MEMORANDUM

From: [redacted] PDLB
To: Files # P960040/S235 and P010012/S255
Subject: INCEPTA, ENERGEN and PUNCTUA CRT-Ds and ICDs – Transparency Memorandum
Date: November 9, 2011
Office: ODE/DCD

The manufacturer, Boston Scientific Corporation (BSC), is seeking approval for the INCEPTA, ENERGEN and PUNCTUA CRT-Ds and ICDs which are included in the bundled files referenced above. In addition, approval is also being sought to modify the COGNIS Models N118 and N119 and the TELIGEN Models E102 and E110 approved May 8, 2008. An overview of the file and our recommendation which takes into account consulting reviews (Clinical, Software, Engineering and Manufacturing/GMP) are included below.

Overview of the File

Background Information

According to BSC, the new pulse generator models, INCEPTA, ENERGEN and PUNCTUA are based on the commercially available TELIGEN and COGNIS family of devices**. Please note as referenced in this memo that the product development names differ from the market names. For example, COGNIS/TELIGEN were developed under the** (b) (4) **project and the INCEPTA, ENERGEN and PUNCTUA devices were developed under the** (b) (4) **project or under the name of** (b) (4)

INCEPTA, ENERGEN and PUNCTUA models have not been marketed in or outside of the U.S. as of the date of this submission. To date, the COGNIS and TELIGEN are approved for sale in the U.S. and other countries.

The manufacturer referenced several field actions which were associated with the TELIGEN, COGNIS and LIVIAN devices and documented that all said field actions have all been resolved. According to the manufacturer, to date, there are no pending field actions related to the marketed COGNIS, TELIGEN and LIVIAN devices.

Pre-IDEs

Pre-IDE meetings/telconferences for (b) (4) and for the use of (b) (4) Field data were held to discuss feature enhancement in the (b) (4) pulse generator models. The meeting minutes as submitted can be summarized as follows:

Regarding the RID Pre-IDE Submission:

- RID is a feature which distinguishes between SVT and VT and was approved in the VITALITY ICDs and the TELIGEN/COGNIS devices.

- A Pre-IDE meeting/teleconference was held on August 5, 2009 with this reviewer, the clinical consulting reviewer and BSC representatives regarding the RID feature enhancement [redacted] (b) (4)

- In the Pre-IDE, bench testing was used to demonstrate proper performance of the RID enhancement and is provided in the referenced files (The sponsor noted that the RID detection algorithm itself is not changing, the feature is enhanced as described above. The enhancement will be supported in the referenced files by firmware [redacted] (b) (4) software [redacted] (b) (4)).

- Physician feedback in use of the enhanced RID algorithm was provided during the Pre-IDE and is included in the referenced files. The feedback will be reflected in the device labeling in that text will be added to the PRM screen that clearly identifies that an increase in specificity for SVTs implies a decrease in specificity for VTs and vice-versa. The labeling will also caution physicians with the trade-offs in a similar fashion.

The testing and clinical experience of the RID algorithm enhancement are discussed further in this review memo under the Clinical Studies section.

Regarding RYTHM IQ Pre-IDE Submission [redacted] (b) (4)

- This Pre-IDE submission encompassed the [redacted] (b) (4) feature which is intended to eliminate unnecessary RV pacing for ICD patients who appear to have normal AV conduction.

- RMS was approved in the CE marked TELIGEN ICDs. BSC is proposing to add an enhanced version of RMS in the next generation devices ([redacted] (b) (4) devices named above). The basic operation of RMS is unchanged. However, with the enhancement, [redacted] (b) (4)

- Support of RMS included the COGENT Study. BSC completed the COGENT-4 Field Following Study which included the COGNIS, TELIGEN and RELIANCE quadripolar lead (4-SITE) field following (COGENT Study). The study included a substudy which evaluated the RMS feature in the TELIGEN devices.

The testing and clinical experience of the RMS feature are discussed further in this review memo.

Description of the Device

The new models for which BSC is seeking approval are as follows:
INCEPTA CRT-D Models N160/N161/N164, ENERGEN CRT-D Models N140/N141, PUNCTUA CRT-D Models N050/N051, INCEPTA ICD Models E160/E161/E162/E163, ENERGEN ICD Models E140/E141/E142/E143 and PUNCTUA ICD Models E050/E051/E052/E053. Approval is also being sought for the modified models - COGNIS Models N118/N119 and TELIGEN Models E102/E110

(b) (4) models (U.S. and OUS) also include the following:

Model #	Feature Set	RF	Description
E160	TELIGEN 160	ISM	ICD VR IS-4
E162	TELIGEN 160	ISM	ICD DR IS-4
F160	TELIGEN 160	SRD	ICD VR IS-4
F162	TELIGEN 160	SRD	ICD DR IS-4
E161	TELIGEN 160	ISM	ICD VR DF-1
E163	TELIGEN 160	ISM	ICD DR DF-1
F161	TELIGEN 160	SRD	ICD VR DF-1
F163	TELIGEN 160	SRD	ICD DR DF-1
E140	TELIGEN 100	ISM	ICD VR IS-4
E142	TELIGEN 100	ISM	ICD DR IS-4
F140	TELIGEN 100	SRD	ICD VR IS-4
F142	TELIGEN 100	SRD	ICD DR IS-4
E141	TELIGEN 100	ISM	ICD VR DF-1
E143	TELIGEN 100	ISM	ICD DR DF-1
F141	TELIGEN 100	SRD	ICD VR DF-1
F143	TELIGEN 100	SRD	ICD DR DF-1
E050	TELIGEN 50	ISM	ICD VR IS-4
E052	TELIGEN 50	ISM	ICD DR IS-4
F050	TELIGEN 50	SRD	ICD VR IS-4
F052	TELIGEN 50	SRD	ICD DR IS-4
E051	TELIGEN 50	ISM	ICD VR DF-1
E053	TELIGEN 50	ISM	ICD DR DF-1
F051	TELIGEN 50	SRD	ICD VR DF-1
F053	TELIGEN 50	SRD	ICD DR DF-1
N160	COGNIS 160	FSB	ISM CRT-D IS-4/IS-1
N162	COGNIS 160	FSA	ISM CRT-D IS-4/IS-1
P162	COGNIS 160	FSA	SRD CRT-D IS-4/IS-1
N161	COGNIS 160	FSB	ISM CRT-D DF-1/IS-1
N163	COGNIS 160	FSA	ISM CRT-D DF-1/IS-1
P163	COGNIS 160	FSA	SRD CRT-D DF-1/IS-1
N164	COGNIS 160	FSB	ISM CRT-D DF-1/ LV-1
N165	COGNIS 160	FSA	ISM CRT-D DF-1/LV-1

