Vista Pharmaceuticals Limited 7/5/17

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS **Warning Letter 320-17-40**

July 5, 2017

Dr. Dhananjaya Alli
Managing Director
Vista Pharmaceuticals Limited
H. No. 7-1-212/a/70 Plot no: 85
Shivbagh, Ameerpet
Hyderabad, Telangana 500 016
India

Dear Dr. Alli:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Vista Pharmaceuticals Limited at APIIC Industrial Estate, Gopalapalli, Narketpalli, Nalgonda, Telangana, from September 19 to 23, 2016.

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 products are 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).

Furthermore, we reviewed the labeling provided by your firm to FDA's electronic Drug Registration and Listing System (eDRLS) of your isoxsuprine hydrochloride USP, 20 mg tablets. After a review of your product's labeling, we conclude that your product, isoxsuprine hydrochloride USP, 20 mg tablets (NDC 61971-065), is misbranded under sections 502(e), (f)(1) and (f)(2) of the FD&C Act, 21 U.S.C. 352(e), (f)(1) and (f)(2) and by introducing it into interstate commerce you are in violation of section 301(a) of the FD&C Act (21 U.S.C. 331(a)).

We reviewed your October 2016 response in detail and acknowledge receipt of your subsequent correspondence.

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

CGMP Violations

1. Your firm failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements (21 CFR 211.67(a)).

On September 19, 2016, during the walk through of your firm's manufacturing areas, our investigators observed that equipment you use for **(b)(4)**, **(b)(4)**, and compression was in a state of disrepair. Specifically, our investigators saw holes and corrosion in three pieces of equipment you use to manufacture **(b)(4)** and a vasodilator drug.

Equipment	**Observation**	**Drug Products Manufactured**
(b)(4) (ID: U1-**(b)(4)**-0-1)	holes in **(b)(4)**corrosion inside and outside of unit	**(b)(4)/(b)(4)** tablets USP, **(b)(4)/(b)(4)** mg tablets isoxsuprine hydrochloride USP, 20 mg tablets
(b)(4) bowl-1	holes in **(b)(4)** missing **(b)(4)** and corrosion on frame	
(b)(4) (ID: U1/**(b)(4)**-001)	holes in **(b)(4)** corrosion	

Prior to our inspection, on March 7, 2016, FDA received a complaint of metal embedded in one of your **(b)(4)/(b)(4)** USP, **(b)(4)/(b)(4)** mg tablets. During our inspection, our investigators noted that when you investigated the complaint, you failed to consider whether the poor condition of your equipment may have contributed to the problem.

In your response you stated that you have replaced the equipment identified as being in a state of disrepair. However, your response is inadequate because it failed to include a retrospective review of **(b)(4)/(b)(4)** USP, **(b)(4)/(b)(4)** mg tablets, and isoxsuprine hydrochloride USP, 20 mg tablets, manufactured for the U.S. market on equipment identified above.

In response to this letter, submit your evaluation of all production equipment to ensure it is fit for the intended use. Conduct and provide the results of a retrospective review of all drugs within expiry distributed to the United States that you manufactured on equipment identified as in a state of disrepair.

2. Your firm failed to establish 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)).

You admitted to our investigators that you had not performed process validation for isoxsuprine hydrochloride USP, 20 mg tablets. Even though you had not validated the manufacturing process for this drug product, your firm distributed at least **(b)(4)** batches to the United States from 2014 to 2016. Manufacturers must design and control manufacturing processes to assure that in-process materials and finished drug products meet predetermined quality requirements consistently and reliably.

In your response, you stated that you were not currently manufacturing isoxsuprine hydrochloride USP, 20 mg tablets and **(b)(4)**. Your response is inadequate. You did not indicate how or when you would complete validation of your manufacturing process for isoxsuprine hydrochloride USP, 20 mg tablets. In addition, you have not conducted a retrospective risk assessment to determine the potential effects of your failure to validate the manufacturing process on the quality of isoxsuprine hydrochloride USP, 20 mg tablets already distributed.

In response to this letter, provide a proposed validation protocol for the isoxsuprine hydrochloride USP, 20 mg tablets. Include your timeframes for completion of validation activities prior to distribution to the United States. Also provide your risk assessment for all batches distributed to the U.S. and within expiry.

Misbranding Violation

Your firm's isoxsuprine hydrochloride tablets (NDC 61971-065) appear to be identical, related, or similar (IRS) to Vasodilan tablets, which are the subject of pending Drug Efficacy Study Implementation (DESI) proceeding 6403. The approval for Vasodilan (NDA 11832) was withdrawn effective March 13, 2009. (See 74 FR 6896, 6897, February 11, 2009), and there is no FDA approved application on file for your product.

