WARNING LETTER

Izeen Pharma Inc

MARCS-CMS 565311 — MAY 16, 2019

Delivery Method: VIA UPS
Product: Drugs

Recipient:

Mr. Janakiram Ajjarapu

Owner

Izeen Pharma Inc

6900 English Muffin Way, Suite A
Frederick, MD 21703
United States

Issuing Office:

Division of Pharmaceutical Quality Operations I

10 Waterview Blvd, 3rd Floor
Parsippany, NJ 07054
United States

WARNING LETTER
CMS #565311

05/16/2019

VIA UPS OVERNIGHT

Mr. Janakiram Ajjarapu
Owner
Izeen Pharma Inc.
6900 English Muffin Way, Suite A
Frederick, MD 21703

Dear Mr. Ajjarapu:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Izeen Pharma Inc. at 6900 English Muffin Way, Suite A, Frederick, Maryland, from June 4 to July 3, 2018.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug product is adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

Inspection of your firm revealed that your firm caused the introduction or delivery for introduction into interstate commerce of levothyroxine and liothyronine (thyroid tablets) in violation of sections 505(a) and 301 (d) of the FD&C Act, (21 U.S.C. sections 355(a) and 331(d)).

Levothyroxine and liothyronine (thyroid tablets) are misbranded under section 502(f)(1) of the FD&C Act, 21 U.S.C. section 352(f)(1). The introduction or delivery for introduction into interstate commerce of this misbranded product violates section 301(a) of the FD&C Act, 21 U.S.C. section 331(a).

We reviewed your July 24, 2018 response in detail, and provide an assessment below.

During our inspection, our investigators observed specific violations including, but not limited to, the following.

1. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

A.) On June 12, 2017, you obtained out-of-specification (OOS) assays for thyroid powder active pharmaceutical ingredient (API), lot 170301, which failed to meet liothyronine and levothyroxine specifications. The assays were found to be significantly above specification (e.g., OOS results from **(b)(4)**. You confirmed the OOS data in your testing of the API samples but did not determine a root cause. The batch was rejected.

Between February 2018 and April 2018, new shipments of the same thyroid powder API batch (lot 170301) were received. On February 28, 2018, another OOS assay result for levothyroxine specifications was obtained, this time below specification (results of individual preparations: **(b)(4)**). The OOS result was confirmed by "repeat testing" and external laboratory testing. In addition, a new OOS assay result was obtained for liothyronine during additional testing (result: **(b)(4)**). Your investigation concluded, without sufficient scientific data, that "there was an issue with bound water in the test sample" and suggested increasing the incubation time during sample preparation beyond the time established in the United State Pharmacopeia (USP). You invalidated the OOS results based on this "possible assignable cause" and used the API batch to manufacture **(b)(4)** lots of thyroid tablets.

Your OOS investigation of February 2018 was inadequate because it did not include a review of previous OOS results; it lacked an evaluation of your API supplier; it lacked a test of your hypothesis; and it did not explain why previous batches of thyroid tablets did not require an extended incubation time of the samples to meet the required specifications. Also, notably, the passing test results from the **(b)(4)** time included values at the extremes of the specifications, including results such as **(b)(4)**. While marginally passing, this data further verified high variability in your API.

B.) On December 5, 2017, you initiated a complaint investigation for thyroid tablets, 60 mg, lots 15617VP-01, 15617VP-02, and 15617VP-03. Several complaints regarding these lots reported tablet size variation, splitting, brittleness, and disintegration upon touching.

Your testing of retain and returned samples determined that all three lots had tablets above the weight variation limit. Testing of retains also revealed that **(b)(4)**.

Your investigation concluded that the root cause of the failure was related to the physical properties of the blend and an unsuitable high-speed compression machine.

As a corrective action, you changed the drug product formulation and the compression machine used in the manufacture of distributed products. However, you failed to evaluate other lots produced using the same manufacturing process and only proposed to recall lot 15617VP-02 in your firm's investigation.

In your response, you stated that you would **(b)(4)**. Your response was inadequate because it failed to provide sufficient evidence of root cause determination and implementation of an effective corrective action and preventive action (CAPA) plan. In addition, your response did not sufficiently address how your quality system will be improved to ensure timely and sound decision-making regarding manufacturing and quality.

