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

Division of Cardiovascular Devices
Pacing, Defibrillator & Leads Branch

File: P010012/S212 and P960040/S198 (PMA/Ss with amendments)

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Device Name: **Pulse Generators – ICD**: TELIGEN ICD Models E103 and E111 (new models); and Models E102 and E110 (labeling only)

Pulse Generators – CRT-D: COGNIS CRT-D Model N120 (new model); and Model N118 and N119 (labeling only)

Lead Reviewer: (b) (6), FDA/CDRH/ODE/DCD/PDLB

Consult reviewers: (b) (6), FDA/CDRH/OC
(b) (6), FDA/CDRH/ODE/DCD Medical Officer
(b) (6), FDA/CDRH/ODE/DCD/PDLB

Recommendation: Approval

Date: November 10, 2010

☒ Background

The subject PMA/Ss were submitted by Boston Scientific Corp. for two requests. Those are:

The labeling changes for all the models, this includes the TELIGEN ICD Models E103, E111, E102, and E110; COGNIS CRT-D Models N120, N118 and N119.

The new models with the 4-sites header, this includes the TELIGEN ICD Models E103 and E111; COGNIS CRT-D Model N120.

FDA letter dated August 10, 2009 was send to the company for requesting additional information, the company submitted the following are the PMA/S Amendments:

Amendment 01 received on October 15, 2009;
Amendment 02 received on February 2, 2010;
Amendment 02 received on February 17, 2010; and
Amendment 04 received on June 30, 2010.

The company submitted the e-mail communications between FDA and company as required, and those communications were documented in the PMA/S Amendments 01 and 03 for the subject file.

Note: The terms, Quadripolar and 4-sites are inter-changeable in this file.

☒ **Device Description**

For ICD: The TELIGEN family contains the following types of PGs:

• VR – single-chamber ICD combining VT therapy with ventricular pacing and sensing

• DR – dual-chamber ICD combining VT therapy with ventricular and atrial pacing and sensing.

Therapies:

This ICD family of pulse generators has a small, thin, physiologic shape that minimizes pocket size and may minimize device migration. Pulse generators within this family provide a variety of therapies, including:

• VT therapy, which is cardioversion/defibrillation therapy used to treat rhythms associated with sudden cardiac death such as VT and VF

• Bradycardia pacing, including adaptive rate features, to detect and treat bradyarrhythmias and to provide cardiac rate support after defibrillation therapy.

Cardioversion/defibrillation therapies include:

• A range of low- and high-energy shocks using a biphasic waveform

• The choice of multiple shock vectors:

  • Distal shock electrode to proximal shock electrode and pulse generator case (TRIAD electrode system)

  • Distal shock electrode to proximal shock electrode (RV Coil to RA Coil)

  • Distal shock electrode to pulse generator case (RV Coil to Can)

Leads:

The pulse generator has independently programmable outputs and accepts one or more of the following leads, depending on the model:

• One IS-11 atrial lead

• One DF-1/IS-12 cardioversion/defibrillation lead

• One GDT-LLHH or GDT-LLHO multipolar connector cardioversion/defibrillation lead

A GDT-LLHH or GDT-LLHO terminal is intended to only be connected to a Boston Scientific device with a GDT-LLHH port, which accepts either a GDT-LLHH or GDT-LLHO lead.

For CRT-D: The COGNIS family contains the following types of PGs:

Therapies:

This CRT-D family of pulse generators has a small, thin, and physiologic shape that minimizes pocket size, and may minimize device migration. Pulse generators within this family provide a variety of therapies, including:

• Ventricular tachyarrhythmia (VT) therapy, which is used to treat rhythms associated with sudden cardiac death such as VT and ventricular fibrillation (VF)

• Cardiac resynchronization therapy (CRT), which treats heart failure by resynchronizing ventricular contractions through biventricular electrical stimulation

• Bradycardia pacing, including adaptive rate features, to detect and treat bradyarrhythmias and to provide cardiac rate support after defibrillation therapy

Cardioversion/defibrillation therapies include:

• A range of low- and high-energy shocks using a biphasic waveform

• A choice of multiple shock vectors:

  • Distal shock electrode to proximal shock electrode and pulse generator case (TRIAD electrode system)

  • Distal shock electrode to proximal shock electrode (RV Coil to RA Coil)

  • Distal shock electrode to PG case (RV Coil to Can)

Leads:

The pulse generator has independently programmable outputs and accepts one or more of the following leads, depending on the model:

• One IS-1 atrial lead

• One IS-1 coronary venous pace/sense lead

• One LV-1 coronary venous pace/sense lead

• One DF-1/IS-12 cardioversion/defibrillation lead

• One GDT-LLHH or GDT-LLHO multipolar connector cardioversion/defibrillation lead

A GDT-LLHH or GDT-LLHO terminal is intended to only be connected to a Boston Scientific device with a GDT-LLHH port, which accepts either a GDT-LLHH or GDT-LLHO lead. The pulse generator and the leads constitute the implantable portion of the pulse generator system.

