DATE: 21 March 2011

FROM: (b) (6)

SUBJECT: P010031/S171 (MASTER); P980016/S211; P890003/S177

CONTACT: DIANE BROWN URIELL; SENIOR REGULATORY AFFAIRS MANAGER; MEDTRONIC, INC

TO: THE RECORD

BACKGROUND/ REASON FOR SUPPLEMENT

Medtronic submitted the Supplements (180-Day) to the subject Pre-market Approval Applications in order to request approval for the Protecta™ XT CRT-D, D314TRG and Protecta™ CRT-D D334TRG Implantable Cardioverter Defibrillators with Cardiac Resynchronization, Protecta™ XT DR D314DRG; Protecta™ XT VR D314VRG; Protecta™ DR D334DRG; and Protecta™ VR D334VRG Implantable Cardioverter Defibrillators, Model SW009 Application Software v1.0, Carelink Monitor Model 2490C upgrade, CardioSight Reader Model 2020A upgrade, and Model 2491 DDMA upgrade.

All aspects of the proposed Protecta Family of Devices are identical to the legacy products EXCEPT software related to support of the following added clinical features:

- **Wavelet for Dual and Triple Chamber Devices**: The Wavelet feature is a single-chamber SVT-VT discriminator that differentiates VT from SVT based on QRS morphology.
- **T-Wave Over-sensing (TWOS) Discrimination**: Therapy withheld depending on pattern analysis and frequency content to compare R-T values in order to identify a VT/VF.
- **VF High-rate Time-out (VF-HRTO)**: Limits duration of withheld tachycardia therapy where ventricular rates are consistently in VF zone.
- **Rhythm Based Synchronization Interval (RBSI)**: (b) (4) difference algorithm still used but relative to the intrinsic rate at the point of detection—based on zone of detection and whether rhythm is polymorphic.
- **RV Sensing Lead Alert**: The feature consists of over-sensing and impedance component to indicate potential lead issues.
- **Sensing Noise Algorithm**: The algorithm compares a set of fast ventricular senses and the associated far field electro gram to discriminate between noise and an event.
- **Optivol 2.0**: Intrathoracic impedance monitor intended to detect chronic heart failure based on increased resistance attributed to fluid.

Medtronic further amended the initial submission in order to 1) add a corrective fix related to charge time out; and 2) incorporate minor evolutionary manufacturing modifications intended to align processes with currently marketed product families.

Review History

The PMA/S was received by the FDA on 22 October 2008. Concerns identified were conveyed to the firm on 22 March 2010. Amendments to the file responding to were received by the FDA on 20 April 2010, 27 August 2010, and 18 January 2011.

REVIEW TEAM

(b) (6), PE, Lead and Software Reviewer, CDRH/ODE/DCD/PDLB
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(b) (6), CDRH/ODE/DCD/CEMB
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(b) (6), Statistician, OSB
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(b) (6), Software Reviewer, CDRH/ODE/DCD/CEMB
(b) (6), MD, Medical Officer, CDRH/ODE/DCD/PDLB
(b) (6), Mechanical Engineer, CDRH/OC/CREB
(b) (6), Supervisory CSO, CDRH/OC/CREB
(b) (6), CSO, CDRH/OC/CREB
(b) (6), Reviewer CDRH/ODE/DCD/PDLB

INDICATIONS FOR USE

The Indications for Use for the Protecta Family of Devices has not changed, per Medtronic (P010031/S171, Volume 1, pages 293-295):

Protecta ICD devices (CRT-D, DR, and VR) are the same as the indications for the Consulta CRT-D (P010031/S84, approved 17 March 2008) and Secura DR/VR ICD (P980016/S114, approved 17 March 2008) which are the same as those of currently marketed devices such as: InSync III Marquis Model 7279 and InSync Sentry Model 7299 (P010031/S18, approved April 8, 2005); Concerto C154DWK (P010031/S057, approved April 17, 2007); and Virtuoso DR D154AWG (P980016/S062, approved May 12, 2006) and Virtuoso VR D154VWC (P980016/S062, approved May 12, 2006):

