Feature (allows the Lower Rate to be decreased during sleep)		X	X	X
Rate Drop Response		X	X	X
Managed Ventricular Pacing (MVP)	X	X	X	X
Conducted AF Response		X	X	X
Atrial Sensing (FFRW rejection – partial, partial + and absolute)	X		X	X
Rate Response				
Rate Profile Optimization		X	X	X
Remote Management				
Telemetry B	X		X	X
Patient Activated Episode Storage (via CareLink Network only)			X	X
Patient Activated AT/AF Query with 2696	X		X	X
Automaticity				
Atrial Capture Management (ACM)		X	X	X
Right Ventricular Capture Management (RVCM)		X	X	X
Lead Monitor with Auto Polarity Switch		X	X	

Follow-up and User Interface Enhancements				
Quick Look II		X	X	X
Rate Response User Interface (RRUI)		X	X	X
Other				
Therapy Guide		X	X	X

The following features of the Advisa device were modified in comparison to its predecessors:

Sensing
- Polarity
- Ventricular Noise Reversion
- Atrial Noise Reversion
- Sensing configuration (i.e. bandpass, threshold, and blanking)

Pacing Output
- Polarity
- Polarity programming confirmation pacing output

Bradycardia Function
- Rate Limit: Upper Tracking Rate, Upper Sensor Rate
- Non-Competitive Atrial Pacing
- Post Ventricular Atial Refractory Period
- Sleep Feature
- Rate Drop Response
- Managed Ventricular Pacing
- Conducted AF Response

AT/AF Detection

Automated Features
- Atrial Capture Management
- Right Ventricular Capture Management
- Lead Monitor, Auto Lead Polarity Switch, Auto Polarity Configuration and Auto Implant Detection
- Battery Measurement Automatic Features
- P&R Wave Measurements
- Lead Impedance Measurements
- Atrial/Ventricular Amplitude

Follow-up Support
- Therapy Guide
- Device Longevity and Replacement Indicators
- Quick Look with Significant Events
- Diagnostic definition of ATP Therapy success
- EP studies
- In-Office Tests
- Patient Diagnostics / Monitoring
- Trans-telephonic Monitoring capability
- Longevity Estimator

Miscellaneous

- POR Operation
- EGM Real Time and Stored Channels
- EGM Storage

Comparisons between the feature in the Advisa device and its predecessor and the reasons for the change are provided by the sponsor in Table 1-9. Details regarding the differences in the Therapy Guide between Advisa and its predecessor (Adapta) are provided in Table 1-10 on pages 1-54 through 1-60.

Hardware

The sponsor notes the following hardware changes:

- Antenna – The telemetry B antenna was modified from that used in the EnRhythm devices to accommodated mechanical packaging requirements. The shape was changed in order to mechanically fit with other components inside the device (Figure 1-3), and the winding of the antenna was changed allowing a better manufacturing layout of the device.
- Left Hand Shield Insulator - The Advisa device will use the same Left Hand Shield insulator material but a slightly different shape. The Advisa insulator has a "tab" at the bottom to provide insulation in the area of the antenna to hybrid connection.
- Feedthroughs - The Advisa feed through has identical external features to EnRhythm. However, internally, Advisa uses a feed through design the same as Adapta. The value of the capacitor will be unique to Advisa.
- Integrated Circuits - The integrated circuits (ICs) for the Advisa devices are based on the IC set approved with Consulta / Maximo II / Secura (P010031/S084 and P980016/S114, approved 17 March 2008) and the IC set manufactured at Medtronic's vendor (b)(4) (b)(4) (P010031/S141 and P980016/S175, submitted 13 January 2009).
    - Microprocessor ((b)(4)) – For CPU, Digital Signal Processing, sensing and pacing engine logic. Same as component in the Consulta / Maximo II / Secura devices.
    - Sensing/EGM/Lead Impedance ((b)(4)) – This is the same as that in the IC set manufactured at Medtronic's vendor (b)(4)
    - Pacing ((b)(4)) – For output pacing. Same as component in the Consulta / Maximo II / Secura devices.
    - LECG Amplifier ((b)(4)) and Input Protection ((b)(4)) – These ICs are related to Leadless ECG capabilities and are included as an extensibility to support future device models. These are not powered up for Advisa devices.
    - Telemetry B ((b)(4)) - This is the same as that in the IC set manufactured at Medtronic's vendor (b)(4)
    - SRAM ((b)(4)) - For memory. Same as component in the Consulta / Maximo II / Secura devices.

