VIA EMAIL AND CERTIFIED MAIL
RETURN RECEIPT REQUESTED

March 27, 2025

Rajen Shah, Owner and Director
Raptim Research, Ltd.
A-226/A-242, MIDC, TTC Industrial Area
Mahape, Navi Mumbai, India 400 710

Dear Dr. Rajen Shah:

This letter addresses significant objectionable conditions observed during the U.S. Food and Drug Administration (FDA or the Agency) inspection conducted at Raptim Research, Ltd. in Navi Mumbai, India between April 24 and 28, 2023, by FDA personnel Kara A. Scheibner, PhD, and Hasan Irier, PhD. Based on significant objectionable conditions observed during the inspection and FDA's own data analyses, FDA issued a General Correspondence Letter (GCL) to you on August 6, 2024, requesting that you provide specific responses to FDA's concerns that you created falsified data that were submitted to FDA. This letter also addresses your September 4, 2024, and October 17, 2024, responses to FDA's GCL (including the corrected attachments received November 8, 2024).[1]

The FDA inspection was conducted as a part of FDA's Bioresearch Monitoring Program that 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 Scheibner and Irier presented and discussed with you the Form FDA 483, Inspectional Observations. We acknowledge receipt of your May 18, 2023, written response to the Form FDA 483.

[1] On February 27, 2025, FDA engaged in a listening session with Raptim, and all information presented was considered as part of FDA's review.

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10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Additionally, as described in FDA's GCL, FDA identified multiple subject skin donor replicates with nearly identical results between Study (b) (4) and Study (b) (4) and between Study (b) (4) and Study (b) (4). FDA's GCL raised concerns that your study data appear falsified in that to produce results from in vitro permeation studies conducted at your facility, it appeared that you reanalyzed or reused skin donor replicates from one donor whose results you knew and recorded them as different skin donor replicates from a different donor in a different study. As a result, FDA's GCL gave you the opportunity to provide substantive scientific explanation of those study data that do not appear possible by chance and would not be expected based on normal physiologic variation.

We acknowledge receipt of your September 4, 2024, and October 17, 2024, written responses to FDA's GCL, including the results of a third-party audit performed for your firm by (b) (4) (b) (4)

Based on our review of the FDA Establishment Inspection Report, the documents submitted with that report, your May 18, 2023, written response to the inspection, and your September 4 and October 17, 2024, written responses (including the corrected attachments received November 8, 2024) to the significant data validity and reliability concerns raised in the August 6, 2024, GCL, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of in vitro bioequivalence studies at your firm. Based on the totality of this information, it is FDA's conclusion that your firm created and caused the submission of falsified data to FDA, as further described below.[2]

FDA's Inspection and Post-Inspectional Data Analysis

During FDA's inspection of your firm between April 24 and 28, 2023, FDA reviewed the conduct of studies that include, but were not limited to, the following:[3]

- **Study** (b) (4): (b) (4) ".
- **Study** (b) (4): (b) (4)

[2] References to "your response" throughout the letter indicate your October 17, 2024, response, including all attachments, unless otherwise specified.
[3] During the inspection, FDA reviewed the firm's conduct of seven studies; however, this letter only discusses the four studies listed.

(b) (4)

”

- **Study** (b) (4) : (b) (4)

”

- **Study** (b) (4) : “(b) (4)

Following FDA’s April 2023 inspection, FDA performed post-inspectional data analyses, which identified anomalous data and poor study conduct associated with studies performed at your firm that were submitted to the Agency in support of certain Abbreviated New Drug Applications (ANDAs). The following studies were identified:

- **Study** (b) (4) : “(b) (4)

- **Study** (b) (4) : “(b) (4)

- **Study** (b) (4) : “(b) (4)

(b) (4)

- **Study** (b) (4) : "(b) (4) "
- **Study** (b) (4) : (b) (4) "
- **Study** (b) (4) : (b) (4) "
- **Study** (b) (4) : "(b) (4)

In the August 6, 2024, GCL, FDA requested that you respond by providing the following information:

- **GCL Request 1**: Provide an explanation for how eight subjects/skin donors from study (b) (4) could have nearly identical (b) (4) concentration profiles across multiple independent test and reference product replicates with eight different subjects/skin donors from study (b) (4)

- **GCL Request 2**: Provide an explanation for how multiple subjects/skin donors from study (b) (4) could have nearly identica (b) (4) oncentration profiles across multiple independent test and reference product replicates with subjects/skin donors from study

(b) (4) .

- **GCL Request 3**: Explain why your firm failed to identify multiple instances of nearly identical drug concentration profiles between two independent (b) (4) in vitro permeation test (IVPT) studies performed for two different sponsors and two independent (b) (4) IVPT studies performed for two different sponsors.

- **GCL Request 4**: Explain how the high incidence of nearly identical drug concentration profiles observed across multiple IVPTs using human skin donors is physiologically and statistically supportable.

