

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



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

**Date:** 28 Dec 2011

**From:** [REDACTED] Biomedical Engineer, FDA/CDRH/ODE/DCD/PDLB

**Subject:** P910073/S091  
Amendments: A001, A002, A003, A004, and A005  
Boston Scientific Corporation  
Endotak Reliance IS-1 defibrillation lead (passive fixation models)

**Recommendation:** **Approval**

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

**Executive Summary**

This PMA supplement was submitted to gain approval for a change to a chemical used to make the steroid-eluting component of the passive fixation models of the ENDOTAK RELIANCE defibrillation lead. The change is to the drug itself, the supplier, and the location on the lead. The current leads have a steroid plug that elutes dexamethasone sodium phosphate (DXP); the sodium phosphate ester (of dexamethasone) is supplied by (b) (4). The firm would like to replace the plug with a steroid eluting collar with dexamethasone sodium acetate (DXA) with the acetate ester of dexamethasone supplied by (b) (4). To accommodate the change from a plug to a collar, some dimensions of the distal tip have also changed.

BSC explains that the reason for the change is the discontinuation of (b) (4) amorphous DXP. As a note, the firm currently uses DXA collars on their active fixation RELIANCE defibrillation leads, but with the drug from a different supplier (b) (4) and with a wider dosage tolerance (1.0 mg +/- 30%) compared to that requested in this submission for the passive models.

A large team of reviewers from CDER, OC, and ODE provided comments during the initial review of this file. A major deficiency letter was sent 4 April 2011 and included concerns and deficiencies regarding the drug testing, documentation, and specifications as well as mechanical testing for the modifications to the tip, animal study results, and manufacturing validation procedures and documentation. Additionally, clarification was asked regarding a new risk identified by the firm (Embolism from a Separated Drug Collar<sup>TM</sup>). Minor concerns were identified for labeling and biocompatibility.

In A003, the firm provided responses to the communicated deficiencies that largely addressed the outstanding concerns: updates were made to the firm's drug specification table and additional testing was conducted on the drug and to address mechanical concerns. The initially concerning adverse event noted in the animal study was justified as was the new clinical risk. Also, the manufacturing documentation requested in FDA's letter was provided and found acceptable.

Two major concerns remained following review of A003, however, resulting in a Not Approvable decision. CDER Biopharmaceutics indicated that the firm's final elution time point and specification were unacceptable. CDER CMC indicated the firm's lack of limit for (b) (4) content in the drug was unacceptable. A minor concern was also communicated regarding the lack of detail on the firm's plan to assess elution in the different lead models that will incorporate the new component.

In A005, the firm provides responses to the Not Approvable letter concerns. A specification regarding the (b) (4) presence has been added and the elution time points and specifications have been updated to incorporate FDA comments. As indicated in detail in this review, at this time all concerns have been addressed; therefore, I recommend approval of the subject PMA Supplement.

#### **Review Team**



#### **Review Clock Background**

This supplement was originally received 12 December 2010. During the review of that PMA/S, the firm provided additional stability data under A001 (received 15 Feb 2011) and detailed animal study results under A002 (received 23 Feb 2011). Major deficiencies were communicated in a letter dated 4 April 2011. The firm's responses to that letter appear in A003 (received 28 June 2011). A004 was submitted to provide additional stability data (received 29 July 2011). A Not Approvable letter was issued 01 Sept 2011 and responses to those outstanding concerns appear in the last amendment, A005.

#### **Indications and Contraindications For Use**

The firm indicates the below Indications for Use is identical to that of the predecessor leads.

"The ENDOTAK RELIANCE leads provide pacing and rate-sensing and deliver cardioversion and defibrillation shocks for AICD automatic implantable cardioverter defibrillator systems."

The contraindications have been updated to reflect the new drug component and dosage:



*LEAD REVIEWER COMMENTS: The changes described in this submission would not affect the indications for use; the changes would affect the contraindications as noted and addressed by the firm. I have no concerns about this section of the review.*

#### **Device Description**

As stated in the submission in section 1.4 of the initial submission:

"The ENDOTAK RELIANCE® /S/G/SG passive fix is a 9 Fr diameter, transvenous, endocardial lead intended for chronic implantation as an integral part of an Implantable Cardioverter/Defibrillator (ICD) or Cardiac Resynchronization Therapy with Defibrillation (CRT-D) lead system."

The leads have three connectors- two DF-1 connectors for each of the RV and SVC coils and one for the pace/sense coil. Leads are available in 59, 64, 70 and 90 cm lengths. (b) (4)  
(b) (4) is used as the external insulation material. The materials (b) (4)

and (b) (4) are used for the pace/sense and shocking conductors, respectively. Each coil is coated with (b) (4) to prevent tissue ingrowth and provide insulation properties.