Firmware and Software Changes

The Advisa DR device uses the same firmware (FW Configuration for (b)(4) Baseline revision

21.1 with RAMware Increment 3) as the FDA-approved Consulta/Secura/Maximo II CRTD/ ICD (P010031/S084 & P980016/S114, approved March 17, 2008 and P010031/S096 & P980016/S127, approved July 11, 2008).

The original submission requested approval for the Model 9995 version 7.1 software, which is based on the version 7.0 software. The 7.1 version modified a look-up table that is used by the battery longevity estimator feature. This modification was required because the Recommended Replacement Time (RRT) trip point voltage was increased to ensure that RRT notification performs as intended with the Delta 26H battery. Additionally, the sponsor notes that the SW XML Translation Utility (XMLTU) has been updated for the MRI SureScan On/Off status. Note: Medtronic is not seeking approval for the Advisa MRI device in this submission. Other incremental changes from the approved Model 9995 version 1.1 software have also been made:

Model 9995 SW version	Description	FDA-Approval Date
1.1	Gen2 market release (testing includes Advisa DR device)	P890003/S131, P010031/S084, and P980016/S114; approved March 17, 2008
1.2	Addition of the Lead Integrity Alert feature for Gen2 (ICD/CRT-D)devices	Under review P010031/S104 and P980016/S135. 180-day PMA-S submitted on October 21, 2008.
7.0	SW Version 1.2 migrated to Windows XPe	Under review P890003/S___. Real-time Review PMA-S submitted on February 20, 2009.
7.1	**Update to battery longevity tables for the Advisa device**	**Subject of this PMA**

Amendment A004 was submitted to request approval for Advisa DR to use Model 9995 Application Software v7.3 and corresponding XMLTU. This is an update from the version originally submitted for this bundled supplement, v7.1. The update was made to address a field issue associated with the Consulta/Secura series of high voltage devices. However, as the Model 9995 v7.3 software and corresponding XMLTU support Advisa DR, the sponsor needs approval to allow Advisa DR to use the updated versions.

CareLink Instruments and Device Data Management Application (DDMA)

The following changes, along with a fix to the XML Translation Utility (XMLTU) were made to the CareLink Monitor Model 2490G, CardioSight Reader Model 2020A, and Device Data Management Application (DDMA) Model 2491.

- CareLink Monitor Model 2490G – The firmware was upgraded to support Advisa device. There were no changes to the CareLink Monitor Model 2490G hardware.
- CardioSight Reader Model 2020A– The firmware was upgraded to support the Advisa device. There were no changes to the CardioSight Reader Model 2020A hardware.
- Device Data Management Application (DDMA) Model 2491 – The (b)(4) (b)(4) and (b)(4) software that were previously approved for the Consulta/Secura/Maximo II CRT-D/ICD DR/VR implantable devices (P890003/S131,

P010031/S084, and P980016/S114; approved March 17, 2008) will now be available for the Advisa device and no changes were needed. The XMLTU has been updated for the MRI SureScan On/Off status. Note: Medtronic is not seeking approval for the Advisa MRI device in this submission.