- **GCL Request 5**: Considering the significant number of repeats and overly flexible acceptance criterion allowing extensive repeats in Studies (b) (4) (b) (4) among others, explain how the Agency can have confidence that your study processes and procedures are not designed to allow repeated testing until desired study results are obtained. In other words, you appear to be testing into compliance – explain how this is not the case.

- **GCL Request 6**: Provide an explanation why your firm failed to improve the rigor of your processes and procedures despite FDA inspections identifying concerns about the high frequency of study run repeats, retrospective data acceptability determinations, and/or quality control/calibration curve (QC/CC) failures in your studies.

- **GCL Request 7**: Determine whether any other studies, including, but not limited to, IVPT and in vivo bioequivalence studies, conducted at your firm have similar data anomalies (e.g., nearly identical drug concentration profiles between independent test or reference replicates from different subjects/skin donors), high frequency study run repeats, retrospective data acceptability determinations, and/or QC/CC failures, and if so, provide an assessment of the impact on each study (if any) and the root cause identified.

- **GCL Request 8**: Provide any reason(s) why the data anomalies identified and discussed in this letter should not raise questions about the reliability of the data reported by your company.

As we explain in more detail below, your responses to the FDA GCL did not resolve FDA's data integrity concerns regarding the data generated from your firm. Your responses and proposed corrective actions do not adequately address FDA's concerns or substantively explain what caused the significant data anomalies present in your studies. Additionally, your responses do not provide a legitimate, scientifically valid reason why the evidence of falsification of data discussed in FDA's GCL should not call into question all in vitro study data generated by your firm. Finally,

your responses do not provide specific corrective action plans that fully address the identified pattern of in vitro and in vivo issues at your firm. We wish to emphasize the following:

FDA's Concerns Regarding In Vitro Study Data Falsification

1. **Your in vitro study conduct resulted in the submission of false information to FDA regarding the measurement of the bioavailability of a drug product or the demonstration that a drug product is bioequivalent to a reference listed drug upon which an applicant relies, or to support a waiver of the requirements for submission of bioavailability or bioequivalence data, and resulted in the failure to adequately describe the analytical and statistical methods used in each study [Sections 505(d) and 505(j)(4)(K) of the FD&C Act (21 U.S.C. 355(j)(4)(K)); 21 CFR 320.21(a) and 314.50(d)(3), 21 CFR 320.21(b) and 314.94(a)(7)].**

   FDA regulations require that applicants submit evidence measuring the in vivo bioavailability of a drug product or evidence demonstrating a drug product is bioequivalent to the reference listed drug or submit information supporting a waiver of the submission of evidence measuring in vivo bioavailability or demonstrating in vivo bioequivalence. FDA regulations also require a description of the analytical and statistical methods used in each bioavailability or bioequivalence study contained in the application. Based on our review of the totality of information, we conclude that your in vitro study conduct resulted in the submission of falsified study data to FDA. As a result, FDA has significant concerns about the validity and reliability of such data generated by your firm that applicants have submitted to FDA in support of ANDAs or New Drug Applications (NDAs).

   As explained in the FDA's GCL, FDA identified significant data integrity concerns for IVPT data generated from four studies at your firm that were submitted to the Agency in support of certain ANDAs. FDA raised concerns about the potential falsification of data from multiple subject skin donors due to observed nearly identical drug concentration profiles between Study (b) (4) and Study (b) (4) and between Study (b) (4) and Study (b) (4) (b) (4) Specifically:

   Studies (b) (4) **and** (b) (4) FDA's analysis of the data from studies (b) (4) (b) (4) ((b) (4) sponsored by (b) (4) and (b) (4) ((b) (4) sponsored by (b) (4)), conducted approximately one month apart by your firm, shows nearly identical individual IVPT concentration profiles for multiple subject skin donors between Study (b) (4) and Study (b) (4) **.** In these studies, each skin donor sample is divided into 20 individual skin donor replicates and each replicate is used to generate an individual IVPT concentration profile. A pattern of nearly identical concentration

profiles of individual skin donor replicates was observed between eight donors in Study (b) (4) (b) (4) and eight donors in Study (b) (4) (referred to by FDA as donor pairs).

Table 1 shows that FDA identified 150 individual subject skin donor replicates that appear to have nearly identical concentration profiles between Study (b) (4) and Study (b) (4) (b) (4). Specifically, eight pairs of subject skin donors (Donor #) from Study (b) (4) have skin donor replicates with nearly identical concentration profiles (point-to-point overlaps) from a different skin donor (Paired Donor #) in Study (b) (4) For each donor pair in Table 1, the drug treatment (test or reference product) is indicated along with the number of pairs of nearly identical concentration profiles (Matching Profile Pairs per Treatment). Of note, the nearly identical concentration profile pairs between different studies were identified across the same treatment (e.g., test product and test product or reference product and reference product) and across different treatments (e.g., test product and reference product or reference product and test product). The pairs identified in Table 1 exhibit point-to-point overlap in their concentration profiles and have nearly identical results (% concentration differences were less than 20% with few exceptions, and many were less than 10%).

