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St. Jude Medical Puerto Rico, PRLLC
Santana Industrial Park
Rd# 2 Km 67.5 Interior Lot 1
Arecibo, PR 00612
Tel 787-650 -1750

Please assign to CSV for review & comment & forward to CB as appropriate

October 22, 2012



Ms. Maridalia Torres Irizarry
District Director
U.S. Food and Drug Administration
San Juan District Office
466 Fernández Juncos Ave.
San Juan, PR 00901-3223

**RE: St. Jude Medical PRLLC , Cardiovascular and Ablation Technologies Division (CATD) and Implantable Electronic Systems Division (IESD) Response to the October 2, 2012 Inspectional Observations (FDA-483) - FEI Number 3006705815**

Dear Ms. Torres:

St. Jude Medical PRLLC , Cardiovascular Ablation Technologies Division and Implantable Electronics Systems Division (hereafter referred to as "SJM PRLLC"), are providing this response to the FDA-483 Inspectional Observations issued to the Arecibo, Puerto Rico Facility on October 2, 2012 by the US Food and Drug Administration. We appreciate the thoroughness of the investigation conducted on our Quality Management Systems by investigators Noreen Muñiz and Adaliz Santaliz. SJM PRLLC is committed to meeting and, wherever possible, exceeding FDA's Quality System Regulations ("QSR") per 21 CFR Part 820.

We recognize and take seriously the significance of the observations in the FDA-483, and are committed to taking all actions necessary to ensure that our systems comply with FDA requirements, and that our products are safe and effective. As described in our detailed response below, in addition to correcting the specific items listed in the FDA-483, we have taken and are continuing to take actions to address systemic issues.

Attachment 1, "Response to the FDA-483," describes the actions we have completed. To facilitate review, the FDA-483 observations are bolded, followed by our response in regular font. Where appropriate, a subset of the original observation may be addressed separately to more appropriately demonstrate or describe the actions taken or commitments made. Supporting documents referenced in Attachment 1, are listed in Attachment 2, "List of Appendices."

We consider the information contained in this letter and its attachments as confidential commercial information and not subject to disclosure under the Freedom of Information Act. Accordingly, we have designated this letter and its attachments as confidential.







Cover Letter

We would like to emphasize that we regard this inspection as highly valuable input for our organization. As further demonstration of SJM PRLLC's commitment to compliance, we would welcome the opportunity to meet with the FDA to further discuss the matters addressed herein, if you deem appropriate. We will contact you shortly to set up a mutually convenient time. Please contact us should you require any assistance in reviewing this letter, or any of the attached documents.

Respectfully,


Angel L. Ortiz

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22 Oct 2012

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Attachments:

1. Response to FDA-483
2. List of Appendices

Distribution List:

Noreen Muñiz
Adaliz Santaliz

U.S. Food and Drug Administration
San Juan District Office
466 Fernández Juncos Ave.
San Juan, PR 00901-3223

Dear Ms. Torres:

To facilitate review, the FDA-483 observations are bolded, followed by our response in regular font. Where appropriate, a subset of the original observation may be addressed separately to more appropriately demonstrate or describe the actions taken or commitments made.

**Observation 1**

**Procedures for receiving, reviewing, and evaluating complaints by a formally designated unit have not been adequately established.**

**Specifically,**

**Procedure #602727, Product Experience Report Handling, PRLLC, established on a site to define the instructions for handling and trending manufacturing related complaints from products manufactured in Puerto Rico and to provide instructions for reporting results to the appropriate SJM Division fails to require complete documentation of activities conducted to ensure a timely investigation (when does the (b) (4) for local investigations start) or describe data analysis conducted as part of complaint trending. Section 7.3, Data Analysis, fails to include the scope and actions associated to the analysis of data as no information is included with the procedure on: how the analysis is conducted and reported to the site for evaluation and action; elements to be evaluated at the site with the reports provided or at least minimum information to be included during the local evaluation of data provided by the Division; scope (period of data reported) of the analysis and source of data reported to justify reported combined defects/product families in order to accurately determine trends (if any).**

SJM PRLLC Response:

Part of observation addressed in the following section:

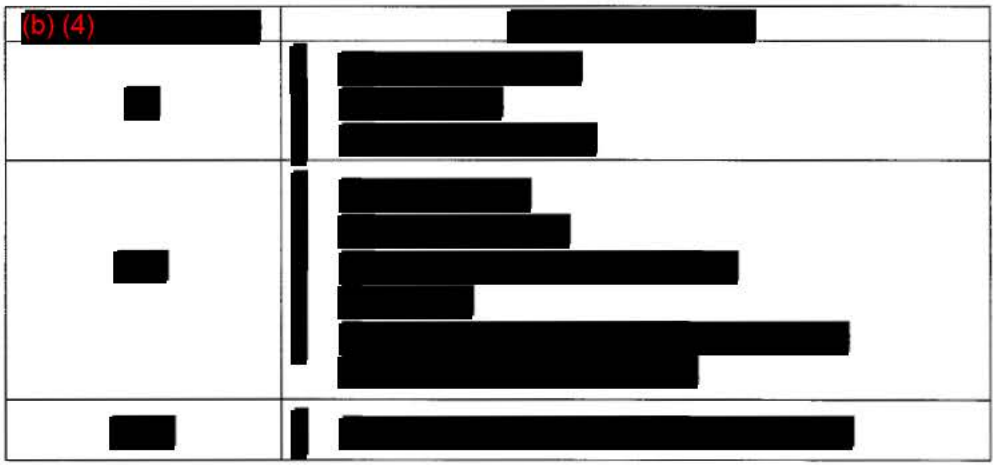
***"fails to require complete documentation of activities conducted to ensure a timely investigation (when does the (b) (4) for local investigations start)"***

Procedure 602727 (Product Experience Report Handling Procedure), Ver. K (see Appendix 1-1), establishes as part of the SJM PRLLC Quality System, a process to handle the Puerto Rico's manufacturing related complaints and trending. It defines requirements to: assign and complete investigations within (b) (4), review Device History Records, handle product return devices for further evaluation, and elevate complaint investigation to the CAPA system (if applicable). In addition, it defines requirements for complaint files maintenance and data analysis.