P165 COGNIS 160 FSA SRD CRT-D DF-1/LV-1
N140 COGNIS 100 FSB ISM CRT-D IS-4/IS-1
N142 COGNIS 100 FSA ISM CRT-D IS-4/IS-1
P142 COGNIS 100 FSA SRD CRT-D IS-4/IS-1
N141 COGNIS 100 FSB ISM CRT-D DF-1/IS-1
N143 COGNIS 100 FSA ISM CRT-D DF-1/IS-1
P143 COGNIS 100 FSA SRD CRT-D DF-1/IS-1
N050 COGNIS 50 FSB ISM CRT-D IS-4/IS-1
N052 COGNIS 50 FSA ISM CRT-D IS-4/IS-1
P052 COGNIS 50 FSA SRD CRT-D IS-4/IS-1
N051 COGNIS 50 FSB ISM CRT-D DF-1/IS-1
N053 COGNIS 50 FSA ISM CRT-D DF-1/IS-1

According to the manufacturer, the electronics of the above models are identical except for the radio frequency. Devices available in North America & Australia have RF modules tuned to operate in the Industrial, Scientific, and Medical (ISM) band and those available in all other OUS markets have RF modules tuned to operate in the Short Range Device (SRD) band. All other differences between the COGNIS & TELIGEN models, the 160/100/50 tiers of models, and FSA & FSB devices are a result of the features available in the devices or the header type that allows for various lead configurations for the physical connections to the device.

INCEPTA, ENERGEN and PUNCTUA are considered “three tiers” within the CRT-D and ICD product lines. Each tier has a specific set of features and functionality (For example, no wireless ECG (new), RhythmMatch threshold (new) and RYTHMIQ (new) in the PUNCTUA and ENERGEN CRT-Ds, however the features except RYTHMIQ are available in the INCEPTA CRT-D. The named features are also available in the PUNCTUA and ENERGEN ICDs with RYTHMIQ added to the INCEPTA DR ICD. Heart rate variability (HRV) (new for ICD) is available in all CRT-D models and in the INCEPTA DR ICD). The manufacturer provided a Table for our review which included the feature and the availability of the feature in the different device models.

The (b) (4) devices provide ventricular tachyarrhythmia therapy, cardiac resynchronization therapy (CRT) and bradycardia pacing support after defibrillation therapy. The cardioversion /defibrillation therapies include:

• A range of low-energy 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 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-1 cardioversion/defibrillation lead

• One DF4-LLHH or DF4-LLHO multipolar connector cardioversion/defibrillation lead

According to the manufacturer, leads with either GDT-LLHH/LLHO or DF4-LLHH/LLHO label are equivalent and are compatible with a device containing either a GDT-LLHH or DF4-LLHH port.

The (b) (4) ICD models include VR and DR devices. These devices provide cardioversion/defibrillation therapy, bradycardia pacing and cardioversion defibrillation therapies and utilize leads which are identical to those mentioned above for the CRT-Ds The pulse generators can be used only with the ZOOM LATITUDE Programming System. The Model 3120 PRM, Model 2868 PRM application software (PRM Software), and an accessory inductive telemetry wand constitute the external portion of INCEPTA, ENERGEN, PUNCTUA, COGNIS and TELIGEN systems. The external components allow interrogation and programming of the device and access to the device's diagnostic features.

According to the manufacturer, the marketed TELIGEN and COGNIS were modified to create the subject newer models (b) (4) which include the following:

- Dual battery options for flexibility during manufacturing
- Inductive telemetry frequency to comply with FCC regulation
- A new header connection which increases header attach strength
- Modified hardware/components and second source suppliers
- Updated software which incorporates enhancements and trends
- Updated labeling which identifies the new models, features and conformance to the DF-4 Standard
- Restructured labeling to reduce redundancy and streamline the information
- Increased shelf life to 24 months
- Added and/or modified 4 diagnostic and detection features (RYTHMIQ, Rhythm ID with RhythmMatch, wireless ECG and heart failure trending data available in the ICD).

The modifications entailed hardware/component changes to the functional components of the COGNIS and TELIGEN (New suppliers were added for some of the components). Certain models were affected by the changes (I = INCEPTA, E = ENERGEN, P= PUNCTUA, C=COGNIS and T=TELIGEN). The changes include the following:

- Header Body - Added two 316 l E-clip components to improve header strength and fatigue life of feedthrough wires and seal plug integrity [redacted] (b) (4) The change in header geometry is intended to improve visibility of the lead at its fully seated position (Affected models - IEP).

  Each device model has a header that accepts a specific lead configuration. Diagrams of specific device headers were provided for our review.

  The seal plugs are identical to the COGNIS and TELIGEN seal plugs. However, the [redacted] (b) (4) has a decreased diameter in I, E and P devices. The change was made to improve the seal and to decrease the likelihood of air bubbles which may lead to oversensing (Design changes addressed this issue in P010012/S023 and P960040/S190 approved March 18, 2009). This additional change was made to further reduce the likelihood of the occurrence).

- Lead Spring - Modified leaf spring leading edge to reduce exposure due to new IS-1 [redacted] (b) (4) and to reduce the risk of springs being oversized (IEP). This change resulted in manufacturing changes which intend to reduce the risk of oversized spring events that may result in high lead impedance and oversensing.

- X-Ray ID – changed to BSC 120 and moved location of ID within the header (IEP).

- Feedthrough Assembly – Moved the location of wire routing within the header (IEP). Feedthrough wire routing adjustments were made to I, E and P CRT-D devices with DF-1/IS-1/LV-1 headers to allow sufficient clearance for the e-clip components.

- PG case – Added [redacted] (b) (4) anchor posts for added header strength, changed laser marking to include DF4 on DF4 models (IEP).

- Front Liner – Added bar to the front liner [redacted] (b) (4) The new liner was approved for use in the COGNIS/TELIGEN via P010012/S245 and P960040/S22. The back liner was not modified from the current COGNIS/TELIGEN design.

- Analog IC – Changed [redacted] (b) (4) which sets frequency of device inductive telemetry communication at [redacted] (b) (4) to comply with FCC regulations (IEP). There are no changes to any of the connections between the analog and the device hybrid as a result of the analog IC change.

- High Voltage Charge Module - Tightened voltage limit for [redacted] (b) (4) diode used in charge module and tightened voltage limit at module and hybrid level (IEP). The component upper limit specification was changed to [redacted] (b) (4) module level upper limit changed to [redacted] (b) (4) and the hybrid level upper limit changed to [redacted] (b) (4) (PMA supplements (P010012/S244 and P90040/S224) were recently approved to include

the new (b) (4) diode in COGNIS/TELIGEN models as well as the new high voltage module with the tighter module level upper limit).

- Transformer – Used in charging the high voltage capacitors. Decreased the number of turns on the primary side of the transformer by (b) (4) to increase high voltage charge frequency and thereby reduce risk of interference with inductive telemetry frequency (IEP). The charge time was increased from (b) (4) seconds to (b) (4) seconds for a maximum energy charge and was updated in the labeling.