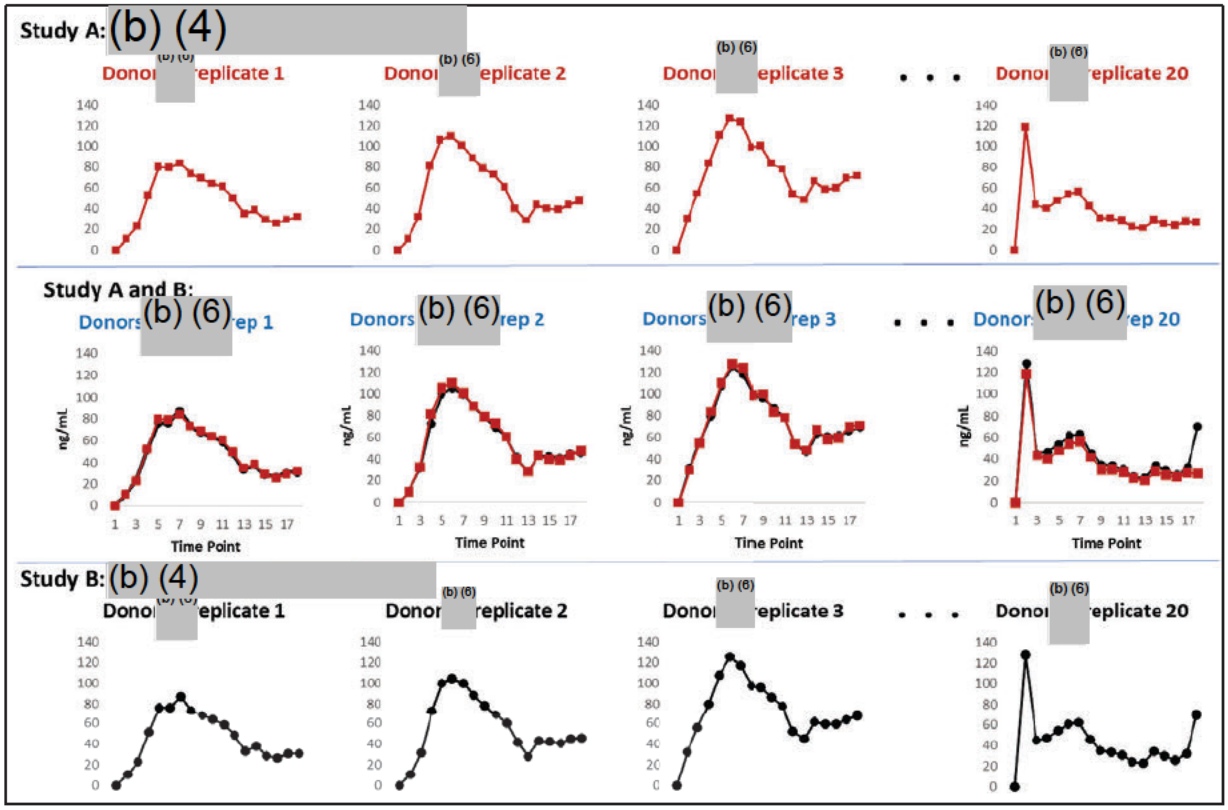
Table 1

Study A: (b) (4)		Study B: (b) (4)		Matching Profile Pairs per Treatment	**Total # of Individual Nearly Identical Profiles**
Donor #	Treatment	Paired Donor #	Treatment		
(b) (6)	Reference	(b) (6)	Reference	5	**10**
	Test		Test	5	
	Reference		Test	10	**20**
	Test		Reference	10	
	Reference		Test	10	**20**
	Test		Reference	10	
	Reference		Test	10	**20**
	Test		Reference	10	
	Reference		Test	10	**20**
	Test		Reference	10	
	Reference		Reference	10	**20**
	Test		Test	10	
	Reference		Reference	10	**20**
	Test		Test	10	

