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Inspections, Compliance, Enforcement, and Criminal Investigations

Advanced Sterilization Products



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Los Angeles District
Pacific Region
19701 Fairchild
Irvine, CA 92612-2506
Telephone: 949-608-2900
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WARNING LETTER

**CERTIFIED MAIL
RETURN RECEIPT REQUESTED**

March 12, 2010

W/L 10-1

William C. Weldon, CEO
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, New Jersey 08933

Dear Mr. Weldon:

During an inspection of your firm, Advanced Sterilization Products, located in Irvine, California on June 1, 2009, through September 28, 2009, investigators from the United States Food and Drug Administration (FDA) determined that your firm manufactures STERRAD models, 50, 100S, 200, NX and 100NX Hydrogen Peroxide Gas Plasma Sterilizers, STERRAD CycleSure Biological Indicator (BI), CIDEX disinfectants (including the CIDEX Activated Dialdehyde Solution), CIDEX Tes Strips, and the Evotech Cleaner and Reprocessor. Under Section 201 (h) of the Federal, Food, Drug and Cosmetic Act (the Act), 21 U.S.C. § 321 (h), these products are devices because they are intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, or are intended to affect the structure or function of the body.

This inspection revealed that the devices are adulterated within the meaning of section 501(h) of the Act, (21 U.S.C. § 351(h)), in that the methods used in, or the facilities or controls used for manufacturing, packaging, storage, or installation are not in conformity with the Current Good Manufacturing Practice (CGMP) requirements for the Quality System (QS) regulation, found at Title 21, **Code of Federal Regulations** (CFR), Part 820. We have received Advanced Sterilization Product's response dated October 16, 2009, concerning our investigator's observations noted on the Form FDA 483, List of Observations that was issued. We address your responses below, in relation to each of the noted violations. These violations include, but are not limited to, the following:

1. Failure to establish and maintain adequate procedures for verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished devices, as required by 21 CFR § 820.100(a)(4).

For example:

a. CAPA 07-000027 was opened on November 30, 2007, to investigate root cause and implement corrective and preventive action for Sterrad Sterilizer models 50 and 100S, based on customer reports of the sterilizers emitting oil mist. Your firm's corrective action was to increase the Preventive Maintenance (PM) frequency for the Sterrad 100S Sterilizer from **(b) (4)**. The field corrective action for CAPA 07-000027 took place from April 28, 2008 through October 31, 2008. However, actions taken by your firm to correct and prevent recurrence of these events were inadequate in that:

i) The effectiveness check performed for this CAPA was not adequate to assess impact on all Sterrad 100S units

affected by the PM change in that, less than three months (or less) had elapsed between completion of the field correction, and completion of the recall effectiveness check for: at least sixty six (66) Sterrad 100S sterilizer units. In addition, your firm received additional complaints **(b) (4)** alleging oil misting had occurred prior to elapse of the **(b) (4)** schedule for the Sterrad 100S.

ii) Your firm's effectiveness check acceptance criteria for CAPA 07-0000027 was established as **(b) (4)** events of oil misting in the Sterrad 50 and 100S sterilizers. However, your firm failed to provide effectiveness criterion and **(b) (4)** for each Sterrad model. In addition, the **(b) (4)** observed for the STERRAD 100S prior to the field corrective action.

b. Your firm initiated CAPA 08-000008 on February 5, 2008, to address 26 customer complaints alleging hydrogen peroxide contact when handling STERRAD CycleSure Biological Indicators (BI's), where media ampoules were found broken following Sterrad sterilization cycles. Your firm identified the root cause as small cracks in the media ampoule causing the ampoules to break during the sterilization cycle and causing hydrogen peroxide to condense on the BI. Your firm's CAPA actions were to revise the CycleSure Instructions for Use by adding the wearing of gloves when handling BI's and ensuring updates of the media ampoule inspection and the handling procedure during the assembly of the BI's. However, your firm did not conduct an effectiveness check to assess whether the actions were effective.

Your firm's response dated October 16, 2009, is not adequate because your firm did not provide a commitment to conduct effectiveness checks on approximately sixty-six (66) STERRAD 100S units after the required field corrective action had been taken. In addition, your firm stated that the **(b) (4)** was set as a collective effectiveness criterion for all STERRAD models but did not provide effectiveness criterion and **(b) (4)** for each STERRAD model. Additionally, your response is inadequate because no assessment was conducted to determine if the actions were effective when the Corrective Actions were implemented. A total of five (5) complaints were received but your firm failed to provide a summary of the complaints and the time period the assessment was conducted.

2. Failure to establish and maintain adequate procedures for the verification of design changes before their implementation, as required by 21 CFR § 820.30(i).