Since the withdrawal of the Vasodilan application, FDA has been made aware of adverse event cases that may be associated with use of isoxsuprine hydrochloride. While it is generally FDA's policy to allow drug products subject to an ongoing DESI proceeding (including drug products that are IRS to those being reviewed under that proceeding) to remain on the market during the pendency of the proceeding, if potential safety issues arise or other violations of the FD&C Act are present, we may take appropriate action. See FDA's guidance document, *Marketed Unapproved Drugs— Compliance Policy Guide*, at **https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070290.pdf (https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070290.pdf)**.

As described below, after reviewing the labeling submitted to FDA's electronic Drug Registration and Listing System (eDRLS), your product is misbranded under sections 502(e) and (f)(1) and (f)(2) of the FD&C Act [21 USC 352 (e), (f)(1) and (f)(2)].

According to the labeling for isoxsuprine hydrochloride tablets (NDC 61971-065 submitted to eDRLS, the product's indications contain the following statements:

Is based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the medications as follows:

> *Possibly Effective:*
> *1. For the relief of symptoms associated with cerebral vascular insufficiency.*
> *2. In peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's disease), and Raynaud's disease.*

Final classification of the less-than-effective indications requires further investigation.

As labeled, the above product is a drug within the meaning of sections 201(g)(1)(B) and (C) of the FD&C Act, 21 U.S.C. 321(g)(1)(B) and (C), because it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and because it is intended to affect the structure or function of the body.

A drug is deemed to be misbranded under section 502(f)(1) of the Act [21 U.S.C. § 352(f)(1)] if its labeling fails to bear adequate directions for use. Under 21 CFR 201.5, "adequate directions for use" means directions under which a layman can use the drug safely and for the purposes for which it is intended. "Prescription drugs," as defined in section 503(b)(1)(A) of the Act [21 U.S.C. § 353(b)(1)(A)], are drugs that, because of their toxicity or potential for harmful effect, method of use, or collateral measures necessary to their use, are not safe for use except under the supervision of a practitioner licensed by law to administer them. Accordingly, adequate directions cannot be written for prescription drugs so that a layman can use them safely for their intended uses.

Due to the toxicity and other potential for harmful effect and the collateral measures necessary to its use, isoxsuprine hydrochloride is not safe for use except under the supervision of a licensed practitioner. In addition, this product is intended for conditions that are not amenable to self-diagnosis and treatment by individuals who are not medical practitioners. For these reasons, it is a prescription drug as defined in section 503(b)(1)(A) of the Act [21 U.S.C. § 353(b)(1)(A)], and adequate directions cannot be written so that a layman can use them safely for their intended uses. Consequently, the labeling of this drug fails to bear adequate directions for their intended uses, causing them to be misbranded under section 502(f)(l) of the Act [21 U.S.C. § 352(f)(1)].

Additionally, a drug is deemed to be misbranded under section 502(f)(2) of the Act [21 U.S.C. § 352(f)(2)] if its labeling fails to bear "adequate warnings against use in those pathological conditions . . . or application, in such manner and form, as are necessary for the protection of users . . . ." We note that the Vasodilan labeling included the following information "β-Adrenergic receptor stimulants such as isoxsuprine hydrochloride have been used to inhibit preterm labor. Maternal and fetal tachycardia may occur under such use. Hypocalcemia, hypoglycemia, hypotension and ileus have been reported to occur in infants whose mothers received isoxsuprine. Pulmonary edema has been reported in mothers treated with β-stimulants. Vasodilan (isoxsuprine HCl tablets, USP) is neither approved nor recommended for use in the treatment of premature labor." The omission of this adequate warning language in your product's labeling may result in patient harm and renders the product misbranded under section 502(f)(2) of the FD&C Act [21 U.S.C. § 352(f)(2)].

We also note other deficiencies in your product's labeling, including, but not limited to omission of inactive ingredients on the label, which renders the drug product misbranded under section 502(e) of the FD&C Act [21 U.S.C. § 352(e].

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.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b) and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

Failure to correct these violations may also result in FDA refusing admission of articles manufactured at Vista Pharmaceuticals Limited at APIIC Industrial Estate, Gopalapalli, Narketpalli, Nalgonda, Telangana, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under the same authority, articles may be subject to refusal of admission, in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B).

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 **CDER-OC-OMQ-Communications@fda.hhs.gov (mailto:CDER-OC-OMQ-Communications@fda.hhs.gov)** or mail your reply to:

Carla Norris
Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4359
10903 New Hampshire Avenue
Silver Spring, MD 20993
USA

Please identify your response with FEI 3003978209.

Sincerely,
/S/
Thomas J. Cosgrove, J.D.
Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research

More in 2017 (/ICECI/EnforcementActions/WarningLetters/2017/default.htm)