Inspections, Compliance, Enforcement, and Criminal Investigations

IsoAid, L.L.C. 8/16/12

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Florida District
555 Winderley Place, Suite 200
Maitland, Florida 32751
Telephone: 407-475-4700
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CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER
FLA-12-41
August 16 2012

Max M. Taghizadeh
President
IsoAid, LLC
7824 Clark Moody Blvd
Port Richey, FL 34668 U.S.A.

Dear Mr. Taghizadeh:

During an inspection of your firm located in Port Richey, Florida, April 12 through April 20, 2012, an investigator from the United States Food and Drug Administration (FDA) determined that your firm manufactures the Advantage Iodine-125™ and Advantage PD-103™ Brachytherapy Seeds, and the Advantage-Strand™/Advantage-Load™ Brachytherapy Kit. 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 these 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, their manufacture, packing, storage, or installation are not in conformity with the Current Good

Manufacturing Practice (CGMP) requirements of the Quality System (QS) regulation found at Title 21, Code of Federal Regulations (C.F.R.), Part 820. We received responses from you dated May 10, 2012 and June 25, 2012, concerning our investigator's observations noted on the Form FDA 483, Inspectional Observations, which was issued to you. We address these responses below, in relation to the noted violations. These violations include, but are not limited to, the following:

1. Failure to adequately ensure that when the results of a process cannot be fully verified by subsequent inspection and test, that the process shall be validated with a high degree of assurance and approved according to established procedures, as required by 21 C.F.R. 820.75(a). For example:

a. The procedures titled IsoAid – Technical File: Advantage I-125 Brachytherapy Seeds, Sterilization Validation Performance Qualification Protocol, EO-PQ-01, Rev. Orig., (Reference B), references using the elements of standard ISO 11135-1:2007, Sterilization of Health Care Products – **(b)(4)**. However, the ISO 11135-1:2007 standard – Requirements for development, validation and routine control of an **(b)(4)** sterilization process for medical devices, does not cover sterilization by injecting **(b)(4)** or mixtures containing **(b)(4)** directly into individual product packages, or continuous sterilization processes. Therefore, your **(b)(4)** sterilizer cannot be validated per the ISO 11135-1:2007 standard requirements.

b. Your firm failed to validate the **(b)(4)** Heat Sealer process for the needle tray package, vial package, and cartridge tray package configurations. There is no documentation establishing your current settings as validated operating parameters for routine heat seal processing.

c. Your firm failed to validate the **(b)(4)** -reader used to evaluate **(b)(4)** Readout Biological Indicators (BIs) used in the conduct of **(b)(4)** sterilization processing to ensure that the lethality of the sterilization process achieves a SAL **(b)(4)** and that the reader and BIs are valid and accurate.

The adequacy of your responses cannot be determined at this time. Your initial response dated May 10, 2012, states that "IsoAid has started working closely with both **(b)(4)** the manufacturer of the sterilizers currently in use and **(b)(4)**, a group that specializes in sterilization validation of **(b)(4)** Sterilizers. IsoAid plans to complete proper revalidation of the sterilizers (following ISO 11135-1), heat sealer and biological indicator (BI) reader within 3 months." Your June 25, 2012 response states that "IsoAid now has decided to explore other **(b)(4)** sterilizer machines. IsoAid is currently performing feasibility testing on **(b)(4)** **(b)(4)** Sterilizer." These responses do not fully detail the corrective actions concerning Brachytherapy devices currently distributed by your firm which are processed using the **(b)(4)** sterilizers. Your June 25, 2012 response also states "Validation protocols for our heat sealer and BI reader are in the development process with the help of validation consultants." The response lacks sufficient details regarding the corrective actions that these processes have been adequately validated.

2. Failure to develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications, as required by 21 C.F.R. 820.70(a). Where deviations from device specifications could occur as a result of the manufacturing process, the manufacturer shall establish and maintain process control procedures that describe any process controls necessary to ensure conformance to specifications.

