

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: 28 Dec 2011

Lead Reviewer: [REDACTED] Biomedical Engineer, FDA/CDRH/ODE/DCD/PDLB
Consultants: Animal Studies-[REDACTED] MD, DVM, FDA/CDRH/ODE/DCD/PDLB
Biocompatibility-[REDACTED], FDA/CDRH/ODE/DCD/CSPDB
Engineering-[REDACTED] FDA/CDRH/ODE/DCD/PDLB
Post Approval Study-[REDACTED], FDA/CDRH/OSB/DEPI/EERB
Clinical-[REDACTED] MD, SGE (review of original PMA/S only)
Clinical-[REDACTED] MD, FDA/CDRH/ODE/DCD/PDLB (review of A001 and A003 only)
Steroid CMC-[REDACTED] PhD, FDA/CDER/OPS/ONDQA/DNDQA I/BRANCH I (review of A001 only)

Subject: P010031/S176 Master File
Refer to File: P980016/S216, P920015/S055, P890003/S179
Amendments: A001, A002, A003, A004, A005, and A006

Sponsor: Medtronic

Device: Quadripolar (M-4) Connector System
Consulta® CRT-D (D204TRM), Maximo® II CRT-D (D264DRM), Secura® DR (D204DRM), Maximo® II DR (D264DRM), and Sprint Quattro Secure Lead Model 6947M

Recommendation: **APPROVAL**

[REDACTED] Lead Reviewer, PDLB	Date	Mitchell Shein, Chief, PDLB	Date
--------------------------------	------	-----------------------------	------

EXECUTIVE SUMMARY

In this bundled submission, Medtronic is requesting approval for a quadripolar lead system consisting of two CRT-D models, two ICD models, and one lead model. The CRT-D and ICD cans are modified to include a single 4-pole receptacle in the header, plus the existing two IS-1 receptacles. The defibrillation lead is modified to include a single 4-pole proximal connector.

Original review of this PMA/S resulted in a Major Deficiency letter (dated 17 March 2010) and a Not Approvable letter (dated 20 April 2011). Responses to all deficiencies contained in those letters were provided in three amendments- A001, A003, and A005. A002 requested a deadline extension in light of the 6 month animal study requested by the Agency. A004 requested manufacturing changes related to the quadripolar lead system devices. A006 requesting inclusion of a software change approved for the predecessor devices while the DF4 devices were under review. Additional discussions under pre-IDE [REDACTED] (b) (4) were also held to obtain clarification on testing requested by the

agency and the acceptability of the firm's approach to addressing the outstanding concerns following the Not Approvable letter.

After review of the materials provided in the original submission and subsequent amendments, the review team now recommends Approval of the quadripolar lead system. More detailed explanations of this decision are provided under specific categories later in this memo.

Regulatory Background

As noted above, several amendments were submitted in relation to the subject files. Several pre-IDEs were discussed before submission of the original PMA/S; pre-IDE (b) (4) was submitted after the firm's receipt of the Not Approvable letter. Below is a timeline of the key events and documents for the subject devices.

Date	Document	Description
19 Dec 2003	(b) (4) received	Regulatory strategy and submission bundling approach
21 Jan 2009	(b) (4) received	General device design and testing
13 Oct 2009	(b) (4) received	Post Approval Study approach (not specific to the DF submission)
04 Dec 2009	P010031/S176 bundle received	---
17 Mar 2010	Major Deficiency Letter sent	46 concerns identified
18 May 2010	A001 received	Responses to all Major Deficiencies except animal study concerns
06 Oct 2010	A002 received	Extension request to complete animal study
04 Feb 2011	A003 received	Responses to animal study deficiency and new design changes
29 Mar 2011	A004 received	New manufacturing changes
20 Apr 2011	Not Approvable Letter sent	7 concerns identified
13 May 2011	(b) (4) received	Pre-IDE to discuss fatigue testing as well as approach to addressing outstanding deficiencies
11 Oct 2011	A005 received	Responses to Not Approvable letter
27 Dec 2011	A006 received	Software change (already approved for predecessor devices)

Indications for Use

As stated on pages 1-92 and 1-93 of the original submission, the indications of use for the devices of the DF4 Connector System are identical to those of the prior IS-1 and DF-1 connector models.