☒ **Indication for Use**

ICD INDICATIONS AND USAGE

The company claims the indications remain unchanged from the commercially available TELIGEN device and are as follows:

> *TELIGEN ICDs are intended to provide ventricular antitachycardia pacing (ATP) and ventricular defibrillation for automated treatment of life-threatening ventricular arrhythmias.*

CRT-D INDICATIONS AND USAGE

The company claims the indications for use remain unchanged from the commercially available COGNIS device and are as follows:

> *COGNIS CRT-D devices are indicated for patients with moderate-to-severe heart failure (NYHA III/IV) who remain symptomatic despite stable, optimal heart failure drug therapy, and have left ventricular (LV) dysfunction (ejection fraction<35%) and QRS duration >120 ms.*

☒ The Review Summary:

Both implantable devices (Teligen and Cognis) were market approved devices, therefore, the purposes of the subject file are requesting the approval of the following:

> 1. To incorporate the '4-site' header to the Teligen and Cognis systems; and
> 2. To modify (expand) the elevated pressure labeling of the Teligen and Cognis systems.

The review summary for the '4-site'header:

The company claims that, the 'new' 4-site lead system was submitted to FDA for review, and the subject file contains the header modifications for interfacing with the 4-site lead system. Note, during the review process of the subject file, the DF-4 Standard was adapted; and the PMA/S file numbers for the 4-site lead system are P830060/S82 and P910073/S77.

Since the subject device's header and the proposed 4-site lead system are related. Therefore, the identical issues for the animal study requirements and/or the clinical study were stated in the FDA letter, (dated: August 10, 2009) to the company with the identical concerns. In addition, some bench tests such as the biocompatibility for the identical materials (note: the connectors in the header contains the identical materials as the connectors of the 4-site lead system) were reviewed interactively within the FDA.

The company submitted the following test reports as part of this PMA/S, Those test reports are:

- Quadripolar Mechanical DVT;
- Current Leakage (High Voltage) Dielectric Strength using Test Pin;
- Insulation Impedance Test using Test Pin;
- Connector Insertion and Withdrawal Force;
- Contact Load;
- Connector Cavity Current Carrying Test;
- Connector Cavity Seal Pressure;
- Connector Cavity Contact Resistance/Stability;
- Connector Cavity Corrosion Testing;
- Simulated Use Testing; and
- Pre-clinical animal testing (GLP).

In addition, the company referenced the following test reports for the Quadripolar Lead Connector Terminal/RELIANCE 4-SITE Leads under *P830060/S062 and P910073/S077,* should be applicable to this file. Those are:

- Mechanical/Electrical Design Verification;
- Flex Fatigue Design Verification;
- Particulate/Cleanliness Design Verification;

- Corrosion Design Verification;
- Terminal Ring Material Design Verification;
- Package and Label Integrity Design Verification;
- Simulated Use Testing;
- Pre-clinical animal testing (GLP);
- Biocompatibility Assessment;
- Shelf Life Assessment;
- Sterilization Assessment;
- Component Qualifications; and
- Process Validations.

The company referenced the following test reports for the Quadripolar 4-SITE Accessories (submitted via a separate PMA/S, *P830060/S062 and P910073/S077*) should be applicable to this file. Those are:

- Mechanical Design Verification;
- Particulate/Cleanliness Design Verification;
- Package and Label Integrity Design Verification;
- Simulated Use Testing;
- Pre-clinical animal testing (GLP);
- Shelf Life Assessment;
- Biological/Biocompatibility/Sterilization Assessment; and
- Component Qualifications.

The review summary for the elevated pressure labeling modifications:

The company requests the labeling modifications for the implantable devices. The following are the purposed of the labeling modifications:

Updated information in Chapter 1 section entitled "Precautions, Environmental and Medical Therapy Hazards" is as follows:

Elevated Pressures.

Elevated pressures due to hyperbaric chamber exposure or SCUBA diving may damage the pulse generator. ~~The pulse generator has been tested to function normally at 1.5 Atmospheres Absolute (ATA) pressure or 15 ft (4.6 m) depth in sea water. For specific guidelines prior to hyperbaric chamber exposure, or if the patient is planning scuba diving activity, contact Technical Services at the number shown on the back cover of this manual.~~ Prior to engaging in activities such as hyperbaric oxygen therapy (HBOT) or SCUBA diving, a patient should consult their attending cardiologist or electrophysiologist to fully understand the potential consequences of these activities relative to their specific health condition.
During laboratory testing, all pulse generators in the test sample continued to function as designed when exposed to more than (b)(4) cycles at a pressure up to (b)(4) ATA. Since the pressure testing was conducted in a laboratory environment, it did not characterize the impact of elevated pressure on pulse generator performance or physiological response while implanted in a human body.

Refer to the system guide for further details regarding elevated pressure exposure (this sentence in physician technical manual only).

Refer to further details regarding elevated pressure exposure ("Elevated Pressures" on page 10-9).

New information is included in Chapter 10 of the system guides, and reads as follows:

ELEVATED PRESSURES

The information provided here is a summary of pressure testing completed by Boston Scientific; it should not be viewed as and is not an endorsement of hyperbaric oxygen therapy (HBOT) treatment or SCUBA diving activities. During laboratory testing, all devices in the test sample (statistically significant) continued to function as designed when exposed to more than (b)(4) cycles at a pressure up to (b)(4) ATA. Pressure for each test cycle began at ambient/ room pressure, increased to a high pressure level, and then returned to ambient pressure. Although dwell time (the amount of time under elevated pressure) may have an impact on human physiology, testing indicated it did not impact pulse generator performance.