For example, your firm's **(b)(4)** Sterilization Procedure, SOP 09-18, Rev. 1, dated October 29, 2009, states in Section 7.18 that, "the sterilization cycle is considered to have been successful only if, all three BIs from the run are negative and the control is positive." The procedure does not include provisions when **(b)(4)** Readout BIs are found positive and your firm fails to document the conduct of any investigation into the **(b)(4)** BI nonconformances for the following sterilization runs:

run #	date	nonconformance reason
0026	12/01/09	failed
0028	12/02/09	failed
0040	12/14/09	failed
0051	12/24/09	failed
0069-1	01/14/10	failed
0967-2	10/11/11	failed
0090-1	02/01/10	all bad
0274-1	06/15/10	not signed off as negative growth
0842-2	07/27/11	reran under 844-2

The adequacy of your responses dated May 10, 2012 and June 25, 2012, cannot be determined at this time because they lack details regarding your corrective actions and their implementation. We acknowledge you have recently updated your **(b)(4)** Sterilization Procedure, SOP 09-18, Rev. 2, to include provisions for when **(b)(4)** Readout BIs are found positive. However, this procedure (Rev.2) does not appear to be signed and dated as issued and effective for use. Further, you failed to provide any documentation of, or plan to review, evaluate, and investigate "…all Sterilization Runs for the past 2 years…" of "…any failures or inadequately approved runs", as stated in your May 10, 2012 response.

3. Failure to validate computer software for its intended use according to an established protocol, when computers or automated data processing systems are used as part of production or a quality system, according to established procedure, as required by 21 C.F.R. 820.70(i). For example, there are no procedures that describe the qualification and maintenance of the Sorting software for decay calculations on brachytherapy seeds sorted into inventory. There are no software verification and validation requirements defined in your firm's procedures, and there are no records documenting that the Sorting software is fully validated for its intended uses. Your firm updated the Sorting software in May 2009, to address a "glitch" when sorting brachytherapy seeds and their respective activity into properly labeled containers; however, your firm failed to validate the updated software prior to implementation for use. There are no procedures or documents that describe changes and version updates to the Sorting software. There are no documents that define the software's features and functions, operating environment, or hardware requirements.

The adequacy of your responses dated May 10, 2012 and June 25, 2012, cannot be determined at this time because they lack details regarding your corrective actions and their implementation. We acknowledge your June 25, 2012 response includes the procedure, Software Validation, SOP 09-27, Rev. 0. However, this procedure does not appear to be signed and dated as issued and effective for use. Further, you have not demonstrated your firm has conducted any software verification and validation activities in accordance with the procedure.

4. Failure to establish and maintain documented instructions, standard operation procedures (SOP's), and methods that define and control the manner of production, as required by 21 C.F.R. 820.70(a)(1), and to fully monitor and control component and device characteristics during production, as required by 21 C.F.R. 820.70(a)(2). For example,

a. Your firm has no written procedures or protocol covering **(b)(4)** residue testing of your manufactured Iodine and Palladium Brachytherapy seeds and Brachytherapy kits consisting of seeds and spacers pre-loaded into synthetic absorbable Brachytherapy sleeves.

b. August 2009 **(b)(4)** residue test performed after one **(b)(4)** **(b)(4)** cycle was completed on combination of needle loaded with titanium seeds and spacers (polymer) in strand material (polymer) plugged with **(b)(4)** wax. The worst case materials were not determined, segregated and tested for **(b)(4)** residues.

c. August 2010 **(b)(4)** residue test performed after two **(b)(4) (b)(4)** cycles is documented as being conducted using dummy seeds stranded in needles, but does not document that spacers and **(b)(4)** wax was included. The worst case materials were not determined, segregated and tested for **(b)(4)** residues.

d. Your manufactured devices are implanted into the human body, but no 30 day or lifetime **(b)(4)** residue testing is documented as completed, or there is no explanation why testing is not needed.

The adequacy of your responses dated May 10, 2012 and June 25, 2012, cannot be determined at this time because it lacks sufficient details regarding the corrective action and also lacks adequate evidence that the corrective action has been adequately implemented. Your May 10, 2012 states "An **(b)(4)** residual protocol that accounts for worst case loads will be established and relevant products will be retested, following the requirements of ISO 10993-7." Your follow-up response of June 25, 2012 states only that "The protocol for testing **(b)(4)** residual in worst case circumstances in the development phase."

5. Failure to establish and maintain procedures for investigating the cause of nonconformities relating to product, processes, and the quality system, as required by 21 C.F.R. 820.100(a)(2), and to adequately document all activities required under Corrective and Preventive Action, and their results, as required by 21 C.F.R. 820.100(b). For example:

a. Your firm initiated three Corrective and Preventive Action (CPA) (#CP021 on July 22, 2008, #CP022 on February 12, 2009, and #CP023 on May 14, 2009) in response to multiple complaints, to include but not limited to: complaints (#C022, #C026, #C027, and #C031) involving out-of-specification radioactivity of Brachytherapy seeds. Review of CPA Forms #CP021, #CP022, and #CP023, disclosed that the documentation of correction and preventative actions was incomplete and not conducted in accordance with Sections 6.3 - 6.5 of CPA procedure SOP 14-01, Rev. 5, dated May 29, 2007. Further, these three CPA Forms do not include the details of any stated investigation conducted, their results, or that the software updates do not have an adverse effect on the finished device.