Battery-Related Changes

This file was placed on Directed Hold (A002) while the sponsor investigated a problem with their Delta 26H battery. The device was erroneously giving an ERI indication during in-office follow-up due to increased current drain during telemetry as a result of unexpected increased battery resistance. The file was lifted from Directed Hold in A003, which included changes made to address this battery issue. These changes included

- Battery Design Changes – Changes to the battery chemistry were made to address the unexpected high resistance.
- Battery Specification Changes – Changes were made to some of the battery specifications based on data from long term, real-time testing, unrelated to the Battery Design Changes. These included changes to the terminal pin, electrical resistance, rated capacity and maximum temperature during processing specifications.
- Device Specification Changes – ERI and EOS trip points have been changed to align with the Battery Specification Changes.
- Manufacturing Change to the Post Sterilization Test (PST) Software – The PST software was changed to program the new ERI and EOS voltages into the Advisa device EEPROM.

Lead Reviewer Comment on Description of Changes

In the original submission, there are conflicting details regarding the changes made in this submission. The major deficiency letter requested clarification of the changes. In their response in Amendment 001, The sponsor notes that the majority of the Advisa features and hybrid are the same as the Secura ICD. However as Secura is an ICD, Advisa is compared to predecessor EnRhythm and Adapta IPGs. The sponsor provides the requested summary table of hardware changes indicating that the hardware changes are to the Filter Feedthrough (FT)/FT capacitor, Telemetry B Antenna, Left Hand Shield Insulator, and Electronic Module Assembly (EMA/hybrid). This response adequately addressed this concern.

Several other minor clarifications of the feature modifications were requested in the major deficiency letter. These included questions regarding Atrial Noise Reversion, Rate Limit, NCAP, Managed Ventricular Pacing, Atrial Capture Management, Ventricular Capture Management, Lead Impedance Measurements, POR Operation, and Upper Tracking Rate. Responses regarding these questions were found to be adequate by myself, (b)(6) *and* (b)(6) (b)(6)*, the original authors of these questions.*

Electrical Testing Review

As noted above, there are several hardware changes that have been implemented for the Advisa device. The sponsor has provided descriptions of these changes as well as non-clinical test plans and reports to support these changes. These have been reviewed in detail by (b)(6) (b)(6) in a memorandum dated May 18, 2009. (b)(6) reviewed the following sections:

- Executive Summary: pages 1-17 to 1-37
- Detailed Device Description: pages 1-39 to 1-41
- Detailed Description of Changes: pages 1-42 to 1-63
- Non-Clinical Testing Overview: pages 1-117 to 1-127
- Electrical Design Verification Test Plan and Report: page 1-223 to 1-252
- Systems Testing and System Validation Test Plans and Reports: pages 2-44 to 2-72 and 2-120 to 2-142

(b)(6) original review noted significant omissions in the submission. First, the descriptions of the hardware changes are not sufficiently detailed and no information regarding component-level testing is provided. Secondly, device-level testing specific to the hardware changes noted in the submission are referenced but could not be located. Third, (b)(6) did not find testing to demonstrate that all of the Advisa features were adequately tested at the system level. In addition to these major issues, (b)(6) raised several more minor clarification questions. These concerns were conveyed to the sponsor in the major deficiency letter. The sponsor provided adequate responses to these deficiencies in Amendment 001 (A001) which were reviewed by (b)(6) in a review memorandum dated August 21, 2009. These are summarized below:

- *Initially, FDA was unable to locate specific testing relevant to the hardware changes in the Device Level Verification report. In A001, the sponsor provides a table that outlines the test plan/report, test name, and page number in the submission for each of the changes.* (b)(6) *reviewed the test requirements and results for these changes as referenced by the sponsor and found the response adequate to address his concerns.*
- *Initially, FDA was unable to locate specific information and component level testing data for the filtered feedthrough, antenna, shield insulator and* (b)(4) *input protection change. In A001, the sponsor provided more detailed information, including figures, test plans, and reports for component level testing for these items.* (b)(6) *reviewed the component level test reports and noted that testing seemed appropriate with acceptable results.*
- *FDA was concerned that electrical design verification testing and limited system level testing did not specifically evaluate all of the features in Advisa in order to thoroughly evaluate the firmware from Secura with the Advisa hardware. In A001, the sponsor notes that the firmware for the Gen2 family of products (Consulta/Secura/Maximo II/Advisa) was planned, designed, and implemented concurrently and that firmware verification testing applied to all. The only differences between Secura and Advisa are that Advisa does not use firmware code for high voltage therapies, wavelet, or Telemetry C. Per the sponsor compatibility of features in various combinations and settings was demonstrated through Gen2 P2-*(b)(4) *firmware testing and in canine studies.* (b)(6) *reviewed this response and found it adequate to address his concerns. He also requested that a software expert review the firmware documentation that was provided.* (b)(6) *reviewed the firmware documentation and found no issues.*