SJM PRLLC is committed to complete our investigations in a timely manner for all Quality Data Sources such as: CAPA, Complaints, Non Conforming Material Reports, and Internal Audit observations, etc. SJM PRLLC has established mechanisms to ensure investigations are completed in a timely manner as follows:

a. CAPA Forum; this forum is established through SOP 602574 (Corrective/ Preventive Action, SJM PRLLC), Ver. S (see Appendix 1-2) with the purpose of providing guidance on investigations to assure timely completion. More specifically, by means of:

i. Per SOP 602727, section 7.2.4.2, monitoring the complaint investigation progress based on the suggested timeframes established in the table below:




ii. Evaluating the investigation to assure that the root cause analysis is performed and that appropriate corrective actions are taken.

iii. Tracking the implementation of the corrective actions.

iv. Reporting the results of completion and pending actions to management.

b. Management Review/Trend forum

i. Analyzing Quality Data Sources by: family, defects, and time frame to identify trends and to ensure that corrective actions are established as needed.

ii. Tracking the aging of investigations and corrective actions for all data sources.

iii. Determining improvements for the Quality Management System and Quality performance.

iv. Identifying resource needs.

v. Reporting to internal/external management the results of the analysis.

c. Plant Objectives; on a (b) (4) basis, Management defines the Plant Objectives including: Quality, Service, and Cost. For the past (b years, one of the Quality Objectives had been to achieve investigation completions within the established due dates. More specifically, the objective of compliance with investigation due dates is monitored by means of:

i. (b) (4) scorecard is discussed in exempt employees meetings.

ii. (b) (4) Reports of compliance with due dates are provided to management.

iii. (b) (4) upper Management meetings to review the status of the Plant Objectives strategies.

In addition, if the investigation cannot be completed within the (b) (4) SJM PRLLC has established, an extension request process which includes a risk assessment of the additional time requested.

SJM PRLLC acknowledges that procedure 602727 (Product Experience Report Handling), Ver. K, is not specific so as to when the (b) (4) clock starts. It could be either when the notification is received from the Designated Complaint Unit or when the complaint is locally assigned for investigation. To address this, SJM PRLLC has updated section 7.2.3 of procedure 602727 to Ver. L (see Appendix 1-3) to read as follows:

> "After the complaint investigation request is received, it will be assigned within (b) (4) days of the request. The investigation Report must be completed within (b) (4) days after it is assigned. Evidence of notification to the Plant by the Designated Complaint Unit will be documented in form 60030668 for Arecibo site and 90074207 for Caguas site and included in the complaint file. Once the investigation is locally approved it is considered closed."

Part of observation addressed in this section:

***"fails to include the scope and actions associated to the analysis of data as no information is included with the procedure on: how the analysis is conducted and reported to the site for evaluation and action; elements to be evaluated at the site with the reports provided or at least minimum information to be included during the local evaluation of data provided by the Division; scope (period of data reported) of the analysis and source of data reported to justify reported combined defects/product families in order to accurately determine trends (if any)."***

SJM PRLLC Response:

Section 7.3 of SOP 602727 (Product Experience Report Handling), Ver. K (see Appendix 1-1), establishes that data analysis shall be performed through the use of Divisional complaint logs and reports. Trends are received on a (b) (4) basis from the Division. Data includes: major offenders (b) (4) charts, and complaints list arranged by product categories (pacers, (b) (4) leads (b) (4) ), (b) (4) ) over the last (b) (4) months.

Section 7.1.3 of SOP 602574, Ver. S, requires the analysis of quality data sources to be performed on a (b) (4) basis and the result of the analysis shall be submitted to the CAPA Administrator to be presented on the trend forum (see Appendix 1-2). To accomplish the analysis of the quality data sources; trend, (b) (4) charts and other data analysis tools are prepared with the data from the prior twelve months and presented by product categories.

Section 7.3.2 of SOP 602727, Ver. K, also establishes that the trend presentation is discussed with Management at the Trend Forum to identify corrective actions when trends are identified. However, SJM PRLLC acknowledges that even though the data analysis is being performed as described above, the data analysis process is not established in the procedure. To address this, SJM PRLLC implemented Procedure 90110817 (Data Analysis), Ver. A (see Appendix 1-5) as part of SOP 602574, Ver. T, to formalize the current practice on how the data analysis is being conducted, based on the process described above.
To address this observation, SJM PRLLC completed the following specific activities:

a. Sections 7.2.2 and 7.5.1 of Procedure 602727 were updated to Ver. L to specify when the (b) (4) clock (to complete the investigation) starts and describes the supporting evidence/ documentation required (see Appendix 1-3).

b. SJM PRLLC also updated other Quality Data sources procedures (CAPA, Complaints, Non Conforming Material Reports, Internal Audit observations, and Event Investigation) to ensure

that the starting point of the days to complete investigations is specifically established (see Appendix 1-4).

c. Procedure 90110817, Ver. A, part of SOP 602574 was implemented to formalize the current practice on how SJM PRLLC performs the Data Analysis for complaints and all other Quality Data Sources. Specifically, this addresses how the data analysis is conducted and reported from SJM Divisions to SJM PRLLC, including but not limited to: the scope (period of data reported), source of data, data arrangements (by product family), and actions associated with the analysis of data (see Appendix 1-5).