In response to this letter, provide:

• A retrospective, independent review of all invalidated OOS (in-process and finished testing) results obtained for API and drug products within expiry. Assess whether the scientific justification and evidence for each invalidated OOS result was conclusive. For investigations that conclusively establish laboratory root cause, determine effectiveness of the CAPA and ensure that other laboratory methods vulnerable to the same root cause are identified for remediation. For any OOS results with inconclusive or no root cause identified in the laboratory, include a thorough review of production (e.g., batch manufacturing records, adequacy of manufacturing steps, raw materials, process capability, deviation history, batch failure history). Provide a CAPA plan that identifies manufacturing root causes and specifies meaningful improvements.
• A fully remediated OOS investigation procedure including, but not limited to, modifications to your retesting practices and the scope of product impact assessments.
• A comprehensive, independent assessment of your overall system for investigating deviations, discrepancies, complaints, OOS results, and failures. Provide a detailed CAPA plan to remediate this system. Your CAPA plan should include, but not be limited to, **(b)(4)**.
• **(b)(4)**.

For more information about handling failing, OOS, out-of-trend, other unexpected results, and documentation of your investigations, see FDA's guidance document Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production at https://www.fda.gov/downloads/drugs/guidances/ucm070287.pdf (https://www.fda.gov/downloads/drugs/guidances/ucm070287.pdf).

2. Your firm failed to establish adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(a)).

(b)(4).

Your manufacturing failures indicate that you do not have an adequate ongoing program for monitoring process control to ensure stable manufacturing operations and consistent drug quality. See FDA's guidance document Process Validation: General Principles and Practices for general principles and approaches that FDA considers to be appropriate elements of process validation at
https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf
(https://www.fda.gov/downloads/drugs/guidances/ucm070336.pdf).

In your response, you indicated that the **(b)(4)**. Your response is inadequate because you **(b)(4)**.

In response to this letter, evaluate drug manufacturing operations to determine the improvements needed to assure you can consistently deliver drug products that meets quality attributes. Provide a data-driven and scientifically sound analysis that identifies all sources of variability including, but not limited to, raw materials and manual steps (e.g., hand scooping). Determine the capability of each manufacturing process step and provide your CAPA plan to reduce process variation.

3. Your firm failed to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity (21 CFR 211.160(b)).

You failed to test thyroid tablet batches for content uniformity. Instead, your firm used a weight variation method as the release test. During the inspection you explained that the weight variation approach is applied to thyroid tablets because the product contains 25 mg or more of thyroid powder. Our review found that the thyroid powder milligram level does not represent the actual amount of the active ingredients in the dosage unit. Your thyroid tablets contain drug substance at microgram levels (see Table A below) and does not meet the criteria listed in USP <905> for the use of the weight variation testing method.

Table A. Thyroid Tablets Content Weight/Label Claim

Product	Actual content of Thyroid Powder per tablet	Label Claim (Quantity of T4 per tablet)	Label Claim (Quantity of T3 per tablet)	Individual Tablet Weight
Thyroid 30 mg Tablets	32.5 mg	19 ug	4.5 ug	68 mg
Thyroid 60 mg Tablets	65 mg	38 ug	9 ug	136 mg
Thyroid 90 mg Tablets	97.5 mg	57 ug	13.5 ug	204 mg
Thyroid 120 mg Tablets	130 mg	76 ug	18 ug	272 mg

Your response is inadequate because your firm continues to assess uniformity of dosage units by weight variation rather than content uniformity.

In response to this letter, provide the following:

• A revision of your test method to determine uniformity of dosage units by content uniformity.
• A thorough assessment of your firm's test methods and specifications to determine if they are scientifically sound and contain clear instructions. Provide a list of drug products tested at your facility using the weight variation method.
• An update of your current manufacturing activities, and future plans related to thyroid tablets.
• Also provide a list of all batches of thyroid tablets and other products manufactured in your facility currently in distribution (lot number, size of the lot, date of manufacture, date of release, date of first shipment). We are aware that your customer initiated a recall of products within expiry.
• A comprehensive review of your laboratory practices, procedures, methods, equipment, and analyst competencies. Based on this review, provide a detailed CAPA plan to fully remediate your laboratory system. Your plan should also include the process you will use to evaluate the effectiveness of the implemented CAPA plan.

4. Your firm failed to establish an adequate written testing program designed to assess the stability characteristics of drug products and to use results of stability testing to determine appropriate storage conditions and expiration dates (21 CFR 211.166(a)).

Your stability program is deficient. You initially established a **(b)(4)**. Your overall ongoing program and data was insufficient to substantiate that marketed batches can reliably meet the new expiry date.

You also failed to follow your stability program protocol. For example:
• You failed to test any lots of thyroid tablets for microbial content during stability.
• You did not test stability lot 15817001-SP (thyroid tablet 120 mg) for disintegration.

