
**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: 9 November 2010

From: (b) (6) Mechanical Engineer, FDA/CDRH/ODE/DCD/PDLB

Subject: P910073/S077 & P830060/S062
Guidant / Boston Scientific Corporation
Endotak Reliance 4-Site Lead Family and Accessories

Contact: Marilee Schaeffer

To: The Record

Recommendation: Approval

Executive Summary

The submission is to add a four-pole connector to approved Reliance defibrillation lead models. Initial review identified 17 deficiencies and a major deficiency letter was sent on 30 July 2009. The major deficiency regarded lack of in-vivo experience. Through discussions within 2 preIDE submissions, the firm and FDA agreed that data from an OUS 4-Site post-approval study, the Foreign Field (FF) study, could be used to address the major deficiency. The firm submitted an incomplete amendment (A001) to allow interactive review of deficiencies 2 through 17 while FF data was being collected. The firm then submitted a small additional change for a new sterilization biological indicator (A002). The firm then submitted a major amendment (A003) to provide the final FF data to address the major deficiency, and to update the A001 responses based on interactive FDA feedback. A final post-approval study protocol and case report forms was submitted on 26 Oct 2010 after interactive review with OSB/Epi. At this time the firm has adequately addressed all deficiencies in the 30 July 2009 letter and an "Approval" decision is recommended for P910073/S077 and P830060/S062.

Submission Chronology

With these submissions, Guidant/BSC introduces a single terminal four-pole connection called 4-Site into existing Guidant/BSC ICD lead/device systems. The 4-Site connector design meets the draft version of the now approved ISO-27186 Active implantable medical devices - Four-pole connector system for implantable cardiac rhythm management devices – Dimensional and test requirements. P910073/S077 requests approval for a modified Reliance defibrillation lead with a 4-Site connector. The submission also requests approval for 4-Site compatible accessories. P830060/S062 requests approval to add the 4-Site Pulling Tip Model 7006 into the Lead Tuner Model 6888 accessory kit approved under that PMA. The initial review found inadequate testing to support approval. A minimum 6 month animal study was considered necessary to collect confirmatory early-chronic performance data for the new terminal. Other deficiencies were identified for engineering, labeling, shelf life and biocompatibility. The firm was issued a major deficiency letter on 30 July 09 with 17 deficiencies. The firm worked interactively with FDA to develop acceptable responses to the deficiencies. Two pre-IDEs were submitted to address the clinical deficiencies (1, 2, 3) while A001

was submitted to address the other deficiencies. A002 was for a minor sterilization change being implemented across the BCS product line. A final amendment A003 was submitted to document all interactive review of all deficiencies to close out the file. Updates to the post-approval study protocol and case report forms were made interactively and submitted on 26 Oct 2010 which addressed Deficiency 3 in the letter dated 30 Jul 2009. Details regarding the review of each submission associated with this review are provided below:

I090770

To address Deficiency 1 in the major deficiency letter (regarding lack of animal study) the firm elected to submit a pre-IDE (I090770) for an alternate proposal to submit human clinical data from an OUS post-approval study for CE mark RELIANCE 4-Site leads. The review team included (b) (6) (clinical), (b) (6) (Animal Studies), (b) (6) (Engineering) and Mitchell Shein (PDLB Chief). FDA reviewed I090770 and agreed that the Field Following (FF) OUS post-approval clinical study was a suitable data source to address the P910073/S077 major deficiency. However FDA indicated that BSC should obtain and submit at least (b) (6) examples of high voltage events at approximately 6 months from implant (either induced or spontaneous would be acceptable).

I100177

The firm submitted this preIDE to present data collected from the Field Following (FF) OUS study. The review team included (b) (6) (clinical), (b) (6) (Animal Studies), (b) (6) (Engineering) and Mitchell Shein (PDLB Chief). Specifically, the preIDE documented extensive collection of clinical data as well as (b) (4). However, the (b) (4) (b) (4) experience was at a maximum of (b) (4) weeks with none nearing the requested 6 month timepoint. During the review of this preIDE, the firm provided additional FF study data on 28 Apr 2010 which contained additional reports of shock events at or after 6 months of implant. The new data was reviewed and FDA provided comments back to the firm stating that the data set was adequate to satisfy the request of Deficiency 1 in the major deficiency letter dated 30 July 09. FDA further agreed in preIDE comments that the handling study presented satisfied the request of Deficiency 2 in the major deficiency letter dated 30 July 2009. FDA did not review content regarding biocompatibility responses or post-approval study responses in under this preIDE.

P910073/S077/A001 & P830060/S062/A001

BSC submitted an unsolicited minor amendment (thus not restarting the review clock) containing responses to Deficiencies 2 to 16. The review team reviewed these responses while the firm developed their approach to address Deficiency 1 through the preIDEs above.

P910073/S077/A002 & P830060/S062/A002

BSC submitted an unsolicited minor amendment containing a new change to gain approval of a new sterilization biological indicator (BI) to be used across all BSC sterilization processes. This same change has already been FDA approved by 30-Day Notice for other BSC PMAs.

P910073/S077/A003 & P830060/S062/A003

BSC submitted the responses to the major deficiency letter including Deficiency 1 in A003. These responses leverage the interactions in the preIDEs and document the FDA agreements regarding the acceptability of the data to address the major deficiency. A003 also contained a summary the interactive review for Deficiencies 2 through 17 including documentation of FDAs feedback regarding the acceptability of the responses. The review of the post approval study (Deficiency 3) is the only concern that has not been fully addressed in A003 as development of the final protocol and case report forms is ongoing.

