U.S. FOOD & DRUG ADMINISTRATION

VIA E-MAIL AND UNITED PARCEL SERVICE

Mr. Umesh Mishra, CEO
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INDIA

Dear Mr. Mishra:

This letter addresses significant objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your firm between November 18 and 22, 2019, by FDA personnel Lori Gioia; Amanda Lewin, Ph.D.; and Gajendiran Mahadevan, Ph.D., representing the FDA. In addition, based on significant objectionable conditions observed during the inspection, FDA's own data analyses, and other information, FDA issued a General Correspondence Letter to you on March 12, 2021 (referred to as "FDA's General Correspondence Letter"), requesting that you provide specific responses to those concerns indicating in FDA's assessment that you created falsified data, which you then submitted to FDA. This letter also addresses your April 12, 2021, response to FDA's General Correspondence Letter.

FDA's Inspection

During FDA's inspection of your firm between November 18 and 22, 2019, FDA reviewed the conduct of the following studies:

- **Study** (b)(4) **, "** (b)(4) [redacted]

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

[redacted]

- **Study** [redacted]

- **Study** [redacted]

- **Study** [redacted]

- **Study** [redacted]

- **Study** [redacted]

- **Study** [redacted]

- **Study** [redacted]

[redacted](b)(4)
[redacted]."

This inspection was conducted as a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research, to help ensure that the rights, safety, and welfare of human subjects have been protected, and to ensure that the data are scientifically valid and accurate.

At the conclusion of the inspection, FDA personnel raised significant concerns about the validity and reliability of bioequivalence and bioavailability data generated at your firm. We note receipt of your December 6, 2019, response to the inspection, and of your April 12, 2021, response to FDA's General Correspondence Letter.

From our review of the FDA Establishment Inspection Report; the documents submitted with that report; your written response dated December 6, 2019; and your April 12, 2021, response to the significant data validity and reliability concerns raised in FDA's General Correspondence Letter, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of bioavailability and bioequivalence studies. We wish to emphasize the following:

You failed to demonstrate that the analytical method used in an *in vivo* bioavailability or bioequivalence study to measure the concentration of the active drug ingredient or therapeutic moiety, or its active metabolite(s), in body fluids or excretory products, is accurate and of sufficient sensitivity to measure, with appropriate precision, the actual concentration of the active drug ingredient or therapeutic moiety, or its active metabolite(s), achieved in the body [21 CFR 320.29(a)].

During FDA's inspection of your firm, FDA found unusual and unexplainable study records demonstrating that you engaged in practices and processes that undermined the analytical methods used at your firm. Upon close review of study reports from your firm, we conclude that those practices and processes resulted in the submission of falsified study data to the FDA. As a result, FDA has significant concerns about the validity and reliability of bioequivalence and bioavailability data generated at your firm that are submitted to the FDA in support of Abbreviated New Drug Applications (ANDAs) or New Drug Applications (NDAs). Examples include, but are not limited to, the following:

1. Study [redacted](b)(4): Subjects' PK study data appeared to separate into two distinct populations, with a change occurring after the midpoint of the study, which would not be expected based on normal subject physiologic variability across a subject population. Specifically, the test product peak drug concentration (C_{max}) appeared to be higher than the

reference product in the first half of the subjects, but the opposite was true for the second half of the subjects.

During FDA's inspection, we requested that you provide a bioequivalence assessment for each group independently, Subjects 1-12 and Subjects 13-24, and compare that assessment to the bioequivalence assessment of all study subjects. We also requested that you calculate the C_{max} and area under the plasma concentration-time curve (AUC_{0-t}) geometric mean ratios (GMRs) with their respective confidence intervals for the two study subject groups, to evaluate the overall trends in terms of the bioequivalence endpoint. The calculations resulting from your analysis (table below) indicated that the (b)(4) GMRs data for Subjects 1-12 were distinct from the data for Subjects 13-24.