For example, your firm initiated CAPA 07-0000022 to address a lack of assurance that information disseminated to customers on medical device compatibility with STERRAD Sterilization Systems (SSS) was current and accurate. Your firm subsequently implemented an online Sterrad Sterility Guide (SSG) to assist Sterrad users in determining which devices have been publicly endorsed by the medical device manufacturers (MDM) for processing in the SSS. However, your firm's CAPA action was ineffective in that your firm failed to verify that all published materials by the MDM were current prior to inclusion of these devices in the SSG as stated in SP 101258 Revision C, Step 4.1. For instance:

a. Your firm used a three year old Customer letter, dated December 7, 2005, to support inclusion of the **(b) (4)** on the SSG, August 6, 2008.

b. Your firm used information indicating that the Sterrad 100S could provide adequate sterility assurance for the **(b) (4)** as justification to add the device to the SSG on August 6, 2008. However this information is over two years old (dated February 3, 2006).

c. Your firm used a two year old cover letter for a user manual (dated March 9, 2006) from the MDM stating that the device, **(b) (4)** is compatible with Sterrad Sterilization Systems and was added to the SSG on August 6, 2008

d. The supporting documentation to support inclusion of **(b) (4)** on the SSG is approximately 1.5 years old and was not included in the audit file at ASP prior to the start of the inspection.

e. There was no documentation accompanying the STERRAD Sterility Audit Form used to add the following device to the SSG: **(b) (4)**. In addition, Documentation used to add **(b) (4)** to the SSG was Dated March 2, 2007.

Your response to this observation dated October 16, 2009, appears to be adequate.

3. Failure to establish and maintain adequate procedures to ensure that those design outputs that are essential for the proper functioning of the device are identified, as required by 21 CFR § 820.30(d);

For example, the "Instruction For Use" (IFU) for CycleSure Biological Indicators (BI) revisions 101011-01 and 101011-02 stated that the BI media color change (from purple to yellow) and/or turbidity change (from clear to turbid) should be evaluated as a positive result. However, your firm did not provide adequate "Instructions for Use" for users to be able to accurately interpret the color change. Also, there were seven complaints **(b) (4)** from users stating that they were unable to identify the positive or negative BI test results. Consequently, your firm failed to establish acceptance specifications for positive CycleSure BI read-out test results in order for users to clearly determine test outcomes for BI's used as positive controls or process challenges.

Your response to this observation dated October 16, 2009, is not adequate because your firm did not sufficiently address the corrective action or the systemic corrective action within the design process to prevent this type of problem from occurring in the future.

4. Failure to establish and maintain adequate procedures for finished device acceptance to ensure that each production run, lot, or batch of finished devices meets acceptance criteria, as required by 21 CFR § 820.80(d).

For example, your firm's procedure titled *Biological Indicator/Chemical Indicator Response of CycleSure Biological Indicator* 14324, document no. TP-I00867, revision B, issue date September 25, 2008, provides a method to evaluate the biological performance of the indicator disc located on the CycleSure Biological Indicator (BI). This procedure is

used for routine lot release testing of the CycleSure biological/chemical indicator. The test methodology and acceptance specifications are inadequate in that:

a. Your firm did not assess each lot of CycleSure BIs for the maximum readout time of 5 or 7 days (depending on date of manufacture) as stated in the CycleSure BI Instructions for Use (IFU). This is exemplified by test documentation for the following lots of CycleSure BI finished--goods: **(b) (4)** for which result read-out times ranged from a minimum of **(b) (4)** and a **(b) (4)**. In addition, your firm received seven (7) complaints alleging that positive result CycleSure Biological Indicators did not maintain a yellow color as indicated by the product IFU. Your firm opened CAPA 09-0000006 on January 15, 2009, to address this issue.

b. Acceptance criteria for biological response test of the CycleSure Biological Indicator are incomplete. The test procedure, *Reporting of Biological Indicator Response* (TP-100867, revision B, section 15.1), does not specify what constitutes a positive test result, but only states that *positive is to be documented as positive and negative is to be documented as negative*. Additionally, this procedure does not require assessment of positive controls or test samples for turbidity, even though the product's IFU provides that a yellow color and/or turbidity should be judged as a positive result. Further, the form for recording BI response tests does not provide a field to document whether a positive result was due to observation of yellow color or turbidity.

c. Test procedure *Reporting of Biological Indicator Response*, TP-100867, revision B, indicates that two BIs are pulled from the lot to be used as a positive and a negative control for each of the two test cycles. Test samples from the same lot are then assessed against these controls for purple (negative) or yellow (positive) color change. However, your firm failed to adequately define the acceptance criteria for the yellow color by not establishing an external standard measure.

Your firm's response dated October 16, 2009, appears to be adequate.

