

Inspections, Compliance, Enforcement, and Criminal Investigations

Zosa, Noli R., M.D. 6/16/09

[hhsbluebird](#) Department of Health and Human Services

Public Health Service
Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

**CERTIFIED MAIL
RETURN RECEIPT REQUESTED**

Ref: 09-HFD-45-06-02

Noli R. Zosa, M.D.
12444 East Washington Boulevard
Whittier, California 90602

Dear Dr. Zosa:

Between October 2, 2008 and October 7, 2008, Ms. Sonya Karsik and Mr. Brian Putz, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol #433 entitled "A Study to Evaluate the Clinical and Microbial Efficacy of 0.6% ISV-403 Compared to Vehicle in the Treatment of Bacterial Conjunctivitis") of the investigational drug besifloxacin hydrochloride ophthalmic suspension (ISV-403), performed for Bausch & Lomb Incorporated.

This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, Ms. Karsik and Mr. Putz presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You failed to conduct the study or ensure the study was conducted according to

the signed investigator statement and investigational plan [21 CFR 312.60].

Specifically, 3 of 4 subjects you enrolled failed to meet enrollment criteria.

a. The protocol inclusion criteria required subjects to "have a clinical diagnosis of acute bacterial conjunctivitis and exhibit purulent conjunctival discharge (crusty or sticky eyelids) and redness in at least one eye. A minimum score of 1 should be present for discharge and a minimum score of 1 for bulbar conjunctival injection".

FDA's investigation found that Subjects 0154 and 0155 were enrolled and received the initial dose of investigational drug despite having the ocular discharge rating of "0 = Absent" for both eyes as documented for both subjects in the Clinical Assessment portion of the electronic case report form (eCRF). Specifically,

- i) For Subject 0154, the Visit 1-Day 1 portion of the eCRF, documented that the subject was diagnosed with "Pterygium nasal". There is no documentation that this subject had bacterial conjunctivitis as specified by the protocol.
- ii) For Subject 0155, the eCRF, pg 36 documented that the subject did not meet enrollment criteria and the Audit Trail Report generated on February 11, 2008, documented that the subject was diagnosed with "Episcleritis," one of the exclusion criteria in the protocol.

b. The protocol exclusion criteria excluded "subjects with suspected viral or allergic conjunctivitis (i.e, severe itching or acute follicular conjunctivitis), or any other disease conditions that could interfere with the efficacy and safety evaluations of the study medication." Our investigation found that both Subjects 0154 and 0155 had the above exclusion criteria marked as "Yes" on the "Exclusion Criteria section of the eCRF.

Your explanation provided during the inspection is unacceptable. You stated that your "system for screening potential study subjects was to see the subject initially, conduct **partial** screening, administer the initial dose of study drug, dispense study medication for home use to the subject, and then send the subject to be seen by the ophthalmologist within a day or so of the Day 1 Visit to complete the screening process." We note that pages 12 and 15 of the protocol specifically state, "the first Day 1 dose of study medication will be administered in the office **after** the initial eye exam and conjunctival culture."

c. The protocol required subjects to be at least one year of age. The eCRF documented that Subject 0156 was only 10 months of age at the time of enrollment. Our investigation found that Subject 0156 was enrolled despite not meeting the age requirement.

When you signed the Statement of Investigator, Form FDA 1572, you agreed to the responsibilities of a clinical investigator that included ensuring that the study is conducted according to the investigational plan and the signed Investigator

Statement, to protect the safety, rights or welfare of the subjects and to comply with all the obligations of a clinical investigator and all other pertinent requirements in 21 CFR 312. We remind you that as a clinical investigator, you retain responsibility for the conduct of the study.

2. You failed to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug [21 CFR 312.62(b)].

Protocol #433 stated the following:

Clinical data will be entered into electronic Case Report Forms (eCRFs). Data on eCRFs must correspond to and be supported by source documentation maintained at the investigational site, unless the site makes direct data entry for which no other original or source documentation is maintained. In such cases, the site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry.

FDA's investigation found that there was no source documentation at your site to corroborate data entered into the eCRF for any of the enrolled subjects, nor did we find documentation regarding which eCRFs were subject to direct data entry, or which procedures were in place to obtain and retain copies of information submitted by direct data entry. The following items, for example, were not found in subjects' files: ophthalmologist assessment reports, visual acuity assessment reports, laboratory reports, subjects' medical charts, bacterial and viral culture laboratory reports for all culture samples collected, and subject's worksheets documenting daily administration of study drug. Therefore, we are unable to verify the accuracy of the data submitted to the sponsor.

3. You failed to maintain documentation of informed consent in accordance with 21 CFR 50 [21 CFR 50.27(a)]

Specifically, 21 CFR 50.27(a) states that except as provided in 21 CFR 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subjects' legally authorized representative at the time of consent.

FDA's investigation found that for all four subjects enrolled, you did not document informed consent by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. The only documentation available at the site to document informed consent was the date recorded in the Informed Consent Section of the eCRFs for all four subjects. During the inspection, you stated that you were unable to locate these records due to the relocation of your office.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each

requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any on-going or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken or will be taking to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Tejashri Purohit-Sheth, M.D., at 301-796-3402; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Tejashri Purohit-Sheth, M.D.
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Good Clinical Practice Branch II
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
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10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,
{See appended electronic signature page}
Leslie K. Ball, M.D.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.

/s/

Tejashri Purohit-Sheth
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