WARNING LETTER

Toxikon Corporation/Labcorp Bedford LLC

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Recipient:

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WARNING LETTER

CBER-22- 001

February 10, 2022

Dear Dr. Desai:

This Warning Letter informs you of objectionable conditions observed during a Food and Drug Administration (FDA) inspection conducted between August 13 and September 14, 2021. An FDA investigator met with you during the inspection to review your conduct of a nonclinical GLP study entitled:

(b)(4)

The FDA conducted this inspection under the Bioresearch Monitoring Program, which includes inspections designed to review the conduct of research involving investigational products 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 (available at **eCFR :: 21 CFR Part 58 -- Good Laboratory Practice for Nonclinical Laboratory Studies**), which are requirements promulgated under section 351 of the Public Health Service Act (PHS Act), 42 U.S.C. § 262, and section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. § 355, among other provisions. At the end of the inspection, the FDA investigator presented a Form FDA 483, List of 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 September 27, 2020 and October 14, 2021 to the Form FDA 483 ("Response Letter"), we determined that you violated GLP regulations in 21 CFR part 58. The violations include, but are not limited to the following:

1. The study director failed to assure that "all experimental data, including observations of unanticipated responses of the test system are accurately recorded and verified" [21 CFR § 58.33(b)].

21 CFR § 58.33(b) provides that "[t]he study director has overall responsibility for the technical conduct of the study, as well as for the interpretation, analysis, documentation and reporting of results, and represents the single point of study control." Multiple mistakes in the study resulted in errors in the calculations of Glomerular Filtration Rate (GFR) and Renal Blood Flow (RBF), which were used in the statistical analyses and reported in the final study report.

i. Plasma volume was used to calculate both renal GFR and RBF. The formula used to calculate plasma volume was incorrect because it was inconsistent with the formula specified in the amended final report submitted October 14, 2021. Plasma volume was calculated by **(b)(4)**.

As demonstrated in the amended final report, which you submitted on October 14, 2021, plasma Volume should have been calculated by **(b)(4)**. This calculation error caused all plasma volumes used to determine GFR and RBF, except for five blood samples which had a Hct of **(b)(4)**, to be incorrect.

Consequently, 32 out of 34 GFR values reported in the final study report and used in statistical analyses were calculated based on incorrect plasma volumes.

The incorrect plasma volume calculation resulted in 133 out of 136 of the RBF values reported in the final study report and used in statistical analyses to be in error.

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

ii. In accordance with the approved study protocol, urine output (mL/min) was used to calculate Renal Plasma Flow (RPF) and GFR, and RPF was used to calculate RBF. The urine output values, however, were incorrectly calculated at the one-hour timepoint during interim calculations. According to the formula in the amended final report, urine output values are calculated as urine **(b)(4)**, meaning that values at the 1-hour timepoint should have been calculated by **(b)(4)**.

Thus, all GFR, RBF, and RPF values based on the inaccurate urine output calculations were subsequently calculated incorrectly.

The erroneous urine output calculations at the one-hour timepoint and respective RPF, RBF, and GFR values were corrected before final analysis and inclusion in the final study report for all animals except:

a. For 33 animals, the RPF value was not corrected for this error before inclusion in the final study report.

b. The urine output, RPF, and RBF values at the 1-hour timepoint for Animal #s 5003 and 5004 were not corrected properly. To correct this error, the urine output value should have been **(b)(4)**. The urine output for these animals at the one-hour timepoint was corrected by a **(b)(4)** at two different times, resulting in a total correction **(b)(4)**. The RPF and RBF values for these two

animals were then calculated based on the inaccurate urine output values and included in the final study report. These inaccurate RBF values were used in the statistical analysis.

Your amended final report dated October 14, 2021 includes corrected data tables. However, as noted in observation 1, values for **(b)(4)**, GFR, RBF and RPF calculations could not be validated due to the PDF formatting of the amended final report, which did not include underlying calculations and formulas utilized. Please provide the data listed in pages 34-43 of the amended report in Excel format that includes all underlying calculations and formulas utilized, including interim calculations.

2. The quality assurance unit failed to "review the final study report to assure that such report accurately describes the methods and standard operating procedures, and that the reported results accurately reflect the raw data of the nonclinical laboratory study." [21 CFR § 58.35(b)(6)]

Sample preparation logs for the **(b)(4)** document the fact that numerous analyzed samples were incorrectly identified. Specifically, inspection of the final study report conducted by the Quality Assurance Unit (QAU) on 10/06/10 failed to identify:

A. Errors in calculations of plasma volume and subsequent errors in calculations of RPF, RBF, and GFR.

B. Failure to correct all errors related to urine output calculations at the 1-hour timepoint.

Your amended report dated October 14, 2021 includes updated data tables outlined in Observation 2. However, GFR, RBF and RPF calculations could not be validated due to the PDF format of the amended report, which did not include underlying calculations and formulas utilized. Please provide the data listed in pages 34-43 of the amended report in Excel format along with all underlying calculations and formulas utilized including interim calculations, as mentioned for Observation 1.A.

A reliable QAU is integral to the successful completion of any GLP study. Without appropriate QAU oversight, the sponsor and FDA reviewers have no assurance that what is reported in the final study report is accurate. Failure to perform QAU functions calls into question the validity of the entire study.

In addition to the violations listed above, you should be aware that FDA's inspection documented several additional violations of GLP regulations. For example, the study director failed to ensure proper identification of multiple blood and urine samples and failed to maintain adequate documentation of concentrations and dilutions of **(b)(4)**. The study director also failed to note unforeseen circumstances and ensure corrective action was taken and documented. Examples include **(b)(4)** and subsequent missed animal dosings. The QAU failed to verify that the final study report accurately reflected the raw data. Examples include

samples with misidentified timepoints and animals that were attributed to the incorrect group that were both included in the final study report. Additionally, the final study report did not include any description of **(b)(4)** issues, mislabeled **(b)(4)** vials, all calculations used in the protocol and the protocol deviations regarding a **(b)(4)** administered.

You appear to have adequately corrected the violations listed in the previous paragraph. Specifically, your response letter, dated September 27, 2021, states that your entire protocol is being reviewed and data analyses will be repeated where required. The letter also states that your current system (Provantis data collection system) allows calculations to be entered and reviewed for accuracy before reporting, therefore decreasing data inconsistency. You report that your current QAU has a fully integrated and configured review process that, along with Provantis, will ensure that proposed calculations and formulas are verified. Your amended final report, dated October 14, 2021, included clarifications of deviations, corrected calculations and root causes of violations listed. These corrective actions may be verified during future FDA inspections.

This letter notifies you of your violations and provides you an opportunity to address the above deficiencies. You should investigate and determine the causes of any violations and take prompt actions to implement corrections to prevent the recurrence of similar violations in current and future studies for which are you are the study director.

This letter is not intended to be an all-inclusive list of deficiencies with your nonclinical studies of investigational new drugs. It is your responsibility to ensure full compliance with the law, including all applicable requirements of the FD&C Act, PHS Act, and FDA regulations.

We request that you respond in writing within fifteen (15) working days from your receipt of this letter. In your response, please provide written documentation of additional actions you have taken or will take to correct the noted violations and to prevent the recurrence of similar violations in current and future studies for which you are the study director.

Failure to adequately address this matter may lead to regulatory action. Failure to respond to this letter and to take appropriate corrective action could result in FDA taking regulatory action without further notice to you. 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 240-402-8928.

We also request that you send a copy of your response to the FDA Office listed below.

Sincerely,
/S/

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

cc:

Anne E. Johnson, Director
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