LEAD REVIEWER COMMENTS: The indications for use of the Consulta ICE CRT-S Model D204TRM, Maximo II CRT-D Model D264TRM, Secura ICD-DR Model D204DRM, Maximo II ICD DR Model D264DRM, and Sprint Quattro Secure Model 6947M lead appear appropriate and acceptable. 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

Medtronic's quadripolar defibrillation system consists of a four-pole lead connector with high and low voltage terminals on a single lead connector and a four-pole device connector bore including sealing rings and contacts to accommodate the four terminals of the lead connector. The system was initially called the "M-4 Connector System" because the ISO draft standard, which uses the term "DF4", was not yet approved. That standard was approved 15 March 2010; therefore, the firm requests to label the new devices as compliant with the final published version of ISO 27186.

LEAD REVIEWER COMMENTS: Conformance to the ISO standard was not obvious in the original submission and a deficiency requesting clear documentation of conformance was sent in the Major Deficiency letter. In response to this deficiency (in A001), the firm provided a clear table detailing how each section and requirement of the standard is met with their connector design and testing. Since conformance to the final published standard has been clearly documented, there are no concerns with approving the subject connector system with the "DF-4" labeling.

The sponsor claims that the clinical functionality and principles of operation of the subject devices are identical to those of the associated market-approved devices since the only difference between the subject models and their predecessors are the modifications to the connector bore of the CRT-Ds and ICDs and the proximal connector of the lead.

The DF4 Connector System uses the same Model 9995 Application Software v1.2, CareLink Monitor Model 2490C upgrade, CardioSightReader Model 2020A, and Model 2491 Device Data Management Application (DDMA) as predecessor devices. The only change made to the programmers is the addition of the DF4 model numbers to the Clinical Information Sheets. All of the DF4 Connector System devices are described in further detail below.

Consulta CRT-D (D204TRM) and Maximo II CRT-D (D264DRM)

The Consulta CRT-D and the Maximo II CRT-D, when compared to their predecessors, are slightly larger. They have identical longevity, telemetry, maximum high voltage, case material, header materials, battery, and SRAM. Devices also have one new Telemetry C antenna, a (b) (4) instead of a (b) (4) connection, and slightly different spacing from the Telemetry C antenna to the lead connections and the case. Of all of the devices of this submission, the Consulta CRT-D has the most complex mechanical configuration and the most extensive feature set.

Secura DR (D204DRM) and Maximo II DR (D264DRM)

The Secura DR and Maximo II DR ICDs, when compared to their predecessors, are slightly larger. They have identical longevity, telemetry, maximum high voltage, case material, header materials, battery, and SRAM. Devices also have one new Telemetry C antenna, a (b) (4) instead of a (b) (4) connection, and slightly different spacing from the Telemetry C antenna to the lead connections and the case.

Sprint Quattro Secure Lead Model 6947M

The Sprint Quattro Secure Lead Model 6947M is an 8.6 French, quadripolar, steroid-eluting, screw-in, ventricular lead with right ventricular (RV) and superior vena cava (SVC) defibrillation coil electrodes. The lead body is constructed from an (b) (4) with a polyurethane overlay. The lead features an extendable and retractable helix electrode, silicone insulation, and parallel conductors and is designed for true bipolar pacing and sensing, cardioversion, and defibrillation therapies. The model is identical to the market-approved Sprint Quattro Secure Lead Model 6947 except for the incorporation of the proximal four pole connector.

Description of Additional Changes proposed in A003, A004, and A006

In A003, the firm proposed several additional design changes that were made in response to corrosion issues that resulted in specimen failing to meet electrical performance requirements following tensile testing.

- Connector ring processing was updated to include (b) (4) to prevent corrosion.
- Several manufacturing processes were updated to clarify instructions in order to prevent damage during manufacture: (b) (4)

Testing was provided in support of the new design changes.

Several manufacturing changes were requested in both A003 and A004, all of which had been approved for the predecessor devices.