(b) (6)	Reference	(b) (6)	Reference	10	**20**
	Test		Test	10	

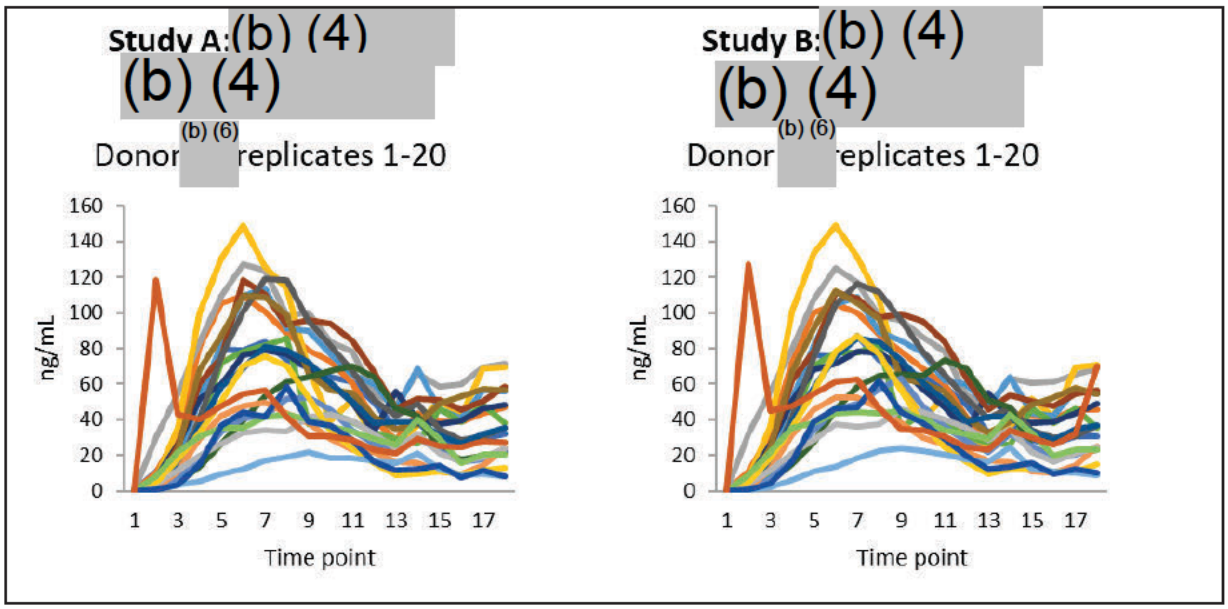
Further, FDA identified that for seven of the eight donor pairs, 20 individual skin donor replicates (representing all replicates for each individual donor) had nearly identical concentration profiles with exactly 20 individual skin donor replicates from a different skin donor.[4] Even more compelling is the fact that the nearly identical replicates occurred in the exact same order (cells 1-20) for both donors. Figure 1 below provides a representative example showing that replicate 1 of Donor (b) (6) n Study (b) (4) aligns with replicate 1 of Dono (b) (6) n Study (b) (4) and this pattern continues up to replicate 20 (4 examples shown Figure 1). These observations contrast with the lack of nearly identical profiles within a single donor, which is demonstrated in Figure 2. Figure 2 provides representative examples showing the high variability among individual IVPT concentration profiles (replicates) from a single donor (Donor (b) (6) rom Study (b) (4) and Donor (b) (6) from Study (b) (4) .

Figure 1



[4] The eighth donor pair included 10 individual skin donor replicates with nearly identical concentration profiles, as described in Table 1 above.

Figure 2



Studies (b) (4) **and** (b) (4) : FDA's analysis of the data from Studies (b) (4) (b) (4) (b) (4) sponsored by (b) (4)) and (b) (4) (b) (4) sponsored by (b) (4), conducted by your firm, shows nearly identical individual IVPT concentration profiles for multiple subject skin donors between Study (b) (4) and Study (b) (4) (b) (4) as is shown in Table 2 below. Nearly identical concentration profiles were observed for eight pairs of subject skin donors. Of note, the nearly identical concentration profile pairs between different studies were identified across the same treatment (e.g., reference product and reference product) and across different treatments (e.g., test product and reference product or reference product and test product). In total, 28 individual subject skin donor replicates appear to have nearly identical results between Study (b) (4) and Study (b) (4)

Table 2

Study C: (b) (4)		Study D: (b) (4)		Matching Profile Pairs per Treatment	**Total # of Individual Nearly Identical Profiles**
Donor #	Treatment	Paired Donor #	Treatment		
(b) (6)	Reference	(b) (6)	Test	5	**10**
	Test		Reference	5	
	Reference		Test	3	**6**
	Test		Reference	3	
	Reference		Test	1	**3**
	Test		Reference	2	
	Reference		Test	1	**1**
	Test		Reference	1	**1**
	Reference		Test	1	**2**
	Test		Reference	1	
	Reference		Test	1	**4**
	Reference		Reference	3	
	Reference		Reference	1	**1**

Your Response to FDA's In Vitro Study Concerns in the General Correspondence Letter

Response to FDA's In Vitro Study General Correspondence Letter Requests 1-4 and Request 7

To address our observation of nearly identical IVPT concentration profiles in the different studies of different sponsor products, FDA's GCL requested that you provide an explanation for the abnormal data identified at your firm (see GCL Requests 1-4 and Request 7 stated above).