Since our pressure testing was conducted in a laboratory environment, it did not characterize the impact of elevated pressure on pulse generator performance or physiological response

while implanted in a human body. Prior to engaging in activities such as HBOT or SCUBA diving, a patient should consult their attending cardiologist or electrophysiologist to fully understand the potential consequences of these activities relative to their specific health condition.

Pressure value equivalencies are provided below.

Atmospheres Absolute	(b) (4)	
Sea water depth[1]		
Pressure, absolute		
Pressure, gauge[2]		
Bar		
kPa Absolute		

If you have additional questions, contact Technical Services at the phone number shown on the back cover of this manual.

1. All pressures were derived assuming sea water density of 1030 kg/m3.
2. Pressure as read on a gauge or dial (psia = psig + 14.7 psi).

The above labeling modification purposed by the company, was reviewed by the FDA medical officer for the clinical issues. The final conclusion of the clinical review indicates the acceptance of the labeling modification.

During the review process, FDA generated few questions, which related to the testing and clinical issues of the purposed labeling modification. The company submitted the additional bench testing information for the header of the implantable device via the PMA/S Amendment 4, dated June 30, 2010. The test reports in Amendment 4 contain the testing of the header under high pressure conditions to prevent the deformation of the materials that is used in the header.

The following are the detailed reviews of this file:

☒ **Bench Testing**

The test reports are listed in the above section (the review summery section). In addition, the company claims all the test reports in the subject are met the specifications.

The following is the deficiencies generated by the reviewer, and the responses from the company to address the deficiencies: Those are:

Deficiency 1: Are there any recall issue for the TELIGEN and COGNIS devices?

The company responses 1: *the advisory letter we sent to all implanting and following TELIGEN and COGNIS physicians. A 21CFR806 report was submitted to FDA.*

The submission that addresses this issue is P960040/S193 and P010012/S207, submitted April 16, 2009. The TELIGEN and COGNIS 4-SITE devices are baselined from the TELIGEN and COGNIS IS-1 devices inclusive of the change described in P960040/S193 and P010012/S207, as detailed in Table 2-2 of P9060040/S198 and P010012/S212.

Reviewer comment: CDRH/OC has been notified. Based on the final CDRH/OC consult review, which indicates this issue is resolved.

Deficiency 2: Has the firmware timing stress test been done for the devices in this submission?

The company responses 2: *Yes. The firmware for TELIGEN and COGNIS 4-SITE models (E103, E111, N120) is the same as for TELIGEN and COGNIS IS-1 models (E102, E110, N118, N119); there are no changes to firmware requested via submission P960040/S198 and P010012/S212. Please see the TELIGEN and COGNIS IS-1 model Real Time Review (RTR) meeting minutes for the submission regarding Software Model 2868 v1.02 and Pulse Generator Firmware v1.04.0, Patch v1.00 (P960040/S155 and P010012/S165, approved May 8, 2008). Per the RTR meeting minutes page 19, Boston Scientific provided a description of the SW analysis tools used for timing and event sequences*.

Reviewer comment: Based on the regulation, the company's response is acceptable for this file, since FDA approved the firmware prior to the subject file, and the subject file does not contain any firmware modification.

Deficiency 3: FDA has concerns that testing was done in an air environment instead of closer to human in-vivo conditions, such as saline. The most important issue is seal integrity in various places on the PG and lead, and the device (PG or Lead) could

see blood ingress under pressure. A test would not be able to determine tiny (i.e. pinhole) leaks in an air test environment, but could determine them in liquid. Boston Scientific should answer the question of whether or not blood could ingress the lead or header in any way under pressure.

The company responses to 3: *The company claims, it has conducted the testing, it was done in a liquid environment rather than air, using* (b) (4) (b) (4) . (b) (4) (b) (4) . *was used as the working fluid in the pressure system of the test.* (b) (4) *t was chosen because and it allows the test to be run as hydraulic instead of pneumatic.* (b) (4)

The testing was conducted for mechanical fatigue, rather than fluid ingression. The reason testing was not specifically conducted for fluid ingression is because the implanted device will reach a stable state in which all air is replaced with liquid and the change in pressure will not affect this state.

After implant, any remaining air in the device or header is replaced with liquid (water and ions), which would typically occur by the time the implant wound is healed. This is due to the fact that all the header materials except the metals diffuse water; these include the Tecothane, medical adhesive, silicone seals, and seal plugs. Once the environment in the device and header is completely liquid-filled, because liquids are incompressible, the pressure change will not change the volume, and there will be no driver to transfer fluid (gas or liquid) between sealed regions. The current carrying and insulation impedance testing included in Exhibit 4-17 of the submittal, and the Mechanical DVT, in Sections 7.6.1, 7.6.2 and 7.6.3 of the submittal, it should still be applied because the pressure change cannot cause transfer of fluid between the sealed regions.

