Inspections, Compliance, Enforcement, and Criminal Investigations

International Isotopes Inc. 10/26/11

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Seattle District
Pacific Region
22201 23rd Drive SE
Bothell, WA 98021-4421

Telephone: 425-486-8788
FAX: 425-483-4996

October 26, 2011

VIA CERTIFIED MAIL
RETURN RECEIPT REQUESTED

In reply refer to Warning Letter SEA 12-03

Stephen T. Laflin, President and CEO
International Isotopes, Inc.
4137 Commerce Circle
Idaho Falls, Idaho 83401

WARNING LETTER

Dear Mr. Laflin:

During our July 18 – 22, 2011 inspection of your facility, International Isotopes, Inc., located at 4137 Commerce Circle, Idaho Falls, Idaho, investigators from the Food and Drug Administration (FDA) determined that your firm manufactures a radiopharmaceutical, Sodium Iodide I-131 solution, and identified significant violations of Current Good Manufacturing Practice (CGMP) regulations for finished pharmaceuticals, Title 21, Code of Federal Regulations, Part 210 and 211. These violations cause your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 351(a)(2)(B)] in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

In addition, this inspection also revealed that your firm is marketing an unapproved drug, Sodium Iodide I-131 solution, in violation of section 505(a) of the Act [21 U.S.C. § 355(a)].

We have reviewed your firm's written response of August 3, 2011, to the Form FDA-483, Inspectional Observations, and note that it lacks sufficient corrective actions.

We acknowledge your firm's written response of September 13, 2011, to the Form FDA-483. However, because this response was received more than 15 business days after the Form FDA-483 was issued, this response has not been considered. We plan to evaluate this response along with any other written material provided as a direct response to this Warning Letter.

The violations observed during the inspection include, but are not limited to the following:

CGMP Violations:

1. Your firm has not conducted at least one specific identity test and has not established the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals [21 C.F.R. § 211.84(d)(2)].

For example, your firm does not perform identity tests for Sodium Iodide I-131. Each batch of incoming

components must be tested for identity of each shipment. In addition, accepting components for other attributes based on the supplier's Certificate of Analysis is only appropriate once you have established the reliability of the results reported on your supplier's Certificate of Analysis and provided that you also have an ongoing program to periodically verify these results.

2. Your firm has failed to calibrate instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met [21 C.F.R. § 211.160(b)(4)].

For example, your firm has failed to establish a written procedure for the calibration of pipettes, scales, and the radioisotope calibrator used in the manufacture of your Sodium Iodide I-131 solution.

3. Your firm has failed to exercise appropriate controls over computer or related systems to assure that the input to and output from the computer or related systems of formulas, other records, or data, are checked for accuracy [21 C.F.R. § 211.68(b)].

For example, your firm's custom software for your Master Batch Production record, referred to as the "I-131 Database," has not been validated. This software is responsible for generating the batch production record, performing calculations to produce varying concentrations of drug product, and generating label information for customer vials and lead pigs.

4. Your firm failed to have written procedures describing, in sufficient detail, the receipt, identification, storage, handling, sampling, testing and approval or rejection of components and drug product containers and closures [21 C.F.R. § 211.80(a)].

For example, your firm's procedures do not address specific storage, handling, sampling, testing, and approval or rejection instructions for the NaOH buffer and bulk and customer containers and closures used in the manufacture of the Sodium Iodide I-131 solution.

5. Your firm has failed to establish written procedures for reconciling the quantities of labeling issued, used, and returned [21 C.F.R. § 211.125(c)].

For example, your firm fails to have written procedures, with sufficient detail, to describe the handling of labeling for the unique customer vials with different concentrations and volumes. Your firm also fails to have written procedures to ensure that strict control is exercised over labeling including reconciliation of the quantities of labeling issued, used, and returned.