Your October 17, 2024, response to GCL Requests 1-4 relied on your third-party auditor's (b) (4) audit report that concluded that "sample receipt, inventory, processing, management, and procedures were found to be void of gaps that could facilitate sample reuse and reanalysis from one in vitro study to another. There was no evidence of sample reuse and reanalysis in any of the studies examined as a part of this audit." Regarding FDA's concern about the nearly identical profiles, your response also included the opinion of (b) (4) IVPT consultant, Dr. (b) (4) which indicated that the profiles in question are not identical and argued that the occurrence of similar profiles across multiple independent test and

reference product replicates was possible. Your response appears to indicate that you believe the occurrence of similar profiles is not, in and of itself, a concern and you also reference the (b) (4) audit report finding that "there was no evidence of sample reuse and reanalysis in any of the studies examined…" Your response includes a reanalysis of bioequivalence for Study (b) (4) that excludes some data. You also stated that you were unaware of any instances of falsified data regarding the use or analysis of study samples in any other studies conducted by your firm.

Based on the explanations and information provided in your response, we find that your response to the GCL is inadequate. Your response, including (b) (4) audit report and the supporting attachments, lacked a full description of the study documents, systems, procedures, and processes you reviewed to address the concerns identified in FDA's GCL. We note that, in general, FDA would not expect study records to document the steps performed to generate falsified data; therefore, a retrospective review must be complete and coupled with valid scientific explanations for the anomalous data. You also did not adequately address FDA's concern about how the validity of your study records and study data can be assured given the significant data anomalies we observed across multiple studies, for multiple products, conducted at your firm. Moreover, your response does not provide FDA an adequate explanation of how eight subject skin donors from two different studies (b) (4) and (b) (4)) had nearly identical (b) (4) concentration profiles across multiple independent test and reference product replicates. Similarly, you did not explain how multiple subject skin donors from another two different studies (b) (4) and (b) (4)) could have nearly identical (b) (4) concentration profiles across multiple independent test and reference product replicates. Overall, your response failed to acknowledge and address the scale and pattern of the nearly identical IVPT concentration profiles identified by FDA.

More specifically, we find your response that well-controlled IVPT study conditions can produce nearly identical individual concentration profiles across multiple independent test and reference product replicates to be inadequate. Nearly identical profiles observed across multiple skin donors in studies supporting multiple different sponsor applications are not expected by normal physiologic variation within a study population. Your argument is also unpersuasive because as Figure 2 shows, your firm's study data exhibits high variability between replicate profiles from single skin donors in the identified studies (as expected through normal physiologic variation). Further, the inclusion of 10 replicates per drug product in the study designs suggests that a high degree of variation was expected. Additionally, your response argues that the nearly identical concentration profiles observed across multiple studies and different donors are supported by research findings cited in multiple articles and presentations. However, your cited sources focus on the similarity of the *means* of multiple individual test and reference product concentration profiles. The use of *means* is not

appropriate to address nearly identical profiles from a *single replicate of one donor with a single replicate of a different donor* and nearly identical profiles across *different studies.*

Your response to GCL Request 1 also argues that the nearly identical concentration profiles are not nearly identical. This argument is not persuasive. Your response does not substantively address the extensive point-to-point overlap between the nearly identical profiles identified by FDA that are clearly shown in Figure 1. Further, our analysis found that with very few exceptions, point-to-point differences between concentrations in the nearly identical profile pairs were less than 20% and many were observed to be less than 10%. In fact, using your own standard procedures to assess reproducibility in your bioanalytical assays are consistent with our conclusion regarding the nearly identical nature of these profiles. We refer to your incurred sample reanalysis procedures, which define samples as bioanalytically reproducible if the difference between original and repeated concentrations is < 20%. As a result, the point-to-point percentage differences described above would meet your firm's own acceptance criteria to be considered reproducible.

Additionally, your response to GCL Request 2 states that your review only found 14 profiles that were "similar" and that when your firm conducted a bioequivalence assessment excluding these 14 similar profiles, Study (b) (4) continued to meet the bioequivalence acceptance criteria. Your response, including (b) (4) audit report, noted that your records did not demonstrate reuse or reanalysis of samples in IVPT studies and that FDA Draft Guidance for (b) (4) was modified in February 2024, making IVPT no longer required for demonstration of bioequivalence of (b) (4).

We note that excluding study data without any substantive scientific basis, and in particular, study data that FDA identified as apparently falsified, does not resolve the underlying issue or provide material information to explain the practices that led to apparent data falsification. Additionally, FDA would not necessarily expect data falsification to be documented in your study records. Therefore, your response stating that your records do not demonstrate the reuse or reanalysis of samples in your IVPT studies is not conclusive and does not explain how the nearly identical (b) (4) study data could occur without falsification. Further, while FDA's February 2024, Draft Guidance for (b) (4) provides multiple recommended options for demonstrating bioequivalence, your reference to the draft guidance does not address the data falsification concern identified by FDA in your firm's IVPT study data.

Finally, your specific response to GCL Request 7 for the IVPT studies raises concerns about the thoroughness of your review. Specifically, your response, including (b) (4) audit report, only notes that five IVPT studies were reviewed, and of those five, only two of the studies had a few identified similar concentration profiles in the samples; however, we note that you did not provide details regarding those samples. You also concluded, without

providing any documentation, that there were no issues related to sample accountability or data integrity for those samples with the similar profiles. Additionally, while you stated that you performed a retrospective evaluation of IVPT studies conducted by your firm in 2024, based on the limited information you provided in your September 4, and October 17, 2024, responses, FDA is unable to verify whether your retrospective evaluation was adequate. As a result, based on the limited information in your responses, FDA cannot determine whether your overall investigation of FDA's data falsification concerns was comprehensive.

