WARNING LETTER

"David M. Lubeck, M.D./Arbor Centers for EyeCare

MARCS-CMS 643531 — NOVEMBER 18, 2022

Delivery Method:

VIA UNITED PARCEL SERVICE

Product:

Drugs

Recipient:

David M. Lubeck, M.D.

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WARNING LETTER

FDA Reference Number: 22-HFD-45-11-02

Dear Dr. Lubeck:

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 April 12 and April 20, 2022. Investigator Yuanyuan Li, representing FDA, reviewed your conduct as the sponsor-investigator of the following clinical investigations:

- Protocol **(b)(4)** , "**(b)(4)**," of an investigational combination product consisting of the investigational **(b)(4)** and **(b)(4)** in combination with **(b)(4)**
- Protocol **(b)(4)**, "**(b)(4)**," of an investigational combination product consisting of the investigational drugs **(b)(4)** and **(b)(4)** in combination with **(b)(4)**

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 rights, safety, and welfare of human subjects have been protected.

At the conclusion of the inspection, Investigator Li presented and discussed with you the Form FDA 483, Inspectional Observations. We acknowledge receipt of your May 10, 2022, written response to the Form FDA 483.

From our review of the FDA Establishment Inspection Report, the documents submitted with that report, and your May 10, 2022, written response to the Form FDA 483, it appears that you did not adhere to the applicable statutory requirements in the Federal Food, Drug, and Cosmetic Act (FD&C Act) and applicable regulations contained in Title 21 of the Code of Federal Regulations, part 312 (21 CFR 312) governing the conduct of clinical investigations and the protection of human subjects. We wish to emphasize the following:

You failed to submit an Investigational New Drug application (IND) for the conduct of a clinical investigation with investigational new drugs that is subject to 21 CFR 312.2(a) [21 CFR 312.20(a), 312.20(b), and 312.40(a)].

FDA regulations require a sponsor to submit, and to have in effect, an IND before initiating a clinical investigation of a drug that is subject to 21 CFR 312.2(a) (see 21 CFR 312.20 and 312.40(a)) in human subjects, unless the clinical investigation qualifies for an IND exemption under 21 CFR 312.2. You failed to comply with these requirements. You initiated and conducted a clinical investigation of investigational drugs subject to section 505 of the FD&C Act (21 U.S.C. 355) without submitting and having in effect an IND[1]. Specifically, you initiated and conducted a clinical investigation of a combination product consisting of the investigational drugs **(b)(4)** and **(b)(4)** in combination with **(b)(4)**, conducted under Protocol **(b)(4)**, without submitting and having in effect an IND. There are no FDA records to indicate that you submitted an IND before initiating and conducting this clinical investigation, in which five human subjects were enrolled.

In your May 10, 2022, written response to the Form FDA 483, you stated that you and an institutional review board (IRB) considered Protocol **(b)(4)** to be a nonsignificant risk (NSR) device study, with the use of **(b)(4)** as a generally recognized as safe (GRAS) substance and as "**(b)(4)**." You further explained that you and the IRB determined that an investigational device exemption (IDE) was not required.

However, the investigational product used in Protocol **(b)(4)** and **(b)(4)** in combination with **(b)(4)** comprises both drug and device components and is therefore a combination product within the meaning of section 503(g) of the FD&C Act (21 U.S.C. 353(g)). Because the primary mode of action[2] of the investigational combination product is attributable to **(b)(4)**, and because **(b)(4)** meets the definition of a drug under section 201(g) of the FD&C Act[3], an IND is required for any clinical investigation of the investigational combination product used in Protocol **(b)(4)**. In addition, Section 10.3.1 of Protocol **(b)(4)** noted that "CDER [Center for Drug Evaluation and Research] has primary jurisdiction for the regulation of this product."

You further stated that subject enrollment commenced after IRB approval. However, on October 29, 2019, the IRB notified you that an IND was required. Subsequently, enrollment was immediately halted, the study was paused, and an IND was submitted to FDA. You then stated that you recommenced enrollment in this study only after FDA received the IND on **(b)(4)**, and the IRB gave approval.

Your written response is inadequate for several reasons, including that neither the IRB approval itself nor your enrollment of subjects after receiving IRB approval met your obligation to have an IND in effect before beginning enrollment and treatment of subjects. Also, while we acknowledge that you halted enrollment and ceased study activities upon learning from the IRB that an IND was required to be submitted to the FDA, the IND you submitted to the FDA and referenced in your written response did not contain Protocol **(b)(4)**. Rather, the IND contained a similar but substantively unique clinical protocol, Protocol **(b)(4)**. Protocol **(b)(4)** clinical investigation of **(b)(4)** and **(b)(4)** in combination with **(b)(4)**, whereas Protocol **(b)(4)** is a **(b)(4)**, **(b)(4)** and **(b)(4)** in combination with **(b)(4)**. Therefore, the IND you submitted containing Protocol **(b)(4)** did not cover the study you initiated under Protocol **(b)(4)**.

Consequently, you initiated a clinical investigation under **(b)(4)** without submitting an IND, and you administered the study drug to all enrolled subjects. Also, we note that an IND does not go into effect upon FDA's receipt of the IND submission4; rather, an IND generally goes into effect 30 days after FDA receives the application, or on earlier notification by FDA that the clinical investigation in the IND may begin (21 CFR 312.40(b)). We emphasize that FDA regulations require a sponsor to submit, and to have in effect, an IND before initiating a clinical investigation that must be conducted under an IND in accordance with 21 CFR 312.40.

Lastly, your response is inadequate because you did not provide a corrective action plan to address how you, as a sponsor-investigator, will determine when an IND is required for clinical investigations of products regulated by FDA, and how you will comply with IND regulations in accordance with 21 CFR 312.2. Without this information, we are unable to determine whether you will comply with IND regulations in the future.

As a sponsor-investigator, you are responsible for compliance with IND requirements, and it is your responsibility to be aware of and to follow all applicable FDA regulations. Your failure to submit, and to have in effect, an IND before initiating a clinical investigation with investigational drugs raises significant concerns regarding the safety and welfare of enrolled subjects, and also raises concerns about the validity and integrity of data collected at your site during the conduct of the clinical investigation.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational combination product. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address any deficiencies and establish procedures to ensure that any ongoing or future studies comply with FDA regulations.

This letter notifies you of our findings and provides you an opportunity to address the above deficiencies. Within 15 business 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 adequately address this matter may lead to regulatory action. If you believe that you have complied with the FD&C Act and relevant regulations, please include your reasoning and any supporting information for our consideration.

If you have any questions, please call Miah Jung, Pharm.D., M.S., at 240-402-3728. Alternatively, you may email FDA at CDER-OSI-Communications@fda.hhs.gov.

Your written response and any pertinent documentation should be addressed to:

Miah Jung, Pharm.D., M.S.
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 5352
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely yours,
{See appended electronic signature page}
David C. Burrow, Pharm.D., J.D.
Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DAVID C BURROW
11/18/2022 11:49:10 AM

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1 Protocol **(b)(4)** did not qualify for any of the exemptions listed at 21 CFR 312.2 from the application of 21 CFR 312.

2 The FD&C Act defines the term *primary mode of action* as "the single mode of action of a combination product expected to make the greatest contribution to the overall intended therapeutic effects of the combination product" [21 U.S.C. 353(g)(1)(C)]. See also 21 CFR 3.2(m).

3 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)(1)].

4 While we recognize that you did not in fact enroll any subjects to Protocol 330019 before the IND went into effect, we note that in your May 10, 2022, response, you highlighted that enrollment in the study was "recommenced only after the IND . . . was received on 2 January 2020."

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