The DVT samples for current carrying and insulation impedance test are pre-conditioned with 10-day soak. The 10-day soak, conducted per ISO 5841-2:2000, 4.2.2.2 and the IS-4/DF-4 standard, preconditions the lead and header by fully replacing the gas with liquid.

Reviewer comment*:* Based on the test reports referenced above, this issue is resolved.

Deficiency 4: Additionally, regarding the Respiratory Sensor feature, how will pressure affect the operation of the feature? If the feature is turned off per submission P960040/S193 and P010012/S207, submitted April 16, 2009 (SMR4), if Boston Scientific ever turned it back on, then how would we address elevated pressure?

The company responses to 4: *The company claims the respiratory sensing feature will be turn-off, per submission P960040/S193 and P010012/S207, submitted April*

16, 2009 (SMR4), the sensor will be turned off via software maintenance release 4 (SMR4).

Reviewer comment*:* Based on the company's statements that the respiratory sensing feature will be turn-off, therefore, it is acceptable for this file.

Deficiency 5: For functions like adaptive pacing and detection of VT/VF, FDA is concerned if we have adequately tested for sensitivity given that use of (b) (4) is new for this connector and the alloy has an unique impedance. FDA believes IS-1 and 4-SITE sensitivity comparison testing is necessary. Note: this is not in regard to RF sensitivity/telemetry sensitivity

One suggestion is if Boston Scientific ran a test (such as with our (b) (4) test device works) where we tested the lead-header interface of IS-1 and 4-SITE when connected to (b) (4) in saline, and compared the results, then we could address this FDA concern.

The company responses to 5: *The conducted the tests for contact resistance (impedance) on both IS-1 and 4-SITE devices to determine if the connection resistance at the header / terminal interface met specifications. This testing is found in Exhibit 4-18, "Quadripolar Header Bore MDVT Report", Section 7.6 for the 4-SITE devices and in the IS-1 submission (P960040/S155 and P010012/S165, approved May 8, 2008), Exhibit 4-14, "IS-1 and LV-1 Spring Contacts MDVT Report" is submitted as part of the 7/1/2009 responses to FDA. The following are the summary:*

> *• The contact resistance of the 4-SITE spring shocking contacts (i.e. impedance) was a mean of (b) (4); this meets the acceptance criteria of "The dynamic contact resistance must be less than (b) (4) Ohms across both shocking contacts". The contact resistance of the 4-SITE spring pacing contact (i.e. impedance) was a mean of (b) (4) ohms for dynamic and (b) (4) ohms for static; this meets the acceptance criteria of "Each of the pacing contacts must exhibit a dynamic contact resistance less than (b) (4) Ohms and a static contact resistance of less than (b) (4) Ohms.";*
>
> *• The contact resistance of the IS-1 spring contact was a mean of (b) (4) ohms for static and (b) (4) ohms for dynamic; this meets the acceptance criteria of "Spring Contact must not exhibit a static contact resistance above (b) (4) Ω and maximum dynamic contact resistance above (b) (4) Ω." These contact resistance values are comparable for IS-1 and 4-SITE devices because the results are within the range of test capability (i.e. noise). More importantly, each device meets Boston Scientific's specifications for that device and the specifications were developed to ensure appropriate performance to meet intended use.*

Additionally, the connection resistance (i.e. contact resistance) at the header / terminal end of the system is order of magnitudes lower than the distal / tip end of the

system. Differences in the impedance at the terminal end of a 4-SITE PG compared to an IS-1 PG are less than (b) (4) *ohm and are insignificant as compared with input and output impedances of the distal / tip end of either system. Specifically they are much less than:*

> *• Tip/ring electrode pacing load impedance:* (b) (4) *of ohms. This value varies depending on the lead type and patient physical anatomy, typically ranging from* (b) (4) *ohms.*
>
> *• Tip/ring sensing source impedance:* (b) (4) *to* (b) (4) *of ohms. This value varies depending on lead tip design and implant patient parameters, typically ranging from* (b) (4) *ohms.*
>
> *• Device pacing output impedance: Several* (b) (4) *of ohms. For TELIGEN and COGNIS devices this equates to the sum of impedance values from two components, the integrated circuit (IC) and two lead switches (one at the end of each electrode). Typical values are* (b) (4) *ohms for the integrated circuit (IC), based on a pace and recharge switch, and* (b) (4) *ohms for two lead switches, for a total of* (b) (4) *ohms pacing output impedance.*
>
> *• Device input sensing impedance: Less than* (b) (4) *K ohm; See Exhibit 4-13, Section*
> *4.7.8 acceptance criteria.*

Based on the contribution of the distal/tip end impedance compared to the terminal end impedance, any difference in the terminal impedances of a 4-SITE device and an IS-1 device will have no consequence on the electrical system sensing performance.

Reviewer comment*:* Based on the additional test reports provided by the company, and the approval of the P960040/S155 and P010012/S165, on May 8, 2008, this issue is resolved.

Deficiency 6: FDA requests a statement certifying that we meet all specifications for the quadripolar connector without any exceptions. If there were any exceptions then clearly state what they are.