Protecta XT CRT-D D314TRG: The indications for use for the Protecta XT D314TRG CRT-D are identical to those approved for Consulta CRT-D D224TRK (P010031/S084, P980016/S114, approved March 17, 2008). "The Protecta CRT-D system is indicated for ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life threatening ventricular arrhythmias. In addition, the device is indicated for use in patients with atrial tachyarrhythmias, or those patients who are at significant risk of developing atrial tachyarrhythmias. The system is also indicated for the reduction of the symptoms of moderate to severe heart failure (NHYA Functional Class III or IV) in those patients who remain symptomatic despite stable, optimal medical therapy and have a left ventricular ejection fraction ≤ 35% and a prolonged QRS duration. 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 ICD-indicated patients with atrial septal lead placement and an ICD indication."
Protecta XT DR D314DRG: The indications for use for the Protecta XT DR D314DRG ICD are

identical to those approved for Secura DR D224DRG (P010031/S084, P980016/S114, approved March 17, 2008). "The Protecta XT DR system is indicated to provide ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life-threatening ventricular arrhythmias in patients with NYHA functional class II/III heart failure. In addition, the device is indicated for use in the above patients with atrial tachyarrhythmias, or those patients who are at significant risk of developing atrial tachyarrhythmias. 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 ICD-indicated patients with atrial septal lead placement and an ICD indication.

• The use of the device has not been demonstrated to decrease the morbidity related to atrial tachyarrhythmias.
• The effectiveness of high-frequency burst pacing (atrial 50 Hz Burst therapy) in terminating device classified atrial tachycardia (AT) was found to be 17%, and in terminating device classified atrial fibrillation (AF) was found to be 16.8%, in the VT/AT patient population studied.
• The effectiveness of high-frequency burst pacing (atrial 50 Hz Burst therapy) in terminating device classified atrial tachycardia (AT) was found to be 11.7%, and in terminating device classified atrial fibrillation (AF) was found to be 18.2% in the AF only patient population studied."

Protecta XT VR D314VRG: The indications for use for the Protecta XT VR D314VRG ICD are identical to those approved for Secura VR D224VRC (P010031/S084, P980016/S114, approved March 17, 2008). "The Protecta XT VR system is indicated to provide ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life-threatening ventricular arrhythmias in patients with NYHA functional class II/III heart failure.

Notes:
• The ICD features of the device function the same as other approved Medtronic market released ICDs.
• Due to the addition of the OptiVol diagnostic feature, the device indications are limited to the NYHA functional class II/III heart failure patients who are indicated for an ICD.
• The clinical value of the OptiVol fluid monitoring diagnostic feature has not been assessed in those patients who do not have fluid retention related symptoms due to heart failure."

Protecta CRT-D D334TRG: The indications for use for the Protecta D334TRG CRT-D are identical to those approved for Consulta CRT-D D224TRK (P010031/S084, P980016/S114, approved March 17, 2008). "The Protecta CRT-D system is indicated for ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life threatening ventricular arrhythmias. In addition, the device is indicated for use in patients with atrial tachyarrhythmias, or those patients who are at significant risk of developing atrial tachyarrhythmias. The system is also indicated for the reduction of the symptoms of moderate to severe heart failure (NHYA Functional Class III or IV) in those patients who remain

symptomatic despite stable, optimal medical therapy and have a left ventricular ejection fraction ≤ 35% and a prolonged QRS duration.

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 ICD-indicated patients with atrial septal lead placement and an ICD indication."
Protecta DR D334DRG: The indications for use for the Protecta DR D334DRG ICD are identical to those approved for Secura DR D224DRG (P010031/S084, P980016/S114, approved March 17, 2008) with the exception that the OptiVol feature is not included in Protecta DR.

"The Protecta DR system is indicated to provide ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life-threatening ventricular arrhythmias in patients with NYHA functional class II/III heart failure. In addition, the device is indicated for use in the above patients with atrial tachyarrhythmias, or those patients who are at significant risk of developing atrial tachyarrhythmias.
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 ICD-indicated patients with atrial septal lead placement and an ICD indication.
Notes:
• The use of the device has not been demonstrated to decrease the morbidity related to atrial tachyarrhythmias.
• The effectiveness of high-frequency burst pacing (atrial 50 Hz Burst therapy) in terminating device classified atrial tachycardia (AT) was found to be 17%, and in terminating device classified atrial fibrillation (AF) was found to be 16.8%, in the VT/AT patient population studied.
• The effectiveness of high-frequency burst pacing (atrial 50 Hz Burst therapy) in terminating device classified atrial tachycardia (AT) was found to be 11.7%, and in terminating device classified atrial fibrillation (AF) was found to be 18.2% in the AF only patient population studied."

Protecta VR D334VRG: The indications for use for the Protecta VR D334VRG ICD are identical to those approved for Maximo II VR D284VRC (P010031/S084, P980016/S114, approved March 17, 2008). "The Protecta VR system is indicated to provide ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life-threatening ventricular arrhythmias in patients with NYHA functional class II/III heart failure."