- *The sponsor's comparison of the Advisa platform to previous platforms (Secura, EnRhythm, and Adapta) did not provide complete information as only key features were described. The sponsor provided a single table with all features in A001.* (b)(6) *found the response acceptable.*
- *FDA was concerned about the addition of an* (b)(4) *-Hz burst capability in a pacemaker platform given the risk of inducing a lethal arrhythmia. The sponsor noted that this feature is also available in the* (b)(4) *pacemaker platform. In addition, the labeling for the feature includes prominent warnings to have external defibrillation capability accessible during such tests. This concern has also been discussed with* (b)(6) *and found to be adequately addressed.*
- *A table had several typographical errors. These were corrected in A001. This table had been reviewed by* (b)(6) *, who noted no concerns.*
- *The Hardware Requirements Specification was not included in the original submission. The sponsor provided it in A001.* (b)(6) *reviewed the information provided and noted no concerns.*
- *The sponsor had noted that the full suite of Electrical Design Verification Testing had been completed for* (b)(4) *implementation of circuitry (* (b)(4) *), and that the other versions have limited impact on* (b)(4) *functionality and verification. The sponsor was asked to provide detailed information about the differences between the versions and an appropriate rationale for the testing completed. The sponsor clarified the differences in A001 and provides a table outlining the rationale for limited testing, which was in most cases because testing was redundant.* (b)(6) *found the response acceptable.*
- *The sponsor was asked to provide additional information regarding the anomalies noted in system level testing. Amendment A001 references the location in the original description where a detailed description of these issues is provided. These were reviewed and found to be acceptable.*

In addition to the changes in the original submission, A003 included an update to the Gen2 Hardware Requirements Specification, which included administrative changes, clarifications, and combining of multiple requirements into single requirements. (b)(6) reviewed these changes and found the changes to be acceptable as documented in an e-mail dated April 1, 2010.

All issues related to electrical testing have been resolved with the submission of A001. (b)(6) (b)(6) **found the electrical testing information provided in the original submission and Amendments A001 and A003 to be supportive of approval and I concur.**

Battery Review

(b)(6) and (b)(6) reviewed the information related to battery changes provided in A003 in consulting memoranda dated March 30, 2010 and March 23, 2010, respectively. Minor concerns were clarified through interactive review with the sponsor. Initial review by (b)(6) focused on the safety of the battery specification changes and their effect on expected device performance, and he concluded that the changes did not raise any new concerns and should not affect the longevity or functionality of the device. (b)(6) reviewed

the design change from a chemistry perspective, noting that the change was safe and should theoretically result in lower impedance. I initiated additional interactive review, along with (b)(6) (b)(6) and (b)(6), to evaluate the actual effectiveness of the redesign in addressing the increased internal impedance that was found in the field. Through this interactive review, the sponsor provided information to support that the new battery will adequately power the device during use and also provided data from comparative resistance testing conducted between the previous and new battery designs. Based on initial submission and subsequent interactive review, (b)(6) and (b)(6) found the changes to be acceptable, and I concur.

In order to implement the changes to the device specifications associated with the battery specification changes (ERI and EOS trip points), a change was made to the PST software to allow the new ERI and EOS values to be programmed into the Advisa device EEPROM. (b)(6) (b)(6) reviewed this software change and noted no concerns in review comment dated May 5, 2010.