6. Your firm has failed to establish written procedures to assure the examination of packaging and labeling materials for suitability and correctness before packaging operations, and the documentation of such examination in the batch production record [21 C.F.R. § 211.130(d)].

For example, your firm's batch record form, "OP-RAD-008 Processing Procedure and Batch Record," documents a second signoff for vial label correctness. However, this form does not also specify an appropriate check for the labeling intended for the inner and outer lead containers. Also, your firm has not established detailed procedures specifying what the labels are to be checked for (i.e., order number, volume, mCi/ml).

In your August 3, 2011, response, your firm has committed to address each observation by a specified date in the future. However, we cannot adequately assess these corrections at this time because your firm has not provided detailed information on the content of the corrections or any evidence of completion of any proposed corrective action. In addition, the deficiencies will need a more comprehensive correction than the actions you have proposed. For example, you have not addressed how you will prevent recurrence of these observations or how you will ensure adequate implementation of each correction (e.g., training, performing an assessment of corrective action effectiveness).

Unapproved New Drug Violations:

In addition to violating CGMPs, you violate the Act by manufacturing Sodium Iodide I-131 solution without an application. This product is a drug within the meaning of section 201(g) of the Act, [21 U.S.C. § 321(g)] because it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. Further, it is a "new drug" within the meaning of section 201(p) of the Act because it is not generally recognized as safe and effective for its labeled uses. Under sections 301(d) and 505(a) of the Act [21 U.S.C. §§ 331(d) and 355(a)], a new drug may not be introduced into or delivered for introduction into interstate commerce unless an application approved by FDA under section 505(b) or (j) of the Act [21 U.S.C. § 355(b) or (j)] is in effect for the drug. Based on our information, you do not have an FDA-approved application for this product.

Although there is no FDA-approved application on file for this drug product, we will allow you to continue

manufacturing this product pending correction of your CGMP violations. This decision is consistent with FDA's commitment to take action against marketed unapproved drugs without imposing an undue burden on patients.

Our general policy is described in the recently amended guidance entitled "Marketed Unapproved Drugs - Compliance Policy Guide (CPG)." See http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070290.pdf[1]. The CPG explains FDA's policies aimed at ensuring that all drugs (prescription and over-the-counter) marketed in the U.S., have been shown to be safe and effective. Other related information can be found on http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/ucm118990.htm[2].

The CPG clearly articulates

- FDA's expectation that illegally marketed products, i.e., products marketed without required FDA approval, be removed from the market;
- FDA's enforcement policies aimed at efficiently and rationally bringing all drugs requiring approved applications into the approval process; and
- that all drugs marketed without required applications are subject to enforcement action at any time, without additional notice.

We highly encourage you to contact FDA's unapproved drugs coordinator, Dr. Sally Loewke, at 301-796-0710 for assistance in communicating with the FDA on the application process for your unapproved drug.

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence or the occurrence of other violations. It is your responsibility to assure that your firm complies with all requirements of federal law and FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice, including, without limitation, injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts. Additionally, FDA may withhold approval of requests for export certificates, or approval of pending new drug applications listing your facility as a manufacturer until the above violations are corrected. A re-inspection may be necessary.

If, as a result of receiving this Warning Letter or in general, you are considering making a decision that will result in a decreased number of finished drug products or active pharmaceutical ingredients produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Program immediately, as you begin your internal discussions, at drugshortages@fda.hhs.gov in order to ensure that your action(s) does not adversely affect the public health.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step being taken to prevent the recurrence of violations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction.

Your reply should be sent to the following address: Food and Drug Administration, Seattle District Office, 22201 23rd Drive SE, Bothell, Washington, 98021-4421, to the attention of Lisa M. Althar, Compliance Officer. Should you have any questions concerning this letter, you can contact Ms. Althar at (425) 483-4940.

Sincerely,
/S/
Charles M. Breen
District Director

cc: Idaho State Board of Pharmacy
P.O. Box 83720
Boise, Idaho 83720-0067

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
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