In addition, you failed to include process validation lots in your stability program to evaluate the effect of significant changes to your formulation (e.g., changed percentage content of two excipients) and a new tablet press machine. You referred to these changes as minor even though you determined the root cause for OOS results of distributed lots was related to the formulation, compression, and physical characteristics of the blend.

In your response, you indicated **(b)(4)**. Your response is inadequate because you failed **(b)(4)** process changes.

In response to this letter, provide a comprehensive assessment and CAPA plan to ensure the adequacy of your stability program. Your CAPA should include, but not be limited to:
• A remediated SOP describing your stability program and a requirement to add lots after changes are made to a manufacturing process.
• Stability-indicating methods.
• Stability studies to support each drug product in its container-closure system before distribution is permitted.
• An ongoing program in which representative batches of each product are added each year to the program to determine if the shelf-life claim remains valid.
• Specific attributes to be tested at each stability interval.

5. Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

A.) Laboratory equipment used to generate analytical data for product release purposes did not have sufficient controls to prevent the deletion or alteration of raw data files. During the inspection, the investigator observed that analysts shared usernames and passwords. The investigator also found that users had administrator rights allowing them to delete or modify high-performance liquid chromatography files.

Your laboratory staff also acknowledged **(b)(4)**.

B.) You used **(b)(4)**. During the inspection, your laboratory staff acknowledged that the **(b)(4)** unit test of thyroid tablets 30 mg, lot 15517VP-03 was incorrect. The recalculated value resulted in an OOS result. The lot was released for commercial distribution and was subsequently recalled.

In your response, you indicated that you are in the process of **(b)(4)**."

Your response is inadequate because you failed to address your quality unit's deficient data review. Your response also lacked a comprehensive assessment and retrospective review of all **(b)(4)**.

Data Integrity Remediation

Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA's guidance document Data Integrity and Compliance With Drug CGMP for guidance on establishing and following CGMP compliant data integrity

practices at https://www.fda.gov/regulatory-information/search-fda-guidance-document... (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-integrity-and-compliance-drug-cgmp-questions-and-answers-guidance-industry)

We strongly recommend that you retain a qualified consultant to assist in your remediation. In response to this letter, provide the following:

A. A comprehensive investigation into the extent of the inaccuracies in data records and reporting including results of the data review for drugs distributed to the United States. Include a detailed description of the scope and root causes of your data integrity lapses.

B. A current risk assessment of the potential effects of the observed failures on the quality of your drugs. Your assessment should include analyses of the risks to patients caused by the release of drugs affected by a lapse of data integrity and analyses of the risks posed by ongoing operations.

C. A management strategy for your firm that includes the details of your global corrective action and preventive action plan. The detailed action plan should describe how you intend to ensure the reliability and completeness of all data generated by your firm including microbiological and analytical data, manufacturing records, and all data submitted to FDA.

FDA Sample Results and Recall of Thyroid Tablets

After the conclusion of the inspection, your customer, **(b)(4)**, initiated a voluntary recall of all batches of thyroid tablets manufactured at your facility because batches contained inconsistent or failing levels of liothyronine and levothyroxine. In addition, FDA sampled thyroid tablets, 15 mg, lot 15918006, at your facility and found that they were not homogeneous and exhibited very high variability. Because of the narrow therapeutic range of this product, it is especially important to prevent patients with hypothyroidism from receiving insufficient or excessive doses.

Responsibilities as a Contractor

Drugs must be manufactured in conformance with CGMP. FDA is aware that many drug manufacturers use independent contractors such as production facilities, testing laboratories, packagers, and labelers. FDA regards contractors as extensions of the manufacturer.

You and **(b)(4)** have a quality agreement regarding the manufacture of thyroid tables USP. You are responsible for the quality of drugs you produce as a contract facility regardless of agreements in place with product owners.