In A006, the firm requested approval for updates made to the Model 9995 programmer application software and the CareLink Device Data Management Application (DDMA) Model 2491 that are intended to address charge time out issues that were noted in the Gen2 ICD devices (the DF1 predecessors to the subject devices). The DF4 devices use the same programmer application software and firmware as their DF1 predecessors, and the change is independent of the connector type. Reference is made to the bundled submission in which the change was approved 11 May 2010 for the predecessors: P010031/S193 (Master File), P980016/S234, and P890003/S188.

Preclinical/Bench

The firm supports the approval of the DF4 Connector System with documentation of functional/mechanical bench testing, packaging and shelf life testing, system validation testing, *in-vivo* physician handling data, and *in vivo* animal study results.

Verification and Validation Testing

The engineering review was performed by myself, CDRH/ODE reviewer [REDACTED] as documented in review memos dated 05 March 2010, 13 April 2011, and 22 December 2011. The firm provided the protocols and results for the following:

- Design Level Verification Testing
- Partial lead Insertion Testing
- Fatigue Testing
- M-4 Device Connector Module Testing
- CRT-D Device Electrical, Mechanical, and EMC Design Verification Testing
- System Validation Testing

Several deficiencies were identified during the initial review regarding engineering issues. Major concerns included the following:

- Conformance to the draft standard was not clearly identified
- Development of all fatigue test parameters was not clearly detailed or rationalized
- Several test anomalies/ deviations appeared at first potentially concerning; additional information was requested
- Testing sample sizes were not thoroughly justified
- Absence of several standard electrical assessments for telemetry

In A001 and A003, the firm provided acceptable response that clarified conformance to the draft standard, sample size justification, and the root cause of the deviations/ anomalies noted during testing. However, follow up concerns were identified based on the firm's more detailed description of the fatigue testing. The absence of several key elements in the testing were noted and communicated in the Not Approvable Letter (for example, preconditioning, proper evaluation of all transition areas, and sample size). In addition, the robustness of the evaluation of the telemetry features was still unclear; further clarification was requested.

A003 included several design changes and testing to assess those changes. Concerns were identified with both the design changes and their supporting testing, which were communicated in the Not Approvable letter; specifically, more information and rationales were requested regarding the passivation process and preconditioning for corrosion testing; in addition further root cause discussion was requested for the failures that resulted in the need for the proposed changes.

In [REDACTED] (b) (4), the firm provided detailed responses to the corrosion testing and telemetry evaluation deficiencies. A very detailed discussion regarding the fatigue testing design was also conducted. The pre-IDE was closed in June 2011 with both the corrosion and telemetry issues having been

addressed and agreement reached between the firm and the Agency regarding appropriate fatigue testing parameters, acceptance criteria, and approach. The testing agreed upon included an assessment to failure of the relevant transition areas around and within the connector region following rigorous preconditioning that is representative of worst case implant handling. Test loading was based on *in vivo* loading estimated using fluoroscopy images; test frequencies and cycle numbers were estimated using literature review kinesiology data for the device patient population. A variety of cycle number and stress (via curvature) amplitude were used to construct a fatigue strength curve. The study hypothesis that at least 90% of all samples would survive to the cycle number representative of 10 years loading with 90% confidence was met. Specimens were x-rayed following loading to ensure that no cable migration through insulation had occurred during testing.

In A005, the firm provided formal responses to the outstanding deficiencies as well as the results from the test to failure fatigue evaluation discussed during (b) (4) A006 included request for approval of software and firmware updates in response to adverse field events.

LEAD REVIEWER COMMENTS: The fatigue testing plan was reviewed by myself.. The firm conducted the testing per the agreed-upon methods, and all results are acceptable and supportive of approval. One interactive email discussion was needed to clarify the distribution of the frequencies used during testing and the ability of all passing specimens to meet electrical specifications post-loading; the firm responded promptly and all issues/confusion have been addressed. No concerns remain.

