Inspections, Compliance, Enforcement, and Criminal Investigations

AMKS TIME RELEASE LAB, LLC 4/10/14

Department of Health and Human Services

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

APR 10, 2014

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

14-HFD-45-04-01

Ismail Elchagea, Ph.D.
President
AMKS Time Release Laboratories, LLC
470 Chamberlain Avenue
Paterson, NJ 07522

Dear Dr. Elchagea:

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at AMKS Time Release Laboratories, LLC (AMKS TRL) between June 17 and July 12, 2013. Mr. Peter Lenahan, representing FDA, reviewed AMKS TRL's conduct as the sponsor of a clinical investigation (Protocol **(b)(4)** of the investigational drug **(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. Lenahan presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your July 30, 2013, written response to the Form FDA 483.

From our review of the FDA Establishment Inspection Report, the documents submitted with that report, and your July 30, 2013, written response, we conclude that AMKS TRL did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We wish to emphasize the following:

1. Failure to submit an IND application for the conduct of clinical investigations with an investigational new drug that is subject to 21 CFR 312.2(a) [21 CFR 312.20(a) and 312.40(a)].

To market a new drug lawfully, a sponsor must obtain approval of a new drug application or abbreviated new drug application under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) [21 U.S.C. 355]. An Investigational New Drug application (IND) is the means through which a sponsor obtains an exemption from this requirement to distribute an investigational drug [21 U.S.C. 355(i)]. FDA regulations require a sponsor to submit an IND application before conducting a clinical investigation of a drug in human subjects, unless the clinical investigation qualifies for an IND exemption.

A marketed drug product is exempt from the IND requirements if all of the following exemption criteria are met:

- The drug product is lawfully marketed in the United States;
- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use and there is no intent to use the investigation to support any other significant change in the labeling of the drug;
- In the case of a lawfully marketed prescription drug, the investigation is not intended to support a significant change in the advertising for the drug;
- The investigation does not involve a route of administration, dosage level, use in a patient population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
- The investigation is conducted in compliance with the requirements for institutional review set forth in 21 CFR part 56 and with the requirements for informed consent set forth in 21 CFR part 50; and
- The investigation is conducted in compliance with the requirements of 21 CFR 312.7 regarding promotion of investigational drugs.

A person planning to conduct a bioavailability or bioequivalence study of an unapproved version of an approved drug product is not required to submit an IND when certain criteria under 21 CFR 320.31 are met.

AMKS TRL's investigational drug **(b)(4)** is not a lawfully marketed drug product in the United States, nor is it an unapproved version of an approved drug product undergoing a bioavailability or bioequivalence study. As a result, before using **(b)(4)** in a clinical investigation, AMKS TRL was required to submit an IND for the drug to FDA, and the IND was required to go into effect under 21 CFR 312.40.

FDA records indicate that AMKS TRL did not submit an IND before conducting the study under Protocol **(b)(4)**, a clinical investigation of **(b)(4)**.

In your July 30, 2013, written response, you state, "Our judgment was that **(b)(4)** was not a drug, we used **(b)(4)** as dietary and food supplement [*sic*]." You also state, "We know that it is characterized as safe in 21 CFR Section 182.1," and "We did the non-clinical and clinical study to obtain enough data to submit to FDA, in order to satisfy the safety and efficiency [*sic*] of **(b)(4)**."

In relevant part, the FD&C Act defines the term *drug* as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals" [21 U.S.C. 321(g)]. We note that Protocol **(b)(4)** describes **(b)(4)** as the "study medication," and the protocol's purpose is to "evaluate the antiviral benefit of **(b)(4)** in human subjects co-infected with hepatitis C and human immunodeficiency virus." Because AMKS TRL was studying whether **(b)(4)** mitigates or treats hepatitis C in humans with immunodeficiency virus infection, it is an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. **(b)(4)** meets the definition of a drug under the FD&C Act; therefore, AMKS TRL was required to submit an IND, which was

required to go into effect before AMKS TRL could initiate any clinical investigations of **(b)(4)** in human subjects.

We acknowledge that in your July 30, 2013, written response, you state that AMKS TRL "is committed to and is working with FDA" and "will not initiate any further study unless the FDA authorizes AMKS to proceed." If properly carried out for clinical investigations that require an IND, AMKS TRL's plan appears adequate to prevent the recurrence of similar violations in the future.

2. Failure to ensure proper monitoring of the investigations and failure to ensure that the investigations are conducted in accordance with the general investigational plan and protocols contained in the IND [21 CFR 312.50 and 312.56(a)].

FDA regulations require that sponsors ensure proper monitoring of clinical investigations and ensure that their clinical investigators conduct those investigations in accordance with the general investigational plan and protocols contained in the IND. Our investigation found that you failed to ensure proper monitoring of Protocol **(b)(4)** and did not ensure that a clinical investigator conducted the investigation in accordance with that protocol. Specifically:

AMKS TRL monitoring failed to identify and correct a clinical investigator's failure to collect study subjects' data on protocol-specific case report forms (CRFs), as required by Protocol **(b)(4)**. We note that during the inspection, you indicated that AMKS TRL did not use any paper CRFs or electronic data capture to record study subjects' data.

In your July 30, 2013, written response, you indicated that AMKS TRL had no written monitoring plan for Protocol **(b)(4)** and monitored the study's progress through verbal discussions with the clinical investigator. We acknowledge that in that written response, you indicated that AMKS TRL has prepared a written monitoring plan and submitted that plan to FDA, along with a new protocol.

Regarding the lack of CRFs, we acknowledge that AMKS TRL has prepared and provided a copy of a CRF with your July 30, 2013, written response.

Your written response is inadequate because you did not include with it a copy of the monitoring plan or provide any details regarding the monitoring plan. As a result, we are unable to determine whether your written monitoring plan appears sufficient to prevent similar violations in the future. In addition, the CRF you provided with your July 30, 2013, written response does not appear to be related to Protocol **(b)(4)**, because there are significant differences between the inclusion/exclusion criteria and laboratory assessments in the CRF you provided, and those for Protocol **(b)(4)**.

3. Failure to maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug [21 CFR 312.57(a)].

As the sponsor of Protocol **(b)(4)**, AMKS TRL was required to maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug **(b)(4)**. These records were required to include, as appropriate, the name of the clinical investigator to whom the drug was shipped, and the date, quantity, and batch or code mark of each such shipment. AMKS TRL failed to maintain adequate records with respect to the investigational drug **(b)(4)**. Specifically, AMKS TRL did not maintain any records showing the shipment or other disposition of the investigational drug.

In your July 30, 2013, written response, you do not address specifically whether AMKS TRL kept written records of the disposition of investigational drug for Protocol **(b)(4)**. However, you do state, "We used to carry the product to the hospital in person because the hospital is close to our facility. But now in the new study we will keep accurate records for shipment as per AMKS TRL has established an S.O.P. To outline the shipment, quantity used, return or destruction of clinical drug

[*sic*].” You also note in your response that records for use were retained in patient files at St. Joseph Hospital.

Your response is inadequate because you provided no documentation or details regarding the AMKS TRL Standard Operating Procedure (SOP) referred to in your response. As a result, we are unable to determine whether this SOP appears sufficient to prevent similar violations in the future.

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 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, please contact Constance Cullity, M.D., M.P.H., at 301-796-3397; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Constance Cullity, M.D., M.P.H.
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Good Clinical Practice Enforcement Branch
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Office of Scientific Investigations
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10903 New Hampshire Avenue
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Sincerely yours,
{See appended electronic signature page}
Sean Y. Kassim, Ph.D.
Acting Director
Office of Scientific Investigations
Office of Compliance
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/s/

SEAN Y KASSIM
04/10/2014

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