The company responses to 6: *The 4-SITE (quadripolar) connector as defined in Design Specification 520018 meets all requirements with no exceptions; see Exhibit 2-01, Quadripolar Connector System Design Specification (doc# 520018) for the requirements related to the connector.*

Reviewer comment: The company's response is acceptable for this file.

Deficiency 7: FDA is concerned that the submission's Exhibit 4-31, "Cyclic Pressure Testing Guideline to Evaluate PG Performance in HBOT and SCUBA Environments, Revision C (100021-854), references the website

http://www.hbomedtoday.com/faq.html#Anchor-Wha-24762 (reference 5 of the document) and that this website lists indications for HBOT, including research on Myocardial Infarction (heart attack). FDA wants to ensure that our company is not looking for an indication to do research on MI. Please address the reason for referencing this website.

The company responses to 7: *The website is referenced in context of supporting information for hyperoxia Hyperbaric oxygen therapy (HBOT) treatment duration, per the following paragraph in Exhibit 4-31 (reference [5]).*

> *Table 3 presents examples of conditions commonly treated using HBOT and associated treatment protocols.*
>
> *Hyperoxia HBOT is typically administered at pressures between 1 and 3 Atmospheres Absolute (ATA) for intervals ranging from 60 to 120 minutes[4].*
>
> *Depending on the response of the individual patient and the severity of the original problem, treatment duration may range from less than 1 week to several months, with the average being 3 to 6 weeks[5]. From the information presented in Table 3, each patient could undergo 1 to 76 total sessions throughout the course of therapy.*

This is provided as background information on the HBOT environment only and is not intended to imply that Boston Scientific CRM is seeking indications related to HBOT research for Myocardial Infarction (MI) for COGNIS and TELIGEN pulse generators. Also note that Table 3 does not include MI as one of the conditions commonly treated using HBOT; therefore, MI is not addressed in Exhibit 4-31. The intention of the website reference is to provide a link to general information about HBOT and specifically to support the treatment duration that is listed as background information in Exhibit 4-31, Section 2.1. Boston Scientific is not requesting a new indication for COGNIS and TELIGEN pulse generators to be used for research of HBOT to treat MI.

Reviewer comment: The company's response is acceptable for this file.

☒ **Animal Studies**

After the FDA consult reviewer completed the review of the animal studies, we requested additional information, and the company inter-actively working with FDA to resolve the requirements for the 4-site lead system, which includes the 4-site header PG as well. The company provided the results and data of the OUS clinical study, and planning to conduct the post market study for the 4-site lead system with the 4-site PG header.

Based on the information provided by the company in the subject PMA/S file, this issue is resolved. Please refer to the post market section for additional information of the Post Market Study Protocol.

☒ **Clinical**

FDA clinician conducted the consult reviews for the proposed labeling modification, the elevated pressure. The following is the concerns, and those concerns were stated in the FDA letter to the company, dated August 10, 2009. The company provided the responses to FDA concerns via the PMA/S Amendment. After further review of the responses from the company, the final FDA conclusion is to accept the purposed labeling modification.

The following is a summery of the clinical review process.

Deficiency 1:

FDA requested clarification as to why the HBOT therapy was done for only 60 minutes when HBOT therapy can be prescribed for up to 120 minutes.

BSC Response: The ability to expose a fatigue failure is based on the stress level of the cycle and the number of cycles, not the duration of the cycle. 60 minutes is also the typical HBOT therapy duration. It is also the time on the draft ISO standard from 2006. Lastly, the sponsor checked that creep deformation, which could cause the generator to fail, and the raw materials used in BSC generators are not susceptible to creep.

Clinical Reviewer Response: BSC provided a sound rationale for not testing beyond the 60 minutes. As a clinician, I am not familiar with creep deformation, but assume that from an engineering standpoint, testing this on raw materials rather than finished product is acceptable.

Reviewer Comment: This deficiency is resolved. The reviewer requested the bench testing, which demonstrates the deformation of the header will not occurred due to the HBOT. The company provided additional test information in the PMA/S Amendment 4 to address this issue (creep). Based on the information in the PMA/S Amendment 4, this issue is resolved.

Deficiency 2:
FDA requested changes to the labeling regarding elevated pressures.

BSC Response:
a) BSC added the following sentence: The [ISO] has not approved a standardized pressure test for implantable pulse generators that experience hyperbaric oxygen therapy (HBOT) or SCUBA diving. However, [BS] developed a test protocol to evaluate device performance upon exposure to elevated atmospheric pressures.

b and d) There are 3 paragraphs; one stating that elevated pressures may damage the pulse generator, two that prior to HBOT therapy the prescribing physician should consult with the patient's cardiologist since HBOT may affect underlying medical conditions, and three that prior to SCUBA the patient should

consult with their cardiologist since this may affect underlying medical conditions. The labeling now includes a list of recommended follow up testing to perform post-HBOT/SCUBA.

c) BSC proposes not to include more detail on the testing done in the labeling but proposes to add the statement," If you have additional questions or would like more detail regarding the test protocol or test results specific to HBOT or SCUBA diving, contact Technical Services…" BSC also proposes to update the System Guide (from (b) (4) *to* (b) (4) *cycles) since that is the minimum number of cycles tested on BSC devices.*

Clinical Reviewer Response: The added sentences to the labeling regarding the elevated pressures are overall acceptable. The labeling clearly states that high pressures may damage the generator. It also states clearly that the underlying medical condition can be affected by HBOT/SCUBA. Lastly, the rationale to not provide further detail on the testing but rather refer the reader to call Technical Services is reasonable.