Study (b)(4) (fasted, (b)(4))				
Subjects	***Parameter***	***GMR Point Estimate (%)***	***GMR 90% Confidence Interval***	***Bioequivalence Determination***
1-12 (n=12)	C_{max}	71.26	64.78 – 78.38	NOT BE
	AUC_{0-t}	85.41	78.45 – 93.00	NOT BE
13-24 (n=12)	C_{max}	141.80	124.27 – 161.82	NOT BE
	AUC_{0-t}	126.89	115.81 – 139.04	NOT BE
Full Study 1-24 (n=24)	C_{max}	100.52	86.88 – 116.31	BE
	AUC_{0-t}	104.11	94.97 – 114.12	BE

Based on your analysis of concentration data for Study (b)(4), you asserted that the study results were correct even though they appear aberrant based on normal subject physiologic variability. You concluded that based on your investigation, "there were no observation or discrepancy [*sic*] found during statistical analysis of the Study (b)(4)-(b)(4)" However, you have failed to resolve FDA's concerns regarding the validity of data for Study (b)(4), given the presence of two distinct populations around the midpoint of the study, which would not be expected based on normal subject physiologic variability across a subject population.

2. Study (b)(4) Multiple subjects' PK data profiles appeared to be identical with overlapping concentration time profiles. (b)(4) and (b)(4) concentration

profiles for several subject pairs were nearly identical, which is not expected based on normal physiological differences, and is indicative of sample substitution. During the inspection, we requested that you plot the concentration profiles for subject pairs that appeared to have nearly identical PK profiles, including Subjects (b)(6) and (b)(6) and Subjects (b)(6) and (b)(6) respectively. The resulting plots from your analysis showed significant overlap between those subject pairs.

During FDA's inspection, you conducted an investigation of those results and reported that "no valid cause or discrepancy in the sample analysis was found." Your conclusion appeared to be based on the results of a repeat analysis showing that specific subjects' concentration values meet acceptance criteria for repeat analysis (that is, the reanalysis found sufficient consistency with the original results); however, your conclusion failed to address the primary concern that multiple subjects had overlapping concentration-time profiles in the original results.

We recognize that a Form FDA 483 was not issued to your firm citing the observations for studies (b)(4) and (b)(4) however, these items were discussed in detail during the inspection. We note that your December 6, 2019, response to FDA's inspection provided no substantive explanation for the unusual trends in the data in Study (b)(4) (b)(4) that is, why the PK data (the C_{max} and AUC_{0-t} GMRs) for Subjects 1-12 vary so drastically from those of Subjects 13-24 – and provided no further explanation for the overlapping concentration-time profiles in Study (b)(4)

We acknowledge that your response did provide a draft SOP, "(b)(4)-SOP-35-02 (Investigation of out of specification results)," detailing a process for investigating results considered out of specification, anomalous, or unexplainable. However, the draft SOP does not address our concerns with studies previously conducted at your firm.

Response to FDA's Inspection Concerns in the General Correspondence Letter

Study (b)(4): FDA's General Correspondence Letter specifically requested that you provide an explanation, if possible, for the divergent PK data between Subjects 1-12 and Subjects 13-24 in Study (b)(4) if the subject samples were not substituted or falsified. Your April 12, 2021, response acknowledged FDA's observations, and stated that you performed an investigation of the clinical, analytical, and statistical conduct at your firm to understand the reasons for the trends in the results, but you could not find any reason for the anomalous data. You indicated that no discrepancies in the conduct of the study or in the reanalyzed data were found that could explain the observed trends.

