U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Michlin, Bernard A., MD 7/13/15

Department of Health and Human Services

Public Health Service
Food and Drug
Administration
Silver Spring, MD 20993

WARNING LETTER
JUL 13, 2015

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref.: 15-HFD-45-07-01

Bernard A. Michlin, M.D.
6367 Alvarado Court, #200
San Diego, CA 92120

Dear Dr. Michlin:

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your clinical site between January 8 and January 23, 2015. Mr. Allen Hall, representing FDA, reviewed your conduct of the following clinical investigations:

- Protocol **(b)(4)**, "**(b)(4)**," of the investigational drug **(b)(4)**, performed for **(b)(4)**; and
- Protocol **(b)(4)**, "**(b)(4)**," of the investigational drug **(b)(4)**, performed for **(b)(4)**.

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

At the conclusion of the inspection, Mr. Hall presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your February 10, 2015, written response to the Form FDA 483.

From our review of the FDA Establishment Inspection Report, the documents submitted with that report, and your written response dated February 10, 2015, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We wish to emphasize

the following:

You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

As a clinical investigator, you are required to ensure that your clinical investigations are conducted in accordance with the investigational plan. The investigational plan requires that the screening visit include safety laboratory tests and urine drug screens. You failed to adhere to these requirements. Specifically:

a. Protocol **(b)(4)** requires the screening visit to include safety laboratory tests (including virology, hematology, and clinical chemistry) of the subjects' blood. Screening blood samples were not collected for the following subjects:

i. Subject 614005
ii. Subject 614009
iii. Subject 614015
iv. Subject 614016
v. Subject 614017
vi. Subject 614019
vii. Subject 614022
viii. Subject 614023

We acknowledge your February 10, 2015, written response to Items a.i., a.ii., and a.iii. above, in which you state that a Quality Assurance Internal Chart Review Tool will be used periodically to ensure that protocol-required procedures are being completed. We also acknowledge your February 10, 2015, written response to Item a.vi. above, in which you state that source documentation standard operating procedures (SOPs) were updated to include specific documentation of all laboratory tests performed. However, although you promised certain corrective measures in your response, you did not specifically address your failure to collect the protocol-specified screening blood samples.

Your response is inadequate because you did not provide documentation of the SOPs you will use for oversight of the studies you conduct. In addition, you did not provide any details of the in-service protocol and specimen-handling training for you and your staff. Without this information, we are unable to determine whether your corrective action plan is adequate to prevent similar violations in the future.

We recognize that Items a.iv., a.v., a.vii., and a.viii. above were not listed on the Form FDA 483 that was issued to you, and as a result, your written response to the Form FDA 483 does not address these issues.

b. Protocol **(b)(4)** requires that a urine drug screen be performed at screening and on Days 1, 2, 3, 4, 8, 15, 22, 29, and 36. Urine drug screens were not performed as follows:

i. For Subject 614011, no urine drug screens were performed on Days 1 or 2.
ii. For Subject 614014, no urine drug screen was performed at screening.

iii. For subject 614019, no urine drug screens were performed on Days 2-4, 8, 22, or 29.
iv. For Subject 614020, no urine drug screens were performed on Days 1-4, 8, 15, 22, 29, or 36.
v. For Subject 614024, no urine drug screens were performed on Days 2 or 3.

We acknowledge your February 10, 2015, written response to Item b.ii., in which you state that periodic checks will be performed to ensure that protocol-required procedures are being completed. However, your response did not specifically address your failure to perform these urine drug screens as the protocol required.

We also acknowledge your February 10, 2015, written response to Item b.iii., in which you state that when these deficiencies were noted, the subject was discontinued from the extension study (Study **(b)(4)**), and that source documentation SOPs were updated to include specific documentation of all laboratory tests performed. However, we note that despite the deficient urine drug screens, you allowed the subject to complete the study; furthermore, you enrolled the subject in the extension study.

Your response is inadequate because you did not provide documentation of the SOPs you will use for oversight of the studies you conduct. In addition, you did not provide any details of the in-service protocol and specimen-handling training for you and your staff. Without this information, we are unable to determine whether your corrective action plan is adequate to prevent similar violations in the future.

We recognize that Items b.i., b.iv. and b.v. above were not listed on the Form FDA 483 that was issued to you, and as a result, your written response to the Form FDA 483 does not address these issues.

Failure to perform screening safety laboratory tests and urine drug screens according to the protocol jeopardizes subject safety and welfare, and compromises the validity and integrity of the data collected at your site.

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 ongoing 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 to prevent similar violations in the future. Failure to address the violations above adequately and promptly may result in regulatory action without further notice. If you believe that you have complied with FDA regulations, include your reasoning and any supporting information for our consideration.

If you have any questions, please contact Allen Lou at 301-796-5652; FAX 301-847-8748. Your written response and any pertinent documentation should be

addressed to:

Allen Lou
Acting Branch Chief
Compliance Enforcement Branch
Division of Enforcement and Postmarketing Safety
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Building 51, Room 5260
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,
{See appended electronic signature page}
Sean Y. Kassim, Ph.D.
Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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/s/

SEAN Y KASSIM
07/13/2015

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