
**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH**



*Division of Cardiovascular Devices
Pacing, Defibrillator & Leads Branch*

Date: 07 Nov 2011

Lead Reviewer: [REDACTED], Biomedical Engineer, FDA/CDRH/ODE/DCD/PDLB

Subject: P010031/S178 Master File
Refer to File: P980016/S218, P890003/S181
Medtronic
M-4 Connector Cardioverter Defibrillators and Software
Protecta XT CRT-D D314TRM
Protecta CRT-D D334TRM
Protecta XT DR D314DRM
Protecta DR D334DRM
Model SW009 Application Software v1.0 Systems
CareLink Monitor Model 2490C
CardioSight Reader Model 2020A
Model 2491 DDMA

Recommendation: APPROVAL

[REDACTED], Lead Reviewer, PDLB

Date

Mitchell Shein, Chief, PDLB

Date

Executive Summary

This bundled submission requests approval for four Medtronic CRT-D and ICD models that incorporate the M-4 Connector System. The IS-1, DF-1 connector versions of the four CRT-D and ICD models were the subject of a previous submission (Master File P010031/S171) approved 25 March 2011. The M-4 Connector System was also the subject of a previous bundled submission (Master File P010031/S176) for which a Not Approvable letter was sent 20 April 2011. After a Not Approvable letter was also sent for the subject bundle (also on 20 April 2011), a pre-IDE (b) (4) was submitted to discuss and eventually reach resolution on the outstanding concerns specific to P010031/S178 (this file). The review of each of these submissions is provided in more detail under the "Review History" section of this memo.

The firm has provided acceptable documentation of the safety and effectiveness of the Protecta M-4 System. The subject devices are qualified by equivalence to the predecessor Protecta and the other M-4 devices for most testing. Initial concerns about the specific tests qualified by equivalence as well

as the specimens and sample size used to conduct systems validation testing and the omission of some sterilization tests were addressed in the amendments submitted to the file. The firm also addressed all deficiencies sent regarding the predecessor and other M-4 devices that would preclude approval of the subject submission. As a note, concerns remain with the quadripolar defibrillation lead, but the approval of that product does not impact the approvability of the subject pulse generators. Since all of the concerns with this file have been addressed at this time, I recommend approval of this bundled submission.

NOTE- For the purpose of this review, "predecessor models" shall refer to those models that incorporate the IS-1 and DF-1 connectors and who are subject in Master File P010031/S171. Reviewer comments appear in indented italics beneath each section of the review. The only change to the predecessor devices is to the connector module.

NOTE- The firm states on page 1-42 that their four pole connector port has been designed and tested in compliance with the Four Pole Connector System Standard ISO/FDIS 27186 (E). The standard was published during the review of this file and, in A003, the firm requested to label their devices as compliant with the final ISO standard as published. This was reviewed and found acceptable; therefore the term "M4" will be replaced with "DF-4" in approved device labeling.

Review Team

Lead Review- [REDACTED], FDA/CDRH/ODE/DCD/PDLB
Engineering- [REDACTED], FDA/CDRH/ODE/DCD/PDLB
Software- [REDACTED], FDA/CDRH/ODE/DCD/PDLB

Key Reviewers of Predecessor Files

Manufacturing- [REDACTED], FDA/CDRH/OC/DOEBA (P010031/S176 and S178 bundles)
Animal Studies- [REDACTED], DVM, MD, FDA/CDRH/ODE/DCD/PDLB (P010001/S176)
Lead Reviewer- [REDACTED], FDA/CDRH/ODE/DCD/PDLB (P010031/S171)

Review History

This Bundle: P010031/S178 (Master), P980016/S218 (Refer to File), P890003/S181 (Refer to File)

02 April 2010: Major Deficiency Letter sent

Main concerns: [REDACTED] (b) (4)

20 April 2011: Not Approvable Letter sent

Main concern: animal study results

DF-1 and IS-1 Connector Predecessor Bundle: P010031/S171 (Master), P980016/S211 (Refer to File), P890003/S177 (Refer to File)

22 March 2010: Major Deficiency Letter sent

Main concerns: [REDACTED] (b) (4)

25 March 2011: Approval Letter sent

M-4 Connector Predecessor Bundle: P010031/S176 (Master), P980016/S216 (Refer to File), P920015/S055 (Refer to File), P890003/S179 (Refer to File)

17 March 2010 Major Deficiency Letter sent

Main concerns: [REDACTED] (b) (4)

(b) (4)

20 April 2011: Not Approvable Letter sent

Main concerns:

(b) (4)

Review is ongoing for these files.

Pre-IDE

(b) (4)

13 May 2011: File submitted

07 July 2011: File Closed

Review topics: (all deficiencies of P010031/S176 bundle)

(b) (4)

Indications for Use

As stated on pages 1-33 to 1-35, the indications of use for the subject devices are identical to those of the predecessor devices currently under review in Master File P010031/S171.