- QHR Battery – Utilized two different battery technologies: Lithium –manganese dioxide cell (manufactured by BSC) or Lithium-carbon (b) (4) (manufactured by (b) (4) by adding a second functionally equivalent battery which according to the manufacturer provides supply chain and manufacturing flexibility (IEP). On the basis of longevity, charge time limits and EOL, both batteries are considered to be interchangeable (according to the manufacturer, the QHR battery with blended chemistries is present in the marketed BSC CONFIENT and LIVIAN devices).

Second Source Suppliers were added for:

- High voltage charge module and super output module (SOM) – Added second source for 4 diodes used in HV charge module and SOM
- Capacitor Lid – Added second source supplier
- System on Chip (SOC) – added an alternate location for burn-in test and final inspection
- ASIC Wafer – Added an alternate facility to (b) (4)

A discussion of the design verification/validation tests which evaluated the changes is provided under the Bench Testing section of this review and includes the engineering consultant's review. The addition of the second source suppliers and other manufacturing changes were addressed by the OC GMP consulting review.

As stated above, BSC is also requesting in the referenced files to modify the commercially available TELIGEN E102/E110 and the COGNIS N118/N119 with a subset of the modifications listed above. These modifications take into account the following:

- Updated software
- Second source suppliers
- Updated labeling and restructured and reformatted labeling

The PRM (Programmer/Recorder/Monitor) System which is used to interrogate and program the subject devices and the software changes can be described as follows:

- The PRM system consists of the Model 2868 PRM software, the Model 3120 PRM and PRM commercially available accessories. The PRM also has operating system software or the utility (MAU) software.

- The software changes included both programming software and pulse generator software (firmware) changes. Changes were made to the marketed COGNIS/TELIGEN firmware to create: (1) COGNIS and TELIGEN PG Software Version A_v1.04.0 Patch_v2.06; and (2) INCEPTA, ENERGEN, PUNCTUA PG Software version B_v1.02 (For which BSC is seeking approval in the referenced files).

- Changes which affect both the PRM and pulse generator software applications (IEP devices) include the following:

    - Programmable RID – programmable correlation from 70.0 percent to 96.0 percent (affects I) (RID with RhythmMatch will have the same nominal settings as RID) – (I)

    - Wireless ECG - allows use of wireless ECG without surface electrodes. Real-time EGM mimics a surface ECG by using a shocking lead (b) (4) to can vector for measuring heart activity – (I devices)

    - Fault detection – system includes detection and displays high battery voltage (IEP)

    - Shock lead impedance integrity test – updated to reduce variability in measurements in the presence of sources of noise (IEP)

    - Heart failure trending data (I ICD), and data recording expanded to include all Brady modes (IEP)

    - Time-to-Explant Indicator – battery management algorithm was updated to include constants for the alternate battery chemistry (QHR) – (IEP)

    - Brady mode transition at EOL – AAI(R) –go to AAI and OFF –go to OFF added at EOL (IEP)

    - RYTHMIQ – based on the RMS which promotes AV conduction by using AAI pacing plus VVI backup pacing and switches to DDD pacing if AV conduction block is sensed; was studied in COGENT (I ICD DR).

    - Monitor only – changed behavior of detection enhancements with a monitor-only zone. With this change the monitor only zone behavior was updated such that detection enhancements will be available in the VT zone after detection in the VT1 zone with no therapy available (uses initial detection parameters rather than redetection for the 2nd detection met event (IEP).

- Changes which were made that applied only to the PG software (IEP devices) included the following:

    - Simultaneous real-time markers – prevent output of the wrong marker

- Telemetry communication – prevent unauthorized user to repeatedly wake the PG and thereby accelerate battery depletion

- Fault detection – prevent continuous beeping of the PG reset following high-rate pacing fault

- Stored EGMs and markers – eliminate marker misalignment

- *Ventricular arrhythmia induction – corrected the PG to transition to post-shock pacing following T-wave shock and Fib induction (reduces possible VF undersensing following induction)

- Atrial arrhythmia induction – made store RV/LV EGMs available during RA EP test

- Temporary brady pacing – PG will now exit temporary brady mode within one cardiac cycle rather than two (restore pacing capture sooner)

- Pacemaker Mediated Tachycardia (PMT) – PMT counter resets properly – no longer prematurely declare PMT)

- Histograms - removed LVPP inhibited events from the Rate histogram interval calculation

- Therapy history – for VT/VT1 episodes, therapy history will report ATP timeout status in the case of shock therapy not available

- Therapy history – in addition, the history storage system was updated to prevent transition to safety mode in certain conditions.

- MV filter – updated to support OUS feature

- Auto lead detect – removed (was used to baseline the respiratory sensor which is not used in U.S. devices)

- Lead impedance integrity test - improve accuracy of the lead impedance test

- Capacitor reform – fixed an issue which could possibly delay transition to EOL by 30 days

- Heart rate trend information – corrected heart rate information

- Daily battery measurements – revised data that is stored during the voltage recovery period following a high current (telemetry or shock event)

- Time-to-Explant Indicator – updated shelf life to 24 months which required updated constants for configuring the battery management algorithm and calculation of the one year remaining point

- RAM validation – improved ability of the firmware to recover from data corruption in specific memory locations – eliminated entering safety mode due to a single event upset corruption

- Storage mode – prevent reset under testing conditions

- *CRT pacing – prevent LV pacing suspension, for suspension to occur, positive LV offset must be present which is only available in OUS devices, with the change, LV pacing behavior was updated and corrected

- Pace clamping and recharge during blanking – prevent VF undersensing by increasing clamping time and decreasing recharge time

- Up rate smoothing – allow full range of sensor driven pacing

- Electrocautery protection mode – electrocautery protection mode was enhanced to prevent entering the safety mode – tolerances were changed and some oscillator faults were disabled in the electrocautery state

- Post shock pacing – the post shock Brady mode becomes effective along with the other post-shock Brady parameters immediately after the post shock delay timer expires

- The modifications which apply solely to the PRM software are listed below:

  - Temp tachy Mode
  - Display of post shock RhythmID
  - Real-time electrograms
  - Telemetry communication
  - EOL telemetry
  - Arrhythmia logbook
  - Pace threshold test
  - Lead tests
  - Pace lead impedance
  - Interactive limits
  - Time-to-Explant indicator
  - Patch mechanism
  - ZOOMView
  - Demo/Disk mode
  - Indications-Based Programming (recommend the feature enhancements,, e.g., RYTHMIQ)
  - Brady MTR/MSR/MPR

- Brady Mode transition at EOL

*Field reports

Validation testing for the software changes (which includes definitions and how identified) are summarized under the Software Development and Validation section and the Animal Testing section of this memo. A discussion of the results of testing is also included in the software consulting reviewer's memo.

Indications for Use

The manufacturer is requesting CRT-D indications for use identical to the proposed indications approved under P010012/S230 (MADIT- CRT). The indications read as follows:

Boston Scientific Cardiac Resynchronization Therapy Defibrillators (CRT-Ds) are indicated for patients with heart failure who receive stable optimal pharmacological therapy:

- Moderate to severe heart failure (NYHA Class III-IV) with EF ≤ 35% and QRS duration ≥ 120 ms

- Left Bundle Branch Block (LBBB) with QRS ≥ 130 ms, EF ≤ 30%, and mild (NYHA Class II) ischemic or nonischemic heart failure or asymptomatic (NYHA Class I) ischemic heart failure.

There are no changes to the ICD indications. The indications read as follows:

Boston Scientific implantable cardioverter defibrillators (ICDs) are intended to provide ventricular antitachycardia pacing (ATP) and ventricular defibrillation for automated treatment of life-threatening ventricular arrhythmias.

Contraindications for Use – According to the manufacturer, there are no contraindications for their CRT-Ds. However, the Contraindications for Use as stated for their ICDs remain. This reviewer contends that since CRT-Ds are ICDs, the listed ICD contraindications also apply to CRT-Ds. No prospective study has been performed to support the claim of no contraindications for BSC CRT-Ds.

Bench Testing

According to BSC, all (b) (4) device models contain the same integrated circuits, hybrids and pulse generator firmware as in the marketed TELIGEN/COGNIS except that the RF hardware in the F1 frequency type models is different from the RF hardware in the F2 frequency type models. Tests described below can also be specific to the device model as it pertains to a specific functionality. The tests below will address the device modifications as described above.

The manufacturer performed a series of bench tests to demonstrate that the device operated and functioned safely and effectively according to design. The tests included electrical design and mechanical verification, component qualification testing, system features testing, simulated use testing, tape testing and safety risk management. In addition, biocompatibility and sterilization assessment and animal studies were performed to support performance to specifications. A discussion of the tests is provided by this reviewer. A review of the bench tests was conducted by this reviewer and also by the engineering consultant. A summary of the bench tests are included below:

Electrical Design Verification Tests

Ripple Effect Analysis (Electrical Hardware verification tests)

- Inductive communication circuit - A Ripple Effect Analysis for the electrical hardware was performed and is as follows: The new frequency of the inductive telemetry communication circuit was changed to operate at about 57 kHz. Tests were done to the (b) (4) rev 10 (earlier name for device series of testing) mixed mode IC to move inductive telemetry transmission from (b) (4) Also the existing HV charging circuit operates across the frequency range of (b) (4) which results in inductive telemetry drop-outs due to high voltage charging due to noise from the high voltage transformer. Therefore, modifications to the transformer/high voltage module as described above were necessary. The modifications to the high voltage transformer will enable it to operate at a higher frequency, moving the transformer's operating frequency out of the telemetry band or nearly out of the band, as well as allowing the copper lid on the transformer to attenuate the noise more effectively. The Ripple Analysis intends to evaluate any potential effects that this could have on the pulse generator system and can recommend any testing that may be required to demonstrate that the transformer design is acceptable. According to the manufacturer, three areas are affected by the change to (b) (4). These areas are: the mixed-mode IC, the high voltage transformer and the software radio (SWR). An assessment/analysis (Design Analysis Testing (DAT) was done for each area and is described below:

  - Mixed Mode IC – The system features tests, programmer software design verification and firmware testing were completely rerun and serve to support performance of the IC. Tape testing was also partially rerun for A-tachy detection. The manufacturer considered qualification of the mixed mode IC was deemed unnecessary because the IC change was a metal-only change (Made to the (b) (4) chip design to allow the device to startup using an inductive telemetry frequency at (b) (4) instead of (b) (4) No new transistors were added to the IC. However, the new testing due to the change consisted of Real-time Drop-out DAT – For 5-Mn02 and 5-QHR batteries (Capacitor reforms were done while observing 4 channels of E-grams on a programmer and noting drop-outs in the real-time display. Repeat testing for all 4 PG-wand orientations and several PG placements and distances was done).

- High Voltage Transformer - By reducing the number of turns on the winding of the transformer, the primary inductance is reduced (This reduces the time that it takes for a shock to reach the peak primary current, which allows the transformer to operate at a higher frequency once it begins operating asynchronously). According to the manufacturer, this change has no impact on the FW or SW interface; therefore the change is managed solely by hardware. According to the manufacturer, the scope of the testing will be limited to hardware except for the system level testing associated with evaluating inductive telemetry performance during charging. The pulse generators used during testing had the transformer design and rev (b) (4) (equivalent to the final configuration) with the telemetry frequency bit modified to match a rev (b) (4). The DAT protocol consisted of the following:

    - Three hybrids with new transformer winding and 3 existing (b) (4) hybrids for comparison were used. The Vcc voltage during charging was monitored and the Vcc amplitude and Vcc ripple on the DUTs were compared to existing (b) (4) hybrids (This test intends to evaluate the performance of the TIKL supply with the new transformer design). (Vcc refers to the 12 volt supply regulated by the analog IC and boosted by the transformer during HV charging. TIKL- a winding on the HV transformer which provides energy to boost Vcc during HV charging).

      The testing on the hybrids with the new transformer also consisted of verifying magnet performance, tachy detection, operation and performance of the charging circuit during telemetry, minute ventilation, MHz oscillator, high voltage supply, RF telemetry, accelerometer channel and sensing.

  Based on the REA, recommended design verification tests on the new transformer involved the following:

    - Repeat (b) (4) EDVT007003 – HV Charge Time
    - Repeat (b) (4) EDVT001101 – Explant to EOL Period, specifically the portion that measures the overall charging efficiency used for longevity calculations.
    - Repeat (b) (4) EDVT005005 – Protection of the patient from AC leakage current during charging.
    - Other recommended tests included: Monitoring the production builds during the Pilot phase in which the Pilot units that will be used for formal testing are built. Evaluating any relevant production test failures to determine if there are any signals that the transformer change will lead to future yield losses, reliability issues, etc. and a full component level qualification of the new transformer including some life testing that simulates many charging cycles. The manufacturer also concluded that a rerun on the (b) (4) design as it pertains to

- QHR battery – The QHR battery was also the subject of REA to determine what electrical DAT and DVT tests are required. The analysis identified the following: (1) A set of new system constants are required for battery management; (2) measurement of the battery energy per charge and measurements of device power consumption – longevity; and (3) because the relative battery voltage measurement was only tested across the (b) (4) range for (b) (4) EDVT002003 will need to be performed to verify that SyRS013755 (System Requirement Specification) is met across the new (b) (4) V range.

