March 29, 2021

UPS Express Mail & Electronic Mail

Neil P. Sheth, M.D.
Synexus Clinical Research, Inc.
5750 West Thunderbird Road, Suite G790
Glendale, Arizona 85306-4678

Dear Dr. Sheth:

This letter informs you of objectionable conditions observed during a Food and Drug Administration (FDA) inspection conducted between November 16, 2020 and November 24, 2020. FDA investigators met with you and your staff during the inspection to review your conduct as a clinical investigator of a clinical study entitled:

(b) (4)

The FDA conducted this inspection under the Bioresearch Monitoring Program that includes inspections designed to review the conduct of research involving investigational products. At the end of the inspection, the FDA investigators presented a Form FDA 483, Inspectional Observations, for your review and discussed the listed observations with you.

Based on our review of the establishment inspection report, the documents submitted with that report, and your written responses dated December 17, 2020, and January 14, 2021 to the Form FDA 483, we determined that you violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published in Title 21, Code of Federal Regulations (CFR) Part 312 (available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=312).
The violations include, but are not limited to the following:

1. Failure 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 section 8.2.2, Use of Electronic Diaries ("eDiary") describes eDiary as a system used to collect 7-day reactogenicity events, solicited local and systemic reactions, and weekly eDiary prompts to elicit an unscheduled Illness Visit if a subject is experiencing(b) (4) symptoms. The protocol states, in pertinent part: "At each dosing visit, participants will record data into the eDiary starting approximately 30 minutes after dosing under supervision of the study site staff to ensure successful entry of assessments."

For at least 23 of 53 subjects whose records were reviewed during the inspection, the eDiary entries were not completed following the Dose (b)(4) visit as set forth in the protocol and illustrated in Table-1. These incomplete eDiary entries conflicted with corresponding source documents completed by site personnel that reflected that the eDiary entries were completed in accordance with the protocol. Specifically, the source document for Dose (b)(4) includes a question: "Was the e-Diary completed and reviewed 30 minutes after observation period?" For these subjects, the "yes" box next to that question was checked, indicating that the eDiary entries were completed and reviewed, when they were not. In addition, during the inspection, one of your study coordinators acknowledged completing the checkbox without reviewing the eDiary for subjects #(b) (6) and #(b) (6) We note that issues regarding incomplete eDiary entries were previously identified by the study monitor during their interim monitoring visits but continued to occur after being identified. For example, for subject #(b) (6) the study monitor identified the issue with incomplete eDiaries during the interim monitoring visit on(b) (6) . However, we observed that there were incomplete eDiary entries for this subject after Dose (b)(4) on (b) (6)

Table -1

Subject number	Date of Dose (b) visit	eDiary entries post Dose (b)
(b) (6)		Not done
		Not done
		Not done
		Not done
		Not done
		Not done
		Not done
		Not done
		Not done

(b) (6)			Not done
			Not done
			Not done
			Not done
			Not done
			Not done
			Not done
			Not done
			Not done
			Not done
			Not done
			Not done
			Not done

In your December 17, 2020 response, you acknowledge the record keeping deficiencies in eDiary entries and describe corrective and preventive actions that include adding additional human resources for the subject study; training of study personnel on study related procedures including, but not limited to, eDiary reviews and review of electronic data capture (EDC) for eDiary completion while subjects are onsite; and retraining the study personnel on Good Documentation Practices. The response also states that since November 30, 2020, you have been personally reviewing a subset of subject records against the eDiary entries to verify completion, accuracy and consistency. However, your response did not provide sufficient detail to fully assess the adequacy of your corrective actions. Specifically, your response did not explain the continued occurrence of these deficiencies after they were identified by the study monitor or provide adequate assurance that your corrective actions have been successfully implemented.

2. Failure to ensure that the investigation was conducted according to the signed investigator statement, the investigational plan, and applicable regulations; failure to protect the rights, safety, and welfare of subjects under your care. [21 CFR § 312.60].

Protocol section 8.2.1, Table 14, and Table 15 with corresponding footnotes, includes follow-up safety calls to be made on specific days after visits 1, 2, and 3 for safety and efficacy assessments, including surveillance for (b) (4) . The protocol also includes follow-up safety calls on Day 8, Day 15, and Day 22 (+3 days window allowance) after the (b) (4) dose of the (b) (4) administration; on Day 36, Day 43, and Day 50 (starting 7 days after the (b) (4) dose with a +3 days window allowance) after the (b) (4) dose that is to be administered (b) (4) days after (b) (4) first dose. The protocol calls for weekly eDiary entries after visit 3 which occurs (b) (4) days (-3/+7 days) after the (b) (4) dose; and site personnel are to follow-up with subjects to confirm health status and remind subjects to complete the eDiary if subjects miss eDiary entries with two-

day window allowance. Further, the protocol includes daily subject follow-up starting Day 2 through Day 14 by telemedicine following initial Illness Visit on Day 1.