Summary of corrective actions in response to Observation 1

| Action | Description | Completion Date |
|---|---|---|
| Update Product Experience Report Handling, PRLLC procedure 602727 by means of CO #C103569 (see Appendix 1-3). | Sections 7.2.2 and 7.5.1 were updated to specify when the (b) (b) clock starts to complete the investigation and to describe the supporting evidence/ documentation required. | 18 Oct 2012 |
| Update Procedures by means of CO #C013569 (see Appendix 1-4):<br>• 602574 "Corrective/Preventive Action", PRLLC to Ver. T, in section 7.4.2<br>• 602575 "Non- Conforming Material (NCMR)" to Ver. T, in section 7.4.5<br>• 602576 "Internal Quality Audits" to Ver. X, in section 7.5<br>• 602626 "Event Investigation" to Ver. R in section 7.2 | Additional improvements to the existing Quality Data Sources procedures (CAPA, Complaints, Non Conforming Material Reports, Internal Audit observations, and Event Investigation) to ensure that the starting points of the days to complete investigations are specifically defined. | 18 Oct 2012 |
| Implementation of Data Analysis procedure 90110817, Ver. A, by means of CO #C103569 (see Appendix 1-5). | Procedure 90110817 was implemented to formalize the current practice on how SJM PRLLC performs the Data Analysis for complaints and all other Quality Data Sources. Specifically, how the data analysis is conducted and reported from SJM Divisions to SJM Puerto Rico including but not limited to: the scope (period of data reported), source of data, data arrangements (by product family), and actions associated with the analysis of data. | 18 Oct 2012 |

**Observation 2**

**Procedures for identifying product during all stages of receipt, production, distribution, and installation have not been adequately established.**

**Specifically,**

1. **The use of the software tool "(b) (4) implemented onsite as reported by local managers in February 2012 and observed in place in the manufacturing/ assembly clean room- specifically in the product inspection stations for HV and CRT Leads- has not been fully documented to support the firm's claim of no impact on production operations for the assembly of leads. Documents issued for the(b) (4) (b) (4) observed in place and in use of the manufacturing clean room were not available nor provided during the inspection or any other documented evaluation to support the firm's claim of reported use "(b) (4) ". The instruction to scan the bar code label on each lead prior to final inspection activities (for "(b) (4) ") is not part of any production record (traveler) or manufacturing available on site.**

SJM PRLLC Response:

The (b) (4) ) tool was implemented with the sole purpose of monitoring the amount of units in the different stages of the manufacturing process. (b) (4) This application is not used to make any quality decisions associated to the product being manufactured. (b) (4) consists of different (b) (4) points located in each product line where the operator scans the unit's barcode label in the traveler to identify its location in the manufacturing floor. This helps to facilitate (b) (4) .

SJM PRLLC acknowledges that the scope and purpose of the (b) (4) tool was not documented as part of the tool implementation. However, we maintain the rationale for this decision because the use of this tool is not a required step for the manufacturing of the device nor does it manage any quality data.

The installation of the (b) (4) tool, including its (b) (4) , did not require qualification based on the following criteria on the intended use:

a. Is not used as a component of the devices,

b. Is not a medical device itself,

c. Is not used for the production of the devices,

d. Is not used in the implementation of the Quality System.

To address the investigator's observation, SJM PRLLC documented guidelines to define the scope, purpose, and to provide the operators with general instructions for the use of the (b) (4) tool (see Appendix 2-1). In addition, SOP 602573 (Validation/Qualification PR LLC) was updated to Ver. V (see Appendix 2-2) to include in section 7.1 the requirement to document the rationale when an implementation of a system is not impacting the manufacture of the device or the quality systems.

To address this observation, SJM PRLLC completed the following specific activities:

a. Implement guidelines [document 90110972 (b) (4) ), Ver. A.] (see Appendix 2-1) to define the scope, purposes and provide the operators with general instructions to use the (b) (4) tool.

b. Update validation procedure 602573 from Ver. U to Ver. V to include in section 7.1 the requirement to document the rationale when an implementation of a system is not impacting the manufacture of the device or the quality systems (see Appendix 2-2).

Summary of Actions in Response to Observation 2.1:

| Action | Description | Completion Date |
|---|---|---|
| Implement documented guidelines (#90110972) for (b) (4) tool use by means of CO #C103705 (see Appendix 2-1). | Define the scope, purpose and to provide the operators with general instructions for use of the (b) (4) tool | 17 Oct 12 |
| Update SOP 602573 to Ver. V in section 7.1 by means of CO #C100102 (see Appendix 2-2). | To include the requirement to document the rationale when an implementation of a system does not impact the manufacturing of a device or the quality systems. | 17 Oct 12 |

**2b. Procedure #603348, Material Handling Control, PRLLC, established on site to assure the effectiveness of material handling controls in place for the manufacture of leads, pacers and ICD's fails to ensure adequate documentation of line clearance activities. Line clearance activities executed as described in the procedure and documented with form #101851, Material Handling Control (MHC) Checklist, does not require documentation of the date when the line clearance (verification of work station to reduce or eliminate the possibility of incorrect materials) was conducted or when the activity was reviewed-there is no documented evidence to ensure that in fact the activity was conducted prior to initiation of assembly activities as reported on the checklist.**

SJM PRLLC Response:

SJM PRLLC has established Instructions 603348 (Material Handling Control), Ver. E, to depict the steps required for line clearance activities (see Appendix 2-3). Form 101851 (Material Handling Control (MHC) Checklist CRM Operations), Ver. D, is used to document the line clearance activities for the different manufacturing operations (see Appendix 2-4). These activities include requirements for the removal of all material, product and components from a work cell after the completion of a designated production work order and prior to start a different work order.

Procedure 603348, Ver. E, defines the following sections that shall be performed in the following order to complete the form 101851:

"Section 7.2.1- Material Handler"
"Section 7.2.2-Review Activities performed by Quality"
"Section 7.2.3-Assembly Manufacturing Operator"

Form 101851, Ver. D, provides space to document the employee signature, employee ID and date for the Material Handler and Quality Review Activities sections (section 7.2.1 and 7.2.2). However, it does not provide space to document the date for the work cell line clearances to be performed by the assembly

manufacturing operator (section 7.2.3). During the manufacturing floor walkthrough with the FDA investigators, it was demonstrated that line clearance activities are being conducted as established in procedure 603348.