Lead Reviewer Comments: The indications for use of the Protecta XT CRT-D D314TRM, Protecta CRT-D D334TRM, Protecta XT DR D314DRM, and Protecta DR D334DRM appear appropriate and acceptable pending their review under Master File P010031/S171. The only difference between the prior and subject models is the connection between the lead and device header, which would not impact the indications of use for the device.

Device Description

The Protecta XT M-4 and Protecta M-4 CRT-D models are multiprogrammable cardiac devices that monitor and regulate a patient's heart rate by providing single or dual changer rate-responsive bradycardia pacing, sequential biventricular pacing, ventricular tachyarrhythmia therapies, and/or atrial tachyarrhythmia therapies.

The Protecta XT M-4 and Protecta M-4 ICD models are multiprogrammable cardiac devices that monitor and regulate a patient's heart rate by providing ventricular tachyarrhythmia detection and therapies, rate-responsive bradycardia pacing and/or atrial tachyarrhythmia detection and therapies.

The main difference between the subject device models and their predecessors is the lead connection:

CRT-Ds: predecessor devices incorporate (b) (4) DF-1 and (b) (4) IS-1 connectors into the device header, while the subject devices have one M-4 four pole connector and two IS-1 connectors.

ICDs: predecessor devices incorporate (b) (4) DF-1 and (b) (4) IS-1 connectors into the device header, while the subject devices have (b) (4) M-4 four pole connector and (b) (4) IS-1 connector.

In addition, the subject devices are slightly larger and heavier. Body thickness, estimated longevity, rate response sensor, capacitors, maximum high voltage, telemetry, case material, header materials, battery, hybrid circuitry partitioning and SRAM are identical.

The subject devices all contain the same firmware and use the same software application. The firmware and software are identical to those of the predecessors submitted under Master File P010031/S171. The Protecta XT M-4 CRT-D device has the most complex mechanical configuration and has the most extensive feature set.

Preclinical/Bench

The firm supports the approval of the subject devices with documentation of testing completed and submitted for the predecessor devices (Master File P010031/S171) and for the M-4 Connector System devices (Master File P010031/S176). Verification and validation testing, risk management activities, and biocompatibility, packaging, and shelf life assessments were conducted on the subject devices themselves as reviewed below. Table 2 indicates in which submission relevant preclinical/bench testing documentation is provided.

Table 1 Testing performed in the current submission as well as in the two prior submissions (P010031/S171 and P010031/S176) .

Component/Subassembly Test	Protecta XT/Protecta Submission (P010031/S171)	M-4 Connector System Submission (P010031/S176)	Protecta XT/Protecta M-4 Submission (current file)
Connector Module		X	Qualified by Equivalence
Design Assurance Unit (DAU) Verification	X	X	Qualified by Equivalence
Electrical Design Verification (EDVT)	X	X	Qualified by Equivalence
Firmware Verification	X		Qualified by Equivalence
Software Verification	X		Qualified by Equivalence
Systems Validation	X	X	X
Animal Testing		X	Qualified by Equivalence
Physician Handling		X	Qualified by Equivalence
Simulation Testing	X		Qualified by Equivalence
Risk Management	X	X	X
Biocompatibility	X	X	Qualified by Equivalence
Packaging	X	X	Qualified by Equivalence
Shelf Life	X	X	Qualified by Equivalence

Verification and Validation Testing

The engineering review was conducted by [REDACTED] of ODE/DCD/PBLD; as documented in her memos, she consulted with software expert [REDACTED]. The firm states that existing testing on the Consulta CRT-D/Secura M-4 models (Master File P010031/S176) and the predecessor Protecta models (Master File P010031/S171) is also appropriate to support approval of the new Protecta M-4 devices. Compared to the other M-4 devices, the subject devices include additional software and firmware to address inappropriate shocks and fluid status monitoring features. These changes were incorporated into the predecessor Protecta devices and tested as indicated in Master File P010031/S171. Several system validation tests were performed to ensure the subject Protecta M-4 devices function properly and are compatible with the other accessories with which they will be used.

Engineering Reviewer Comments: The use of previously submitted testing to support approval of the subject devices is appropriate and acceptable. The differences between the devices tested and those subject in this submission should not affect the outcome of most of the tests. The Major Deficiency letter sent included a request for further justification on the absence of several tests for the subject devices such as component qualification, device level verification, firmware verification, and software verification. The firm's response (essentially that the software and firmware were not impacted by the requested connector module change) was deemed appropriate under P010031/S178/A002 and no concerns were included in the Not Approvable letter.

Initial concerns regarding the sample size of and the samples used in the systems validation testing were also sent in the Major Deficiency letter. The firm's response in P010031/S178/A002 addressed the concern since the differences between the samples evaluated and those to be marketed would not impact the results of the testing performed. No concerns remain.