You also indicated that (b)(4) is a highly variable drug based on published studies, and the PK data from study (b)(4) were consistent with the published variability of

(b)(4) You indicated that because your evaluation of the secondary PK parameters (T_{max}, $T_{1/2}$, K_{el}, and K_a) showed no unusual trends comparable to the aberrant primary PK parameters (C_{max} and AUC_{0-t}), the "detailed pharmacokinetic data" do not indicate any abnormality. You further state that randomization is carried out to distribute any variability throughout a study and to minimize any kind of group effect; however, you state that there is no possibility that variability can be concentrated in a specific sequence or group. Thus, in the absence of any other reason, you stated that a rare observance of subgroup characteristics may have been observed in the study, and you suggested that a possible interaction between the drug formulation and the subjects could be the reason for the divergent PK data.

Your above response to the FDA's General Correspondence Letter is inadequate because you failed to resolve FDA's concerns related to data anomalies between two distinct subject populations. FDA's concern is not with the variation of the Study (b)(4) data that your response focuses on; rather, our concern is for non-random distribution of subject data into distinct sub-groups. However, even if we accept that (b)(4) is a highly variable drug, as you mention, we would expect that fact to make it ***less*** likely to observe the two distinct, sequential subject populations for the test and reference (T/R) ratios for C_{max} and AUC_{0-t} found in Study (b)(4) Further, your evaluation of the secondary PK parameters does not address or alleviate FDA's concerns with the study's having two distinct populations in the primary PK parameters (C_{max} and AUC_{0-t}). We note that distinct subject populations are not expected for any PK parameters in a randomized, well-controlled study. In addition, you failed to adequately explain why randomization did not eliminate any group effect in Study (b)(4) (b)(4) as would be expected, or how the "specific distinctive unknown formulation-subject interactions" address the unusual trends in the primary PK parameters beyond mere conjecture. As such, your response does not resolve FDA's concerns for the non-physiologic PK trends in Study (b)(4) that deviate significantly from a normal population distribution from a group of healthy volunteers.

Study (b)(4): FDA's General Correspondence Letter requested that you explain how Study (b)(4) could have nearly identical (b)(4) and (b)(4) concentration-time profiles in multiple subject pairs, if the subject samples were not substituted or falsified. To address that request, your April 12, 2021, response details that you removed the subject data that FDA identified as concerning and you re-analyzed the bioequivalence statistical determination, which showed that the study still met the bioequivalence criteria without the anomalous data. We note that your response provided no justification for removing subject data, identified by FDA as possibly substituted, from your statistical re-analysis of Study (b)(4) Thus, removal of the subject data from the re-analysis does not alleviate our concern that data generated by your firm were falsified. Your response did not resolve FDA's concerns related to how the unexpected, non-physiologic PK study data were generated, which undermines our ability to ensure that the remaining data were not also falsified.

Based on FDA's inspection findings of anomalous PK study data at your firm and your responses' failure to adequately address or refute FDA's significant concern that subject samples in Studies (b)(4) and (b)(4) were substituted or falsified, the facts support that your firm engaged in practices and processes that undermine the reliability and validity of the analytical methods used at your firm and the study data generated by your firm.

Post-Inspection FDA Data Analyses

In addition, FDA's March 12, 2021, letter to your firm identified similar and significant anomalous PK data trends to those described above in a number of other studies performed at your firm that were submitted to the Agency in support of certain ANDAs. Specifically, the letter raised concerns about unexpected, non-physiologic PK data from eleven of your firm's studies: (b)(4) and (b)(4); (b)(4); (b)(4) and (b)(4); (b)(4) and (b)(4) (b)(4); (b)(4) (b)(4); and (b)(4) - (b)(4)

For those studies, FDA requested that you provide an explanation for the anomalous PK data identified; that is, that you explain the study data (1) showing multiple pairs of subjects with overlapping time-concentration profiles, (2) showing distinct groups of subjects where the T/R ratio for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for most subjects in the subgroups is above or below 1, or (3) having both concerns. (See request for response number 2 in FDA's March 12, 2021, letter.)

In your April 12, 2021, response, you acknowledged the observations regarding PK data anomalies from FDA's inspection and letter of March 12, 2021. You stated that you carried out retrospective investigations into the clinical, analytical, and statistical conduct of the additional studies identified in FDA's March 12, 2021, letter. You indicated that your investigations did not identify any cause to explain the anomalous data, and you stated that the data were not abnormal, arguing that the PK parameters were within the expected range of variability and any overlapping time-concentration profiles were consistent with normal variation. We note that for each of the studies (except for Study (b)(4), you also provided reports of repeated PK statistical analysis that excluded the anomalous data identified by FDA from the bioequivalence determinations.

In addition, for studies with distinct groups of subjects relative to the T/R ratio for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ (that is, for Studies (b)(4); (b)(4) and (b)(4); (b)(4); and (b)(4), you argued that while randomization for those studies is expected to distribute any variability throughout a study and minimize any group effect, there remains a non-zero possibility that variability can be concentrated in a specific sequence or group. For Studies (b)(4) and (b)(4), you indicated that inter-subject variability was lower than intra-subject variability, and thus one was more likely to observe overlapping profiles between subjects for those studies.

Your explanations fail to resolve FDA's concerns. We do not agree with your response that the anomalous data identified by FDA for each study were not a concern because the results were within normal variation. FDA's concern is not that the data were outside of normal variation, but rather the lack of expected variation among select subjects with overlapping time-concentration profiles and the T/R ratio for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ showing distinct subgroups.

We do agree with your statement that randomization should have eliminated any group effect observed in the study. As such, we find that your claim that variability in the data was due to randomization is unsupported and inadequate to explain those studies' having distinct groups of subjects where the T/R ratio for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for most subjects is above or below 1. As to your response's specific claims for Studies (b)(4) and (b)(4), we note that the likelihood of overlapping profiles is based on the total variability of the study, which is calculated from both inter-subject and intra-subject variability. Thus, the total variability in each study would suggest that any overlapping profiles between subjects should be infrequent, and therefore your argument does not explain the presence of numerous overlapping profiles in the studies.

Additionally, FDA does not agree with your removal of the subject data that FDA identified as being concerning during FDA's inspection and in FDA's General Correspondence Letter, because you provided no justification for the removal. Thus, your arbitrary approach does nothing to resolve the FDA's concerns with how the anomalous data were generated by your firm, and therefore does not address how the reliability of any study data generated by your firm can be ensured.

Taken together with your response to FDA's inspection findings for Studies (b)(4) and (b)(4), as noted above, your April 12, 2021, response fails to provide adequate explanation(s) for the observed anomalous time-concentration overlaps and PK trends (that is, distinct groups of subjects in which the T/R ratios for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ are above or below 1). As such, FDA's concerns regarding study data generated by your firm remain; that is, Panexcell's study data are inconsistent with normal variation or distribution found in a healthy population, and are not expected by chance across the significant number of studies identified by FDA.

FDA's Specific Request for Responses

We also note that FDA's General Correspondence Letter, specifically requested that you explain the following (listed as request for response numbers (3) through (6) in the letter):

(1) Why your firm failed to identify and assess the data anomalies observed on inspection

(2) How multiple studies conducted at your firm could have numerous instances of overlapping subject sample concentrations and unusual PK trends that deviate significantly from normal population distribution of data from a group of healthy volunteers

(3) Whether any other bioequivalence or bioavailability studies conducted at your firm have similar PK data anomalies, and if so, an assessment of the impact of each study, if any, and the root cause for any identified data anomalies

(4) Any reason why the evidence of falsification of data discussed in this letter should not raise questions about the validity of all data reported by your company

Regarding those requests, your April 12, 2021, response explained that you are a small-sized contract research organization and may have unintentionally missed the errors due to ignorance. You noted that based on concerns identified by the European Medicines Agency (EMA) (which were noted in FDA's March 12, 2021, letter), your firm implemented corrective measures to prevent a recurrence of similar concerns identified by EMA. Notably, your suggestions that unintentional errors may be the basis for the significant data anomalies identified by FDA seems to contradict your other statements that your investigations found that no mistakes or intentional errors existed to explain those data anomalies.