  Regarding QHR battery voltage measurement, the manufacturer concluded that the existing MnO2 requirement applies to both battery chemistries. This is because the accuracy of the measurement circuit depends on the hybrid circuitry and not the battery chemistry. Also because the associated circuitry is identical to the COGNIS/TELIGEN, therefore it was concluded that no (b) (4) EDAT or EDVT testing is required. Regarding longevity, since (b) (4) includes a HV transformer change, charging power will need to be retested. In addition, according to the manufacturer, a series of tests will be performed to support longevity estimates.

  The battery as mentioned above in the (b) (4) devices contains dual battery chemistries (layers of (b) (4)) which, according to the manufacturer, was discussed with FDA and the international community. According to the manufacturer, the regulatory acceptability for the use of dual battery chemistries per model was based on existing precedents as quoted directly from the PMA application. Based on regulatory approval, the strategy for the new tachy product (b) (4) (IEP devices) include the following:

• Utilize two batteries under one model.
• Batteries will have different chemistries but common performance.
• Two vendors fabricate these batteries: BSC & (b) (4)
• Component traceability is provided by PG serial number for effective management of inventory in-case of an issue.
• Labeling outlines the battery models, vendor, and longevity performance characteristics.

Electrical Design Verification Tests

The EDVTs encompassed primarily the device changes and the impact on telemetry communication, battery management, sensing, pacing, shocking, EMI and other features. The EDVT as referenced in the file includes mechanical design, firmware design, system design, electromagnetic compatibility, and programmer software verification testing. The verification tests included were run on the (b) (4) design, specifically targeted at the changes as noted in the (b) (4) Electrical Ripple Effects Analysis (REA), QHR REA and the System REA as noted above. The tests included the following:

- Regarding coulometer (summation of all three sources of charge consumption – hardware coulometer, high voltage charging and beeper) calculations, tests were performed to confirm the accuracy of battery charge usage during high voltage charge and beeper operation. Hybrid assemblies were subjected to a test protocol which included high voltage and beeper activity. The tests intended to ensure that the calculation of charge usage due to beeper operation is within ±25% of the actual charge consumed from the battery due to beeper operation. The results of testing confirmed the accuracy of the battery charge consumption for beeper operation.

- Regarding external recovery, 15 units were tested. Recovery was evaluated with different lead configurations and polarities. Fifteen units were tested. The results reported that all units passed and met the acceptance criteria of an upper limit of 15 seconds.

- Regarding battery management, the test protocol involved an analysis based on measured device data, battery modeling, system constants and calculations. The manufacturer stated that direct testing on real batteries was impractical and therefore, data were collected on an "externally powered devices using a power supply" to measure power consumption (The output was a calculation). The data analysis encompassed taking four measurements, namely, background power, HV charging, RF telemetry and beeper power on each device (VR, DR and CRT-D). RF telemetry measurements were made using OUS devices since, according to the manufacturer, they use more power during RF telemetry than U.S. devices. Fifteen samples of each device were used. For HV charging, RF telemetry and beeper measurements 15 devices were configured CRT-D. According to the manufacturer, the results of testing demonstrated that the acceptance criteria were met and all tests were passed. In addition, according to the REA, it was recommended that, EDVT evaluate fifteen pulse generators with QHR (silver vanadium) and 15 pulse generators with Manganese Dioxide batteries placed in an oven at 37 degrees C for one hour. A high voltage cap dump and a cap reform would be commanded and the charge times (min, max and average charge times) would be determined and the data would be compiled for analysis. Accordingly, these data would be used to evaluate BOL and charge time of the subject devices.

According to the manufacturer some parameters and device modifications were verified under equivalence (Testing done as per (b) (4)

Some of the [redacted] (b) (4) design/features considered as unaffected by the change included the following:

- Runaway pacing protection/high rate pace monitoring
- Hardware coulometer capacity, write protection, and saturation behavior and. coulometer PG resets
- Coulometer high current alert
- Battery voltage management accuracy, aborting average battery measurement
- Sensing/pacing function
- RA, RV and LV thresholds
- Capability of sensing channels to produce 8 bit 200 Hz e-grams and 12-bit 400 Hz e-grams
- Capability of the RA sense channel and LV sense channel to receive the signal from the appropriate electrodes
- Internal shock recovery blanking and refractory periods, AV interval
- Protection of patient with DC leakage current during charging and with charged capacitors
- [redacted] (b) (4) defibrillation testing, device delivered shock and HF surgical exposure, ultrasound immunity, electrostatic discharge immunity evaluation, AC magnetic fields
- EMI (induced lead current testing, malfunction due to EMI, temporary responses to continuous wave sources, sensing EMI as cardiac signals (1 kHz – 150 kHz)
- Charge times, biphasic shocks, shock pulse width, external high voltage present fault detection
- Lead impedance measurement accuracy
- Measurement telemetry noise and interaction
- MV measurements
- Magnet sensor response time

Overall, the ICD/CRT-D [redacted] (b) (4) features, identical to those in the [redacted] (b) (4) series or earlier devices (which all may not be named above) were verified according to equivalence [redacted] (b) (4) EDVT). The complete series of tests were described and the results were included in the [redacted] (b) (4) EDVT Report, Revision B, and were provided for our review. According to the manufacturer, all results PASSED per the methods and acceptance criteria established in the [redacted] (b) (4) EDVT Protocol (100042-838). In addition, all testing from the [redacted] (b) (4) EDVT Report (553834-417) that is used for equivalency also PASSED. There were no protocol deviations affecting the test methods or acceptance criteria.

Standards, considered as acceptable were referenced as used in the Electrical EDVT testing.

<u>Mechanical Design Verification Tests</u>

<u>Ripple Effects Analysis</u> (Mechanical hardware)

The mechanical hardware changes as described above for the (b) (4) subject devices include:

- Liner change (bar near the accelerometer to hold the broken beams in the accelerometer pocket
- Capacitor bonding change - (b) (4)
- Addition of the QHR battery cell
- New analog IC – Activates existing part os the IC, the change supports the FCC inductive telemetry fix and feature additions.
- New charging circuit transformer - has fewer (b) (4) than the current COGNIS/TELIGEN 100-008 transformer, also supports the FCC inductive telemetry fix.
- X-Ray tag change – A new tag was created for the (b) (4) devices.

As stated above the REA determined the mechanical design verification tests required due to the changes. The manufacturer stated that there would be changes which would impact the assembly and manufacturing processes. Testing would be required because of the liner change, cap bonding, QHR cell, analog IC and the transformer changes, all which impact the device internal atmosphere. In addition, it was noted that environmental tests would also be required because of the changes.

Rev C of the REA addressed the e-clip change from the earlier Rev A and B. The difference in the revision change is the radius for the interior cutouts. The cutout radius changed from (b) (4). The REA analysis noted that no further evaluation testing was required (The other noted changes were either addressed under PMA supplement review and/or EDVT and MDVT).