Of the 31 subjects whose records were reviewed during the inspection, one follow-up call was missed for 10 subjects, and for 15 subjects two or more follow-up calls were missed. In addition, illness visits were missed for 2 subjects and telemedicine calls following illness visits were missed for 3 subjects. We note that issues regarding missed safety calls, illness visits, and telemedicine calls following illness visits were previously identified by the study monitor during their interim monitoring visits but continued to occur after being identified. For example, for subject #(b) (6) the study monitor identified the missed safety call on Day 8 during the interim monitoring visit on (b) (6) . However, safety calls continued to be missed for this subject after the issue was identified (e.g., on Day 36, Day 43, and Day 50). Examples are illustrated in Table-2.

Table-2

Subject	Date of Dose[b] (b) (4)	Protocol procedures	Not performed
(b) (6)		Telemedicine call following illness visits	Day 2 (b) (6)) and Day 3 (b) (6)) following illness visit on Day 1 on (b) (6)
		Safety phone call	Day 43
		Illness visit	No illness visit was documented regarding subject reporting fatigue and decreasing nausea and note of a temperature of "101 something" on progress notes dated 9/9/2020 and 9/11/2020 following vaccination on (b) (6)
		Safety phone call	Day 36, 43, and 50
		Safety phone call	Day 8, 36, 43, and 50
		Safety phone call	Day 36
		Safety phone call	Day 36 and 50
		Safety phone call	Day 8, 36, 43, and 50
		Safety phone call	Day 15, 36, 43, and 50
		Safety phone call	Day 36 and 50
		Safety phone call	Day 15, 36, and 50

(b) (6)	Safety phone call	Day 43
	Safety phone call	Day 36 and 43
	Safety phone call	Day 22 call was out of window, conducted the same day as the Day 29 visit (visit 2)
	Telemedicine call following illness visits	Days 2 through 9 (b) (6) (b) (6) following illness visit on (b) (6) ((b) (4) detected from illness visit swab on report generated on 11/6/2020).
	Safety phone call	Day 22 and 43
	Telemedicine call following illness visit	Days 3 and 4, (b) (6) and Days 6 and 7 ((b) (6) - following illness visit on (b) (6) (b) (4) detected from illness visit swab on report generated on 11/19/2020).
	Safety phone call	Day 15
	Safety phone call	Day 8
	Illness visit	During the day 15 call (on (b) (6)) symptoms including shortness of breath and cough were noted. However, no illness visit was scheduled by the site. The subject was hospitalized from (b) (6) - (b) (6) and tested (b) (4) (dose on (b) (6)).
	Safety phone call	Day 8 and 36
	Safety phone call	Day 8 and 22
	Safety phone call	Day 22 and 36
	Safety phone call	Day 36 and 43
	Safety phone call	Day 8
	Safety phone call	Day 36
	Safety phone call	Day 8 and 22
	Safety phone call	Day 22
	Safety phone call	Day 8 and 15
	Safety phone call	Day 8

In your December 17, 2020 response, you acknowledge the deficiencies in your study conduct and failure to follow the protocol procedures regarding follow-up safety calls and illness visits.* You further state that you did not believe the deficiencies identified above had an impact on the subject safety as additional follow-up procedures were performed during the study and will continue for an additional (b) (4) after dosing.

You also describe completed and initiated corrective and preventive actions, and you state that you will not screen new subjects on any ongoing studies and that you will not initiate any new studies until the corrective actions are fully implemented. Among your corrective and preventive actions, you state in the December 17, 2020 response that (i) you personally reviewed or oversaw the review of records for all 262 subjects for safety issues; and (ii) an independent medical peer review of the source records for the 262 subjects enrolled at the site is in process, to identify any subject safety issues and provide appropriate medical oversight. In your January 14, 2021 response, you state that the independent medical peer review was completed on January 08, 2021, and this medical peer review did not identify any additional safety concerns for the subjects enrolled at your site. We acknowledge your corrective actions; however, the adequacy of your corrective actions cannot be evaluated due to a lack of supporting documentation regarding the findings from the medical peer review.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational new drugs. It is your responsibility to ensure adherence to each requirement of the law, including the Federal Food, Drug, and Cosmetic Act (FD&C Act) and all applicable FDA regulations.

We request a written response within fifteen (15) business days of your receipt of this letter. In your response, please provide written documentation of the actions you have taken or will take to correct any violations and to prevent the recurrence of similar violations in current and future studies for which you are the clinical investigator. If you believe that you have complied with the FD&C Act and FDA regulations, please include your reasoning and any supporting information for our consideration.

Your response should be sent to me at the following address: U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, Document Control Center, 10903 New Hampshire Ave., WO71-G112, Silver Spring, MD 20993-0002. If you have any questions regarding this letter, please contact the Division of Inspections and Surveillance, CBER at 240-402-8979.

* We note that the materials collected during the inspection do not reflect a notification to the institutional review board (IRB) regarding these deviations from protocol procedures in your study conduct. We remind you that under 21 CFR 312.66, an investigator must assure that he or she will promptly report to the IRB all unanticipated problems involving risk to human subjects or others.

We also request that you send a copy of your response to Eric Pittman, Director FDA ORA-OBIMO West, 550 West Jackson Street, Suite 1500, Chicago, Illinois 60661.

Sincerely,

Mary A. Malarkey, Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc:

Eric Pittman
Director, FDA ORA-BIMO West
550 West Jackson Street, Suite 1500
Chicago, Illinois 60661

(b) (4)