The changes related to the battery are acceptable for approval.

Electromagnetic Compatibility (EMC) Review

(b)(6) performed the EMC review for this supplement. His consulting review is documented in review memoranda dated May 14, 2009 and July 30, 2009. (b)(6) reviewed the EMC Design Verification Plan and Report (pages 1-171 to 1-222) and found that the sponsor provided documentation to support all required and numerous optional EMC tests. (b)(6) noted device interactions during (b)(4) injection testing below (b)(4) kHz and requested clarification from the sponsor on the types of device interactions observed, the sensitivities at which they occurred and why those interactions were considered acceptable. The sponsor responded interactively in e-mail dated May 18, 2008. (b)(6) reviewed the sponsor response and had an additional follow-up question which was conveyed as a Minor Deficiency under "Electromagnetic Compatibility Testing" in the major deficiency letter. This issue is summarized below:

- *The sponsor was asked to verify that device interactions for EMI at low frequencies during the "Behavior during Application of Modulated Interference from (b)(4) Hz to (b)(4) GHz" test occurred during testing below (b)(4) kHz. The sponsor was also asked to justify the acceptable (b)(4) sensitivity level. In A001, the sponsor clarifies that all device interactions occurred at frequencies below (b)(4) kHz. The sponsor also notes that the (b)(4) setting for sensitivity is chosen based on the expected amplitude of the cardiac signal, and not on a transient EMI environment. (b)(6) found this response acceptable and noted no issues related to EMC for this submission.*

All issues relate to EMC have been resolved with the submission of A001. (b)(6) found the electrical testing to be supportive of approval and I concur.

Software Review

(b)(6) performed the consulting review for the software and firmware changes in this submission. (b)(6) review is documented in memoranda dated June 8, 2009 and September 1, 2009. She reviewed all documentation provided to support the

firmware/software changes described above for the Advisa™ DR A4DR01 Implantable Pulse Generator, Model 9995 Application Software v7.1, CareLink Monitor Model 2490G upgrade, CardioSight Reader Model 2020A upgrade, and Model 2491 DDMA upgrade. **She found the documentation to be sufficient but with three clarification questions that were addressed in Amendment A001 as described below:**

- *The sponsor had indicated that a fix to the* (b)(4) *utility was made in the Gen 2 Advisa Battery SW V7.1 Maintenance Release Plan, but the motivation and scope of the change was unclear. In A001, the sponsor clarified that the subject change as made to support the future Advisa MRI device, and does not affect Advisa DR.*
- *The sponsor was asked to clarify how memory was re-allocated to provide for storage of arrhythmia episodes.*
- *The sponsor was asked to clarify why changes were made to the Battery Modeling/Longevity Projection methodology and to better describe what changes were made. The sponsor described the changes and how they differ from the Adapta and EnRhythm longevity estimation methodologies due to the different battery chemistries. The sponsor also provided additional information regarding validation of the algorithm, which compared lifetest data to the battery performance model.*

As noted above, the sponsor submitted A004 to request approval for the Advisa DR device to use the Model 9995 Application Software v7.3 and corresponding XMLTU. None of these changes in this update affect the Advisa DR devices and are wholly described and documented in P010031/S193, which is for the Consulta CRT-D and was reviewed under Real-Time Review (RTR) by (b)(6) The sponsor also submitted an unsolicited minor amendment to P010031/S193 and also to the subject supplement (A005) for completeness. This amendment requests approval to integrate the firmware updates in A004 using the existing inline manufacturing test and was included in the RTR. I participated in the RTR and concur with (b)(6) (b)(6) recommendation to approve the supplement, and thus fund the changes proposed in A004 and A005 to be acceptable as documented in a review memorandum dated May 11, 2010.