Material handlers, quality and manufacturing personnel are formally trained on procedure 603348 Ver. E and form 101851 Ver. D (see Appendix 2-5). Therefore, they are instructed to follow the order of the activities to complete the line clearance. Data from periodic internal audits for this year (2012); confirmed that employees audited were following the sequence established in the line clearance procedure 603348, Ver. E, as per training provided.

To address this observation, SJM PRLLC completed the following specific activities:

a. Form 101851, was updated to Ver. E (see Appendix 2-6) to include additional space to document the date in Table A. Evidence of this change was provided to the FDA investigator during the inspection.

b. To systematically address the investigator's findings the following activities were conducted:

   i. A total of (b) (4) PRLLC and (b) (4) Divisional Forms were reviewed (see Appendix 2-7). Changes were made to those that did not provide space to document the date.

   ii. SOP 602816 (Quality and Environmental Records, PR LLC) was updated to Ver. J (see Appendix 2-8) to establish in section 7.9 the requirement that the employee signature/initial shall be accompanied with the date.

Summary of Actions in Response to Observation 2.2:

| Action | Description | Completion Date |
|---|---|---|
| Update form 101851 to Ver. E, by means of CO #C101707 (see Appendix 2-6). | Include additional space and the requirement for date documentation in Table A. | 26 Sep 12 |
| Review PRLLC and Divisional Forms, verify if PRLLC and Divisional Forms have a space to document the date. Changes for PRLLC documents were implemented. (see Appendix 2-7). | Add space to document the date. | 17 Oct 12 |
| Update SOP 602816 to Ver. J, by means of CO #C103645 (see Appendix 2-8). | Establish the requirement that the employee signature/initial shall be accompanied with the date in section 7.9. | 17 Oct 12 |

**Observation 3**

**Process validation activities and results have not been approved and adequately documented.**

**Specifically,**

**Activities conducted on site describing the performance qualification report for the (b) (4) executed as described on protocol #90084631, 12/2011, and reported as successful on protocol report #90087565, January 2012, failed to include full documentation of activities conducted as executed including:**

a. **Full description of product samples reportedly manufactured at Woodridge, MN, and Caguas, PR, for the exercise in order to demonstrate that actual product used during the validation exercise is equivalent/similar to (b) (4) (justification for use, accurate size/ material description, comparison of "native units"/"demo units"/"clinical units"/"PCD" or product challenge devices vs. actual product units). Differences between packaging presentation described as "shipping crates", "shipping carton", and "shipping boxes" were not documented and were used interchangeably throughout the written protocol to describe/same product presentations.**

Part of observation addressed in the following section:

***"Full description of product samples reportedly manufactured at Woodridge, MN, and Caguas, PR, for the exercise in order to demonstrate that actual product used during the validation exercise is equivalent/similar to (b) (4) (justification for use, accurate size/ material description, comparison of "native units"/"demo units"/"clinical units"/"PCD" or product challenge devices vs. actual product units)".***

SJM PRLLC Response:

(b) (4) validation protocol #90084631 (see Appendix 3-1) was generated to validate (b) (4) (b) (4) in Arecibo PR. Protocol section 7, stated a description of the four (4) types of samples used in the (b) (4) validation; Native product, IP-PCD, EO/EC residual samples and dunnage (filler) units.

The native product samples are defined as follows: (b) (4) The native product samples must have successfully passed all inspection criteria with the exception of visual defects.

( b ) (

SJM PRLLC acknowledges that the procedures do not include a definition for samples (such as demo units) used in the validations; nevertheless Manufacturing Procedure 650221 (Demo Units), Ver. 11 (see Appendix 3-2) established the requirement to manufacture a Demo unit. Demo units are valves that are originated as clinical product and due to visual defects in the manufacturing process are converted to DEMO (see Appendix 3-2). These units are manufactured utilizing the same components and processes as a clinical unit based on MP 650221 and MP 650054 (Mechanical Heart Valve, Repair product and JSA Microbial sample processing), Ver. AM (see Appendix 3-3). The travelers included in validation

attachments confirm that units used for the validation were DEMO units and represent the components and processes of a clinical unit.

To add additional clarification on the terms used in this protocol/report the following table includes each of the terms and their relation to (b) (4) product being validated:

Equivalency comparison between (b) (4) and actual product used during this validation/report:

| Term utilized in protocol | Relation to (b) (4) for this protocol |
|---|---|
| Demo (b) (4) | (b) (4) |
| Demo Units | (b) (4) |
| Native Units | (b) (4) |
| Clinical Units | (b) (4) |
| PCD's | (b) (4) |

Procedures and (b) (4) reports were enhanced with the addition of these definitions. Redlined procedure 650221, Ver. 12, with the changes in the definitions section and 650054 Ver. AM were presented to the investigator during the inspection (see Appendix 3-4).

Protocol section 7 stated the use of "(b) (4)". Although we acknowledge that referring to (b) (4) can be interpreted as a range (b) (4)), later in the same section of the protocol it is established that sample size (b) (4) (there is no size (b) (4) will be used for validation. The (b) (4) size samples are the (b) (4) sizes of the product that represent a typical worst case scenario in terms of Bioburden and load density for routine (b) (4) and the ones used for this validation.

To address this observation, SJM PRLLC completed the following specific activities:

a. Procedure 650221 (Demo units) was updated to Ver. 12 (see Appendix 3-4) to include a specific definition of a DEMO unit in the definition section.

b. An addendum to validation report 90087565 was completed to clarify the definition of samples used (see Appendix 3-5).

c. SOP 602573 (Validation/Qualification) was updated to Ver. V (see Appendix 3-6) in section 7 and Appendixes A, B, and F to include requirements for sample descriptions. When non-clinical units are used, the appropriate rationale shall be included in the material section of the protocol/reports.

d. Checklist of validation templates was updated to include verification of sample description in all protocols and reports (see Appendix 3-7).

e. Validation protocols and report templates were updated to include a definition section. This change will ensure that acronyms and definition of samples are described in validation protocols and reports (see Appendix 3-7). A review of all (b) (4) and product transfer validations in Arecibo since 2010 was performed to ensure all samples used in the validations were defined. Two out of (b) (4) validations evaluated were updated (see Appendix 3-8).