DEVICE DESCRIPTION

The Protecta ICD devices are multi-programmable, implantable cardioverter defibrillators (ICDs) and the Protecta CRT-D devices are multi-programmable, cardiac resynchronization therapy implantable cardioverter defibrillators. The Protecta CRT-D provides biventricular pacing for cardiac resynchronization therapy.

PRECLINICAL/BENCH

The modifications to the device system relate to the implanted device (RAM, firmware, specifications, labeling), external device programmer (RAM, software, specifications, labeling), and device data management application (software).

BIOCOMPATIBILITY/MATERIALS : Not applicable

ANIMAL STUDIES: Not applicable

ELECTRICAL SAFETY: Review of the proposed modification to the RAMware indicates adequate evaluation of electrical safety concerns in terms of modified device parameters. Specifically, increasing the ERI and EOL thresholds initiates earlier notification of battery failure. Of some note, increased telemetry features resulted in greater battery depletion than anticipated.

MECHANICAL SAFETY: Not applicable

SOFTWARE: Review of the proposed modification to the firmware and software indicates adequate testing for approval of the subject. The documentation provided sufficiently details adequate software development in alignment with previous practices. Further, the features proposed within the subject were rigorously studied as evidenced by the documentation presented in accordance with the FDA Software Guidance Document.

The following deficiencies were identified by (b) (6), (b) (6), and (b) (6) regarding the software and firmware modifications:

1- The original submission did not contain the entire Software Requirements Specification (SRS) document. The entire SRS document was submitted and deemed adequate by (b) (6) and (b) (6), who had the initial concerns on this matter.

The remaining software and firmware deficiencies were submitted by (b) (6):

2- Revised software development life-cycle documentation was requested to account for changes due to field issues. This deficiency represented a Major Unsolicited Amendment extending the review clock to 05 Sept 2010. The software was designated as a "Major" level of concern since "failure or latent flaw in pacemaker or ICD firmware has the potential to directly result in death or serious injury to the patient." No further issues are noted.

3- One of the unresolved anomalies associated with the programmer software potentially presents an issue related to patient safety. After clarification it was determined that these anomalies no longer presented concern for the safety and effectiveness of the device.

4- A viable traceability matrix describing modifications within various system applications (devices, CardioSight Reader, CareLink Monitor, DDMA) was not submitted. A viable traceability matrix describing modifications within various system applications (devices, CardioSight Reader, CareLink Monitor, DDMA) was provided by the firm. No further issue is noted.

5- The modifications to the (b) (4) software platform relate to various clinical applications intended to deliver appropriate shock and minimize inappropriate shock by refining various input variables. The complex software logic necessary requires interaction of the clinical features. A discussion of mitigations associated with significant risks identified was not provided within the hazard analysis. The firm provided a response and the significant risks associated with the newly incorporated features as well as the mitigation strategies were adequately defined. No further issue is noted.

CLINICAL DATA: Review of the clinical data included both a medical officer and statistical analyses. Issues identified were resolved during interactive review. The sponsor modified labeling to comply with FDA guidelines. Some concern from the statistician was noted regarding specific raw data. However, FDA has not required such data within previous applications: Team consensus determined the summary data provided adequate for approval.

(b) (6) provided deficiencies to the firm requesting more information on the wavelet sequential algorithm contained in the Clinical Study volume and clarification on various other features and algorithms in the device. The firm provided clarification on all issues and this satisfied all concerns from (b) (6) who recommended approval of the supplement.

(b) (6) identified the following deficiencies:

Deficiency 1. You have provided results of (b) (4) testing but no accompanying electronic data. Please provide data in electronic form with appropriate documentation. Please refer to the following link for presentation format: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm136377.htm.

Deficiency 2. You refer to subject demographics for the clinical studies used, but do not appear to have provided this information with your submission. For reviewer convenience, please provide tables that show subject demographics and clinical data for subjects used for simulated testing of all algorithms. In addition, please justify why these data adequately represent the intended use population for each (all) of the devices for which you are seeking approval.

The firm responded to the above two deficiencies stating that submitting this data would be overly burdensome. (b) (6) did not agree with this response and left it up to the team to decide if another deficiency should be sent to the firm.

Deficiency 3. Since the (b) (4) algorithm will replace the (b) (4) algorithm in dual - chamber ICDs and the (b) (4) algorithm in single - chamber ICDs, comparison of both sensitivity and specificity of (b) (4) + (b) (4) with (b) (4) appears pertinent. You have provided only a comparison of the sensitivity of (b) (4) + (b) (4) with that of (b) (4), please provide a comparison of specificities, and add graphs of sensitivity and specificity of (b) (4) t for the range of SVT limits to Figure 1 (page 4 - 49). The firm provided a response that was acceptable. There are no further concerns on this deficiency.