b. Your firm initiated CPA #CP019 dated 3/31/2008, in response to Complaint #CP021 dated February 19, 2008. CPA Form #CP019 indicates that rough handling of packages containing **(b)(4)** cartridges in green pig (lead lined container) caused some of the cartridges to crack due to high speed impacts pushing down on the plunger of the **(b)(4)** cartridge. The documentation does not include the details of any stated investigation conducted, their results, or that the reconfiguration of the **(b)(4)** cartridge does not have an adverse effect on the finished device in accordance with Sections 6.3 - 6.5 of procedure CPA, SOP 14-01, Rev. 5, dated May 29, 2007.

c. Your firm initiated a corrective action to check each vial containing Brachytherapy seeds prior to shipment for radioactive contamination in response to Complaint #CP025 dated November 14, 2008, regarding a customer finding radiation contamination after a vial swipe on one vial (wipe 1: 2200 dpm and wipe 2: 709 dpm). Your firm stated to our investigator that the origin of contamination could not be determined. This corrective action was not documented in accordance with CPA, procedure SOP 14-01, Rev. 5, dated May 29, 2007.

Your firm's responses dated May 10, 2012, and June 25, 2012, are not adequate because the responses do not specifically address the deficiency cited. We acknowledge you have recently updated your procedure, Corrective and Preventive Action, SOP 14-01, Rev. 6, to clarify provisions for investigation including determination of potential causes of nonconformances. However, this procedure (Revision 6) does not appear to be signed and dated as issued and effective for use. Further, you have not demonstrated your firm has implemented the revised CAPA procedure for the nonconformances identified in the CPA Forms referenced above.

6. Failure to adequately maintain a record of the complaint investigation by the formally designated unit, as required by 21 C.F.R. 820.198(e). For example, Section 7.1 of the procedures for handling complaints, Complaint Handling Procedure, SOP 14-02, Rev. 5, dated May 29, 2007, requires that your firm maintain records that are accurately completed of all complaints received meeting the definition of a complaint. However, your firm documented receiving multiple complaints including Complaint #C021 - February 19, 2008; Complaint #C022 - July 21, 2008; Complaint #C024 - August 11, 2008; Complaint #C025 - November 14, 2008; Complaint #C026 - December 30, 2008; Complaint #C027 - April 15, 2009; and Complaint #C031 - August 20, 2009, involving cracked **(b)(4)** cartridges, out-of-specification Brachytherapy seed radioactivity, and leaking Brachytherapy seed, but failed to consistently document the nature and details of the complaints received as well as the dates and the results of investigation, and any corrections that may have been taken.

The adequacy of your responses dated May 10, 2012 and June 25, 2012, cannot be determined at this time because it lacks sufficient details regarding the corrective action and also lacks adequate evidence that the corrective action has been adequately implemented. We acknowledge your June 25, 2012 response includes the revised, Complaint Handling Procedure, SOP 14-02, Rev. 6; however, this procedure does not appear to be signed and dated as issued and effective for use. Further, you have not demonstrated your firm has conducted the complaint handling activities promised in your response in accordance with the revised procedure.

7. Failure to establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements, as required by 21 C.F.R. 820.50. Failure to establish and maintain the requirements, including the quality requirements that must be met by suppliers, contractors, and consultants. 21 C.F.R. 820.50(a). For example, your procedure for Purchasing, SOP 06-01, Rev. 3 and Vendor Survey, Form No. 06-01-04, Rev. 1 are inadequate in that they do not require an evaluation and qualification determination of vendors, suppliers, and contract service providers listed on your firm's Approved Vendors List prior to February 28, 2003. There is no documentation that **(b)(4)**., the supplier of extruded titanium tubes used in the manufacture of Brachytherapy seeds, was qualified or re–qualified as a supplier. Your firm has been purchasing extruded titanium tubes from this vendor since prior to 2003.

The adequacy of your responses dated May 10, 2012 and June 25, 2012, cannot be determined at this time because it lacks sufficient details regarding the corrective action and also lacks adequate evidence that the corrective action has been adequately implemented. We acknowledge your June 25, 2012 response includes the revised procedure, Purchasing, SOP 06-01, Rev. 4 and Vendor Survey, Form No. 06-01-04, Rev. 2; however, this procedure does not appear to be signed and dated as issued and effective for use. Further, you have not demonstrated your firm has reassessed current vendors of critical products and services as promised in your response, in accordance with the revised procedure.