Summary of actions in response to observation 3a:

| Action | Description | Completion date |
|---|---|---|
| Update MP 650221 to Ver. 12 in definitions section by means of CO #C101340 (see Appendix 3-4) | Include a specific definition of a DEMO unit. | 09 Sep 12 |
| Generate addendum to validation report 90087565 (see Appendix 3-5). | Clarify the definition of samples used during validations. | 20 Sep 12 |
| SOP 602573 was updated to Ver. V in section 7 and Appendixes: A, B and F section 6 by means of CO #C100102 (see Appendix 3-6). | Include requirements for sample descriptions and a rationale when non-clinical units are used. | 17 Oct 12 |
| Update checklist from validation templates referenced in SOP 602573 by means of CO #C100102 (see Appendix 3-7). | Include verification of sample descriptions in all protocols and reports. | 17 Oct 12 |
| Update validation protocols and report templates referenced in SOP 602573 by means of CO #C100102 (see Appendix 3-7) | To include a definition section | 17 Oct 12 |
| Review all (b) (4) and product transfer validations in Arecibo since 2010 (see Appendix 3-8). | Generate addendum for the identified validations that did not include sample definitions. | 17 Oct 12 |

Part of observation addressed in the following section:

***Differences between packaging presentation described as "shipping crates", "shipping carton", and "shipping boxes" were not documented and were used interchangeably throughout the written protocol to describe/same product presentations.***

SJM PRLLC Response:

Draft procedure 90097987 ((b) (4) ), Ver. A (see Appendix 3-9) was developed to provide the instructions for handling/shipping (b) (4) product to the Arecibo (b) (4) site. The procedure describes the following two packaging configurations in section 5:

a. Carton: Plastic shipping box where the product is placed.
b. Case: Black shipping case.

SJM PRLLC acknowledges that the words used to identify the packaging material in draft procedure 90097987, Ver. A were not consistent. The carton was referred to as a shipping box and carton in the document text, and the case was referred to as shipping case, shipping crates, black case and black shipping case in the document text; however the use of carton and cases were not interchanged in draft procedure 90097987, Ver. A, nor in the execution of the validation.

Carton (P/N 300688-001-Shipping Carton, Plastic) used to transport the (b) (4) unit to the (b) (4) site was referred to as shipping box in the (b) (4) validation protocol #90084631. There are no other shipping terms used interchangeably throughout the (b) (4) protocol #90084631 or report #90087565 (see Appendixes 3-1 and 3-10 respectively).

In addition to the draft of the manufacturing procedure 90097987, Ver. A, procedure 602744 (Shipping PRLLC), Ver. AC, used for handling of product prior and after (b) (4), was reviewed to assure consistency in the terms used to describe different packaging materials. No discrepancies were found (see Appendix 3-11). Therefore the use of different terms used in the (b) (4) draft procedure 90097987, Ver. A, did not have any impact on the conduct of the (b) (4) validation.

To address this observation, SJM PRLLC completed the following specific activities:

a. The different packaging materials used for (b) (4) were defined in section 5 of draft manufacturing procedure 90097987, Ver. A (see Appendix 3-9).

b. Manufacturing Procedure 650673 was updated to Ver. R (b) (4) ", used for (b) (4) processing, (b) (4) in (b) in section 5 to add the shipping material description in a definition section (see Appendix 3-12).

Summary of actions in response to observation 3a:

| Action | Description | Completion date |
|---|---|---|
| Update definitions section of draft procedure 90097987 Ver. A by means of CO #C095362 (see Appendix 3-9). | To define the different packaging materials used for (b) (4) product. | 19 Oct 12 |
| Update Manufacturing Procedure 650673 to Ver. R in definitions section by means of CO #C103172 (see Appendix (3-12). | To define the different packaging materials used for (b) (4) product. | 17 Oct 12 |

**b. Documented evidence to support the lack of product functional testing reported. The protocol reports that functional tests would not be required solely because the cycle under validation at Arecibo ((b) (4) ) is "the same" as the cycle conducted by the external contractor located at Minnesota-US. Impact on the product and seal integrity was not documented of different environmental conditions (including shipping) from product manufactured-shipped to Minnesota/Caguas and (b) (4) in Puerto Rico.**

(b) (4) validation protocol #90084631 was generated to validate (b) (4) process in Arecibo PR (see Appendix 3-1). The cycle parameters validated in Arecibo chamber #1 for (b) (4) product are equivalent to the cycle parameters validated at Steris MN. Although SJM PRLLC, Arecibo is a new (b) (4) validated in Arecibo has the same parameters for (b) (4) Therefore no changes to the (b) (4) were made for (b) (4) in Arecibo.

Even though the shipping configuration for transportation of product to the (b) (4) site did not change, the (b) (4) are different. SJM PRLLC acknowledges the fact that the package integrity shall be evaluated. For this reason a package integrity test evaluation for product manufactured

at Caguas had been initiated prior to the inspection and documented under protocol #90088394/report #90108482 (see Appendix 3-13). The protocol for this evaluation was presented to the investigator during the inspection. For product manufactured at Woodridge, the package integrity test evaluation was initiated during the FDA investigation and documented in protocol #90108920 and report #90110676 (see Appendix 3-14). Results from both qualifications confirmed there was no impact on packaging integrity due to the (b) (4) in Arecibo for products manufactured in Caguas and Woodridge.

**To address functional testing portion of this observation refer to response for observation #4.**

To address this observation, SJM PRLLC completed the following specific activities:

a. Generated an addendum to (b) (4) report #90087565 to include reference to the Packaging validations conducted for product manufactured in Caguas and Woodridge (see Appendix 3-5).

b. Updated SOP 602573 (Validation/Qualification PR LLC) to Ver. V (see Appendix 3-6) in section 7.8.1.6 to require a documented assessment on the need for Packaging integrity testing for new cycles and products introduction.

c. Successfully completed package integrity validation under protocol #90088394 and report #90108482 conducted for product manufactured in Caguas meeting all validation tests requirements (see Appendix 3-13).

d. Successfully completed package integrity validation conducted under protocol #90108920 and report #90110676 for product manufactured in Woodridge meeting all validation tests requirements (see Appendix 3-14).