Review Team

Engineering: (b) (6) , FDA/CDRH/ODE/DCD/PDLB
Animal Studies: (b) (6) , FDA/CDRH/ODE/DCD/PDLB
Clinical: (b) (6) , FDA/CDRH/ODE/DCD/PDLB
Biocompatibility: (b) (6) , FDA/CDRH/ODE/DCD/CSPB
Epidemiology: (b) (6) , FDA/CDRH/OSB/DPS
Materials: (b) (6) , FDA/CDRH/OSEL/DCMS

Device Description

This supplement was submitted by BSC / Guidant to gain approval of Endotak Reliance defibrillation leads and accessories with a 4-pole "4-Site" connector'. A submission for an ICD with a 4-Site header was submitted separately under P960040/S198 (Teligen/Cognis) and is not included in this review. Reliance 4-Site leads are integrated bipolar endocardial steroid eluting pace/sense and defibrillation leads with the following variable characteristics identified by model number:

- Active and passive fixation models
- Single and dual shock coil models
- (b) (4) coated and uncoated shock coil models

The following modifications were made to the approved Reliance lead family to create the Reliance 4-Site models:

- Cable conductor(s) for defib coils changed from (b) (4) coated (b) (4) stainless steel to (b) (4) coated (b) (4) .
- Added (b) (4) tubing over the existing silicone tubing to enhance abrasion resistance from the connector extending 7 inches distal
- Modified suture sleeve to 3 grooves, same material and similar geometry
- Minor labeling updates for 4-site connection

The following characteristics of the approved Reliance lead family are unchanged for the Reliance 4-Site lead family:

- Passive fixation (tines) and active fixation (helix) versions
- Single and dual coil configurations
- Models with coils (b) (4) adhesive backfill or (b) (4) coating
- Same conductor pace/sense conductor coil design and material
- Same (b) (4) lead body from mid-lead through distal tip
- Same shock coils, distal tip, fixation mechanism (both passive and active), and drug (b) (4)

The Reliance 4-Site lead and its components were compared with the IS-1/DF-1 version in illustrations provided in the submission. In addition, illustrations of the lead body cross section between the connector and the proximal shock coil (for a two shock coil model) were provided in the submission. Note that Reliance leads are "integrated bipolar" and therefore there is no dedicated lead body conductor for the ring electrode. Rather it is electrically connected to the distal shock coil cable conductor. A table was provided on in the submission (Table 2-6 from page 2-14) to present a comparison of the Reliance IS- 1/DF-1 lead to the new Reliance 4-Site lead noting all differences.

The 4-Site connector meets the draft DF-4 standard. The following Endotak Reliance 4-Site defibrillation lead models are included in this submission:

- Models: 0262, 0263 Uncoated Single coil, Passive fixation
- Models: 0265, 0266 Uncoated Dual coil, Passive fixation
- Models: 0272, 0273 Uncoated Single coil, Active helix fixation
- Models: 0275, 0276 Uncoated Dual coil, Active helix fixation

- Models: 0282, 0283 (b) (4) coated Single coil, Passive fixation
- Models: 0285, 0286 (b) (4) coated Dual coil, Passive fixation
- Models: 0292, 0293 (b) (4) coated Single coil, Active helix fixation
- Models: 0295, 0296 (b) (4) coated Dual coil, Active helix fixation

The Endotak Reliance 4-Site Lead's four-pole lead connector is shown in the photograph below:



Accessories Description

This supplement was submitted by BSC / Guidant to gain approval for the following lead accessories, included within the lead package and also separately packaged as detailed below:

- 4-Site Terminal Tool Model 7001
- Lead Cap Kit Model 7007
- 4-Site Lead Pulling Tip Model 7006
- Lead Tunneler Model 6888

Stylets

The leads are packaged with 4 stylets (b) (4) firm and (b) (4) soft). These are the same stylets used for the Reliance IS-1/DF-1 leads. They also are available in a Stylet Accessory Package.

Model 7001 4-SITE Terminal Tool

The terminal tool details are presented on submission page 2-34. The terminal tool clamps onto pin and used to deploy/retract helix as well as to connect analyzer clips to during implant checkout. It is packaged sterile. This tool is packaged with the lead and also packaged as an individual accessory. A sample was provided and was found to function as intended with the 4-Site lead sample. A (b) (4) fixation handle is provided with the Terminal tool to rotate the connector pin to deploy the helix. The fixation handle is illustrated below and the sample was found to function as intended and described on submission page 2-28.

Model 7007 Lead Cap Kit

The lead cap kit details are presented on submission page 2-39.

The platinum cure silicone rubber lead cap is used to isolate and cover the quadripolar lead connector when it is not inserted into an ICD or CRT-D. It is packaged sterile and has a suture groove to secure the cap to the lead. The lead cap is packaged with the lead and also packaged as an individual accessory.

Model 7006 Lead Pulling Tip

A stainless steel (b) (4) lead pulling tool is described in detail on submission page 2-41. The 4-Site connector fits into one end of this stainless steel bullet shaped slug which can be used subcutaneously to move the lead from the venous access site to the device pocket if needed. This is not packaged sterile. The pulling tip is packaged individually and also included in the previously approved Model 6888 Lead Tunneler Accessory Kit.

Model 6888 Lead Tunneler

This is a kit that includes the 4-Site lead pulling tip (above) as well as a lead tunneling handle and two rods and tips for IS-1 and DF-1 connector also. This kit is not packaged sterile. The Model 6888 Lead Tunneler kit is the only device requested for approval under P830060/S062.