Packaging and Shelf Life

The engineering review memos also discussed Packaging and Shelf Life considerations. The packaging used with the other M-4 devices will be used for the subject devices as well. A shelf life identical to both the other M-4 devices and the predecessor Protecta devices (18 months) is requested.

Engineering Reviewer Comments: The qualification by similarity proposed by the firm for both packaging and shelf life appears acceptable. The changes implemented with the new connector module should not affect the acceptability of an 18 month shelf life. An initial concern regarding the differences between the predecessor and subject devices (volume, mass and dimensions) was sent in the Major Deficiency letter. The firm's response in P010031/S178/A002 highlighted small differences that would not impact packaging integrity detrimentally. No concerns remain.

Physician Handling

Physician handling was assessed as part of the M-4 Connector System submission (Master File P010031/S176). No additional information is provided in the subject submission.

Lead Reviewer Comments: The clinical review of the M-4 Connector System indicated a number of initial concerns regarding the potential for misuse of the new connector and its accessory as well as and the specific feedback provided by the participants in the handling assessment. These concerns were provided to the firm in a Major Deficiency Letter sent under P010031/S176. The firm's response in P010031/S176/A003 highlighted the training methods to be used with the new devices and the assessments of individual study participants. This response addressed all physician handling concerns as indicated in the lead reviewer's memo for that file. No concerns remain.

Animal Testing

In vivo animal testing was reported as part of the M-4 Connector System submission (Master File P010031/S176). No additional information is provided in the subject submission.

*Lead Reviewer Comments: The animal study review of the M-4 Connector System indicated a number of concerns that were provided to the firm in a Major Deficiency letter sent 17 March 2010. Both the duration of the study (3 months instead of FDA-expected 6 months) and the results (pathology and well as electrical measures) were concerning. The *in vivo* performance in an animal model of the subject Protecta M-4 devices would be similar if not identical to that of the previously reviewed M-4 Connector System. Therefore, all concerns with the M-4 Connector System were sent to the sponsor in the Major Deficiency letter for the subject submission as well.*

The firm performed an additional animal study (as documented under the M-4 Connector System bundle) to address FDA concerns. The results were submitted under P010031/S176/A003 and, while the duration of 6 months was now acceptable, the results still presented concerns. Further justification for the difference between electrical measurements of the predecessor and subject devices were requested in the Not Approvable letter sent for both P010031/S176 and the subject file (P010031/S178).

The firm submitted a pre-IDE (b) (4) to discuss the results of their animal study (as well as other outstanding concerns under the subject file and the M-4 Connector System file). The lower R-wave amplitude in the test group noted by the animal study reviewer was rationalized by the firm as acceptable based on the frequency of occurrence, absence of related electrical anomalies, absence of concerning pathology findings, and method of measurement. The firm's rationale was found acceptable by [REDACTED] and no concerns remain.

Clinical Data

No clinical data was provided to support approval of the Protecta M-4 devices.

Lead Reviewer Comments: The device's functionality and performance should not change with the alteration of connector type in such a way that bench testing, handling testing (conducted on the other M-4 devices), and animal study results (provided for the other M-4 devices) would not adequately assess the new risks. For this reason, I agree with the firm that no clinical data is necessary to support approval of the new devices.

Labeling

The labeling, clinician manuals, and device package labels of the subject devices are based on the submitted labeling for the predecessor device and the other M-4 devices. The patient manuals were updated for the predecessor devices, but not as a result of the connector module change. As indicated in the summary of this memo, the DF-4 ISO standard (ISO 27186) was published during the course of review; the firm requested that their product be labeling as compliant with the published standard under P010031/S178/A003.

Lead Reviewer Comments: I reviewed the labeling changes submitted, paying special attention to the description and visual representation of the new connector system. The changes were clearly referenced and described by the firm in Volumes 2-10 of the submission. Several editorial changes were made and are adequately justified and described. No concerns were identified during the initial review of thus PMA/S or communicated in any letter to the firm.

The review of P010031/S178/A003 indicated that there were no concerns with the subject device being labeled as compliant with the ISO standard for the DF-4 connector. No concerns remain with this section of review.

Sterilization

The subject devices will be sterilized using the same (b) (4) process as the predecessor Protecta devices and the other M-4 devices. The testing provided in the Consulta/Maximo II/Secura M-4 Connector System submission (Master File P010031/S176) also included samples of the subject Protecta and Protecta XT M-4 devices. Product bioburden and tolerable contact limits were assessed after a (b) (4) process. Residual (b) (4) irritation was also assessed. All test criteria were met and demonstrate conformance to AAMI/ANSI/ISO guidelines. Lethality, bacterial endotoxin, and packaging/load configurations were not evaluated. Two deviations were noted, but did not affect the outcome of the testing performed.