This deficiency is resolved.

☒ **Sterilization**

N/A

☒ **Statistical**

N/A

☒ **Biocompatibility**

Based on the information is the subject file, the following is the deficiencies raised by FDA reviewer for the biocompatibility information that is related to the implantable device under the high pressure environment, and the responses from the company:

Deficiency 1: Regarding the sufficiency of biocompatibility data for (b) (4), if a seal breaks when the device is under pressure, then the biocompatibility would need to be for direct body/blood contacting and not indirect. Please discuss the applicability of the biocompatibility data to the elevated pressure environment.

The company responses: Tests done for (b) (4) per Exhibit 4-07 (biocompatibility assessment, 553834-442 Rev D) are applicable for either indirect contact or direct contact metal components. These tests were:

- Physicochemical
- Cytotoxicity

- Hemolysis
- Short-term Implant (7-14 days)
- 90 Day Implant

The majority of ISO biocompatibility tests are not applicable for metals since they are based on extraction properties for polymers. These materials have established implant histories, per the references listed in Table 2 of Exhibit 4-07 of the submittal.

Additionally, (b) (4) was submitted as a new direct blood contact material for the RELIANCE 4-SITE leads in comparison to the RELIANCE IS-1/DF-1 leads, per P910073/S077 and P830060/S062. The biocompatibility report for (b) (4) was provided as Exhibit 4-8 of the RELIANCE 4-SITE submission, also approved by FDA. The testing reported in the (b) (4) biocompatibility report was performed in support of legacy products dating back to 1998 made of the identical material; this testing supports biocompatibility of the PG based on no changes to processes that would affect biocompatibility.

Reviewer comment: Based on the additional information provided by the company, FDA approved the (b) (4) in P910073/S077 and P830060/S062, this issue is resolved.

Deficiency 2: FDA is concerned that if a seal breaks under pressure then it would cause corrosion at a different rate (increased) and Boston Scientific's 30-day test would not be sufficient. Please discuss the applicability of the 30-day corrosion test to the elevated pressure environment.

The company responses: *The 30-day corrosion test is applicable in an elevated pressure environment because, as discussed in Response 1.A, the implanted device and header reaches a steady state in which it is liquid-filled there will be no change in pressure and no transfer of liquids to cause damage to seals. Boston Scientific's corrosion test was done per ASTM F746-04 standard method, which is a standard test method for pitting or crevice corrosion of metallic surgical implant materials.*

However, if pressure did create an additional transfer of fluid, Boston Scientific's corrosion testing addresses this condition. Exhibit 4-20, Corrosion Assessment, summarizes testing conducted per another report, Corrosion Performance of Quadripolar Connector Spring

Contacts DVT Report (doc# 554837-403) was submitted as part of the 7/1/09 e-mail to FDA.(This e-mail was submitted to FDA as part of the PMA/S Amendment as well.)

For this testing, both lips of all seals were intentionally slit; this degree of damage is not seen when inserting the lead into the PG or in any other expected use of the system. Dual redundant lips are provided on each seal to restrict transfer of saline, even if one lip is compromised.

In this study the test conditions for seal damage are more severe then would be expected in service, including during or following elevated pressures. Though the primary challenge was intentional damage to the seal lips, specimens were tested in extreme conditions for several other factors including the number of shocks, shock energy, pacing amplitude, pulse width and pulse rate.

The study was designed to evaluate the stability of the system over the initial 30 days of service. If corrosion were to occur the process would begin with an initiation phase. This study was intended to evaluate susceptibility to initiation of corrosion. If corrosion never initiates then it cannot progress to the point of component or system failure. Therefore, a life test for corrosion is not necessary based on establishing that the device is resistant to initiation of corrosion.

The study was designed to determine whether corrosion processes would initiate under conditions that are more extreme then are expected during use. For this study, acceptance criteria were established to detect changes in system performance that would indicate the onset of corrosion. Since highly corrosion resistance materials are used in this design it was expected that there would be no evidence of onset of corrosion even under conditions exceeding those expected in use.

The results demonstrated that the system is stable over the interval when onset of corrosion would be apparent. No evidence was detected of the onset of corrosion at the electrical interface between the lead and PG.

In summary, the results of the corrosion testing conducted on the quadripolar connector spring contacts, per the attached, supports the required corrosion resistant performance of the device during or following elevated pressures based on the following:

- (b) (4) *is an extremely corrosion resistant alloy of* (b) (4) *Cobalt,* (b) (4) *Nickel,* (b) (4) *Chromium and* (b) (4) *Molybdenum.*

- *Testing was performed with intentionally damaged seals that exceed normal implant conditions, so as to allow fluid ingress into the critical contact zone of interest.*

- *Testing was performed using extreme device settings to promote corrosion initiation Therefore, if header conditions during or following elevated pressures should result in liquid ingression, the corrosion testing has adequately assessed this condition and demonstrated the device meets requirements.*

Reviewer comment: Based on the additional test reports with the explanations, this issue is resolved.