All issues related to software have been resolved with the submission of A001. (b)(6) **found the software documentation provided in the original submission and in Amendments A001, A003, A004 and A005 to be supportive of approval and I concur.**

Mechanical Testing Review

The sponsor performed testing to qualify mechanical and thermal environmental performance of the Advisa devices and provided their Mechanical Design Verification Test Plan and Reports for our review. The Advisa DR MRI device (model A3DR01) was used as the test model for mechanical qualification testing. This is acceptable as all Advisa DR models have the same hardware and firmware and only differ by labeling and radiopaque symbol. The device build seems appropriate (appropriate software and firmware versions) for testing as well. Note that the test plan and reports describe thermal and mechanical testing, as well as mechanical MRI testing. As the Advisa MRI device is not under review in this submission, *I did not review the mechanical MRI test plans or results.*

The tests performed (visual inspection, device functional tests, physical dimensions, storage temperature, temperature cycling, temperature shock, mechanical vibration, free fall drop, shielded cyclic deflection, barometric pressure, and destructive analysis) are appropriate as are the sample sizes used for testing, which range from (b)(4) to (b)(4), although destructive analysis was performed in only (b)(4) samples.

Thermal and mechanical design verification testing was successfully completed. All thermal and mechanical device environmental specification requirements were met. Two deviations were noted in the report and the sponsor deemed these acceptable. I have reviewed these minor deviations and concur that their resolution is reasonable. **I have no issues with the mechanical testing or its results.**

Animal Testing Review

(b)(6) performed the review of the animal testing information provided in this supplement. (b)(6) review is documented in memoranda dated May 28, 2009 and August 21, 2009. In brief, the sponsor conducted two GLP animal studies for the Advisa device. The first study included a more extensive array of testing than the second study, which was conducted to demonstrate that incremental changes to the Advisa device did not have an adverse effect on device operation. For the first study, (b)(6) found the testing and results acceptable for the most part, but has a concern regarding the observation of (b)(4) (b)(4) and (b)(4). (b)(6) did not find a justification for the limitation in testing that was made for the second study, and requested that additional information be provided so that the appropriateness and completeness of testing could be assessed. The sponsor responses in A001 are summarized as follows:

- *The sponsor indicated that the features excluded in the second study were either for a different device (i.e. for CRT vs DR), or were appropriately verified in firmware testing.*
- *The shorter study duration and smaller sample size for the second study were appropriate because the longer duration for the first study was required to test a feature that is not available for the Advisa IPG, and (b)(4) animal was required because the the Advisa IPG had fewer lead configurations ((b)(4)) to test.*
- *The sponsor clarified that the (b)(4) and (b)(4) that were observed were expected for a (b)(4) model likely based on differences in conduction velocity and depolarization in comparison to humans.*

All issues related to animal testing have been resolved with the submission of A001. (b)(6) found the animal testing to be supportive of approval and I concur.

Sterilization Review

The sponsor notes that the sterilization for the Advisa devices is the same as the approved sterilization for other approved implantable devices. The sponsor has provided the "Product Sterilization Strategy for the Medtronic Gen2 (P2 DR, CRT-P and D2) Product Family in the (b)(4) EtO™ Sterilizer System." The Gen2 P2 DR refers to the Advisa device. Notably, the document states that sterilization qualification testing is not required for the Gen2 P2 DR product family. The Gen2 P2 DR product family will be sterilized and aerated using a (b)(4)-minute gas exposure

process in the (b)(4) EtO sterilizer system at Medtronic-CRDM facilities. Aeration must be performed for a minimum of (b)(4) hours to a maximum of (b)(4) hours following (b)(4) sterilization cycle on the (b)(4) minute process; for the second and third sterilization cycles, a minimum of (b)(4) hours to a maximum of (b)(4) hours of aeration is required. **I have no issue with the sterilization documentation provided.**