Summary of actions in response to observation 3b:

| Action | Description | Completion date |
|---|---|---|
| Generate an addendum to report #90087565 (see Appendix 3-5). | Include the reference to the Packaging validations conducted for product manufactured in Caguas and Woodridge. | 20 Sep 12 |
| Update SOP 602573 to Ver. V in section 7.8.11.6 by means of CO #C100102 (see Appendix 3-6). | Add the requirement to document assessment for the need of Packaging integrity testing for new cycles and products introduction. | 17 Oct 12 |
| Complete Package integrity validation under protocol #90088394 and report #90108482 (see Appendix 3-13). | Validate Package integrity for product manufactured in PR. | 20 Oct 12 |
| Complete Package integrity validation under protocol #90108920 and report #90110676 (see Appendix 3-14). | Validate Package integrity for product manufactured in Woodridge. | 20 Oct 12 |

**Observation 4**

**Device packaging and/or shipping containers are not designed and constructed to protect the device from alteration or damage during processing, storage, handling, and distribution.**

**Specifically,**

**Protocol #90088394 approved on site on July 2012 for the packaging Integrity Performance Qualification of (b) (4) Products (b) (4) at Arecibo Site, and executed to provide documented evidence to demonstrate that the packaging tray integrity of (b) (4) units is maintained after a (b) (4) cycle, fails to report impact on product manufactured at Woodridge, Minnesota-US and (b) (4) at Arecibo, Puerto Rico or justification for lack-of. The protocol includes only tests conducted on product manufactured at Caguas (PR) transferred to Arecibo (PR)- but fails to include tests on product manufactured at Woodridge and shipped to Arecibo (as proposed on PMA P810002/S080) or documented evidence to support the lack of such tests.**
**In addition, protocol #90088394 reports that functional tests on product is not required because it was completed under protocol #873526 (January 2008), which only includes tests on product manufactured at Caguas (PR) and (b) (4) at Minnesota. No documented evidence is included with either protocol to support the firm's conclusion of no impact on the product and seal integrity under different environmental conditions (including shipping) for the new proposed (b) (4) site vs. the two proposed manufacturing sites.**

Part of observation addressed in the following section:

***Protocol #90088394 approved on site on July 2012 for the packaging Integrity Performance Qualification of (b) (4) Products (b) (4) at Arecibo Site, and executed to provide documented evidence to demonstrate that the packaging tray integrity of (b) (4) units is maintained after a (b) (4) cycle, fails to report impact on product manufactured at Woodridge, Minnesota-US and (b) (4) at Arecibo, Puerto Rico or justification for lack-of. The protocol includes only tests conducted on product manufactured at Caguas (PR) transferred to Arecibo (PR)- but fails to include tests on product manufactured at Woodridge and shipped to Arecibo (as proposed on PMA P810002/S080) or documented evidence to support the lack of such tests.***

SJM PRLLC Response:

SOP 602573 (Validation/Qualification PR LLC), Ver. U (see Appendix 4-1) assures that processes or operations are identified and validated or qualified in accordance with St. Jude policies, FDA QSR and ISO-13485:2003 requirements, by defining the steps necessary for qualifications or validations in SJM PRLLC.

In response to this observation, we have reviewed our validation process. After evaluating our procedure 602573, Ver. U, two areas of opportunity were identified:

a. In Appendix A (Qualification/Validation Protocol Format), section 2.0 "Scope" instructs the protocol owner to describe the extent of the qualification and establishes the areas to be covered by the qualification (for example: facilities involved, equipment affected by the qualification). However, the procedure could be more specific requiring that product from other manufacturing sites be included as part of the validation requirements, and/or a documented justification for lack of.

b. In Appendix A (Qualification/Validation Protocol Format), section 8.0 "Sample Size Determination" instructs the protocol owner to document a logical and justifiable way to determine the appropriate sample size. The instruction is limited to the rationale or justification on how many samples have to be documented. However, the procedure could be more specific on the rationale and justification for the product selection (product family and/or model, etc.) to be used.

We have retrospectively reviewed all validations generated from 2010 to 2012 and qualification protocol #90084631 and report #90087565 reviewed by the investigator was the first validation that included product from multiple sites (see Appendix 4-2).

St Jude Medical PRLLC acknowledges that product from Woodridge was not included as part of protocol #90088394 (see Appendix 4-3). To address this gap a new protocol #90108920 was generated and executed. The purpose of this validation was to provide documented evidence that the packaging tray integrity of (b) (4) ) units built in Woodridge is maintained after units are submitted to a (b) (4) in (b) (4) Chamber #1-(b) (4) located at the SJM Arecibo PRLLC Facility. The validation reports: #90108482 and #90110676 (see Appendix 4-4) concludes that the Performance Qualification Exercise has met the acceptance criteria established in the Performance Qualification Protocols: #90088394 and #90108920. Therefore it is concluded that the packaging integrity of (b) (4) products is maintained after units were submitted to (b) (4) in (b) (4) Chamber #1.

Part of observation addressed in the following section:

***In addition, protocol #90088394 reports that functional tests on product is not required because it was completed under protocol #873526(January 2008), which only includes tests on product manufactured at Caguas (PR) and (b) (4) at Minnesota. No documented evidence is included with either protocol to support the firm's conclusion of no impact on the product and seal integrity under different environmental conditions (including shipping) for the new proposed (b) (4) site vs. the two proposed manufacturing sites.***

SJM PRLLC Response:

In response to this observation, a Technical Report #90111066 (See Appendix 4-5), was developed to provide supplemental rationale for why product functional testing is not required as referenced in the protocol 90088394, section 7.2. The report provides rationale from two perspectives:

a. Simulated Shipping/Distribution, Humidity, and Thermal Shock.

b. (b) (4)

Rationale for no functional testing from *shipping/distribution, humidity, and thermal shock* perspective for protocol 90088394, section 7.2:

> The Technical Report concluded that Performance qualification protocol #90088394 provides evidence that the sterile barrier system of the (b) (4) product is maintained after units are submitted to a (b) (4) in (b) (4) Chamber #1 at SJM Arecibo PRLLC facility. Additional product functional testing does not need to be performed because it is covered within the scope of the testing completed in the (b) (4) performance validation (TR 872040) and (b) (4) package validation (TR 872047) (see Appendix 4-6).