☒ **Shelf Life**

N/A

☒ **Packaging Change w/ the description**

N/A

☒ **Post Market Issues**

The company agreed to conduct a post market study for the 4-site lead system with the PG 4-site header PG. The proposed protocol for the post market study was reviewed and accepted by FDA. The title of this post market study is, The Longitudinal Surveillance Study of the 4-SITE Lead/Header system (LSS of 4-SITE)

The primary purpose of this post market study is to evaluate, document, and report on the appropriate clinical performance, the long-term reliability and the functional integrity of the 4-SITE Lead/Header system consisting of a 4-SITE compatible ICD or CRT-D. The study design is a single arm study, 95% free complication for the lead and header. The subject study is for a maximum of (b) (4) centers, a minimum of (b) (4) 'successful' implanted subjects with a 5 years follow-up period. The follow-up periods are: (month, (months, (b) months, then (b) (4) follow-up until the 60th months.

Inclusion criteria for this post market study:

- Has been or will be implanted with the 4-SITE lead;
- Has been or will be implanted with a BSC commercially available 4-SITE compatible PG;
- Plans to remain in the long-term care of his/her enrolling Investigator;
- Is willing and capable (or appropriate legal representative) of authorizing access to and use of health information as required by an institution's IRB; and
- Is willing and capable (or appropriate legal representative) of providing authorization for participation in the study.

Exclusion criteria for this post market study:

- More than 14 days have passed since implant;
- Any of the required data listed below is missing:
    - o RV lead and PG date of implant.
    - o RV lead and PG model and serial numbers.
    - o RV lead implant attempts/repositioning (whether more than one lead or lead position was attempted to achieve a successful lead implant).

o RV lead electrical measurements for final lead configuration (sensing,
pacing threshold, and impedance).
o Documented assessment of Adverse Event status since implant.

• Are unable or unwilling to comply with the protocol requirements.

☒ **Manufacture/QSR/GMP**

CRDH/OC conducted the manufacture/QSR/GMP consult review for the file, a number of the manufacture deficiencies were generated, and those deficiencies were stated in the FDA letter dated August 10, 2009. The company provided the responses to address those deficiencies in PMA/S Amendment 01, dated October 14, 2009. Another CDRH/OC consult review was conducted for the responses. The final consult review indicates the acceptance of the company responses.

The following is the CDRH/OC review summary with the deficiencies and the company responses:

1. *Please provide a procedure that follows the requirements of the Quality System Regulation, 21 CFR 820.30(a), and relates how the development process is incorporated into the design control requirements.*

2. *Please provide a design development plan that follows the Quality System Regulation, 21 CFR 820.30(b). The information provided in the procedure should describe or reference, and assign responsibility for the implementation of Design Inputs, Design Outputs, Design Review, Design Verification, Design Validation, Design Transfer, Design Changes, and Design History File.*

Reviewer comment **(1 & 2):**

The firm submitted the procedure 005253, CRM Product Development Process. The activities associated with design inputs, design outputs, design review, design verification, design validation, design transfer, design changes and design history file are identified and a link to the appropriate procedure describing the implementation of that activity is also provided. This is found to be adequate.

3. *A procedure describing the design input process was not submitted. Please provide the design input procedure that follows the requirements of the Quality System Regulation, 21 CFR 820.30(c), that is used for the identification and control of design inputs for the device under review. It should describe the process for addressing incomplete, ambiguous, or conflicting requirements and should explain how inputs are documented, reviewed, and approved.*

Reviewer comment **(3):**

The firm submitted the procedure 005245 Rev O, System Requirements/ System Design. This procedure describes how inputs are documented, who reviews the design inputs, the review criteria and the use of the peer review process to approve the document. This is found to be adequate.

4. *A procedure describing the design output process was not submitted. Please provide the design output procedure that follows the requirements of the Quality System Regulation, 21 CFR 820.30(d), which defines an adequate and measurable evaluation of conformance to design input requirements and provides a list of the outputs that are considered essential for the proper functioning of the device. Also included should be acceptance criteria.*

Reviewer comment **(4):**

The firm submitted following procedures that are related to design output activities:

Procedure 042240 Rev J – Design Documentation
Procedure 007037 Rev L – Product Information Control
Procedure 006389 Rev L – Product Development Traceability
Procedure 044671 Rev F – Performing a Hardware Design Output Spec
FMEA Procedure 005247 Rev Q – Hazard/Safety Analysis
Procedure 044590 Rev B – Stratification of System Requirements
Procedure 007022 Rev I – Safety Risk Management Process

A review of the above procedures found the process to be satisfactory per 21 CFR 820.30(d).

5. *A procedure describing the design review process was not submitted. Please provide the procedure that follows the requirements of the Quality System Regulation, 21 CFR 820.30(e), and defines how formal design reviews are planned and how you ensure that formal design reviews are conducted at appropriate stages of the design and development process for the device under review.*

Reviewer comment **(5):**

The firm submitted the procedure 005256 Rev T, Design Reviews indicating design reviews and peer reviews are conducted at pre-determined milestones. It also indicates that the reviews are cross functional. This is found to be adequate.