TVI Tool

The Reliance 4-Site lead is packed with a Transvalvular Insertion (TVI) tool, which is an accessory device designed to work with hemostatic introducers to prevent cosmetic damage to the (b) (4) covered shocking coils(s) for Reliance G/SG Leads. There have been no changes to the TVI tool with the creation of the Reliance 4-Site leads.

The description of the accessories contained in the original submission was considered acceptable.

Indications For Use

The indications for use of the Endotak Reliance 4-Site lead is unchanged from the approved Endotak Reliance IS-1/DF-1 defibrillation lead models:

ENDOTAK RELIANCE leads provide pacing and rate-sensing and deliver cardioversion and defibrillation shocks for ICD systems.

The indications for use of the Reliance 4-Site lead was considered acceptable.

Review of Clinical, Animal Study, Engineering and Biocompatibility

The clinical review was performed by (b) (6) and his initial review was provided in a memo dated 2 Jun 2009. The animal study review was performed by (b) (6) and his initial review as provided in a memo dated 10 Jun 2009. The engineering review was performed by Mark Fellman and documented in memos dated 30 Jul 2010, 8 Oct 2010, and 3 Nov 2010. The biocompatibility review was initially performed by (b) (6) in a memo dated 10 Jun 2010 and then the deficiency response review was provided by (b) (6) in a memo dated 21 Apr 2010.

Clinical / Animal Study Review Issues

The clinical, animal study, and engineering reviews all found that the submitted data was not adequate to support approval of the 4-Site lead. The following deficiencies were identified and sent to the firm in a major deficiency letter dated 30 July 2009. Responses to the deficiencies and ultimate resolutions are described below each deficiency.

1. You submitted a 1-day acute GLP study to evaluate the compatibility and functionality of the 4-Site lead/connector and a representative 4-Site header assembly in 4 dogs. FDA does not consider this data sufficient to assure the chronic safety and effectiveness of the Reliance 4-Site lead and new connector design for market approval. The design, material, and accessory changes should be evaluated in a chronic animal study to provide confirmatory electrical and mechanical performance data. Please provide an animal study of at least 6 month duration to demonstrate that the current Reliance 4-Site lead is safe and effective. The following additional study recommendations are provided for consideration:

The firm intentionally did not provide a response to this deficiency under A001. The firm submitted a pre-IDE (I090770) to propose submission of data from the RELIANCE 4-SITE International Field Following (FF) study in lieu of a chronic GLP animal study. The FF protocol is copied as Exhibit 1 in A003. The FF study is an International Post Market Study, initiated upon receiving CE mark. The International FF is a 375 total patient study (maximum of 450 enrollments) encompassing up to 50 total centers. The study includes collection of

data at implant, pre-discharge and (b) -month (b) month, (b) month, and (b) month follow-up for the purpose of meeting the following study objectives:

- Objective 1: Appropriate Detection of induced Ventricular tachyarrhythmias (VT/VF)
- Objective 2: Appropriate induced Ventricular Tachyarrhythmia (VT/VF) Shock Conversion
- Objective 3: Appropriate pacing thresholds at follow-up with the RELIANCE 4-SITE defibrillation lead
- Objective 4: Appropriate shock and pacing lead Impedances as a measure of lead integrity over 12 month time
- Objective 5: Appropriate sensing and absence of artifacts / non-sustained / sustained episodes resulting from transient potentials (artifacts) originating from incomplete lead / header contact
- Collection of handling and implant data

- a. The study should use 4-Site leads, devices, and accessories that are of final design, production, and packaging.

Response/Analysis: FDA reviewed the response to this deficiency under preIDE I090770 and found it acceptable as documented in A003/Exhibit 2. In A003, the firm restates that the FF study includes RELIANCE 4-SITE leads, TELIGEN and COGNIS 4-SITE pulse generators and 4-SITE accessories that are of final design, production and packaging in the EU; the connector design, production and packaging are identical to US product with the exception of labeling, which is equivalent. This response is acceptable to address Deficiency 1a.

- b. Use of active fixation dual shock coil 4-Site lead models is recommended to evaluate operation of the fixation mechanism and all conductor paths.

Response/Analysis: In preIDE I090770, the firm presented information concerning the number of active fixation models included in the FF study. At that time there were 81 active fixation models being studied. FDA provided feedback, presented as A003/Exhibit 2, which documents the agreement that this fully addresses Deficiency 1b.

- c. A detailed handling assessment by physicians should be included as part of the implant protocol for both the 4-Site lead, 4-Site device (including set screws) and the 4-Site accessories.

Response/Analysis: In preIDE I090770, the firm presented the FF study protocol including data collection for system/connector handling and implant assessments. FDA reviewed this information and found the FF study protocol adequate to address this concern providing data for over 150 implants by EPs under true clinical conditions with human patients. The FF study handling assessment data was presented in A00/Exhibit 3 (section 4) and in Exhibit 6. The results indicate that the 4-Site system "Exceeds" or "Meets" expectations 81.6% of the time, or 95.5% of the time if "no replies" are excluded. The firm has documented acceptable 4-Site handling and implant characteristics in clinical use under the FF study and this fully addresses Deficiency 1c.

- d. The chronic animal study should include data of the lead electrical performance such as: Pacing capture thresholds, P and R-wave signal amplitudes, Pacing lead impedances, Defibrillation Testing and lead integrity check.