Rationale for no functional testing from (b) (4) perspective for protocol #90088394, section 7.2:

Performance qualification report #90108482 provides evidence that the (b) (4) system of the (b) (4) product is maintained after units are submitted to a (b) (4) (b) (4) in (b) (4) Chamber #1 at SJM Arecibo PRLLC facility. Additional product functional testing does not need to be performed due to a change in the (b) (4) facility because functional testing is covered within the scope of the testing completed in the (b) (4) Performance Validation" (TR 872040) and (b) (4) package validation (TR 872047) (see Appendix 4-6).

Summary of Corrective Actions in Response to Observation #4

| Action | Description | Completion date |
|---|---|---|
| Validations Assessment (see Appendix 4-2) | Assess validations generated from 2010 to 2012 for similar situation (validation covering products from different sites). | 18 Oct 12 |
| Complete Validation Protocol #90108920 /Report #90110676 (see Appendix 4-4) | Provide documented evidence that the packaging tray integrity of (b) (4) ) from units built in Woodridge is maintained after being (b) (4) at the SJM Arecibo Facility. | 12 Oct 12 |
| Technical Report #90111066 Approval (see Appendix 4-5). | Provide supplemental rationales for why product functional testing is not required as referenced in the protocol #90088394, section 7.2. | 19 Oct 12 |
| Update SOP 602573 to Ver. V by means of CO #C100102 (see Appendix 4-7). | Add requirements in section 7.6.3 and in section 2 of Appendixes: A, B, E and F to include product from additional sites.<br>Add requirements for sample types utilized in section 7.8.1.6. (product, family, etc.) . | 17 Oct 12 |

**Observation 5**

**Software validation activities and results for computers or automated data processing systems used as part of production have not been adequately documented.**

**Specifically,**

**Not all activities reported on the (b) (4) #60025082, Rev A., including test requirements/design/procedures and acceptance criteria for the verification of the (b) (4) used to control the (b) (4) cycle, were fully documented to comply with the requirements described on the plan. For example, section 8.4 of the (b) (approved on June 2009) includes the 21 CFR Part 11 Compliance and System Security requirements, describing procedures and levels of access to be granted for users accessing the controller. However, no formal procedure was established on site for the implementation of the security requirements prior or during the executions of the protocol control users with access to the system. Furthermore, no documented evidence was included with the execution of the plan to confirm that compliance with the system security was in fact executed.**

Part of observation addressed in this section:

1) ***"Not all activities reported on the (b) (4) #60025082, Rev A., including test requirements/design/ procedures and acceptance criteria for the verification of the (b) (4) controller used to control the (b) (4) cycle , were fully documented to comply with the requirements described on the plan. For example, section 8.4 of the (b) (approved on June 2009) includes the CFR 21 Part 11 Compliance and System Security requirements, describing procedures and levels of access to be granted for users accessing the controller."***
2) ***"Furthermore, no documented evidence was included with the execution of the plan to confirm that compliance with the system security was in fact executed."***

SJM PRLLC Response:

The (b) (4) ) #60025082 (also identified as (b) #1065, Rev. 1.0), Rev A, (Verification for (b) (4) (b) (4) ) (see Appendix 5-1) "(b) " was generated for the (b) (4) located at the St. Jude Medical PRLLC, Arecibo, Puerto Rico site. The (b) (4) system operates under the "(b) (4) " environment which includes the security (user access) features and the (b) (4) " application which provides the operational capabilities and user interface for the (b) (4) The (b) (4) system is certified 21 CFR Part 11 compliant by (b) (4) (system manufacturer).

Refer to the following figure for a general depiction of the various interfaces of the (b) (4):


The changes to the (b) (4) process steps that were required as part of Protocol #90084631/Report #90087565(Validation of Arecibo PR (b) (4) Chamber #1 for (b) (4) of (b) (4) Product) (see Appendix 5-2) were documented as part of (b) (4) (b) (4) #1065, addendum #07 (see Appendix 5-3). The changes were: an (b) (4).

For the inclusion of (b) (4) into the system, section 8.4 (21 CFR Part 11 compliance and system Security) of the (b) was not required due to the following:

a. Section 8.4 of the (b) #60025082 (#1065) was verified and documented as part of the original execution of (b) #1065, Rev 1.0 and approved on October 2009 (see Appendix 5-4). Section 8.4 verified: that the system requires user ID and password, confirmation of the levels of security within the system, and that the system maintains audit trails of changes. The changes related to the (b) (4) validation did not affect the "(b) (4)" environment that controls the system security access. (b) #1065, addendum #07 was executed to verify the (b) (4) addition of a (b) (4) (see Appendix 5-3). These changes impacted only the (b) (4) " application, which is not related with security features of the (b) (4) ("(b) (4) (b) (4) " environment). The test sequence of (b) #1065, addendum #07 consisted of:

   i. Documentation verification of the software document 60025082.

   ii. Running the currently validated (b) (4) to confirm that the changes incorporated with the inclusion of the (b) (4) cycle ((b) (4) ) did not affect the (b) (4).

   iii. Performing a verification of the (b) (4) (b) (4) cycle Parameters printout to confirm the presence of the (b) (4).

Part of observation addressed in this section:

3) ***"However, no formal procedure was established on site for the implementation of the security requirements prior or during the executions of the protocol control users with access to the system."***

SJM PRLLC Response:

A verification of the (b) (4) (validation protocol #90084631, report #90087565) was performed in order to determine if all the personnel that operated the (b) (4) had received their system access prior to the execution of the validation protocol. The evaluation confirmed that all the operators of the (b) (4) during the execution of the validation protocol, had been granted their system access and no discrepancy was found.