8. Failure to establish and maintain procedures to control the design of the device in order to ensure that specified design requirements are met, as required by 21 C.F.R. 820.30(a). For example, your design control procedure, Design and Development Planning, SOP 04-01, Rev. 4, dated May 29, 2007, is not fully established to control the design process for the manufacture of Brachytherapy seeds and Brachytherapy kits, in that:

a. Your design control procedure fails to include a mechanism for addressing incomplete, ambiguous, or conflicting requirements.

b. Your design control procedure, Document and Data Control, SOP 05-01, Rev. 4 dated May 29, 2007, and your Document Change Order Form No. 05-01-01, Rev. 2 do not ensure that all requirements for the conduct of design changes are included in the procedures or document change order form such as, validation or where appropriate verification of design changes before their implementation.

c. The Brachytherapy Kit design process does not include a validation protocol for the conduct of the design validation for manufactured kits, in accordance with the design control procedure, Your firm does not maintain a design history file for Brachytherapy Kits documenting results of design validation, including identification of the design, method(s), the date, and the individual(s) performing validation.

The adequacy of your responses dated May 10, 2012 and June 25, 2012, cannot be determined at this time because they lack sufficient details regarding all corrective actions and also lack adequate evidence that the corrective action have been adequately implemented. We acknowledge your June 25, 2012 response includes the revised procedure, Design and Development Planning, SOP 04-01, Rev. 5. However, this procedure does not appear to be signed and dated as issued and effective for use. You have not demonstrated your firm has addressed incomplete, ambiguous, or conflicting requirements for Product Nos. 2010 & 3010 and 2011 & 3011, in accordance with the revised procedure. Your June 25, 2012 response also includes a protocol for the conduct of design validation for the Brachytherapy Kit. You have not provided evidence that design validation for the Brachytherapy Kit has been conducted as promised in your response, in accordance with the newly prepared protocol.

This inspection also revealed that your devices are misbranded under section 502(t)(2) of the Act, 21 U.S.C. 352(t)(2), in that your firm failed or refused to furnish material or information respecting the devices that is required by or under section 519 of the Act, 21 U.S.C. 360i, and 21 C.F.R. Part 803 - Medical Device Reporting (MDR) regulation. Significant deviations include, but are not limited to, the following:

9. Failure to develop, maintain and implement written MDR procedures, as required by 21 C.F.R. 803.17. For example, your firm identified and provided Complaint Handling Procedure, SOP 14-02, Rev. 5, dated May 29, 2007, to the FDA investigator, as your firm's MDR procedures. SOP 14-02 does not include the regulatory requirements to develop, maintain, and implement written MDR procedures.

We have reviewed your response and have concluded that it is inadequate because you have not addressed the regulatory requirements to develop, maintain, and implement written MDR procedures. We acknowledge your June 25, 2012 response includes the newly created procedure, Medical Device Reporting, SOP 14-05, Rev. 0. However, this procedure does not appear to be signed and dated as issued and effective for use. Moreover, there are no internal systems in your newly created procedure that provide for:

- Timely and effective identification, communication, and evaluation of events that may be subject to MDR requirements, as required by 21 C.F.R. § 803.17(a)(1);

- A standardized review process or procedure for determining when an event meets the criteria for reporting under the MDR regulations, as required by 21 C.F.R. § 803.17(a)(2); and

- Timely transmission of complete medical device reports to manufacturers or to FDA, or to both if necessary, as required by 21 C.F.R. § 803.17(a)(3).

In addition, there are no documentation and record-keeping requirements, in your procedures listed above, for:

- Information that was evaluated to determine if an event is reportable, as required by 21 C.F.R. § 803.17(b)(1).

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 violations 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 device have been corrected.

Please notify this office in writing within fifteen (15) business days from the date you receive this letter of the specific steps you have taken to correct the noted violations, as well as an explanation of how you plan to prevent these violations, or similar violations, from occurring again. Include documentation of the corrections and/or corrective actions you have taken. If your planned corrections and/or corrective actions will occur over time, please include a timetable for implementation of these activities. If corrections and/or corrective actions cannot be completed within 15 business days, state the reason for the delay and the time within which these activities will be completed. Your response should be comprehensive and address all violations included in this letter.

Your response should be sent to:

Salvatore N. Randazzo, Compliance Officer
555 Winderley Place, Suite 200
Maitland, Florida, 32751

Refer to the Unique **Identification Number 329180** when replying. If you have any questions about the content of this letter please contact: Salvatore N. Randazzo at (407) 475-4712.

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 management 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/
Emma R. Singleton
Director, Florida District

Page Last Updated: 10/05/2012
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