<u>Mechanical Design Verification Tests</u>

The (b) (4) or subject devices are considered as mechanically equivalent except for the pulse generator (PG) size and weight and the header. As a result of the REA, the tests performed on the (b) (4) devices are described below. In some cases equivalency is declared to devices previously tested

- PG size and weight dimension test – The minimum sample size was three of each of 5 configurations (15). Measurements of height, weight and volume were made and considered acceptable based on the stated criteria. Device markings were also confirmed.

- Device Header – Verification of connector assembly (header) insulation and device internal atmosphere were confirmed using internal documents as referenced below. It was noted that wire route modifications in specific models required testing. Therefore, current leakage and insulation impedance tests with representative leads were performed to ensure that the lead seals, wire insulators and silicone backfill

provide electrical isolation to the lead contacts in a saline tank environment in accordance with BSC internal documents/requirements. Forty-five CRT-D (DF1/IS1/LV1 – Models N164, N165 and P165) connectors and 45 quadripolar connector assemblies were used in the testing). Wire routes were modified presenting worst insulative case relative to the changes among all of the headers. A description of the test protocol was provided for our review. The results reported that the acceptance criteria were met and all tests were PASSED.

Current Leakage (High voltage) dielectric tests of seal plugs and electrical impedance test of seal plugs were performed to ensure that the connector assembly seal meets leakage current requirements and that the seal plugs provide adequate electrical insulation in accordance with the noted BSC internal documents, respectively. A description of the test protocols and the acceptance criteria were provided for our review. The results of testing reported that the criteria were met and all tests were passed. Also tests were performed to verify IS-1 compatibility verification and to ensure legibility of the X-ray identifier.

The device with header configurations was sterilized with 3 sterilization cycles and was subjected to a series of environmental tests. The tests included mechanical shock, vibration, thermal shock, temperature cycling. The test protocol was described with reference to the internal electronic notebook (ELN) where the raw data were recorded. The test results reported that all tests were passed.

Equivalency to those devices previously tested was also used for the connector assembly and seal system of the (b) (4) devices to assess parameters, e.g., hermeticity, current leakage, DF-1 current carrying requirements, insertion/withdrawal and impedance set screw lead retention and contact resistance.

Several Standards and internal documents used during mechanical verification/validation testing were referenced. No concerns about the documents identified.

<u>Component Qualification/Safety Risk Assessment</u>

A series of tests were performed on component changes to the (b) (4) devices. A complete description of the test protocol, which included supplier validation and design verification and operating life test, was provided for our review. The test results reported that the components met the acceptance criteria with at least 90% confidence and 95% reliability and passed all tests with no safety risks identified. The components evaluated included the following:

- E-clip (used for fastening the header to the PG on the (b) (4) models)
- Connector ring/leaf spring
- X-ray identifier
- Anchor post with backfill plug E-ring
- Front liner
- Analog IC

- Zener diode/high voltage charge module
- Transformer
- QHR battery
- Capacitor lid (used in the assembly of the capacitor assembly).
- IC Ball Grid Array (BOG)

Overall the tests supported the reliability of the components.

Failure Mode, Effects and Criticality Analysis (FMECA)

The objective of the FMECA is to detect failure modes and ensure that the necessary controls are in place either to detect the event or prevent its occurrence. Twenty one COGNIS based models and 24 TELIGEN based models are covered under this (b) (4) report. The severity index 0- none – 1- limited, 2- moderate, 3 –severe and 4- life threatening), occurrence index (1-remote, 2- low, 3- moderate and 4-high), and criticality index (0-2- low risk, 3-9 medium risk and 12 or 16- high risk) along with the controls in place were assigned to each component named above and other critical components deemed identical in earlier COGNIS/TELEIGEN devices. The assignment took into account the different failure modes and potential causes and effects of failure. In most of the cases, the occurrence index was remote to low, severity index of 4 and criticality index of 6 -8. There were no concerns regarding the information provided.

System Features Testing

System features testing included: verification of device packaging for each device model; confirmation through programmer sessions that correct features are available in the appropriate models; confirm programmable nominals as indicated; verify battery status (ERI and EOL) based on HV charge time and during programmer session; user requests e.g., reset counters, disable capacitor reform; programmer journaling; and verification of appropriate operation of different pacing modes, features and various utility functions. The results noted that all tests were passed.

Simulated Use Testing

The use of the system was validated through simulated clinical use conditions with emphasis placed on the interface between the system and the user. The system met the acceptance criteria except for one failure pertaining to the RV threshold test with LV offset, the observations were not reproducible. No patient safety concerns were identified.

Arrhythmia Testing

Appropriate sensing of human heart signals was validated. Tape testing with rhythms, e.g., normal sinus, atrial fibrillation/flutter combined with various ventricular rates, normal sinus, ventricular tachycardia rates and ventricular fibrillation, sinus

tachycardia, ventricular tachycardia and ventricular fibrillation was performed. The devices' ability to detect: monomorphic rhythms above the VT rate threshold, polymorphic rhythms above the VT rate threshold and that start-of-charge is initiated within 10 seconds of the start of the polymorphic rhythm meeting the criteria for a VT/VF rhythm and that various combinations of A-Fib were sensed appropriately were assessed. Initial and average redetection times were recorded. The results reported that all tests were passed.

Gold Database (Human EGM data) Tape Testing

Validate that the tachyarrhythmia detection algorithm in I, E and P devices is clinically equivalent to COGNIS/TELIGEN in discriminating between VT, SVT when challenged with a formal test set of human EGM data. The testing determined the sensitivity, specificity and time to detection of the subject device with the Rhythm ID SVT inhibit feature enabled and the RhythmMatch threshold set to the nominal value (94 percent). The average sensitivity was reported as 100 percent (55/55 number of VT/VF episodes), specificity at 96.2 percent (25/26 – number of SVTs) and a detection time of 10 seconds. In the case where the correlation coefficients were below nominal RhythmMatch threshold of 94 percent, the test was re-run with RhythmMatch threshold of 90 percent and the therapy was appropriately inhibited. This was considered as an example of how SVT discrimination can be improved with the ability to program the RhythmMatch. Based on the test results, the design verification tests as described were passed.

Biocompatibility

Biocompatibility guidelines were based on ISO 10993. The device was subjected to full biocompatibility testing with the exception of short-term muscle implant test, thrombogenicity and chronic toxicity (The short-term implant and chronic toxicity tests were performed on the individual materials and the results from the material testing were used to justify not performing the testing on the subject devices). All device/materials were rendered biocompatible.

Sterilization

Sterilization validation was performed to verify that the COGNIS/TELIGEN devices can be incorporated into the present validated sterilization cycles. No external changes were made to the COGNIS/TELIGEN which would be of interest in affecting the sterilization process. The changes consists primarily those of the header which are surrounded by the (b) (4) header and covered in the same medical adhesive as the previous design. The results of tests verified the validation of the sterilization cycles according to the Boston Scientific internal requirements for (b) (4) sterilization processes.