Specific to the drug component:



The nominal dose of DXA is 0.87 +/- 0.08 mg.

**Detailed Description of Change**

The firm lists the design changes in Table 2-2 on pages 2-7 and 2-8 in the initial submission. A visual is also provided in that initial submission (Figure 2-3). The changes are summarized in brief below for convenience.



CDER CMC and biopharmaceutics reviewed the steroid change; OC reviewed the manufacturing supplier changes; and ODE reviewed the animal study and preclinical testing in support the safety and effectiveness of the new drug component and the changes made to the distal end of the lead.

As a note: Both (b) (4) are glucocorticosteroids which suppress the inflammatory response believed to cause threshold rises typically associated with implanted pacing electrodes. The body responds to both in an identical fashion: "Upon exposure to plasma, (b) (4) are hydrolyzed to form dexamethasone (DX), the therapeutically active agent."

**Preclinical/Bench Evidence**

A Ripple Effects Analysis (summary in Table 5-2 in the initial submission) was performed to understand what tests needed to be conducted to evaluate the mechanical and electrical effects of the proposed changes to the lead tip. Based on the results of that analysis, the following testing was conducted:

- Tine Strength
- Axial Load Durability
- Introducer Compatibility

*LEAD REVIEWER COMMENTS: I reviewed the engineering aspects for this submission as documented in the Engineering Review memos. I identified several initial concerns that were all addressed within A003 as follows:*

- *Distal tip flex fatigue testing was not conducted to support approval of this submission; the rationale based on loading at the modified area was provided in A003 and found acceptable.*
- *The testing conducted on the specimens was not described in enough detail to understand what loads were being applied where and, therefore, to determine whether or not the testing was sufficient to address the modification proposed. The descriptions provided in A003 and interactively via email were found acceptable.*
- *Preconditioning of test specimens was not thoroughly discussed and did not appear to have been conducted for several of the tests. In A003, the firm provided a rationale that was found acceptable.*
- *The firm did not clearly identify in the initial submission whether test specimens were of final manufactured form. In A003, this confirmation was provided and found acceptable.*
- *Initially, it appeared that the tine angle change might be related to field events and that the proposed change might allow damaged specimen to pass inspection. The firm clarified in A003 that the (b) (4) is not a post market concern and that the change proposed in this PMA/S is identical to that already approved for other marketed leads. This rationale was found acceptable.*

*Since all concerns were addressed in A003, no engineering deficiencies were included in the Not Approvable letter and, therefore, no further information on this section is provided in A005. All engineering issues have been addressed at this time and no concerns remain.*

### **Animal Testing**

The firm provided results from a 90-Day, GLP animal study conducted on 33 canines to characterize the peak steroid effect on electrical performance of leads with the proposed changes. The study, which was conducted in 2005 and 2006, compared pacing thresholds on passive fixation leads with a (b) (4) collar to both the current design (b) (4) plug) and no steroid (dummy collars). Note that the DXA collar tested was that currently used in the active fixation models of the RELIANCE defibrillation leads; the differences between the active fixation collar and that proposed is the manufacturer ( (b) (4) ) and the dosage (1.0 mg +/- 30% vs 0.87 mg +/- 10%).

*LEAD REVIEWER COMMENTS: The animal study provided was reviewed in detail by Judith Davis, DVM, during the initial review. She indicated that the provided data supports the firm's objectives for the study (i.e. (1) the steroid reduces pacing thresholds and (2) the steroid acts similarly to the predecessor steroid, (b) (4), but still noted one concern with a failure mode observed ( (b) (4) ) that was conveyed in a Major Deficiency Letter. The firm's response was reviewed by (b) (6) in A003 and found acceptable. No concerns were communicated in the Not Approvable letter and no additional information was provided in A005 regarding this testing. All animal study issues have been addressed at this time and no concerns remain.*

### **Drug Component**

The firm has requested specific changes to the drug component of the subject leads:

(b) (4)

- Dosage from 0.7 +/- 0.25 mg per lead to 0.87 +/- 0.08 mg per lead
- Location from within lead to outside on lead tip
- Presentation of drug from a plug to a collar

The firm submitted characterization testing of and specifications for their drug substance and finished product, analyses for various batches, manufacturing information and a drug elution test method in support of their requested changes. Each are thoroughly described in the respective CDER review memos.