Response/Analysis: In preIDE I090770, the firm presented the FF study protocol including the electrical data fields to be collected in the study. The collected electrical performance parameters are listed in the FF study protocol presented in A003/Exhibit 1. FDA found the scope of the data and method of collection to be acceptable in their feedback presented in A003/Exhibit 2. This response satisfied Deficiency 1d.

- e. Electrical performance data should be collected at implant and follow-ups at weeks (b) (4), (b) (4).

Response/Analysis: In preIDE I090770, the firm presented the FF study protocol stating that FF data will be collected at implant, pre-discharge, (b) month and (b) months. Data will also be available for (b) subjects at (b), (b) and (b) weeks. FDA found that the proposed data collection sequence was acceptable in preIDE feedback copies in A003/Exhibit 2. The firm provided the actual FF data in A003/Exhibit 3/Section5. The electrical performance data for pacing capture threshold, R-wave amplitude, and pacing lead impedance were reviewed and found to be consistent with expected values and acceptable to address Deficiency 1e.

- f. Defibrillation performance data should be assessed at implant, week (b) and week (b).

Response/Analysis: In preIDE I090770, the firm presented the FF study protocol to collect acute and chronic (spontaneous) defibrillation data. FDA agreed that this source could be used to satisfy Deficiency 1e in replacement of the requested GLP data. FDA indicated that the dataset submitted to support PMA/S approval include data for at least 10 spontaneous or induced shock events at greater than 4 weeks from implant, with 5 of the 10 at approximately 6 months from implant as copied in A003/Exhibit 2. In preIDE I100177, the firm presented initial data for the FF study spontaneous shocks which was not sufficient to address the concern. However during review of I100177, the firm submitted documentation of additional spontaneous events which met the 6 month criteria as copied in A003/Exhibit 8. The data was reviewed and found sufficient by FDA as documented in A003/Exhibit 9. The clinical study report data set included data for 100 VT/VF conversions at implant. The clinical report presented under Exhibit 3 includes data for 90 spontaneous high energy 41 Joule shocks delivered in 31 patients. Appropriate high energy shock delivery was verified in all cases with shock lead impedance values between (b) and (b) ohms (within recommended range of 10 to 80 ohms). The scope of data greatly exceeds the animal study data requested under this deficiency. The firm has fully addressed Deficiency 1f.

- g. You should provide a post-study analysis of the lead, connector terminal and header components including evaluation of helix operability at time of termination, set screw operation, mechanical integrity, insulation, seal performance and corrosion resistance.

Response/Analysis: During interactive discussions and through preIDE 090770, the firm presented rationale to support that bench testing, corrosion testing, and in-vivo system diagnostics and monitoring would provide sufficient evidence that the mechanical integrity of the 4-Site connection was safe and effective. FDA agreed with the firm's rationale which was supported by extensive collection of human clinical data compared with the limited animal study suggested under the deficiency. The clinical study report was presented in A003 Exhibit 3 and no particular failures indicating device design problems were identified. BSC indicates that 102 4-Site leads are out of service and that 73 have been returned for analysis. All have been visually inspected and technical analysis is complete. No signs of seal performance issues or corrosion were identified. The firm has adequately addressed Deficiency 1g with evidence that the lead, connector terminal and header have passed rigorous testing and demonstrate good early chronic clinical performance through returned product analyses.

- h. The animal study should include also pathology examination of the tissue adjacent to the lead fixation and connector assembly.

Response/Analysis: During interactive discussions and through preIDE I090770, the firm presented rationale to support that bench testing, corrosion testing, and in-vivo system diagnostics and monitoring would provide sufficient evidence that the connector system was working correctly. The firm justified that system diagnostics and performance parameters would be triggered prior to any potential tissue damage adjacent to the connector from issues

like current leakage. The rationale was considered by the animal study reviewer and engineering reviewer under I090770 and found acceptable to address Deficiency 1h as documented in A003/Exhibit 2. There were no findings in the FF study report A003/Exhibit 3 that indicated any concern that could be related to seal integrity or current leakage. The concern under Deficiency 1h has been adequately addressed.

2. In addition to the 4-Site connector, you have made other changes to the lead that could affect handling and performance such as the new polyurethane outer tubing, thicker tubing, new cable alloy, new suture sleeve, and new/modified implant accessories. Please provide a summary which documents how the 4-Site lead changes and accessories have been evaluated to justify that additional premarket human clinical study is not necessary. Provide test reports and data for any completed pre-clinical or clinical studies supporting clinical evaluation or reference where this information is located in the current submission. You should reference additional data that you plan to collect in a future animal study and post-approval study to support your response.

Response/Analysis:

In A001, the firm provided a listing of mechanical bench testing on page 2 copied from the original submission. The firm provided a listing of accessory testing on page 3 including simulated use testing and acute GLP animal study testing. The firm noted one unexpected observation with a terminal tool spring clip and documented an acceptable quality system response. The firm states that additional confirmatory information will be collected post-approval. The firm submitted additional information to address Deficiency 2 under preIDE I100177. FDA agreed that the scope of lead and accessory handling data to be collected under the FF study was acceptable to address Deficiency 2 as documented in A003 Exhibit 7. Handling surveys were also supplied under I100177. The data showed that all observations were resolved at implant and that there were no adverse events associated with system handling including accessories as documented in A003 Exhibit 8. FDA reviewed the information and agreed that the accessory handling data collected under the FF study was acceptable as documented in A003 Exhibit 9. The clinical study summary presented in A003 Exhibit 3 was reviewed again and no concerns for accessory use were identified. The firm has fully addressed Deficiency 2.