Packaging/Design Verification

The tests consisted of shelf life testing (accelerated and real-time aging – 18 months and 2 years) and sterile barrier integrity (dye penetration tests). Since the subject devices have identical packaging as the marketed COGNIS/TELIGEN, therefore the devices were not to be tested, and were listed as equivalencies regarding each test performed. The results of testing showed that the packaging system was not adversely affected by exposure to sterilization cycles, climatic conditioning and distribution simulation. Tests were performed as per ASTM D4332-01(2006) – climatic conditioning, ASTM F1980-07- aging; and ASTM F1929-98 (2004)-dye penetration. The results of accelerated and real-time aging tests are not yet available, the tests have not been finished.

Software Development/Validation

The software development/validation data were reviewed in-depth by the Software consulting reviewer. A summary of the validation processes for purposes of the referenced file is included below.

- The tests as described below were performed using COGNIS/TELIGEN (160/100/50) pulse generator models, the Model 3120 Programmer Recorder Monitor and the COGNIS/TELIGEN Model 2868 programmer Application Software (The COGNIS Model N119 was used in the majority of the tests since it contains the full feature set). The tests involved Regression Analysis and Ripple Effects Analysis testing which included a series of validation tests intended to verify the functionality of the telemetry communication, telemetry security and system performance. The tests performed included evaluations of the following: automatic switching between RF and inductive telemetry; the inductive telemetry range for 57 kHz and no drop-outs in real-time display. In addition other tests consisted of evaluation of emergency functions, lead impedance, Indications Based Programming, battery management and firmware integration testing. Based on the test results, all (b) (4) devices which includes COGNIS/TELIGEN and the subject devices with pulse generator firmware version B_v1.02.00; the COGNIS/TELIGEN Model 2868 Programmer Application SE version v1.02; and the (b) (4) SMR5 (Software Maintenance Release 5) FW patch version A-v1.04.0 Patch 2.06 met the requirements and passed all tests. There were cases of uncorrected failures which were addressed by the consulting reviewer.

Animal Testing

The manufacturer provided adequate justification regarding why GLP studies were not required for the changes as described for the subject devices. A summary of animal tests performed using the COGNIS/TEIGEN is as follows:

- One pig was used to validate the performance of the Wireless ECG signal (b) (4) wanded telemetry operating in living tissue) The tests intended to evaluate if the

devices were able to measure and transmit intracardiac electrogram signals and display information of sufficient quality to make a clinical diagnosis as compared to a surface ECG. The tests involved evaluations of wireless signal quality from combinations of sensing and pacing and during threshold testing. The displayed and printed EGMs were evaluated by a panel of clinical experts and were found to be acceptable. Tests were also performed to demonstrate that the system provided acceptable PRM/PG telemetry in the following cases: (1) while the PG was in the sterile packaging and shipping container; (2) while the PG was implanted in living issue and surrounded by a coil of leads; and (3) while the PG was in the intended clinic environment (Several features were activated and the telemetry was observed). The results of testing reported that all tests were passed and the system performed as intended.

- Post Shock Tag-On Study - Three pigs and one canine were used in the study to evaluate oversensing and undersensing post shock with atrial pacing. Several mitigations were proposed. The intent of the study was to evaluate the proposed mitigations in reducing the post shock artifact amplitudes which have been contributing factors in oversensing and undersensing. The results of testing verified that the proposed mitigation settings do not appreciably change the amplitude and waveform post-pace in both the RA and RV e-grams.

Clinical Studies

A summary of the clinical studies by this reviewer is included below.

Regarding the Rhythm ID, the nominal value of 94% was shown to be safe and effective in the [redacted] (b) (4) study. During the pre-IDE discussions, we asked whether physician feedback was obtained about reprogramming the FCC threshold. BSC reported that overall the general consensus was that there were no real concerns. As a result of the feedback, BSC decided to do the following:

- Show the beat to beat FCC correlation values with the EGMs and markers and the decision point as part of the episode summary.

- Add to the PRM screen and the labeling to caution physicians with trade-offs (increasing specificity of SVT and decreasing sensitivity of VTs).

- Show the measured FCC value for all tachy episodes as long as a RhythmID template has been acquired.

- Program the devices to a 3 zone monitor only configuration and program the lowest tachy zone to the lowest setting (90 bpm).

- Regarding the Reverse Mode Switch (RMS) study, the purpose of the primary effectiveness objective was to ensure effective clinical performance of the RMS in the TELIGEN 100 HE DR device.

- In the COGENT substudy with RMS randomized to OFF and ON, the data demonstrated a significant reduction in RV pacing when RMS was used.

- The conclusions from the COGENT study reported that the adverse events were evaluated between implant and one month follow-up (Additional evaluation was at the physician's discretion). A total of 120 patients were implanted with the TELIGEN 100 HE DR device and 97 patients were enrolled in the RMS study. Of the 114 with RMS programmed ON, there were 3 adverse events. The RMS-related adverse event free rate was 97.4 percent with a lower confidence limit of 93.3 percent.

- BSC proposes to add the clinical and statistical results from the COGENT study in the device labeling.

- Regarding the COGENT-4 Field Following study, the study was performed at 27 OUS sites. The purpose of the study was to evaluate and document appropriate clinical performance of the TELIGEN 100 HE DR ICD system and the COGNIS CRT-D systems. An optional substudy in the TELIGEN DR patient evaluated the safety and effectiveness of the RMS feature found in this mode. Additional data e.g., as Quick Convert ATP feature performance, number and appropriate function of RMS mode switches, percentage of BiV pacing in COGNIS 100 HE patients and adverse events (The 4-Site defibrillation lead included BSC dual coil, passive fixation, single coil, active fixation lead). In addition the TELIGEN/COGNIS devices incorporated the capability of interrogating the device via RF telemetry).

- The data from the COGENT-4 study demonstrated that the COGNIS/TELIGEN 100 HE devices performed safely and effectively and that the RMS feature functions safely and reduces RV pacing in patients with the feature turned ON (5.2%) versus OFF (18.7%; absolute difference of 13.5%; p=0.01.

Manufacturing and Quality System

The manufacturing information and quality controls were reviewed by the OC consulting reviewer.