Regarding the software change- the change appears acceptable and has already been approved for predecessor devices as of 11 May 2010 (under P010031/S193 bundle including P980016/S234 and P890003/S188 as well). The change itself (and its acceptability) would not be impacted by the DF4 connector and, therefore, I have no concerns with approving for the subject devices. In addition, it appears that all appropriate testing was conducted and deemed acceptable by FDA during the review of the requested changes. No concerns remain.

Packaging and Shelf Life

The firm requests a 24 month shelf life for the new lead and an 18 month shelf life for the Consulta/Maximo/Secura devices. In support of the requested, the firm provided the following test reports:

- Package Qualification Testing
- Shelf Life Testing

Note that packaging testing was conducted on the Model 6947M lead, but not on the Consulta/Maximo II/Secura DR CRTs.

Several clarifications were requested in the Major Deficiency letter:

- A detailed difference between the specimens assessed during testing and those that were subject in the supplement was not provided.
- Test reports assessing peel strength following aging were not provided.

In A001, the firm provided the requested clarification and additional test reports (for both 4 years aging and peel strength), both of which were deemed acceptable by myself as the engineering reviewer. The design changes in A003 were deemed to not impact the packaging or shelf life considerations, therefore, no concerns regarding this topic were sent in the Not Approvable Letter.

LEAD REVIEWER COMMENTS: The firm has addressed the initial concerns and, no concerns remain.

Physician Handling Assessment

Physician handling was assessed in a swine with RV, RA, and LV leads previously placed by a veterinarian. Only device placement and lead connections were tested. The eight physicians of the study used all DF4 implant tools and were given 2-4 minutes of training with the aid of a tip card. Physicians interrogated the DF4 device (using the ACI tool), and impedances were recorded to verify proper connections. Results were successful, but the firm indicated that feedback on visibility of the color band would be used to improve customer training materials.

The clinical review of the original submission was performed by [REDACTED], SGE. He identified several concerns that were communicated to the firm in the Major Deficiency letter:

- Physician concerns/complaints/recommendation did not appear to have been taken into account with labeling and design; clarification was requested.
- A thorough discussion of the differences between the new tools compared to the predecessors and their ease of use was not provided.

The firm's responses were provided in A001 and were reviewed by Dr. [REDACTED]. The firm provided the follow up clarification regarding mitigation for erroneous insertion (physical limitations of bore and pin), usability of the new tools including visualization of the blue band on the connector tip, and the details of the handling assessment results.

LEAD REVIEWER COMMENTS: The firm has successfully completed a physician handling study to assess to usability of the device. Initial concerns were addressed appropriately under A001 and no concerns remain.

Animal Testing

In the firm's original submission, results from three separate 3- month GLP animal studies were provided to demonstrate the performance of the new connector module. This duration was deemed insufficient by animal study reviewer Dr. [REDACTED], and a 6 month minimum study was requested in light of the absence of clinical data on the substantially modified connector. In addition several concerning results were noted in the original reports. Four deficiencies were provided in the Major Deficiency letter relating to the results themselves and the need for a longer study.

In A003, the firm provided results from a newly-conducted 6 month GLP animal study on 16 canines. Eight canines were implanted with the subject lead and eight with the predecessor lead. The primary objective of the study was to show equivalence to clinically significant boundaries for pulse width threshold and high voltage pulse delivery since these measurements could be impacted by a new header/connector design. Secondary objectives included measuring and comparing R-wave sensing amplitude and pacing impedances.

Dr. [REDACTED] indicated that the results looked promising from the 6 month report (and it was encouraging that the concerns noted in the original report were not also noted in the 6 month report); however, several key electrical parameters were reported only as averages vs as individual measurements. This last concern was communicated to the firm in the Not Approvable letter.

In [REDACTED] (b) (4), the firm provided the individual measurement for the animal study as well as the graphical analyses requested. Interactive follow up on the adequacy of this response were conducted and resolution was reached after closure of the pre-IDE. The firm provided an email 5 July 2011 to respond to [REDACTED] question regarding the consistently lower minimum R-wave amplitude in the test group compared to the control group. They pointed to the acceptability of the raw numbers as well as the absence of concerning results from pathology review.