You are required to ensure that drugs are made in accordance with section 501(a)(2)(B) of the FD&C Act for safety, identity, strength, quality, and purity. See FDA's guidance document Contract Manufacturing Arrangements for Drugs: Quality Agreements at https://www.fda.gov/downloads/drugs/guidances/ucm353925.pdf (https://www.fda.gov/downloads/drugs/guidances/ucm353925.pdf)

CGMP Consultant Recommended

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements. Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for fully resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

Unapproved New Drug Violations

Your levothyroxine and liothyronine (thyroid tablets) are “drugs” within the meaning of section 201(g)(1) of the FD&C Act (21 U.S.C. section 321(g)(1)) because they are articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals and/or an article (other than food) intended to affect the structure or any function of the body of man or other animals. Labeling statements documenting the intended uses of your products include, but are not limited to, the following:

Levothyroxine and liothyronine tablets, labeled with statement of intended use:
1. As replacement or supplemental therapy in patients with **(b)(4)**. This category includes cretinism, myxedema, and ordinary hypothyroidism in patients of any age (children, adults, the elderly), or state (including pregnancy); primary hypothyroidism resulting from functional deficiency, primary atrophy, partial or total absence of thyroid gland, or the effects of surgery, radiation, or drugs, with or without the presence of goiter; and secondary (pituitary), or tertiary (hypothalamic) hypothyroidism.
2. As pituitary TSH suppressants, in the treatment or prevention of various types of euthyroid goiters, including thyroid nodules, subacute or chronic lymphocytic thyroiditis (Hashimoto's), multinodular goiter, and in the management of thyroid cancer.
3. As diagnostic agents in suppression tests to differentiate suspected mild hyperthyroidism or thyroid gland autonomy.

Further, this drug is a “new drug” within the meaning of section 201(p) of the FD&C Act (21 U.S.C. section 321 (p)) because it is not generally recognized as safe and effective for use under the conditions prescribed, recommended, or suggested in its labeling.

Under section 505(a) of the FD&C Act (21 U.S.C. section 355(a)), new drugs may not be introduced or delivered for introduction into interstate commerce unless applications approved by FDA under either section 505(b) or (j) of the FD&C Act (21 U.S.C. section 355(b) or (j)) are
effective with respect to such drugs. There are no FDA-approved applications in effect for your
product listed above. The introduction or delivery for introduction (or the causing thereof) into interstate commerce of new drugs in violation of section 505 is prohibited under 301(d) of the FD&C Act (21 U.S.C. section 331(d)). Consequently, your marketing and distribution of these products without approved applications violate provisions of the FD&C Act.

Misbranded Drugs Violations

According to section 502(f)(1) of the FD&C Act, 21 U.S.C. section 352(f)(1), a drug is misbranded if, among other things, it fails to bear adequate directions for its intended use(s). “Adequate directions for use” means directions under which a layman can use a drug safely and for the purposes for which it is intended (21 CFR section 201.5).

Levothyroxine and liothyronine (thyroid tablets) are intended for conditions that are not amendable to self-diagnosis and treatment by individuals who are not medical practitioners and are prescription drugs. Prescription drugs, as defined in Section 503(b)(1) of the FD&C Act, (21 U.S.C. 353(b)(1), are drugs “because of its toxicity or potential for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drugs.” It is impossible to write adequate directions for use for prescription drugs (as defined by regulation 21 CFR 201.5) for drugs that are limited to prescription status.

Adequate directions for use cannot be written for levothyroxine and liothyronine (thyroid tablets). Moreover, levothyroxine and liothyronine (thyroid tablets) are not exempt from the requirement that the labeling bear adequate directions for use because there is no FDA-approved application in effect for levothyroxine and liothyronine (thyroid tablets) nor is there an effective IND. (See 21 CFR sections 201.100(c)(2) and 201.115.) As such, levothyroxine and liothyronine (thyroid tablets) are misbranded under section 502(f)(1) of the FD&C Act, 21 U.S.C. section 352(f)(1). The introduction or delivery for introduction into interstate commerce of this misbranded product violates section 301(a) of the FD&C Act, 21 U.S.C. section 331(a).

Conclusion

Violations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations, for determining the causes, for preventing their recurrence, and for preventing other violations.

Correct the violations cited in this letter promptly. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction. Unresolved violations in this warning letter may also prevent other Federal agencies from awarding contracts.

Until these violations are corrected, we may withhold approval of pending drug applications listing your facility. We may re-inspect to verify that you have completed your corrective actions. We may also refuse your requests for export certificates.

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic reply to orapharm1_responses@fda.hhs.gov (mailto:orapharm1_responses@fda.hhs.gov). Your written notification should refer to the Warning Letter CMS #565311.

If you have any questions, contact Compliance Officer Liatte Closs at liatte.closs@fda.hhs.gov (mailto:liatte.closs@fda.hhs.gov) or James Mason at james.mason@fda.hhs.gov (mailto:james.mason@fda.hhs.gov).

Sincerely,
/S/

Diana Amador-Toro
Program Division Director/District Director
U.S. Food and Drug Administration
OPQO Division I/New Jersey District

More Warning Letters (/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters)