Oeyama-Moto-Medical Group Foundation, LLC 5/21/18

U.S. FOOD & DRUG ADMINISTRATION

10903 New Hampshire Avenue
Silver Spring, MD 20993

WARNING LETTER

MAY 21, 2018

VIA UNITED PARCEL SERVICE

Benedict S. Liao, M.D.
Oeyama-Moto Medical Group Foundation, Inc.
3106 East Garvey Avenue South
West Covina, California 91791-2344

Ref.: 17-HFD-45-05-01

Dear Dr. Liao:

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at Oeyama-Moto Medical Group Foundation, Inc., West Covina, California, from August 7 to August 11, 2017. Mr. Johann M. Fitch and Drs. Mark J. Seaton, Zhou Chen, and Eias A. Zahalka, representing FDA, reviewed your conduct of the following nonclinical laboratory studies of the investigational drug **(b)(4)**:

- "Toxicity of **(b)(4)** in Mice by Oral Administration" (2008)
- "Toxicity Study of **(b)(4)** in Mice by Repeat Oral Administration" (2016)
- "Toxicity Study of **(b)(4)** in Rabbits by Repeat Oral Administration" (2016)
- "**(b)(4)** Toxicity Study in Rabbits by Repeat Intramuscular Administration" (2016)
- "Toxicity Study of **(b)(4)** in Hamsters by Repeat Oral Administration" (2016)

- "Toxicity Study of **(b)(4)** in Dogs by Repeat Oral Administration (**(b)(4)** Subchronic Toxicity Test in Animal Species of Dogs)" (2016)

This inspection was conducted as a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the data are scientifically valid and accurate, in accordance with Title 21 of the Code of Federal Regulations (CFR), part 58 – Good Laboratory Practice (GLP) regulations.

At the conclusion of the inspection, FDA representatives presented and discussed with you Form FDA 483, Inspectional Observations.

From our review of the FDA 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 nonclinical laboratory studies. We wish to emphasize the following:

1. Your testing facility management failed to assure that there was a Quality Assurance Unit (QAU), which was responsible for monitoring each study and was entirely separate from and independent of the personnel engaged in the conduct of the studies, for each nonclinical laboratory study [21 CFR 58.31(c), 21 CFR 58.35(a)].

The testing facility management must ensure that there is a Quality Assurance Unit (QAU) responsible for monitoring each nonclinical laboratory study, to assure management that all facilities, equipment, personnel, methods, practices, records, and controls are in conformance with the GLP regulations. For any given study, the QAU must be entirely separate from and independent of the personnel engaged in the direction and conduct of that study. This separation will allow the QAU to provide an objective and unbiased assessment that each nonclinical laboratory study is conducted in accordance with the approved protocol and standard operating procedures (SOPs); that the final study report reflects the raw data accurately; that the facility is compliant with GLP requirements; and that the findings from inspections are reported to management and the study director to allow implementation of corrective actions.

Your testing facility management failed to adhere to the above GLP requirements. Specifically, there were no records indicating the presence of a functional QAU, or records of any QA activities at the facility. In addition, you indicated during the FDA inspection that you were the study director as well as the head of the QAU. However, this practice undermines the QAU from performing its required functions separate from and independent of the personnel engaged in the conduct of nonclinical laboratory studies. You also indicated that a veterinarian for the study from **(b)(4)**, was a member of the QAU; however, that veterinarian signed a statement denying that he was a QAU member.

Considering your test facility management's overall lack of responsibility to implement basic essential elements of GLP compliance, the quality and integrity of the study data cannot be assured because there was no QAU oversight of the nonclinical laboratory studies conducted at your testing facility.

2. Your testing facility failed to establish standard operating procedures (SOPs) in writing setting forth nonclinical laboratory study methods that are adequate to insure [*sic*] the quality and integrity of the data generated in the course of the studies, as well as to ensure appropriate handling and care of animals [21 CFR 58.81 (a) and (b)].

A testing facility must establish and follow written SOPs for nonclinical laboratory studies, to ensure consistency in study conduct and thus the quality and integrity of data generated in the studies. Your testing facility did not adhere to these requirements. Specifically, no SOPs were established for the nonclinical laboratory studies, including but not limited to animal room preparation, receipt, identification, storage, handling, mixing, method of sampling of the test and control articles, collection and identification of specimens, histopathology, and data handling, storage, and retrieval.

In addition, you had no SOPs for housing, feeding, handling, and care of animals, as required by 21 CFR 58.90.

During the inspection, you indicated that as a surgeon, you knew all operation procedures, and therefore you did not agree that SOPs needed to be established. Nevertheless, the testing facility is required to establish SOPs in writing, setting forth nonclinical laboratory study methods that are adequate to ensure the quality and integrity of the data generated during the studies, as well as to ensure appropriate handling and care of animals. FDA must conclude that the methods followed at your testing facility for animal care and handling and for conducting nonclinical toxicity studies were neither effective nor adequate to ensure data quality and integrity.

3. As the study director, you failed to assure that all experimental data were accurately recorded and verified; all data entries were dated and signed or initialed; and that all changes did not obscure the original entry, indicated the reason for change, and were dated and signed or identified at the time of the change [21 CFR 58.33(b), 21 CFR 58.130(e)].

As the study director, you must ensure that all experimental data, including observations of unanticipated responses of the test system, are accurately recorded and verified. In addition, all data entries must be dated on the date of entry and signed or initialed by the person entering the data. Any changes in entries must be made so as not to obscure the original entries, must indicate the reason for such change, and must be dated and signed or identified at the time of the changes. Specifically:

a. You failed to ensure that all experimental data were accurately recorded and verified.

i. For the toxicity study in mice conducted in 2008, the study summary report describes the study as being conducted in 2009; also, the body weight records indicate the animal species as "rat" instead. There were no source records to verify the purchase of test systems including mice, hamsters, and rabbits.

ii. For the toxicity study in dogs, dose calculation worksheets for nine dogs show body weight measurements and test article administration in June and July 2016; however, purchase records indicate that eight of the nine dogs were purchased in August 2016, which makes the data entered before August 2016 invalid. In fact, during the FDA inspection, you acknowledged that the data entered before the dosing in August was inaccurate and did not reflect real-time data entry.

b. You failed to ensure that all data entries and changes to data were dated on the date of entry and signed or initialed by the person entering the data. The following data entries and changes to data were not signed and dated. In addition, for all data changes, you failed to ensure: (1) that the

original entries were not obscured; (2) that the reason for all changes was indicated; and (3) that all changes were dated and signed or identified at the time of the changes.

i. For the toxicity studies in mice, hamsters, and dogs, body weight records included dosing dates but did not include the signature or initials.

ii. For the toxicity study in dogs, original entries in the body weight records were obscured and did not indicate the reason for the changes, the date of the changes, or the signature or identification of the individual making the changes.

iii. For the toxicity study in rabbits by repeat oral administration, the original data entries for Rabbits A1, A2, and B3 in the **(b)(4)** Result Report for LDH and iron were obscured and did not indicate the reason for the changes, the date of the changes, or the signature or identification of the individual making the changes.

Because you failed to ensure that all experimental data were accurately recorded and verified, and that all entries and changes in entries were properly documented, FDA has concerns about the integrity of the data generated from the nonclinical toxicity studies conducted at your testing facility.

4. Your testing facility failed to assure that all raw data, documentation, protocols, final reports, and specimens generated as a result of the nonclinical laboratory study were retained, and that archives for orderly storage and expedient retrieval of all raw data, documentation, protocols, specimens, and interim and final reports were provided [21 CFR 58.190(a), and (b)].

All raw data, documentation, protocols, final reports, and specimens (except for specimens obtained from mutagenicity tests, and wet specimens of blood, urine, feces, and biological fluids) generated as a result of the nonclinical laboratory studies must be retained. In addition, archives must be provided for the orderly storage and expedient retrieval of all raw data, documentation, protocols, specimens, and interim and final reports.

You failed to comply with the above requirements to retain and to provide archives for storage and retrieval of all raw data and specimens. Specifically, not all histopathology specimens and slides generated during the conduct of the nonclinical toxicity studies were retained. Only a limited number of animal specimens and tissue blocks were found at the testing facility during the inspection.

You were unable to provide all data requested during the inspection; you indicated that you were unsure where the data was, and that it might be at your home. You indicated that there was no designated space at the testing facility for retention and archiving. You also acknowledged during the inspection that the majority of specimens, slides, and raw data for the hamster study and for the rabbit studies were lost.