Post-Market Issues

The review of this submission for post-market issues was provided by OSB/Epi reviewer (b) (6) (b) (6) in formal memos dated 9 Nov 2009 and 8 Nov 2010. The following deficiency for a post approval study was identified in the first review and the resolution is described below.

3. Approval of a new four-pole connection without collection of chronic premarket human clinical data will need to be supported by a robust plan to monitor and evaluate chronic performance post approval. You have indicated on page 1-14 that you plan to complete a post approval study for the 4-Site lead. A five year study similar to that of the Acuity Spiral lead model, but also including suggestions contained in a April 3, 2009 correspondence, is considered appropriate. The study should collect implant data to document safe use of the 4-Site lead/device and accessories, and evaluate chronic performance for a time period that includes device change-out and returned product evaluation of the new connector terminal and header. Please provide a draft post-approval study protocol for review.

Response/Analysis:

The firm provided a post approval study (PAS) draft protocol in Exhibit 2 of the A001. The firm proposes to use their Longitudinal Surveillance Registry (LSR) to monitor the post-market performance of the 4-Site Lead/Header system. The 4-Site LSR is a prospective study intended to evaluate the chronic complication free rate of the 4-Site Lead/Header system to verify long-term functional integrity. The study will enroll at least (b) (6) patients at up to (b) (6) centers and follow a minimum of (b) (6) patients for 5 years. Status reports will be issued every (b) (6) months. The review of the PAS protocol submitted in A001 was found

generally acceptable. However, the review identified 8 deficiencies regarding details of the study including protocol, definitions, and case report forms. The firm provided an updated draft protocol to address the concerns as copied in A003 Exhibit 12. Interactive review between BSC and FDA/OSB/Epi continued as documented in A003 Exhibits 13 to 16 (Protocol), A003 Exhibits 17 to 38 (Case Report Forms) and A003 Exhibit 39 (Informed Consent). FDA provided feedback on these draft documents in an email dated 3 Sep 2010 copied as A003 Exhibit 40. BSC and FDA/OSB/Epi have continued to work interactively to resolve remaining concerns identified in the 3 Sep 2010 email (A003 Exhibit 40). The OSB/Epi reviewer provided an email and final review memo on 8 Nov 2010 indicating that the firm had submitted an acceptable final protocol and final case report forms. At the request of OSB/Epi, the firm should be asked to submit the final protocol (Version 4.0 dated 26 Oct 2010) and final CFRs (Version 1, Revision A, dated 26 Oct 2010) within a PMA Supplement following approval.

Engineering Issues

The review of this submission for engineering issues was initially provided by Mark Fellman in a review memo dated 30 Jul 2009. The following deficiencies for engineering issues were identified and the resolutions are described below.

4. You present a DVT report for intracardiac and subcutaneous buckle flex fatigue in Exhibit 4-20. In this document you state that your lead testing for the intracardiac region was performed at one orientation and (b) (4) cycles. FDA expects lead testing of intracardiac regions to be evaluated to 400 million cycles and at multiple axes, and to have preconditioning steps representative of handling and implant. Please provide additional test data or a detailed analysis and justification to support the validity of the testing you performed, including test validation, in regards to the expectations listed above.

RESPONSE SUMMARY:

The firm provided a detailed analysis and justification supporting the validity of flex fatigue testing on Reliance 4-Site leads in Exhibit 3 of A001. BSC provides a detailed justification for their quantitative accelerated life testing methods. The firm states that the Reliance IS-1/DF-1 leads have had acceptable reliability in over 8 years of service, particularly with respect to fatigue performance. The firm provides detailed information on confirmed flex fatigue failures of Reliance leads and a chart showing the fracture locations on page 13 of 14 in Exhibit 3 of A001. There was only 1 fracture at the distal tip. The firm concludes by stating that the intracardiac region of Reliance 4-Site and IS-1/DF-1 leads are equivalent in all respects that are relevant to fatigue performance. The firm commits to enhance test data for future submissions where the design of the intracardiac portion of the lead differs from marketed leads.

FDA ASSESSMENT:

In A001, the firm has provided a valid justification that the lead tip of the 4-Site model is identical to the approved IS-1/DF-1 model and that the approved model has had acceptable fatigue performance. The firm understands that accelerated testing may not be accepted in the future and that 400 million cycle multi-axes, preconditioned requirements may be imparted in future submissions. The response is acceptable.

Biocompatibility Issues

The review of this submission for biocompatibility issues was initially performed by (b) (6) in a memo dated 10 Jun 2009. The biocompatibility deficiency responses were reviewed by (b) (6) in memos dated 21 Apr 2010 and 6 May 2010. The following deficiencies for biocompatibility issues were identified and the resolutions are described below.

5. Please provide copies of the biocompatibility test reports summarized in Exhibit 4-61 for the Terminal Tool and Fixation Handle. Alternatively, identify the submission number, date, appendix and page number for where this information has been previously submitted.

RESPONSE SUMMARY:

In A001, the firm provided biocompatibility test reports for the Terminal Tool and Fixation handle in Exhibits 4, 5, 6 and 7.

FDA ASSESSMENT:

The response to Deficiency 5 submitted in A001 was reviewed. The requested documents were provided for cytotoxicity, sensitization, intracutaneous reactivity and implantation. No concerns were identified. The testing and results were found acceptable to address Deficiency 5.