LEAD REVIEWER COMMENTS: Dr. [REDACTED] found the firm's responses as presented via email 5 July 2011 acceptable. The additional data provided by the firm was supportive of their conclusion that the new connector has acceptable electrical performance in the animal model.

These new results in fact show that only two animals had low R-wave amplitudes and that all results were in a clinically acceptable range. No concerns remain.

Steroid Comparison Testing

The steroid and distal tip components of the Model 6947M lead are identical to those of the Model 6947 lead. The firm provides evidence of similar manufacturing processes and equivalent in vitro elution performance. During pre-IDE discussions prior to submission of the original PMA/S, FDA indicated that the firm should provide documentation of the drug substance, MCRD composition, content, and elution methods/profile; in addition, the pre-IDE review team indicated they did not anticipate needing a separate review from CDER. The only difference between the subject lead model and its predecessor is the container closure system. Clarification on these differences was requested in the Major Deficiency Letter.

In A001, the firm provided a table comparing the packaging materials of the subject lead to its predecessors and other Medtronic marketed leads. They also noted that all testing submitted under this PMA/S was conducted on samples packaged using the new material (b) (4) vs the predecessor material (b) (4). Specific to the steroid issue: An updated Certification of CMC Equivalence of Models 6947M and 6935M to Legacy Leads noting the differences in packaging was provided in Attachment Q of A001.

(b) (4) of CDER found the firm's response in A001 acceptable and the differences in material to be fairly minor from a drug perspective (especially considering that a similar (b) (4) material is used with other Medtronic-marketed leads); however, she indicated that the firm should commit to placing a batch of product packaged in the new (b) (4) container/closure system into their stability program in order to demonstrate that the new container doesn't affect the stability of the drug component on storage. This concern was communicated in the Not Approvable letter.

In A005, the firm agreed to place such a batch into the stability program.

LEAD REVIEWER COMMENTS: The firm has acceptably addressed the steroid issues sent in the both the Major Deficiency and Not Approvable letters; therefore, no concerns remain.

Clinical Data

No clinical data was provided to support approval of the new DF4 Connector System.

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, and animal study results could not adequately assess the new risks. For this reason, I agree with the decision made during discussion of pre-IDE (b) (4) that no clinical data is required to support approval of the subject devices.

Labeling

The labeling of the DF4 Connector System family of leads and devices is based upon those of the predecessor models. Both "M-4" and "DF4" labeling sets were provided in the original PMA/S with the understanding that "M-4" will be used until the ISO draft standard is approved, at which point the label "DF4" will be used. Since the standard was published while the subject submission was under premarket review, though, this change was requested in the subject PMA/S.

The firm provided all lead and device package labels, lead technical manuals, and device clinician manuals. A change table was provided for the Model 6947M, Secura DR D204DRM, and the Consulta CRT-D D204TRM and Maximo II D2xxTRM.

Several concerns with the labeling were identified in the Major Deficiency letter:

- Specific warning to compatibility with DF-1 and IS-1 connectors was not provided.
- Device and system description pages were inadequate.
- Several text phrasing choices were inappropriate
- Rationale for changes to text and instructions were not provided in detail.

The firm's responses in A001 were reviewed by the lead reviewer and (b) (6). The firm added warnings and descriptive text as requested; in addition, clarification on the changes to text and instructions were provided. Only one concern remained after review of A001: the firm appeared to be referencing pacing configurations that were not supported by premarket data. This concern and request for the editorial change to the text of the labeling was communicated in the Not Approvable letter.

In A005, the firm agreed to remove the problematic sentence regarding pacing configurations to alleviate phrenic nerve stimulation.

LEAD REVIEWER COMMENTS: The firms addressed all of the initial labeling concerns in A001. The response to the last concern is appropriate- the firm has agreed to remove the text FDA requested be removed. No concerns remain.

Also, as indicated in the Device Description section of this memo, conformance with the standard was demonstrated in A001; therefore no concerns remain with designating the subject lead as DF4 compliant.