Biocompatibility

The biocompatibility of the tissue-contacting materials used in the Advisa DR device has been established in previous PMA applications. These materials are all currently used in Medtronic's commercially available Consulta / Maximo II devices (P010031/S084 and P980016/S114, approved 17 March 2008). The sponsor provides a biocompatibility certification to support approval. **This is acceptable.**

Packaging and Shelf Life

The sponsor notes that the inner and outer sterile packaging and shelf box packaging for the Advisa device is the same as that for the Adapta device. The sponsor has provided the Advisa DR Device DAU Package Design Verification Plan and Report for our review. Their packaging testing included a suite of functional, visual, vibration, temperature and humidity conditioning, drop, and sterilization and aeration tests. Two shelf box discrepancies were noted during initial visual inspections, and I concur with the sponsor that these have been adequately addressed. All testing requirements were met and the packaging is considered acceptable for use.

The sponsor provides a Gen2 P2 Shelf Life Report to support an 18-month shelf life for the Advisa device.

Packaging and Shelf Life documentation are acceptable.

Risk Analysis

The sponsor conducted risk analysis and assessment for the Advisa system according to ISO 14971. They have provided a Summary Risk Management Report for the Advisa device as well as for the Application Software Version 7.1 for our review. I have reviewed the risk documentation for the Advisa device. The risk documentation for the software falls under the scope of (b)(6) software review.

In this report, the sponsor presents the risk management process and summarizes the risks assessments for:

- Device operation in its anticipated environment
- Device design features
- Device design implementation
- Random component failures over the life of the device
- Device manufacturing processes

Of note, for "Device design implementation," the sponsor noted three potential design issues that introduce incremental risk for the Advisa device. Two of these regard battery longevity

estimation and one regards VSP disabling. Additional information regarding these issues was requested in the Major Deficiency letter (as minor deficiencies). The responses provided by the sponsor are summarized here:

- *The sponsor provides information to describe the probability of occurrence of battery depletion without indication. I have discussed the clinical scenario described by the sponsor for the occurrence of this issue with clinician* (b)(6)*, who concurs that the incremental risk of this issue is reasonable and that the likelihood of occurrence is remote.*
- *The sponsor clarifies that this risk is outdated as the risk assessment was conducted prior to the software update included in this submission.*
- *The sponsor describes a clinical scenario where ventricular pacing might be inhibited due to interaction between Managed Ventricular Pacing and Mode Switch. I have discussed this issue with clinician* (b)(6) *who agreed with the sponsor's assessment that the incremental risk of this issue is acceptable.*

System Validation and Verification Testing did not identify any new hazards. The sponsor concludes that all identified system hazard scenarios have been either mitigated or are at an acceptable level of residual risk. **The sponsor's risk management activities are acceptable.**

Clinical Review

Although this submission did not include new clinical data for review, (b)(6) was consulted for her clinical review of the feature modifications (Tables 1-9 and 1-10) and the labeling. Her review is documented in memoranda dated May 19, 2009 and August 21, 2009. With regard to the feature modifications, (b)(6) notes "I do not have any issues with the features proposed [in Table 1-9] and from a clinical standpoint do not see any interaction or lack of appropriateness with these features." She also finds no issue with the Therapy Guide suggestions given in 1-10.

(b)(6) minor concerns are noted above under "Description of Changes." All were resolved with A001. **From a clinical standpoint, the feature modifications are acceptable.**

Labeling Review

The sponsor provided clinician and patient manuals and device package labeling for our review. (b)(6) **reviewed the manuals and had requested minor clarifications which were resolved in A001.**

I reviewed the package labeling and find that it includes the appropriate markings as symbols along with English text for package contents, prescription use, sterility, serial number, temperature information, device image, use-by date, and single-use status. These are acceptable. The sponsor also provided a USB Keytag Label and USB Shipper Label for our review. **I have no concerns with these.**

The sponsor notes that no changes have been made to the patient or device labeling for the CareLink Monitor Model 2490G and CardioSight Reader Model 2020A. The clinician information

sheets for these two products have been updated to add the Advisa model to the list of compatible devices. **This is acceptable.**