In conclusion, based on the explanations and information provided in your responses, we find your September 4, and October 17, 2024, responses to FDA's GCL inadequate because they fail to identify the root cause of the data integrity issues FDA has observed in your studies. Your responses also fail to provide a substantive explanation to address FDA's specific data integrity concerns that your IVPT studies are falsified. It is not expected that multiple donors would produce nearly identical individual drug concentration profiles between two (b) (4) studies and two (b) (4) studies submitted to FDA by different sponsors. While similarity within and between donors may occur within an IVPT study, you failed to explain how different subject skin donors in different studies, for different sponsors, could have nearly identical individual drug concentration profiles. Your response failed to acknowledge that the replicates for a single subject skin donor within a single study did not show the same nearly identical drug concentration profile trends, which were observed between different donors from different studies.

While we acknowledge that corrective or preventive actions (CAPAs) were described in your September 4, and October 17, 2024, responses, those proposed actions do not appear sufficient to avoid recurrence of the identified concerns related to in vitro studies with respect to future studies conducted by your firm. For example, without any credible explanation for the cause of the anomalous IVPT data identified by FDA, FDA cannot be assured that your CAPAs include actions that will address the data falsification concerns FDA identified or prevent falsification of data in the future. Additionally, your response and CAPA did not explain or include adequate actions to address the failure of your quality management system to identify or address the observed nearly identical concentration profiles between different donors in different studies for different sponsors.

FDA's In Vivo Study Concerns and Your Response to the General Correspondence Letter

FDA notes that our April 2023 inspection of your firm identified processes and practices that raised concerns regarding our ability to verify the reliability and validity of the bioanalytical methods used at your firm. Based on the totality of information before the Agency, including close review of the inspection findings and your firm's study records, FDA notified you in the August 6, 2024, GCL of our concerns regarding your in vivo study conduct and requested that

you respond to specific questions (see GCL Requests 5-7 stated above) to address those concerns. Our review of your GCL response of October 17, 2024, and our conclusions regarding our April 2023 inspection are discussed below.

In summary, your procedures for the retrospective rejection of acceptable study data and inappropriate use of the internal standard response raise significant concerns regarding your firm's study data. Your defined processes and procedures do not appear scientifically justified and result in inconsistent study practice in the form of frequent repeat analysis of valid sample results and failure to perform repeat analysis on invalid sample results. As a result, FDA remains concerned about the reliability of your methods and the reliability of study results generated using those methods. As further described below, FDA will require that you take actions to address these concerns and will continue to evaluate the extent to which you have addressed these concerns as part of FDA's review process.

Response to FDA's In Vivo Study General Correspondence Letter Requests 5-7

FDA's GCL requested explanations to address our observations from FDA's inspections that certain in vivo studies conducted by your firm failed to follow established processes and procedures and used inconsistent and non-validated procedures to justify rejecting runs that met your established acceptance criteria, thereby allowing repeated testing of samples until desired results were obtained (see GCL Requests 5-7 stated above).

Your October 17, 2024, response to GCL Requests 5-7 stated that the BE studies selected for review by (b) (4) did not contain retrospective rejection of analytical batches, high numbers of repeat analyses, or incurred sample reanalysis (ISR) failures and that data reviewed in audited studies were found to be reliable. Additionally, you did not agree with FDA's concern that your procedures and practices created "overly flexible acceptance criterion," stating that you have complied with FDA's established requirements and are aligned with prevailing industry practices. Your response also stated that reanalysis of samples does not inherently represent a lack of compliance, and there are valid reasons for reanalysis, although the established criteria in relevant SOPs must be met. You also stated that your analysis of the six in vivo studies listed in GCL Request 5 found only one study ((b) (4) had a high number of repeat analyses (defined by the firm as >10% of total study samples) and that it was only relevant to the metabolite data, which was not used to determine BE.

As discussed below, based on the explanations and information provided in your response, we find that your response to the GCL is inadequate. Regarding the retrospective rejection of acceptable runs from Study (b) (4) your response to the GCL was similar to the May 18, 2023, written response to the Form FDA 483, stating that rejection of these runs was justified. As noted in the GCL, during the inspection an examination of your firm's documents for five

subjects (Subjects (b) (6) showed that you retrospectively rejected valid, acceptable data following the repeat analysis of these runs, which was inconsistent with your established processes and practices. Further, your firm rejected an ISR run from (b) (4) (b) (4) (ISR04), which met your pre-established run acceptance criteria for (b) (4) (b) (4) Your responses to GCL Requests 5 and 6, and the (b) (4) audit report, did not specifically address why you allowed retrospective rejection of acceptable runs for Subjects (b) (6) and for ISR04. Your response did not explain or provide scientific justification for your retrospective rejection of runs based only on the area response of CCs and QCs when the validated method relies on the analyte-to-internal standard (IS) response ratio. Further, your response did not address the impact of using original results from the run for ISR04 on the overall ISR results. For these reasons, among others, your response did not adequately address our concern that your practices allow testing into compliance. We also note that the March 2019 inspection, which was also described in the GCL, raised similar concerns regarding rejection and repeat analysis of acceptable runs.