We acknowledge that your response also indicated that you self-identified two additional studies, (b)(4) and (b)(4) to assess whether other bioequivalence or bioavailability studies conducted at your firm had similar PK data anomalies to those identified by FDA. You stated that for those studies, you reviewed the concentration-time profiles and PK analysis and did not identify any anomalous data in those studies. In addition, your response also explained that your firm does its best to follow international and regulatory guidance, and that you are willing to evaluate any other studies if identified and requested by FDA and to perform any additional bioanalytical analyses at the direction of the FDA. For Studies (b)(4) and (b)(4) while we agree with your assessment that no data anomalies were observed in either study, we are unable to determine whether your firm performed a comprehensive evaluation of all bioequivalence and bioavailability studies conducted at your firm to date, based on the information provided in your response.

In your April 12, 2021, response letter, you indicated that as a corrective action and to improve on any unintentional errors that might have resulted in the PK data anomalies, your firm has initiated various system improvement measures to prevent recurrence of such incidences. You specified that you (1) prepared and implemented policies, in particular, SOPs for "Data Integrity" and "Verification of similar PK profiles"; (2) changed the organizational structure and hierarchy, including the hiring of new management and the establishment of policy and procedures for identifying staff training needs; (3) implemented facility infrastructure

improvements; and (4) improved Quality Management System conforming to standards and applicable regulatory requirements.

We acknowledge the corrective actions your firm has taken or will take specific to the implementation of system improvements in response to the significant concerns raised by FDA's inspection and FDA's General Correspondence Letter.

Your response to FDA's General Correspondence Letter is inadequate because you failed to adequately address (1) FDA's concerns for what caused the anomalous PK trends, (2) why multiple studies conducted at your firm could have multiple instances of overlapping subject sample concentrations, and (3) any legitimate, scientifically valid reason why the evidence of falsification of data discussed in the FDA's General Correspondence letter should not raise questions about the validity of all data generated by your firm.

Your failure to identify and address how numerous studies could each have multiple instances of overlapping subject sample concentrations and/or anomalous PK trends raises significant concerns about the bioavailability and bioequivalence data generated at your firm that are submitted to FDA in support of Abbreviated New Drug Applications (ANDAs) or New Drug Applications (NDAs). Your firm engaged in practices and processes that undermine the reliability and validity of the analytical methods used at your firm and the study data generated by your firm.

This letter is not intended to be an all-inclusive list of deficiencies regarding bioavailability and bioequivalence studies conducted at your firm. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations and to ensure the integrity of all data generated at your firm that are submitted to the FDA in ANDAs or NDAs.

The manner in which Panexcell conducted the studies noted above causes FDA to believe that the reliability and validity of study data generated by your firm cannot be ensured. Put simply, because you have been responsible for the creation of false data in the studies discussed here, we have no reason to believe that any data that you have produced are reliable. Thus, FDA has determined that all study data from all studies conducted at your firm must be rejected.

Please be advised that we are not requesting that you respond to this letter. You are responsible to ensure that your firm adheres to each requirement of the law and relevant FDA regulations if you are involved in the conduct of studies that are submitted to FDA. You should address any deficiencies and establish procedures to ensure that any ongoing or future studies comply with FDA regulations. This may include, among other things, that your firm documents your implementation and following of processes and procedures that are sufficient to promptly identify, assess, and resolve any aberrant study data from studies conducted at

your firm, including issues similar to those identified by the FDA. Note that we may conduct a future inspection to verify your corrective actions and future compliance with FDA regulations.

We appreciate the cooperation you showed to FDA personnel Lori Gioia, Amanda Lewin, and Gajendiran Mahadevan during the inspection.

Should you have any questions regarding this letter, please e-mail Sean Kassim at sean.kassim@fda.hhs.gov, or David Burrow at david.burrow@fda.hhs.gov, or write to:

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Sincerely yours,

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