*LEAD REVIEWER COMMENTS: Two separate reviews from CDER were conducted to understand if the firm's proposed changes and supporting evidence are acceptable from both a Chemistry, Manufacturing and Controls (CMC) perspective and a Biopharmaceutics perspective. The CMC reviews of the initial submission and the subsequent amendments were conducted by Dr. [REDACTED]; the Biopharmaceutics reviews were conducted by Dr. [REDACTED]*

*CMC-[REDACTED] identified several concerns with the firm's drug specifications in the initial review- several standard specifications were absent and several acceptance criteria were inappropriate. Several of the reports cited in the firm's submission were not provided initially, but were included in the amendments that followed. In addition, several shelf life and stability data issues were identified in the initial PMA/S- the requested shelf life was not supported by data, but sufficient data was provided in A004. The 24 month requested shelf life was deemed acceptable in [REDACTED] review of A003 and A004.*

*One concern remained after [REDACTED] review of A003 and A004: the firm had not specified an appropriate limit for the [REDACTED] (b) (4) content of the drug. This concern was communicated as a major deficiency in the Not Approvable letter. In the firm's response in A005, they provide a proposed limit for the [REDACTED] (b) (4). This specification was found acceptable by [REDACTED] as indicated her consult email for A005.*

*Biopharmaceutics-[REDACTED] identified several concerns with the firm's elution testing and specifications. In the Major Deficiency letter, concerns regarding the specific time points and specifications for each were communicated. In response, the firm proposed additional and modified elution criteria in A003. These criteria was still deemed inappropriate in that the final elution time point was too low and did not reference a lower bound (only a range). This concern was communicated in the Not Approvable letter. The firm's response (in A005) revised the final elution specification and time point further. Some initial confusion regarding what the firm was proposing was resolved via email interactively and, as indicated in her review memo, [REDACTED] found the firm's elution specification in A005 acceptable.*

*The Major Deficiency letter also requested complete elution profiles (or rationale for not providing them) for all of the models of the subject lead family, which includes several brand names as well. The firm indicated in their response in A003 that they believe the differences between the models of the lead family would not impact elution; after interactive discussions, FDA agreed that the firm could collect comparison data for each of the four branch names (vs each model number) of the subject lead family after PMA approval. As a minor deficiency in the Not Approvable letter, FDA requested a detailed plan on how the firm plans to collect that data. The firm's response in A005 was reviewed by [REDACTED] and found acceptable with respect to data collected and time points of interest.*

### **Packaging, Shelf Life, and Sterilization**

The firm indicates that no changes are proposed to the packaging, sterilization methods, or shelf life of the market approved RELIANCE leads.

*LEAD REVIEWER COMMENTS: No changes have been proposed for this section of the review. In addition, the proposed modifications to the drug would not affect the ability of the previous review of packaging, sterilization or shelf life of the lead (from a non steroid perspective) to apply for this submission. Therefore, as the engineering reviewer, I have no concerns with this section of the review. As a note, the shelf life of the drug is reviewed separately above and concerns were initially presented by CDER and resolved under A003 and A004.*

### **Biocompatibility**

The firm conducted a biocompatibility assessment in accordance with ISO 10993-1:2009 to determine what testing needed to be repeated on the subject device due to the proposed changes. They noted that no new materials (other than the changes to the drug component) are incorporated into the subject device. However, one of the tined neck suppliers uses a slightly different manufacturing process than that of the predecessor device: (FMI 355281-001 is the predecessor, 002 is the new model.) The firm provides a detailed table indicating the type and date of each biocompatibility test performed on the materials incorporated in the predecessor leads (and, therefore the subject lead).

*LEAD REVIEWER COMMENTS: Initial concerns regarding the new manufacturing process were communicated in the Major Deficiency letter. The firm's response in A003 was acceptable as it indicated that the processing of the new firm contains fewer chemicals so is, therefore, less of a biocompatibility risk. No concerns remain with the biocompatibility of the subject devices.*

*Note that the biocompatibility issue was resolved under A003; therefore, no deficiencies on this topic were communicated in the Not Approvable Letter and no additional information was received in A005.*

### **Clinical Data**

No clinical data was provided to support approval of this submission based on the following key similarities between the devices studied previously and those subject in this submission:

- Handling
- Acute pacing threshold performance
- Location of steroid

In addition, the firm notes that the proposed steroid collar is identical in material (b) (4) and construction (collar) to the market approved active fixation models of the same lead.