Sterilization

The (b) (4) sterilization process used to sterilize all bradycardia pacing leads was approved 31 October 1995 under P850089/S032. The process is considered an (b) (4). This method is accepted by all major guidelines, including AAMI, ANSI, DHSS and ISO/CEN. These same guidelines and standards are used to validate and qualify the sterilization process with respect to maximum allowable bioburden, microbial lethality characteristics, and minimum sterilization process specifications. All tissue-contacting products have a sterility assurance level of at least (b) (4).

Sterilization testing was not conducted on samples of the Sprint Quattro Secure Model 6947M because this new lead presents fewer challenges to sterilization than a previously qualified "worst case" lead, Model 4068. The two leads were compared based on geometric design and dimensions. The "worst case" lead has a sealed lumen design, while Model 6947M has an open lumen design.

No concerns were sent in either the Major Deficiency or Not Approvable letter.

LEAD REVIEWER COMMENTS: The conclusion that testing is not required on this new lead model is appropriate. The Model 4068 (CapSure Fix pacing lead) presents a higher burden of sterilization due to its sealed lumen. This same analysis was determined to be acceptable during the review of the prior model, Model 6947. The sterilization validation performed on the "worst case" lead was in accordance with accepted standards, and I have no concerns with respect to the sterilization of Model 6947M.

Bioburden

Bioburden and endotoxin testing was not addressed for the new Model 6947M lead. The firm states in Volume 2, page 18, that this testing was previously addressed for the 6947 lead product family per JH010891MM and JH000461-A. However, once the 6947M leads are built in the manufacturing environment, bioburden and endotoxin testing will be performed on a routine basis.

No concerns were sent in either the Major Deficiency or Not Approvable letter.

LEAD REVIEWER COMMENTS: I believe the sponsor's assumption that bioburden testing is not

required due to previous testing is acceptable. I believe the bioburden for the current lead, Model 6947M would present no greater challenges than the prior model, Model 6947, so the same conclusions can be drawn.

Biocompatibility

The biocompatibility review was conducted by (b) (6) of ODE. All materials in the DF4 Connector System are identical to those of the market-approved predecessor devices with the exception of the material used on the lead to create a seal between it and the header. The new lead connector uses (b) (4) in the seal zone component, which indirectly contacts tissue. The (b) (4) material has been used in other Medtronic products, and its Biocompatibility and Biostability information were provided by the firm in Volumes 2 and 3 of the original submission. During pre-IDE conversations (b) (4) FDA indicated that biocompatibility information for the lead and CRT-D/ICD, including chronic toxicity and carcinogenicity testing, would be required in a PMA supplement.

In the original submission, FDA could not locate several of the referenced biocompatibility test reports. In addition, no rationale for not conducting implantation testing was provided and no details on the plasma treatment of the new (b) (4) material were provided. These concerns were sent to the firm in the Major Deficiency letter.

In A001, the firm provided the 5 requested test reports as well as a scientific rationale for the absence of implantation testing of the (b) (4) material and additional details regarding the (b) (4) process. Ms. [REDACTED] reviewed the firm's response and found the rationale for not conducting implantation testing acceptable. Also- since the (b) (4) treated surface is not patient contacting, no further concerns were identified. However, the firm did not (in the newly provided test reports) thoroughly specify the processing differences between each test article and the final lead material or provide a rationale for why these differences would not impact testing results. Such rationale was requested in the Not Approvable letter.

In (b) (4), the firm provided the requested rationale and relevant documentation. However, the rationale was deemed insufficient. After pre-IDE closure, the firm provided additional discussion and rationale via email on 3 Aug 2011: a very clear table indicating the differences between the tested and subject materials is provided. [REDACTED] found the clarification provided helpful and supportive (in combination with the provided rationale) of not repeating the omitted biocompatibility tests for the new material.

LEAD REVIEWER COMMENTS: The firm addressed the outstanding biocompatibility concerns with additional documentation and rationale that was deemed acceptable by biocompatibility reviewer [REDACTED]. The differences between the manufacturing processes of the three components of the subject lead that are not identical to those of the predecessor compared to those of the predecessor are minor and would not impact biocompatibility. The one new tissue contacting material (b) (4) was fully tested. There are no further concerns with this section of review.