6. To support your claim that biocompatibility testing is not needed on the redesigned Reliance 4-SITE leads, you provided a rationale in Exhibit 4-9 of your submission, outlining the differences between previous PMA approved devices as well as biocompatibility tested products. Please address the following regarding your rationale:
 - a. For all of the certifications provided in Tables 2.1 and 3.1 of Exhibit 4-9, where exceptions were noted (i.e. there are differences between the 4-SITE leads and the marketed devices or test articles), please provide additional information specific to the change and each individual type of material to support your conclusions that the changes will not impact the biocompatibility of the final device. For example, discussions regarding the potential for chemical interactions with water, the potential for specific chemical-chemical interactions, and/or material transition temperature information may be helpful to your response. While some of this information appears to have been provided in Exhibit 4-07, more detailed rationales are needed to better understand the information used to support your conclusions.
 - b. In several of the certifications, you indicated that Attachment 1 of the exhibit provided data to demonstrate that the noted exception does not alter the chemistry of the material, and therefore, biocompatibility of the approved product or testing on the biocompatibility test article can be applied to the final sterilized device. The referenced Attachment 1 information was not found. Please resubmit this Attachment, or identify the location of this data in your submission.
 - c. For the new ASTM F1314 material used to make the "DSB Cable" you indicated that both Attachments 1 and 2 of the exhibit provided data to demonstrate that the change in formulation does not significantly alter the chemistry of the alloy, and therefore additional biocompatibility testing is not needed." As noted above, Attachment 1 was not found, and Attachment 2 did not provide sufficient information on your specific product to confirm that changes in formulation of the base material will not impact the chemicals presented to the patient from your final device. In addition to final product corrosion testing, please provide additional details regarding the chemicals available at the surface and/or from the bulk that might leach out over the implant life.
 - d. In accordance with ISO 10993 part 1, pacing and defibrillator leads are implant products in contact with cardiovascular tissue and circulating blood, with a permanent duration of contact (>30 days). For this type of product, CDRH recommends the following tests be considered: cytotoxicity, sensitization (guinea pig maximization with both polar and non-polar extracts), irritation (or intracutaneous reactivity), acute systemic toxicity, material-mediated pyrogenicity, hemocompatibility (including indirect and direct contact hemolysis, in vivo thrombogenicity, and direct contact complement activation (C3a and Sc5b-9)), subchronic toxicity, implantation, chronic toxicity, genotoxicity (Ames; Mouse Lymphoma Assay or Chromosomal Aberration Assay; and In Vivo Mouse Micronucleus Assay or Peripheral Blood Micronucleus Assay), and carcinogenicity. In Table 3.1, you reference biocompatibility test report numbers, but did not describe the type of testing conducted on each of the material components. For each material component that was tested, please identify the specific biocompatibility studies that were conducted on the components,

summarize the findings of the studies and identify the location of this data in previous submissions to the FDA. If this data has not been previously submitted to the FDA, please provide it for our review. As a part of your response, please include a justification for omission of any recommended biocompatibility studies identified above.

- e. Please expand your justification for omission of final product biocompatibility testing to address the potential for chemical interactions between material components.

RESPONSE SUMMARY:

In A001, the firm provided information to address each part of Deficiency 6 starting on page 11 of 41 and within Exhibits 8 through 21.

FDA ASSESSMENT:

The response to Deficiency 6 response in A001 was reviewed. The following review assessments were made:

- a. *The firm provided updates in Table 2.1 and 3.1 regarding material comparisons to other devices and similar materials that were tested and found biocompatible. The firm also provided biocompatibility test reports for 4-Site device materials. The additional information was found acceptable to address Deficiency 6a.*
 - b. *The firm provided the requested location for an attachment which contained data referenced in a test report. The response addressed Deficiency 6b.*
 - c. *The response addressed the concern regarding differences in (b) L and (b) (4) stainless steel. The firm documents that a chemical analysis was performed and also notes that the SS cables are fully encapsulated inside the lead body. The response to address Deficiency 6c was found acceptable.*
 - d. *The testing performed for (b) silicone rubber and (b) (4) appropriate and adequate. However it was noted that the silicone rubber is mixed with (b) in the terminal boot and was this was not fully tested. The testing for the (b) heat-shrinkable tubing was considered adequate. An additional concern regarded lack of testing for the terminal pin and terminal ring. While A001 was under review, the firm submitted I100177 asking for informal feedback to the 2 identified biocompatibility questions from Deficiency 6d. The response addressed the terminal pin concern was addressed, but additional information was required for the (b) issue. This feedback was provided to the firm by email dated 6 May 2010 copied in A003/Exhibit 41. The firm provided additional information and testing by email on 6/3/2010 presented as A003/Exhibits 12, 42, and 43. This information was reviewed. The levels of (b) released in testing were very low and there was no safety concern. With the additional information, the response to Deficiency 6d was found acceptable.*
 - e. *The firm provided a table listing all the component to component transitions and material interfaces. The firm justified that these were unchanged from the approved Reliance lead. The response was found acceptable to address Deficiency 6e.*
7. Please provide copies of the biocompatibility test reports for the Reliance 4-SITE leads summarized in Exhibits 4-12 and 4-13.

RESPONSE SUMMARY:

In A001, the firm provided biocompatibility test reports to address this deficiency in Exhibits 22 through 26.

FDA ASSESSMENT:

The response to Deficiency 7 in A001 was reviewed. The requested bioburden, hemolysis, and cytotoxicity test reports were submitted. The testing and results were found acceptable to address Deficiency 7.