*LEAD REVIEWER COMMENTS: The need for clinical data to support the proposed changes was discussed at a PDLB Rounds meeting on 16 March 2011. Members of the review team including (b) (4), DVM and (b) (4) were also present to answer questions. The team discussed the two part argument provided by the company: (1) the plug and collar in general provide similar results and both decrease pacing threshold and (2) the collar studied in the animal study is similar enough to the collar proposed in the submission that the animal study data (studying the old collar) should be sufficient. CDER indicated the animal study data was probably sufficient from their perspective as long as the questions regarding testing and particle size were addressed adequately. In particular, the new supplier of (b) (4) appeared to have larger particle sizes that may impact in vivo elution (and therefore effectiveness) (b) (4). (b) (4) also noted that the tolerance of the proposed collar is within the specifications of the older, studied collar. The PDLB Rounds team agreed that the firm's two part argument seemed acceptable if the firm could address all of CDER's concerns (especially with regard to elution rate given the changes in (b) (4)). In their responses to FDA deficiencies and concerns in A003 and A005, the firm has indeed adequately addressed all of the Agency's concerns and therefore, no additional testing (animal or clinical) is required to support approval.*

### Labeling

The firm indicates labeling was updated to reflect the new drug and dosage as well as comply with current labeling standards. No redlined copy was provided initially, but was requested as a minor concern in the Major Deficiency letter. Tables describing the labeling changes were provided in A003.

*LEAD REVIEWER COMMENTS: I reviewed the labeling changes noted in the tables provided in A003 and have no concerns. Note that the labeling issue was resolved under A003; therefore, no deficiencies on this topic were communicated in the Not Approvable Letter and no additional information was received in A005.*

### Risk Management

In the original submission, the firm provides updated versions of their Safety Risk Management Report in exhibit 5-20 and their Hazard Analysis in exhibit 5-19. One new risk was identified due to the proposed changes: Embolism from Separated Drug Collar. A specific document was provided analyzing this single risk (exhibit 5-20 in the initial submission).

*LEAD REVIEWER COMMENTS: The new risk identified was discussed with clinician [REDACTED] on 14 March 2011. He indicated the firm should provide additional information regarding the size of the potential thrombi (example- is it the whole steroid collar), the clinical context for the size (i.e. do other objects of that size cause issues), and the circumstances under which it may come off. The firm responded to this deficiency (provided in the Major Deficiency letter in A003) with the requested information, indicating that the drug collar is rather small and pliable with little potential for embolism in the lungs. I spoke with [REDACTED] at that time (while A003 was under review) regarding the acceptability of the firm's response. He indicated that the firm's rationale seemed appropriate and had no concerns with approval. (In addition, the drug collar has already been approved for other leads.) No concerns remain.*

*Note that the risk management issue was resolved under A003 and A004; therefore, no deficiencies on this topic were communicated in the Not Approvable Letter and no additional information was received in A005.*

### Manufacturing

To implement the changes proposed, the firm indicated the following areas of the Quality System were impacted:

- Design Changes
- Purchasing Controls
- Process Validation
- Final Acceptance Activities

*LEAD REVIEWER COMMENTS: The manufacturing changes were reviewed by [REDACTED] of OC. He indicated initial concerns with Purchasing Controls, Process Validation and Final Acceptance Activities. The firm had not completely described their supplier evaluation process or demonstrated appropriate controls over each individual supplier. Additionally, the firm provided a protocol only (vs protocol and results) for the Process Validation activities and provided only two of the four documents for review under the Final Acceptance Activities section. [REDACTED] on Detail at the time the firm's responses (in A003) were received by FDA, so [REDACTED] reviewed the amendment. As indicated in his review memo (documented under A003), the firm adequately addressed the initial concerns and no concerns remain.*

*In addition, [REDACTED] provided feedback regarding the status of the proposed drug substance testing facilities from CDER's Office of Compliance- at the time the Not Approvable letter was issued, one site [REDACTED] had not been inspected for drug testing. Since*

inspection is required prior to PMA approval, the firm opted to withdraw its application for the (b) (4) (as documented under the review of A003 and A004). No concerns remain with this issue.

*Note that all of the manufacturing issues were resolved under A003 and A004; therefore, no deficiencies on these topics were communicated in the Not Approvable Letter and no additional information was received in A005.*

### **Pediatric Support Statement**

In accordance with 515A(a)(2) of the Act, the firm included a statement regarding the pediatric subpopulation that suffers from the disease their device can treat and an estimate of the number of affected patients (approximately 1% of ICDs are implanted in pediatric patients according to one cited article from 2005).

*LEAD REVIEWER COMMENTS: The firm has sufficiently addressed the requirements for Pediatric Subpopulation. The information provided appears accurate and restates current HRS/ACC/AHA guidelines for pediatric ICD use. The firm also clearly states the limitations of current literature research on the pediatric population use. I have no concerns with this section.*