Regarding the failure to include all acceptable CCs and QCs in calculating the acceptable IS response range for Studies (b) (4) which we observed from an examination of your firm's documents during the April 2023 inspection, you did not adequately explain or provide scientific justification for why it was appropriate to accept CCs and QCs in one context (run acceptance), but it was also appropriate to reject/exclude them in a different context (acceptable IS response range calculations). Such justification was not provided in your responses to GCL Requests 5 and 6, in the (b) (4) audit report, during the April 2023 inspection, or in earlier versions of your repeat analysis SOP. The (b) (4) audit report noted that your current repeat analysis SOP has removed the criterion allowing exclusion of acceptable CCs and QCs from calculation of the acceptable IS response range.

While we acknowledge your statement that the repeat analysis SOP has been revised, the implementation of the earlier versions of the SOP facilitated the inconsistent treatment of CCs and QCs dependent on context, the repeat analysis of samples with valid results, and more critically, the failure to reanalyze samples with invalid results. Thus, we are unable to verify the adequacy of your procedures and remain concerned about the accuracy and reliability of your study data. We note that the March 2019 inspection, which was also described in the GCL, also raised concerns regarding how the IS acceptance range was calculated. Thus, you have not adequately addressed prior IS issues at your firm.

Regarding the high number of sample repeats due to IS variability, as observed in the March 2019 and April 2023 inspections and described in the GCL, your responses to GCL Requests 5 and 6 did not adequately address this issue for Studies (b) (4) (b) (4) (noted in GCL Request 5), or Studies (b) (4) (b) (4) (noted in the GCL as studies from the March 2019 inspection). For example, the

(b) (4) audit report indicated that Studies (b) (4) and (b) (4) were examined but provided insufficient details regarding the documents that were reviewed relevant to those studies.

We also note that you have not adequately addressed GCL Request 7 in your GCL response or in the (b) (4) audit report. To date, you have not provided a root cause for the high percentage of samples with unacceptable IS responses across multiple methods and multiple analytes. Your lack of a root cause analysis for these issues prevents FDA from conducting an informed evaluation of their potential impact on the reliability of your methods. The high number of repeat analyses due to IS variability observed across Studies (b) (4) (b) (4) is concerning, particularly given that there were no matrix effects or other relevant concerns in the validated methods.

The (b) (4) audit report stated that you initiated a CAPA for in vivo studies. However, the in vivo CAPA (CAPA/USFDA/24/001-02) described in the audit report was not submitted with the GCL response or included with the audit report. You stated that as part of the CAPA, you repeated the BE assessment for studies, including (b) (4) (b) (4) either using original concentration data or excluding affected concentration data. You stated that in all cases the BE analysis met the acceptance criteria, and therefore, the inspectional observations had no impact on the studies. However, you have not provided sufficient information in your GCL response to allow FDA to verify your conclusions. Specifically, your response did not provide your proposed CAPA report, and as a result, we have insufficient details to assess your conclusions, including what original concentration data were used, what concentration data were excluded, and the impact of the high frequency of IS-driven repeat analysis on BE.

Overall Conclusions

Your failure to acknowledge, identify, and address the evidence of in vitro data falsification identified by FDA for multiple data points, multiple subjects/samples, and multiple individual studies, across multiple applications, and for multiple applicants, undermines the integrity of the FDA application review process. These facts create a risk that any products relying on such data are not bioequivalent. Absent a demonstration of bioequivalence, FDA cannot conclude that such products can be expected to have the same clinical effect and safety profile as their respective reference listed drugs when administered to patients under the conditions specified in the labeling. Put simply, because you have been responsible for the creation of false in vitro study data in the scope and manner discussed above, we have no reason to believe that any in vitro data that you have produced are reliable. Therefore, FDA has determined that all study data from all in vitro studies conducted at your firm must be rejected.

With respect to in vivo studies, FDA remains concerned about the reliability of your methods and the study results generated using those methods. As further described below, FDA will require that you take actions to address these concerns. FDA has evaluated and will continue to evaluate the extent to which you have addressed these concerns as part of FDA's review process.