Drug Component/Labeling Issue

The drug component used on Reliance 4-Site leads is identical to the drug component on approved Reliance leads. There are no changes to the distal tip design, materials, or manufacturing processes. Therefore no formal drug review as obtained from CDER. However, the firm was asked to update their labeling to include the drug dose information in the following deficiency from the major deficiency letter dated 30 Jul 2009.

8. You presented steroid dosage DVT testing in Exhibit 4-26. The results demonstrate that the dose is within your stated specification for active and passive fixation drug components. Since the distal tip and drug components are unchanged from the approved Reliance lead models, a full CDER review was not required. However, at this time, you should update labeling to include the nominal drug dose based upon your test results. The drug name and dose should be clearly indicated on the sterile package, technical manual device description, and specification sheet.

RESPONSE SUMMARY:

In A001, the firm presented updated labeling as requested in the Deficiency. The firm documents that the Reliance design specifications are (b) mg maximum dose of dexamethasone acetate (DXA) for active fixation leads and maximum (b) mg dose of DXA for passive fixation leads. The nominal dose of DXA for passive fixation leads is (b) mg. The nominal dose of DXA for active fixation leads is (b) mg. The updated physician technical manuals (PTM) are presented in Exhibits 27 to 30 of A001. The updated box and try labels are presented in Exhibits 31 to 34 of A001.

FDA ASSESSMENT:

In their A001 response, firm has documented the nominal and maximum dose of DXA for both passive and active fixation Reliance leads. The firm has updated their labeling with this information as requested in the deficiency. The response to Deficiency 8 is acceptable.

Other Minor Deficiencies (Engineering, Shelf Life, Labeling)

A number of minor deficiencies were identified during the engineering review presented in a memo from Mark Fellman dated 30 Jul 2009. The following deficiencies for engineering issues were identified and the resolutions are described below.

9. The labeling included in your submission indicates that the Reliance 4-Site leads will have a lubricious coating. Please provide information regarding the coating formulation, location, and specifications or identify where this information is presented in the submission.

RESPONSE SUMMARY:

In A001, the firm states that information on the lubricious coating was provided under P910073/S035, approved 2 Nov 00. There has been no change to the coating on the Reliance 4-Site models compared to the approved IS-1/DF-1 models. The information on the lubricious coating was repeated in this A001. The silicone derived coating is supplied as coated tubing by Applied Membrane Technology, Inc (AMT) using a proprietary technology described on page 26 of 41 of A001. The coated tubing is used from the connector down to the first shock coil. Coated tubing is also included between the shock coils on dual coil models. The firm summarizes the testing on the coating for coefficient of friction and biostability which were presented with the previous approval of the coating.

FDA ASSESSMENT:

The firm has documented the location, composition, and testing of the lubricious coating on 4-Site leads. The coating is unchanged in all regards from the approved coating for Reliance IS-1/DF-1 lead models. The response to Deficiency 9 is acceptable.

10. You presented a shelf life assessment for Reliance 4-Site leads in Exhibit 4-14. Please confirm that the test samples used for accelerated and real-time testing are of final design using final manufacturing processes and personnel. You should justify that any changes from the final design or production would not alter shelf life testing results.

RESPONSE SUMMARY:

In A001, the firm states that test samples used for accelerated and real-time testing are representative of final design using manufacturing processes and personnel that are representative of final manufacturing. However the firm notes several differences and provides justifications of why they would not alter shelf life testing results on page 27 of 41 of A001. The firm documents their change order process for design and manufacturing changes occurring after design verification tests (DVT). "Pilot A" test articles were used for Real-Time shelf life testing. However "Alternate" test units were used for Accelerated shelf life testing. The Alternate units had flaws which would not affect the results such as wrinkles, blemishes, scratches, foreign matter, and slight dimensional variations. Use of Alternates was peer reviewed and found acceptable for shelf life testing.

FDA ASSESSMENT: The firm has provided documentation that the samples used for shelf life testing were either production units or acceptable replacements. The response to Deficiency 10 is acceptable.

11. Evaluation of the lubricious coating integrity and function was not found in your shelf life testing in Exhibit 4-14. Please provide data to show that the lubricious coating is not affected by aging to support your requested 2 year shelf life for the Reliance 4-Site lead models.

RESPONSE SUMMARY:

In A001, the firm states that information on the lubricious coating was provided under P910073/S035, approved 2 Nov 00. There has been no change to the coating on the Reliance 4-Site models compared to the approved IS-1/DF-1 models.

FDA ASSESSMENT: The firm has documented that the lubricious coating is identical to the market approved Reliance IS-1/DF-1 leads in their response to Deficiency 9 above. The data support a 2 year shelf life for the previous lead model. Since the body material and coating are identical, there is no further concern regarding a 2 year shelf life for the coating on the 4-Site lead. The response addresses the concern of Deficiency 11.

12. In the submission, you requested expiration dating of 4 years for the 4-Site accessories. This request appeared to be based on package testing. Please identify where shelf life testing for the 4-Site accessories is located in the submission or provide this information.

RESPONSE SUMMARY:

In A001, the firm provided reference to the original S077 submission Ex 4-67 and Ex 4-68 where shelf life assessment and testing of accessories is documented. Real time and accelerated testing is presented for the lead cap, fixation tool and handle, and sterile package.

FDA ASSESSMENT: The firm has provided appropriate assessment and testing to demonstrate that the accessories can be approved with a 4 year shelf life when packaged in the accessory kit. The response to Deficiency 12 is acceptable.

13. Figure 14 in the user manual appears to show an illustration with the old suture sleeve design. Please update the figure as appropriate.