The absence of raw data and specimens collected during these nonclinical toxicity studies, and the absence of proper storage of raw data and specimens, raises significant concerns about the integrity of the study records and data.

5. For mixtures of articles with carriers, your testing facility management failed to assure that tests were conducted by appropriate analytical method to determine the uniformity of

the mixture, the concentration of the test or control articles in the mixture, and the stability of the test and control articles in the mixture, as applicable [21 CFR 58.31(d), 21 CFR 58.113].

According to the protocols for the animal toxicity studies described above, the test article **(b)(4)** (from **(b)(4)**) was to be dissolved in 0.5% of Tween-80 solution or Vitamin C solution to a specific final concentration based on the animal species and the route of administration being studied; however, the formulation mixtures were not analyzed for concentration of test or control article, uniformity, and stability before or during dosing.

Specifically, for mixtures of articles with carriers, the testing facility must ensure that tests by appropriate analytical method are conducted to determine the uniformity of the mixture, the concentration of the test or control articles in the mixture, and the stability of the test and control articles in the mixture, as applicable. Testing to determine the stability of the test and control articles in the mixture must be conducted, either before the study initiation or concomitantly, according to written SOPs that provide for periodic analysis of the test and control articles in the mixture. However, none of these analyses were done. We acknowledge that a microbiological analysis of the product **(b)(4)** was performed in May 2017; however, that analysis was conducted after the completion of the toxicity studies.

Because your testing facility failed to ensure that for mixtures of articles with carriers, tests by appropriate analytical method were conducted to determine the uniformity of the mixtures, the concentration of the test or control articles in the mixtures, and the stability of the test and control articles in the mixtures, FDA is concerned about the uniformity of the mixtures, the concentration of the test or control articles in the mixtures, and the stability of the test and control articles in the mixtures used in the nonclinical toxicity studies conducted at your testing facility. Therefore, FDA cannot assure the quality and reliability of the study data.

6. For each study, study protocols lacked the information required by 21 CFR 58.120(a).

The protocols of nonclinical toxicity studies in mice, hamsters, rabbits, and dogs conducted at your testing facility did not adhere to the GLP requirements for such protocols. Specifically, the protocols did not have a date of approval by the sponsor and did not contain sufficient details, including but not limited to:

a. A statement of the purpose of the specific study
b. The name and address of the testing facility at which the study is being conducted
c. The procedure for identification of the test system
d. The methods for the control of bias
e. The frequency of tests, analyses, and measurements to be made
f. The records to be maintained

During the FDA inspection, you indicated that you considered FDA's guidance *Subchronic Toxicity Studies with Non-Rodents*, Redbook 2000: IV.C.4.b., as the protocol for the toxicity study in dogs. We note that while this FDA guidance is intended to provide general recommendations, it does not include the study-specific information (described in **6.** a.-f. above) required to comply with the basic GLP requirements.

The lack of approved study protocols for each toxicity study, with all required information, raises concerns about the conduct of the studies and about the quality and reliability of study data.

As evidenced by FDA's inspection findings, your testing facility management failed to fulfill the primary responsibilities to establish appropriate policies and procedures intended to ensure the quality and integrity of nonclinical data for FDA submission. Furthermore, the deficiencies found in your oversight as the study director and the absence of an independent QAU indicate that your testing facility failed to fulfill the core responsibilities to remain GLP-compliant. As a result, FDA is concerned about the validity of nonclinical data generated by your testing facility.

This letter is not intended to be an all-inclusive list of deficiencies with the nonclinical laboratory toxicity studies of an investigational drug conducted at your testing facility. 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 comply 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 noted above adequately and promptly may result in regulatory action without further notice. If you believe you have complied with FDA regulations, include your reasoning and any supporting information for our consideration.

If you have any questions about this letter or the inspection, please call Adam Donat, Branch Chief, Compliance Enforcement Branch, at 301-796-5316. Your written response and any pertinent documentation should be addressed to:

Adam Donat, M.S.
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Compliance Enforcement Branch
Division of Enforcement and Postmarketing Safety
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
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Building 51, Room 5352
10903 New Hampshire Avenue
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Sincerely yours,

{See appended electronic signature page}

David C. Burrow, Pharm.D., J.D.
Director
Office of Scientific Investigations
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/s/

DAVID C BURROW
05/21/2018

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