5. Failure to establish and maintain procedures for identifying valid statistical techniques required for establishing, controlling and verifying the acceptability of process capability and product characteristics, as required by 21 CFR § 820.250(a).

For example, your firm does not have adequate statistical rationale to support the techniques used in trending of customer complaints per your firm's procedure SP-14122, "Complaint Trending and Escalation Process," revision F, issued October 02, 2008.

Your firm's response dated October 16, 2009, is not adequate because your firm has not provided adequate statistical rationale for your firm's Complaint Trending and Escalation Process procedure. Please contact the Center for Devices and Radiological Health's (CDRH) Office of Compliance (OC) with further responses.

Our inspection also revealed that the STERRAD® CycleSure® Biological Indicator (BI) is adulterated under section 501(f)(1)(B) of the Act, 21 U.S.C. § 351(f)(1)(B), because you do not have approved application for pre-market approval (PMA) in effect pursuant to section 515(a) of the Act, 21 U.S.C. § 360(e)(a), or approved applications for an investigational device exemption (IDE) under section 520(g) of the Act, 21 U.S.C. § 360G(g). These devices are also misbranded under section 502(o) of the Act, 21 U.S.C. § 352(o), because you did not notify the agency of your intent to introduce the devices into commercial distribution, as required by section 510(k) of the Act, 21 U.S.C. § 360(k) in that a notice or other information respecting the modification to the device was not provided to the FDA as required by section 510(k), 21 U.S.C. § 360(k), and 21 CFR § 807.81(a)(3)(i).

Specifically, the STERRAD CycleSure Biological Indicator (BI), K071014, was cleared for the standard method of frequent monitoring of the STERRAD Sterilizer cycles. The device contains the following changes or modifications that could significantly affect the safety and effectiveness of the device and requires a new 510(k) premarket notification clearance application:

1. The "Instructions For Use" for the STERRAD CycleSure Biological Indicator (BI) were changed to instruct the user to read the BI results within 5 days of incubation instead of 7 days of incubation.
2. A change in the **(b) (4)** component of the CycleSure Biological Indicator (BI) device which is intended to prevent microbial contamination during incubation, and **(b) (4)** into the CycleSure BI during the STERRAD sterilization process.

Your firm's response dated October 16, 2009, appears to be adequate. We acknowledge that your firm has submitted a new premarket notification clearance application **(b) (4)** as of July 8, 2009.

A follow up inspection will be required to fully assess the adequacy and sustainability of your corrective actions.

You should take prompt action to correct the violations addressed in this letter. Failure to promptly correct these violations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil money penalties. Also, federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts. Additionally, premarket approval applications for Class III devices to which the Quality System regulation deviations are reasonably related will not be approved until the violations have been corrected. Requests for Certificates to Foreign Governments will not be granted until the violations related to the subject devices have been corrected.

We are requesting that you submit to this office on the schedule below, certification by an outside expert consultant that he/she has conducted an audit of your establishment's manufacturing and quality assurance systems relative to the requirements of the device QS regulation (21 CFR, Part

820). You should also submit a copy of the consultant's report, and certification by your establishment's Chief Executive Officer (if other than yourself) that he or she has reviewed the consultant's report and that your establishment has initiated or completed all corrections called for in the report. The initial certifications of audit and corrections and subsequent certifications of updated audits and corrections (if required) should be submitted to this office by the following dates:

- Initial certifications by consultant and establishment - August 1, 2010.
- Subsequent certifications - August 1, 2011 and August 1, 2012.

Please notify this office in writing within fifteen (15) working days from the date you receive this letter of the specific steps you have taken to correct the noted violations, including an explanation of how you plan to prevent these violations, or similar violations, from occurring again. Include documentation of the corrective action you have taken. If your planned corrections will occur over time, please include a timetable for implementation of those corrections. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your written response should be sent to:

Alonza E. Cruse
District Director
U.S. Food and Drug Administration
19701 Fairchild
Irvine, CA 92612-2506

If you have any questions about the content of this letter please contact: Ms. Mariza Jafary, Compliance Officer, at 949-608-2977

Finally, you should know that this letter is not intended to be an all-inclusive list of the violations at your facility. It is your responsibility to ensure compliance with applicable laws and regulations administered by FDA. The specific violations noted in this letter and in the Inspectional Observations, Form FDA 483 (FDA 483), issued at the closeout of the inspection may be symptomatic of serious problems in your firm's manufacturing and quality assurance systems. You should investigate and determine the causes of the violations, and take prompt actions to correct the violations and to bring your products into compliance.

Sincerely,
/S/

Alonza E. Cruse
District Director
Los Angeles District

Attachment

Cc: Acting Branch Chief
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