RESPONSE SUMMARY:

In A001, the firm updated the user manual to correct the error.

FDA ASSESSMENT: The updated user manual was reviewed and the change was found acceptable. The response addresses the Deficiency 13 concern.

14. A new precaution in the Physician Manual regarding the terminal pin indicator is described on page 9-4. Using the lead and header samples provided to FDA, the terminal pin was not easily seen when inserted into the header. You described additional labeling changes based on European field data and also handling studies in an email to FDA dated June 16, 2009. Please provide an update on any design or labeling changes regarding assurance that the terminal pin is fully inserted into the header and that visual indicators are adequate.

RESPONSE SUMMARY:

In Table 10 of A001, the firm listed the labeling changes they made to address the concern for full insertion of the terminal pin and visualization.

FDA ASSESSMENT: The firm added text to instructions and warnings in the user manual to better describe visualization of the terminal pin insertion indicator beyond the set-screw block. No other changes are proposed. The instructions are included in the User Manual (A001, Exhibit-27). The response was reviewed by the clinical reviewer and found to address the concern. The response to Deficiency 14 is acceptable.

15. You have added a large number of precautions regarding safe handling and use of the 4-Site terminal and Terminal Tool by physician users as listed in Table 9-2 and found in the Exhibits of Section 9. Please provide copies of your training plan and documentation for physician users to assure that the 4-Site terminal and accessories are used correctly and damage is not inflicted.

RESPONSE SUMMARY:

In A001, the firm provided copies of the terminal tool training presentation (Ex-37), field following product survey (Ex-38), and implant experience survey (Ex-39).

FDA ASSESSMENT: The firm has provided the requested documentation regarding physician feedback and training for the terminal tool. The clinical reviewer reviewed the response and found the training material appropriate and acceptable. The response to Deficiency 15 is acceptable.

16. You present instructions for use of the Terminal Tool in Exhibit 9-11. In this document, you include a "Note" that the stylet must be fully inserted during fixation or repositioning. The instructions imply that the 4-Site lead can not be implanted without use of a stylet and go against the practice of slightly retracting the stylet during helix fixation to reduce the likelihood of perforation. Please provide information to clarify this issue.

RESPONSE SUMMARY:

In A001, the firm clarified the labeling regarding use of the stylet during repositioning and helix fixation. Instead of saying the "stylet must be fully inserted during fixation and repositioning" the text has been modified to say "Once the lead is positioned in the desired location, the stylet may be fully inserted to stabilize the lead tip during fixation".

FDA ASSESSMENT: The updated labeling was reviewed by the clinical and engineering reviewers. The initial response in A001 did not address the concern. FDA worked interactively with the firm to agree on acceptable text. The firm presented updated text by email on 14 Jul 2010 which was reviewed and found acceptable.

17. You provide a sample package label for the Lead Pulling Tip in Exhibit 9-16. The package label does not include a statement that the contents are not sterile. Please add text indicating the contents are not sterile or provide a justification for omitting this information from the package label.

RESPONSE SUMMARY:

In A001, the firm updated the labeling for the lead pulling tip to include "Contents are not sterile".

FDA ASSESSMENT: The response has addressed the concern of Deficiency 17.

Review of New Change Included in A002: Biological Indicator

During the interactive review of this file, the firm notified FDA in I100177 that they are changing the biological indicator (BI) used during sterilization processes for all Boston Scientific products. FDA agreed that the firm could add this change to S077 as long as the 30-day notice for the change was reviewed and approved by FDA/OC and also that the specific device did not affect the considerations of approval (FDA email copied as A002 Exhibit 7). BSC submitted this change under A002. They provided documentation that the new BI had been approved for other PMAs in A003.

FDA Assessment: The firm included a copy of the FDA approval for this change as a 30-day Notice in A003 Exhibit 47 with an approval date of 12 Jan 2010. In A003, the firm included a sterilization assessment report for 4-Site lead and accessories concluding that the change to BI is not impacted by the device type. The change does not affect the sterilization equipment, cycle parameters, or process. The firm has justified that the new BI can be approved for the 4-Site system under this supplement S077.

Review of New Change Included in A003: Labeling Change

During the interactive review of the file, the firm notified FDA that they wanted to update the technical specifications sheet for the 4-Site lead. Two changes were proposed in I100177. The first was a correction to the maximum tip helix penetration depth due to a typographical error. The second was to remove several intermediate diameter parameters from the specifications sheet. FDA provided feedback under I100177 as copied in A002 Exhibit 7 and BSC presented FDA with a revised specification sheet in A003 Exhibit 8. FDA agreed that the revised specification sheet would be acceptable as documented in A003 Exhibit 9.

FDA Assessment: The firm has presented the updated 4-Site lead specification sheet in A003 as agreed to under review in I100177. The updated specification sheet corrects the typographical error, and modifies the presentation of lead diameter in a way that was considered acceptable to FDA. The technical specification sheet updates can be approved under this supplement S077.

Conclusion & Recommendation

Through a long and interactive process with FDA, Guidant / Boston Scientific Corporation has addressed all deficiencies contained in the major deficiency letter dated 30 Jul 2009. The supplement can be approved with the condition to conduct a post-approval study according to the 26 Oct 2010 protocol and case report forms. The firm will be asked to submit the final post-approval study protocol and case report forms to FDA in a new supplement following approval of S077.

(b) (6) [redacted] Lead Reviewer, PDLB Date

(b) (6) [redacted] Chief, PDLB Date