Note that the sponsor has also included reports from those studies that support the previously approved features available in the Advisa device. These include:

- Atrial Therapies
- Capture Management Managed Ventricular Pacing (MVP)
- Atrial Fibrillation Symptoms Mediated by Pacing to Mean Rates (AF SYMPTOMS) Study
- Atrial Septal Pacing Efficacy Trial (ASPECT)
- Atrial Therapy Efficacy and Safety Trial (ATTEST)
- Atrial Capture Management (ACM) clinical study
- Kappa 700 Clinical Study
- EnRhythm Clinical Study
- GEM III Model 7275 MVP Study
- Marquis MVP Download Study

Through interactive review, the sponsor noted that these clinical study reports are each individually published and made available to end users via Medtronic's website. They are considered labeling. The content has not changed from previously approved labeling (Concerto/Virtuoso CRT-D and ICD devices; P010031/S0031, approved May 12, 2006 and Consulta /Maximo II / Secura CRT-D and ICD devices). **This is acceptable.**

Manufacturing Review

The Advisa devices will be manufactured at the same manufacturing facilities that are approved for the Consulta/Maximo II/Secura devices (P010031/S084 and P980016/S114) and EnRhythm IPG (P980035/S038).

The sponsor provides the manufacturing process flow for the Advisa device, as well as a listing of manufacturing changes. The sponsor notes that the changes have either been approved by FDA (via 30-day manufacturing changes or Real Time Review PMA-S submissions), or already reported to FDA through the Annual Reports or will be reported to FDA in upcoming Annual Reports, or are changes applicable only to Advisa.

The manufacturing changes were referred to the Office of Compliance/Division of Enforcement B/Cardiac Rhythm and Electrophysiology Devices Branch for review. The review of the manufacturing changes was divided between (b)(6) and (b)(6). They provided consulting review memoranda dated May 18, 2009 and August 21, 2009 ((b)(6)) and May 14, 2009 ((b)(6)), respectively. (b)(6) found 16 of the 19 changes that he reviewed to be acceptable, but requested additional information on the remaining three**. The sponsor provided the requested information in A001 and** (b)(6) **found the responses acceptable.**

In (b)(6) review of changes 19 changes, he found that 15 were approved by Office of Compliance and that four changes were still under review. The original 30-day notices for these 4 changes were found to be inadequate. A 135-day conversion letter was sent to the firm along

with a list of deficiencies. A Minor Deficiency asked the sponsor for an update to the status of those manufacturing changes. In A001, the sponsor indicated that 2 of the 4 changes had been approved and that the remaining two would not be implemented until the master submission for those changes was approved. **This is acceptable.**

The sponsor also submitted A006 to request approval of 19 manufacturing changes that have already been approved for other approved devices. These were reviewed by (b)(6) of Office of Compliance/Division of Enforcement B/Cardiac Rhythm and Electrophysiology Devices Branch, who indicated that 16 of 19 changes were acceptable for approval (see Attachment A). The remaining three changes are design changes and I have reviewed these. These three changes were approved for other devices under master files P980035/S162, P980035/S169, and P980035/S182 through the real-time review paradigm. There are no concerns with applying these changes for the Advisa device as well.

Conclusion and Recommendation

The original submission was found to be deficient, and later found to be approvable pending resolution of QSR issues (PGMP) after review of A005. While on hold, the sponsor submitted A006, which was found to be acceptable by the Office of Compliance/DOEB/CREBD as noted above. A memorandum from (b)(6) dated March 9, 2011 (Attachment B) indicates that issues related to QSR non-compliance have been resolved and that the hold status for this PMA is lifted. Therefore, this supplement may now be approved.

Based on the information provided in this submission and associated amendments, consulting reviews, and interactive review with the sponsor, I recommend approval of this supplement.

(b)(6) Lead Reviewer Date

(b)(6), Branch Chief Date
FDA/CDRH/DCD/PDLB