Lead Reviewer Comments: The provided sterilization testing was deemed appropriate for the other M-4 devices and is also appropriate for the subject devices. The testing meets all standard guidelines and was conducted using sterile-packaged final products. All test criteria were met; the two noted deviations are acceptable and do not impact the test results. An initial concern regarding the absence of lethality, bacterial endotoxin, and packing/load configuration testing was sent in the Major Deficiency letter. The firm's response in P010031/S178/A002 was found acceptable as indicated in the lead review memo for that file: lethality testing was completed, worst case testing results (for a different device) were provided for the bacterial endotoxin evaluation, and further description of the packaging configuration was presented. No concerns remain.

Biocompatibility

The firm indicates that the materials and manufacturing processes of the subject devices are identical to those of the other M-4 devices and, therefore, can be qualified by equivalency. The additional software and firmware of the subject devices would not affect the results of biocompatibility testing.

Lead Reviewer Comments: The qualification by similarity is appropriate for the biocompatibility testing. I agree with the firm's conclusion that the software and firmware changes implemented in the subject devices would not affect the biocompatibility testing results since the materials

and manufacturing processes are identical. I have no concerns about the biocompatibility of the subject devices.

Manufacturing

The sponsor identifies the manufacturing facilities of the subject devices on page 1-46 as those used for the predecessor devices and the M-4 connector devices. The manufacturing process flow is provided on page 1-47 and is similar to that used for the predecessor devices, with the only difference being the procedure required to [REDACTED] (b) (4). As stated on page 1-48, the processes used to construct the new connector system are identical to those used with the M-4 Connector System devices subject in P010031/S176.

Several other manufacturing changes were reported in the original PMA/S: 23 had already been approved by FDA (via 30-Day Notices or Real Time Review PMA supplements), 11 were being reviewed under Annual Reports, and 3 were specific to the subject devices and, therefore, have not been previously submitted.

Lead Reviewer Comments: The manufacturing changes already approved by FDA appear appropriate for the subject devices as well- the Protecta M-4 devices present no new risks associated with the implementation of these 23 changes.

The 11 changes that were being reviewed under Annual Reports are also acceptable for the subject devices pending their approval in the files already submitted to FDA. The sponsor was asked to provide an update to FDA regarding the status of previously submitted changes in the Major Deficiency letter for this file. The firm's response in P010031/S178/A002 indicates all changes were approved. The extension of approval to the subject bundle was discussed with OC Branch Chief Josh Simms and deemed acceptable.

The three changes specific to the subject devices appear acceptable, but approval of the two that were under review in Master File P010031/S171 was required prior to approval in the subject devices. The only new change, the [REDACTED] (b) (4) change, was reviewed and appears appropriate and acceptable- I have no further concerns about this change. The change was implemented to improve manufacturing and, as the sponsor states, was not in response to a recall, field issue, or field corrective action. As of 25 March 2011, P010031/S171 was approved (and with it the outstanding manufacturing changes requested also in the subject bundle). No concerns remain with these three changes.

In A004, the requested 10 manufacturing changes (all already approved for predecessor devices) be approved for the subject devices. OC Branch Chief Josh Simms indicated this approach was acceptable since the changes were recently approved. No concerns were conveyed to the firm in regards to these changes.

In A005, the firm requested 20 additional already-approved manufacturing changes be approved for the subject device system as well. I have reviewed the changes themselves and do not believe any would impact Mr. Simm's assessment of the approach under A004; therefore, I believe the 20 additional changes should be approved here and have no further concerns with this section of the review.

Post Approval Study

The Post Approval Study (PAS) provided in the M-4 Connector System submission (Master File P010031/S176) included the study of the subject Protecta M-4 devices. No additional information is provided in the subject submission.

Lead Reviewer Comments: The PAS review of the M-4 Connector System under P010031/S176 indicated a number of concerns were provided to the firm in a Major Deficiency letter sent 17 March 2010. The firm had presented a general PAS platform which was difficult

to navigate. FDA's concerns focused on the absence of several key PAS elements such as a clear study design and hypothesis, objectives, study population and sample size, follow-up visit, etc. The firm responded in P010031/S176/A003 with a modified protocol that addressed the outstanding concerns and, therefore, no concerns remain with this section of review.

Risk Management

Medtronic conducted a formal risk management assessment for the predecessor Protecta devices (Master File P010031/S171). For the subject devices, a Risk Management Upgrade Report was issued and the Protecta Summary Risk Management Report was updated to include a new failure mode (baseline Telemetry C failure) as identified in the System Validation Testing of the subject devices.

Lead Reviewer Comments: The firm has properly addressed risk management by identifying the areas in which the new connector system would affect the potential risks and hazards to the patient. The Upgrade Report appears extensive, and I have no concerns about the incremental risks the connector module change will introduce to patients relative to the predecessor devices.