Field Reliability Assessment

According to the manufacturer, (b) (4) is a continuation of the (b) (4) product platform and thereby inherits corrective actions for (b) (4) products." The manufacturer included a Table of the Field Reliability Assessment. The Table listed the Trend/failure mode, Trend root cause, corrective action, (b) (4) design team assessment, and (b) (4) design team mitigation, estimate of (b) (4) effectiveness, the (b) (4) Trend failure rate and the severity and occurrence index. The manufacturer noted the following Trends which were considered to present potential issues in that the "Estimate of Effectiveness"

of the corrective action (CA) implemented for [redacted] (b) (4) was less than 100%. The Trends, [redacted] (b) (4) estimate effectiveness and the CAs include the following:

- TR94020 Sensing issues – 50% [redacted] (b) (4) estimate effectiveness) , CA - noise sensing algorithm, MDVT of header components
- TR94030 Defibrillator output bridge transistor damage - 0%, CA - no mitigation planned for [redacted] (b) (4) TELIGEN/COGNIS has a method by which it mitigates against an excessive current draw condition when shock into a shorted lead occurs.
- TR94035- Set-screws, IS-1, IS-4 - 50% - CA – [redacted] (b) (4) set-screw implemented
- TR997001 - Rapid battery depletion – 50% - CA new battery technologies, EDVT and longevity prediction analysis
- TR97037- Oversensing - 50%, CA- noise sense algorithm, MVDT
- TR98016 Device does not meet expected longevity- 50 %, CA battery technologies, EDVT
- TR99006 Undersensing – 0%, CA none planned (COGNIS/TELIGEN functioned appropriately
- TR09838 Set-screw issues - 50%, CA- [redacted] (b) (4) set-screw, MDAT, MDVT
- TR99009 Leaky tantalum capacitors- 50%- CA- validation processes
- TR99011 Battery weld failures - 50%, CA-quality awareness training
- TR99016 Battery depletion undetermined – 0%, CA - EDVT, prediction analysis
- TR99030 Lead insertion difficulty – IS-1- 25%, IS-4- 25%, CA- insertion force testing
- TR00007 Device failures following radiation – 50%, CA – new design of SRAM, DVT tests
- TR00041 Devices found in OFF mode- 50% - CA – changed feature in Programmer software
- TR00063 Telemetry idle/no telemetry – 50%, CA- symptoms addressed in safety core – [redacted] (b) (4) inherits
- TR02019 Feedthrough wire to backfill tube short – 50%, CA- No backfill tube on COGNIS/TELIGEN design, EDVT, MDVT
- TR02028 Fault code 07 – 50%, CA- Adds check on system clock,

Other TRs with [redacted] (b) (4) estimate effectiveness of 50% or less include additional failure modes involving sensing, set-screws and battery, The manufacturer noted that recent [redacted] (b) (4) trends, e.g., TR08018 - "Difficulty Securing Leads in [redacted] (b) (4) Setscrew and White Seal Plug Header Design" and TR0901 - "Loose Headers" were among those Trends which presented potential issues. The trends are being addressed by design/corrective actions, as noted above, incorporated in the [redacted] (b) (4) models.

[redacted] (b) (4) <u>Reliability Prediction</u>

The manufacturer provided documentation regarding reliability predictions performed for the [redacted] (b) (4) models. The [redacted] (b) (4) as described above is an enhancement of the COGNIG/TELIGEN platform with hardware changes to the transformer, alternate QHR battery to existing MNO2 battery and ASIC to support inductive telemetry frequency change [redacted] (b) (4) The performance reliability prediction was determined

by gathering and analyzing identical or similar component field reliability data from precedent products. Highlights of the prediction report include the following:

- Life expectancy of 5 years for the defibrillator and CRT-D shall be greater than 99.5 %.
- The reliability prediction for the COGNIS/TELIGEN with the IS4/IS1 (N160) header is 99.67% at 5 years and the IS-4 (E160) header is 99.71% at 5 years (Based on implanted devices only). These predictions also apply to the (b) (4) models (INCEPTA, ENERGEN and PUNCTUA).

Device Labeling

A copy of the device labeling was provided for our review. The labeling was provided for the PUNCTUA CRT-D High Energy (HE) Defibrillator – (41 J stored and 35 J delivered), the ENERGEN CRT-D (HE) Defibrillator, the INCEPTA CRT-D High Energy (HE) Defibrillator and the TELIGEN 100 High Energy (HE) Defibrillator. The labeling appears to be in order. There are no significant concerns about the labeling.

Discussion

According to the manufacturer, from an electrical design perspective, the differences between (b) (4) are in the Analog Integrated Circuit (IC), the transformer component used for HV charge and the battery used to power the device. These are indeed changes which could significantly impact device performance. Ripple Analyses and a series of EDVT, MDVT and component reliability testing were provided for our review. However, based on the review of the test data, this reviewer was not clear regarding the actual tests performed to qualify the new components for their intended use. It appeared as if the qualification/validation tests were done, however, the data were not presented in a manner so that the test protocol and results obtained could be easily discerned. In several cases, component testing was based on equivalence in that the (b) (4) was deemed identical to the (b) (4) and therefore no additional tests were warranted. We requested additional information to support equivalency.

The Ripple Effects Analyses recommended certain tests, however we could not find evidence that the tests were done and/or there was no clear justification, as mentioned above, for equivalence. Also in several cases, test data and results were referenced as being contained within internal documents. The questions regarding qualification of the device changes revealed that this reviewer was unsure and not entirely clear about the tests performed and the “equivalences’’ made. Therefore we could not attest to the data as presented as being acceptable to support qualification and validation of the device modifications. There were many clarifications which could not be addressed interactively; therefore the questions were included in a letter. There were also concerns about the Trends (failure modes) identified in the (b) (4) which are now being inherited by (b) (4)

The first set of questions involved clarifications and documentation regarding the bench tests performed. Specifically, we requested additional data to support the qualification of the device changes as noted above from TELIGEN/COGNIS to (b) (4) In Amendment 001, the manufacturer responded satisfactorily to most of the deficiencies and, in addition, requested software, firmware and manufacturing changes to the INCEPTA/ENERGEN/PUNCTUA models. The changes noted that the QHR battery as specified above will not be used in the (b) (4) devices. Other changes included the following:

- Firmware - updated shock lead impedance measurement for the commanded shock algorithm; therefore the firmware is updated from Version B_v1.02.00 to Version B_v1.02.00, patch_v1.01.

- Software – update display of correct parameter values (e.g., VF rate, VT rate and RMS/RHYTHMIQ) and EGM; therefore the patch is downloaded to the devices

- Manufacturing – modify the fixture used for E-clip engagement during the bonding header to case manufacturing step.

The review of these data was done by the software consulting reviewer and the OC/GMP manufacturing reviewer. There were software concerns noted to be included in errata sheets. No additional concerns were identified.

The review process continued with additional component/qualification testing deficiencies and others which required additional clarifications and documentation, namely, component testing, transformer qualification, battery longevity, on-going testing to support device reliability, second source suppliers and trends inherited by (b) (4) In Amendment 002, the manufacturer provided the requested data and addressed the remaining issues interactively. The responses were considered acceptable to support device performance to specifications.

In Amendment 003, the manufacturer provided data to support expiration dating of 18 months for the devices. There were no concerns regarding the data submitted.

Recommendation

The manufacturer has responded satisfactorily to the deficiencies listed in our deficiency letters and has provided acceptable test results to support 18 month expiration dating. Therefore approval of the referenced files is recommended.