Manufacturing

The manufacturing of the DF4 Connector System devices includes the same processes of the legally marketed predecessor devices. The only difference between the devices is the header assembly containing the quadripolar connector bore. Routine validation is performed in accordance with the Association for the Advancement of Medical Instrumentation. Medical Device- Validation and routine control of (b) (4) sterilization (ANSI/AAMI/ISO 11135:1994). The manufacturing flow chart for the devices is included on page 177 of Volume 1 of the original PMA/S.

During the initial review, the only concern identified with respect to manufacturing was the absence of confirmation that all specimens tested in bench testing were of final, manufactured form. In A001, the firm provided clear documentation of the similarities and differences between samples tested and

final manufactured specimens. In most cases, there were no differences; in those that differences were apparent, the justification was provided for these differences. These justifications were deemed acceptable and no further concerns were communicated in the Not Approvable letter.

LEAD REVIEWER COMMENTS: The one issue identified during initial review was addressed in A001. The firm appears to have the proper controls in place to ensure acceptable manufacturing; manufacturing sites are all currently used for other market-approved products and the differences requested for the subject device relative to the predecessor would not impact the adequacy of the controls in place or sites themselves. No concerns remain.

The firm was on the OAI list at the time of the original submission. After removal from the list, several manufacturing changes (A003 and A004) were submitted. These changes were deemed acceptable by Office of Compliance. The firm is no longer on the OAI list at this time, therefore, Approval can be recommended.

Post Approval Study

The post approval study (PAS) review was performed by [REDACTED] (b) (6) of OSB. The post approval study proposed by the firm calls upon an updated System Longevity Study Clinical Platform Protocol in combination with a Data Analysis Plan. The platform was discussed in general during the review of pre-IDE [REDACTED] (b) (4). The primary objective of the DF4 PAS is to demonstrate that the complication-free probability is greater than 92.5% at five years post-implant for the high voltage DF4 connector, although individual adverse event rates with 95% confidence bounds will be provided as well. The nonrandomized, multi-site, world-wide study will include approximately 1,778 subjects from 150 centers globally, but have no more than 50% of patients from non-US sites. The sponsor provided descriptions of the inclusion/exclusion criteria, sample size, data collection methods, follow up visits, and enrollment plan in the original PMA/S.

Initial review identified several specific concerns with the firm's proposal, although, in general, the firm's approach was not specific enough to be used as a PAS protocol. Several critical elements such as a study design and hypothesis, study population description, and statistical analysis plan were missing from the overall platform. Fifteen deficiencies were provided in the Major Deficiency letter requesting a more detailed protocol and communicating concerns with various portions of the provided platform.

In A001, the firm provided a revised PAS protocol combining the platform with a DF-4 specific Analysis Plan. A clear list referencing the location of each specific PAS element within the Protocol and Analysis Plan was also provided. The epidemiology reviewer found the firm's responses acceptable- all deficiencies provided previously were appropriately addressed and no issues were communicated in the Not Approvable letter.

LEAD REVIEWER COMMENTS: The initial concerns regarding the lack of clear and detailed objectives, hypotheses, and other necessary elements of a PAS protocol were addressed in A001 appropriately. No concerns remain.

Risk Management

Medtronic conducted a formal risk analysis and risk assessment for the leads and devices of the new DF4 Connector System according to the ISO standard 14971. All components of the system were found to be safe and acceptable for patient implantable use from a safety perspective. No incremental risks of critical harm due to the use of new or modified features were identified compared to the predecessor devices. The following documents are provided in Volume 4 of the initial submission as evidence of the Risk Management activities conducted: M-4 Project Summary Risk Management Report, Model 6947M Design FMEA, Top Down FMEA, M-4 Partial lead Insertion Report, and Risk Management Upgrade Report- Gen2 to Gen2M4.

LEAD REVIEWER COMMENTS: Each document provided was reviewed under the initial

submission and no concerns were found relative to the residual risks of the system. All risks are appropriately mitigated and the risk-benefit analysis is supportive of approval.