The table below depicts a cross-reference of the personnel involved in the operation of the (b) (4) during the execution of the (b) (4) protocol:

| Cycle # | Cycle Description | Cycle Start Date | Operator | Date System Access Granted |
|---|---|---|---|---|
| (b) (4), (b) (6) | | | | |
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SJM PRLLC acknowledges an area of opportunity in regard to granting access to the (b) (4) system; specifically, formalizing the actual process of granting access. A Standard Operating Procedure (SOP) 90108848, Ver. A, (see Appendix 5-5) to address access requests to the (b) (4) system was created. This SOP also incorporated the use of a form (form 90108842 Ver. A) to document the access requests. Both documents had been released under Change Order (CO) #C101366 with an implementation date of 20 Sep 12. Copies of the implemented documents and CO were provided to the investigator prior to her departure from the SJM Arecibo site.

The current method of granting security access to the computerized systems consists of:

a. The system administrator determines if users met applicable training requirements.

b. The system administrator notifies the Information Technology (IT) Access Administrator making the request of access to the system.

c. The IT Access Administrator grants Access to the user.

The area of opportunity with the steps mentioned above is that they are not part of a formal procedure, therefore, as an additional corrective measure from a system perspective, the existing Standard Operating Procedure (SOP) 603162 (IT General Security Management, PR LLC) was updated to Ver. D to establish the requirements to grant access controls to computerized systems (see Appendix 5-6). Furthermore, as part of the update of SOP 603162, the document 90108848 and form 90108842 will be incorporated under the scope of procedure 603162.

To address this observation, SJM PRLLC completed the following specific activities:

a. Standard Operating Procedure (SOP) 90108848, Ver. A, and form 90108842, Ver. A, were created to address access requests to the (b) (4) system (see Appendix 5-5).

b. Standard Operating Procedure (SOP) 603162 "IT General Security Management" was updated to Ver. D to establish the requirements to grant access controls to computerized systems (see Appendix 5-6).

Summary of corrective actions in response to Observation 5

| Action | Description | Completion Date |
|---|---|---|
| Create SOP for access requests for (b) (4) system by means CO #C101366 (see Appendix 5-5). | Incorporates the steps to be followed at the time of requesting and granting user access to the (b) (4) system. | 20 Sep 12 |
| Update SOP 603162 to Ver. D by means of CO #C103574 (see Appendix 5-6). | Include enhancements in regard to the access control to computerized systems. | 17 Oct 12 |

**Observation 6**

**Procedures for product handling have not been adequately established.**

**Specifically,**

**Procedure # 90097987, (b) (4) , including instructions for the preparation for shipment to Arecibo of (b) (4) units and handling during (b) (4) and (b) (4) (which included activities executed for protocol #90084631, 12/2011, and report #90087565) fails to include an accurate depiction of units used for shipping materials and accurate depiction of responsibilities per areas involved ("trained inspectors" vs. "shipping") in the process of handling units shipped to Arecibo for (b) (4) and subsequent shipment to another site for further processing after (b) (4) .**

Part of observation addressed in this section:

***"Procedure # 90097987, (b) (4) , including instructions for the preparation for shipment to Arecibo of (b) (4) units and handling during (b) (4) and (b) (4) (which included activities executed for protocol #90084631, 12/2011, and report #90087565) fails to include and accurate depiction of units used for shipping materials"***

SJM PRLLC Response:

As mentioned in observation 3 response, the draft procedure 90097987, Ver. A, used for handling of product prior and after (b) (4) was reviewed to ensure consistency in the terms used for different packaging presentations in the definitions section (see Appendix 6-1).

To address this observation, SJM PRLLC completed the following specific activities:

a. The different packaging materials used for (b) (4) were defined in draft procedure 90097987 in the definitions section (see Appendix 3-8).
b. Manufacturing Procedure 650673 ((b) (4) , (b) (4) ), Ver. P, used for Pre and post (b) (4) processing, (b) (4) (b) (4) was updated in section 5 to add the shipping material description in a definition section (see Appendix 3-12).

Part of observation addressed in this section:

***"an accurate depiction of units used for shipping materials and accurate depiction of responsibilities per areas involved ("trained inspectors" vs. "shipping") in the process of handling units shipped to Arecibo for (b) (4) and subsequent shipment to another site for further processing after (b) (4) ."***

SJM PRLLC has established procedures to control and define format for standardization of documents. QS Work Instruction 90011296 "Document Format/Content", Ver. K, defines the format and content requirements for controlled documents (see Appendix 6-3).

Draft procedure 90097987, Ver. A, "(b) (4) ", includes section 4.0 "Responsibilities" as required on procedure 90011296. SJM PRLLC acknowledges that the trained operator and trained inspector responsibilities in this procedure were placed together and could imply that

both perform the same activities. Section 4.0 was revised along with the procedure body to clarify operator and inspector responsibilities (see Appendix 6-1).

To address this observation, SJM PRLLC completed the following specific activities:

a. Updated responsibilities section of the draft of document 90097987, Ver. A, to separate the responsibilities of trained operators and inspectors and procedure body to enhance operator and inspector responsibilities (see Appendix 6-1).

b. To address this in a systemic way, PRLLC procedures and divisional documents were revised to assure the responsibilities are clearly defined. A total of 425 documents were revised/updated as required (see Appendix 6-4).

Summary of corrective actions in response to Observation 6

| Action | Description | Completion Date |
|---|---|---|
| Update draft procedure 90097987, Ver. A, by means of CO #C095362 (see Appendix 6-1). | Enhance trained operator and trained inspector responsibilities. | 19 Oct 12 |
| Revise and update PRLLC procedures and divisional documents (see Appendix 6-2) | Systemic review of 425 documents to clearly define the responsibilities. | 18 Oct 12 |