Deficiency 4.You state on page 4 - 49 that one hybrid episode was excluded from the statistical analysis since it was not classified as either SVT or VT/VF during simulation. It would appear that this is an "indeterminate" test result and should not be ignored in your analyses. Please provide a worst case analysis that treats this observation as being incorrectly classified by the (b) (4) + (b) (4) algorithm. (Please see FDA Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic tests available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071148.htm for some discussion of this issue.) The firm provided a response that was acceptable. There are no further concerns on this deficiency.

Deficiency 5. Please comment on the distribution of SVT and VT/VF episodes used for your testing with respect to episodes near the "grey zone" between VT/VF and SVT. (A disproportionately large number of episodes closer to the "extremes", which are less challenging to classify, may present your algorithm in a better light than warranted.) The sponsor indicated that no data was available to answer the question. (b) (6) found this to be unacceptable, however, due to the lack of data, follow-up would on the deficiency would be unproductive.

Deficiency 6. For Secondary objective #2 (page 4 - 22) the rules used for re - classifying episodes for the manual analysis appear to be different from those used in primary objectives #1 and #2. Please provide analyses using the same rules and/or explain and justify the reason for the differences.

Deficiency 7. Please provide patient demographics for patients whose episodes formed part of the records used for testing. (This would entail two sets of demographics for EMPIRIC and WAVE subjects, one for the sensitivity and the other for the specificity estimation.)

RV Lead Noise Discriminator:
Deficiency 8. You state that (b) (4) randomly selected episodes from the SCD HeFT clinical study. However, you have not stated how many different subjects this corresponds to, please do so.

OptiVol2.0

Deficiency 9. You state (page 4 - 411) that 3 subjects were excluded "... because no device data was collected for these subjects during the study." Please explain why such data was not collected and discuss whether lack of data from these patients could have biased the study results.

Deficiency 10. The firm indicates several reasons for non-availability of Daily impedance data none of which appear to be clinical (except perhaps "incalculable values". Please discuss if any clinical causes may result in data not being available and if so, please explain why you believe such exclusions would not bias the results of your study.

Deficiency 11. You state that the goals of your OptiVol (b) (4) plan are "... to demonstrate that OptiVol2.0 algorithm decreases the false detection rate and does not substantially decrease sensitivity for detection of critical clinical events ... compared to the presently approved OptiVol algorithm." Thus is appears that you intend to show superiority of OptiVol2 with regards to false detection rate and non - inferiority with respect to sensitivity. However, you state that "Establishing performance criteria and a minimum sample size are not necessary for this characterization." This is not clear. Your stated goals cannot be established without such criteria. In addition, the limited analyses on limited data (b) (4) events for OptiVol and (b) (4) events for OptiVol 2.0) you have presented do not allow for such determinations.
Please define your statistical goals prospectively and provide suitable statistical evidence to substantiate your claims.

Deficiency 12. You state that a given OptiVol threshold will be used for Fluid index detection for both versions of the OptiVol algorithm. If this threshold is not fixed for the algorithm, then performance of your algorithm across various thresholds in the range of clinical interest should be provided (for instance an ROC or partial - ROC analysis).

Deficiency 13. It appears that you could have multiple events from same subject in your data. Please clarify if statistical dependence between events from the same subject has been accounted for in your analyses.

Deficiency 14. You state that for the OptiVol comparison 95% CI for sensitivity was computed using the (b) (4) method. Please provide model details and output. (Please also note above deficiency regarding statistical goals for this analysis.)

(b) (6) indicated that the raw data from the bench testing would be preferable and that sufficient data was not provided to assess that the study samples, using retrospective data, were representative of the intended use population. However, she deferred to the team for final consensus. The team indicated overall approval.

(b) (6) also provided input regarding approval of the labeling, indicating that the proposed labelling was acceptable.

Manufacturing: The following deficiency was sent regarding manufacturing changes:

Deficiency 26.The submission lists several modifications previously approved in a 30 - Day/135 - day PMA - S or under current FDA review. FDA requires evaluation of the proposed changes based on the new product families. Please provide a 30 - day notice for each of these changes. The firm submitted a 30-day notice for all changes that required one.

(b) (6) and (b) (6) indicated no further deficiencies regarding the clinical or manufacturing aspects. According to (b) (6), the Warning letter for this firm has been lifted so the supplement can be approved.

CONCLUSION – The entire review team recommended that the supplement be **Approved**.

22 March 2011

(b) (6), Reviewer, PDLB Date

(b) (6), Chief, PDLB Date