Additionally, based on our review of the information and our evaluation of your GCL response, prior to your firm conducting future studies that are intended for FDA submission, you must address FDA's concerns and incorporate controls to ensure the accuracy and reliability of your study conduct going forward, to include, but not limited to:

1. A detailed corrective action plan that describes how you intend to ensure the reliability and completeness of all the data you generate, including in vitro and in vivo bioavailability or bioequivalence data and all other data submitted to FDA.
2. A root cause investigation of your data integrity lapses, including evidence that the scope and depth of your corrective action plan is commensurate with the findings of the investigation and risk assessment. Indicate whether individuals responsible for data integrity lapses remain able to influence in vitro and in vivo bioavailability or bioequivalence studies, or FDA-related study data generated at your firm.
3. An assessment of the extent of data integrity deficiencies at your firm. Identify omissions, alterations, deletions, record destruction, non-contemporaneous record completion, and other deficiencies. Describe all parts of your firm's operations in which you discovered data integrity deficiencies.
4. A current risk assessment of the potential effects of the observed failures on the integrity and quality of both the in vitro and in vivo studies conducted by your firm.

FDA intends to confirm these actions during a future inspection.

Additionally, we acknowledge that you have previously engaged with (b) (4) to audit your operation. In response to this letter:

5. Provide the CAPA plans and full CAPA report for CAPA/USFDA/24/001-01 – "Similar Profiles issue in IVPT studies." Ensure that the following are included in your submission of this CAPA report:

    a. Confirm that the Data Integrity Risk Assessment policy discussed in your GCL response and in (b) (4) audit report has been implemented, and provide all documents relevant to this policy including but not limited to: 1) how risk is defined; 2) how the policy will be implemented; and 3) how the policy will be

reviewed.

b. Confirm that the Laboratory Information Management System barcodes for management of in vitro samples described in (b) (4) audit report have been implemented, and provide relevant SOPs and additional documents guiding use, maintenance, and review of this system.

c. Detail the interim measures describing the actions you have taken to ensure reliability and completeness of all the data you generate, including in vitro bioequivalence data submitted to FDA.

d. Detail the long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, and management oversight, including measures to detect overlapping profiles, designed to ensure the integrity of your company's in vitro data.

6. Provide the CAPA plans and full CAPA report for CAPA/USFDA/24/001-02 – "Procedural issues in in vivo bioequivalence studies." Ensure that the following are included in your submission of this CAPA report:

   a. Provide additional details and documentation for the reanalysis of bioequivalence conducted for Study (b) (4) including the comprehensive dataset used for the reanalysis. Ensure you specify subjects/samples/data where 1) original concentrations were used; and 2) concentration data were excluded.

   b. Detail the interim measures describing the actions you have taken to ensure reliability and completeness of all the data you generate, including in vivo bioavailability and bioequivalence data submitted to FDA.

   c. Detail the long-term measures describing any remediation efforts and enhancements to procedures, processes, methods, controls, systems, and management oversight, including measures to detect overlapping profiles, designed to ensure the integrity of your company's in vivo data.

7. Provide all SOPs that have been revised and updated following the April 2023 inspection. Include redlines to highlight all changes made to the documents.

8. Provide an amended table of in vivo studies conducted at Raptim, which was included with your September 2024 GCL response, to include all studies completed from April 2023 to the present. Also include the specific analyte(s) assessed in each study, analytical dates, and the study sponsor.

9. Provide an amended table of in vitro studies conducted at Raptim, which was included with your September 2024 GCL response, to include all studies completed from June 2022 to the present. Also include the specific analyte(s) assessed in each study, the study sponsor, analytical dates, and the specific type of in vitro study.

We also note that FDA's GCL specifically asked you to explain the following:

- **GCL Request 8**: Provide any reason(s) why the data anomalies identified and discussed in this letter should not raise questions about the reliability of the data reported by your company.

For the reasons explained above, we find your response to GCL Request 8 inadequate. To reiterate, your response fails even to recognize the evident falsification of in vitro study data identified in the GCL, and we cannot be sure that any in vitro data previously generated by your firm are reliable or that implementation of any CAPAs or SOP updates will be sufficient to prevent continuation of the conduct that resulted in the issues FDA has identified.

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 FDA in ANDAs or NDAs.

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 FDA. Note that we will conduct a future inspection to verify your corrective actions and future compliance with FDA regulations.

This letter notifies you of our current findings and provides you with an opportunity to address the deficiencies described above. We request that you notify this office in writing, within 30 business days of your receipt of this letter, of the actions you have taken or will take to address any violations noted above and to prevent their recurrence. You may provide additional information for our consideration as we continue to assess your activities and practices.

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

Sean Kassim, Director
Office of Study Integrity and Surveillance

Office of Translational Sciences
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
United States

David Burrow, Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
United States

Sincerely yours,

SEAN KASSIM -S

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Date: 2025.03.27 07:12:49 -04'00'

Sean Kassim, PhD
Director
Office of Study Integrity and Surveillance
Office of Translational Sciences
Center for Drug Evaluation and Research

DAVID BURROW -S

Digitally signed by DAVID BURROW -S
Date: 2025.03.27 07:15:51 -04'00'

David Burrow, PharmD, JD
Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research