6. *A procedure was describing the design verification process was not submitted. Please submit the procedure that follows the requirements of the Quality System Regulation, 21 CFR 820.30(f), which is used to verify the device design for the device under review. The procedure should*

describe the process that confirms the design outputs meet the design input requirements and the mechanism for resolving any discrepancies. Further, the procedure should define the method of recording design verification activities for the design history file and should include: verification results, identification of the design, verification methods, dates of verifications, and individual(s) performing the verifications.

Reviewer comment **(6):**

The firm submitted the procedure 006318 Rev T, Design Verification and Validation. This procedure describes how Design Verification Tests are performed to demonstrate that system design outputs meet device level requirements. The procedure also defines how to resolve discrepancies and the method of recording the results, methods, dates and individuals performing the verification in the design history file. This is found to be adequate.

7. *A procedures describing the design validation process was not submitted. Please provide the procedure that follows the requirements of the Quality System Regulation, 21 CFR 820.30(g), which is used to define the design validation activities.*

Reviewer comment **(7):**

The firm submitted the procedure 006318, Design Verification and Validation, describing how a design validation is performed to demonstrate that the system meets user needs and intended uses.

8. *A procedure which describes the design transfer process was not submitted. Please submit the procedure that follows the requirements of the Quality System Regulation, 21 CFR 820.30(h), which is used to transfer design output to manufacturing. The procedure should describe the final review process and the approval of the design. What documents are included in the device master record should also be addressed.*

Reviewer comment **(8):**

The firm submitted following procedures that are related to design transfer activities:

Procedure 007080 Rev J – Design Release Requirements
Procedure 041577 Rev G – Design History File (DHF), Device Master Record (DMR) and Device History Record (DHR)
Procedure 005418 Rev K – Manufacturing Transfer Process

A review of the above procedures found the process to be satisfactory.

9. *A procedure which discusses how changes made to the design are controlled was not submitted. Please submit the procedure that follows the requirements of the Quality System Regulation, 21 CFR 820.30(i), that is used to control design changes after the original design has been transferred to manufacturing. The procedure should also include verification and validation activities, how the change is approved and implemented, the review process, and the approval authorities.*

Reviewer comment **(9):**

The firm submitted the procedure 007041 Rev S, Engineering Change Process, which is followed once design has been transferred to manufacturing. A review of the procedure found it to be satisfactory.

10. *A procedure describing the establishment and control of the design history file was not submitted. Please submit the procedure that is used to establish and maintain the contents of the design history file in accordance with the requirements of the Quality System Regulation, 21 CFR 820.30(j).*

Reviewer comment **(10):**

The firm submitted procedure 007037 Rev L, Product Information Control, which outlines a procedure for maintaining the contents of the Design History File (DHF).

11. *To meet the requirements of 21 CFR 820.20(e), you have provided procedure CP5000 and CP7000, Quality System Manual to document your quality system procedures at Saint Paul and Ireland manufacturing facility respectively. You indicate in document CP7000 section 9.13.5 that the Ireland manufacturing facility does not have a complaint handling function. All complaints are handled through the Saint Paul site via 028564 Product Experience Handling Policy. Please explain how complaints related to the devices manufactured at the Ireland manufacturing facility are disseminated Ireland's CAPA system and Management Reviews. Please provide document 028564, Product Experience Handling Policy.*

Reviewer comment **(11):**

The firm indicated that the procedure 028564, Product Experience Handling Policy, which applies to all worldwide employees, agents, and temporary workers from the Boston Scientific CRM business and therefore includes the Clonmel, Ireland manufacturing site. All complaints are ultimately transmitted to St Paul based department. The firm also provided procedure 006643, Management Controls. As per the procedure, the meeting agenda typically includes review of process performance for CAPA items. This is found to be adequate.

12. *You submitted document # 100015-405 that includes Operational Qualification (OQ) performed for the Clean 2 Foreign Material (FM) removal from the IS2 lead barrels. Results indicate that vacuum process was performed on (b)(4) units out of (b)(4) selected units. Please provide a rational that (b)(4) samples are sufficient to derive conclusion that the process adequately meets desired specification.*

Reviewer comment **(12):**

The firm indicated that it recognizes that this OQ testing did not demonstrate the statistical level outlined in its protocol due to the fact that the test instructions were unclear and thus all (b)(4) samples were not subjected to vacuuming. Subsequently, a new test plan was devised and re qualification was conducted. A review of the revised results found them to be adequate.

☒ **Labeling**

With the exception of the labeling modifications for the elevated pressure and 4-site header, the company claims all other the labeling information were approved by FDA prior to the subject file. With above, the Labeling of this file is acceptable.

Note: The elevated pressure labeling information is located in the clinical section.

Recommendation:

The post approval study protocol has been accepted by OSB as of November 10, 2010. The title for the post approval study is, The Longitudinal Surveillance Registry of the 4-SITE Lead/Header System (LSR of 4-SITE).

Based on the information in the submission, I am recommending the approval of this file.

(b) (6) **Date**
Reviewer

Mitchell Shein **Date**
Branch Chief, PDLB

Please refer to P960040/S198 for the Review