DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

06/17/2024

Vishal Dhawan
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Dear Vishal Dhawan:

This letter addresses significant concerns the U.S. Food and Drug Administration (FDA or the Agency) has notified you of regarding bioavailability (BA) and bioequivalence (BE) studies conducted at your site. Based on the totality of information before the Agency, including FDA's data analyses communicated to you in a General Correspondence Letter (GCL) on 2/12/2024 and in an additional email on 3/18/2024, and your subsequent responses received 2/26/2024 and 4/13/2024, it is FDA's conclusion that your site has created and caused the submission of falsified data to FDA, as further described below. References to "your response" indicates your 2/26/2024 communication unless otherwise specified.

As described in our 2/12/2024 GCL, FDA identified significant data anomalies in numerous studies conducted by your site. In five of your studies,[1] we identified multiple pairs of study subjects that have nearly identical data (i.e., overlapping point-to-point concentration-time profiles). Additionally, in two of these studies, we identified individual study subjects that produced nearly identical results when treated with the test drug and the reference drug.[2] While it would be unusual for two subjects in a single study to have nearly identical data, this occurred for multiple pairs of subjects, in multiple studies, and, in some instances, occurred in such a way (i.e., across multiple concentration peaks) that makes the nearly identical data even more unlikely. It does not appear possible to FDA that these data were generated from a group of healthy subjects by chance, and these results would not be expected based on normal intra- and/or inter-subject physiologic variation.

In one of these five studies,[3] we also found an anomalous data trend, with the results for the first half of the subjects tested for the maximum drug concentration (Cmax) test/reference (T/R) ratio

[1] Study (b) (4), Study (b) (4), Study (b) (4), Study (b) (4), and Study (b) (4).
[2] Study (b) (4) and Study (b) (4).
[3] Study (b) (4).

showing a typical random distribution pattern we would expect to see in a normal, healthy population, and the second half of subjects registering results that lacked a random pattern and remained consistently similar with the T/R ratios at or around 1. The distinct patterns for the subject data for these two groups within a study is a significant deviation from the normal population distribution of data from a group of healthy volunteers, especially for a drug with low variability, and does not appear to be possible to have authentically occurred by random chance.

In another one of these five studies,[4] we found that the original, valid test data for multiple test subjects was rejected and replaced with reanalyzed data, even though the original test data met the study's acceptance criteria. Our analysis shows that the study would have failed using the original, valid data and that the improper substitution of this reanalyzed data changed the final result.

In our 2/12/2024 GCL, we requested that you respond by providing the following information:

1) explanation for the anomalous pharmacokinetic data and unjustified substitution of data from repeat analysis identified by FDA with respect to the studies discussed in the GCL;
2) explanation of why your site failed to identify and assess the data anomalies;
3) explanation of how your overall system of process and procedures contributed to or permitted multiple studies conducted at your site to have numerous instances of overlapping subject sample concentrations;
4) explanation for whether and to what extent the findings of the European Medicines Agency's (EMA's) human medicines committee (CHMP) should affect our assessment of the data generated by your site in support of FDA applications;
5) any other bioequivalence or bioavailability studies conducted at your site that have similar pharmacokinetic data anomalies, and an assessment of the impact of any such data anomalies on each study, if any, and the root cause for any identified data anomalies; and
6) any reason why the evidence of falsification of data discussed in the GCL should not raise questions about the validity of all data reported by your company.

As we explain in more detail below, your response did not resolve FDA's data integrity concerns regarding the data generated from your site. It does not adequately address FDA's concerns for what caused the significant data anomalies present in your studies, and it does not provide any legitimate, scientifically valid reason why the evidence of falsification of data discussed in the FDA's 2/12/2024 GCL should not call into question the validity of all data generated by your firm.

Your Response to the General Correspondence Letter

FDA has reviewed your response to the 2/12/2024 CGL and the additional information you submitted on 4/13/2024. In the following sections, we address the topics covered in the response in the order set forth in your response.

[4] Study (b) (4)

1. Your Quality Management System

You assert that your quality management system (QMS) is robust, and all aspects of your site's activities are appropriately controlled, including clinical, bioanalytical, and statistical departments and all processes and procedures for collection, analysis, and reporting of data. You also note your training program is robust and you have personnel with quality expertise across key functions. Further, you assert that your inspection history by various agencies, sponsor vendor qualification, third-party monitoring and sponsor audits, internal quality assurance, and regular QMS and SOP updates ensure your QMS is adequate.

It is concerning to the Agency that your response of 2/26/2024 suggests that your QMS is adequate when it failed to recognize and address the data quality problems raised in our 2/12/2024 GCL. FDA would expect that if your site and your QMS were in fact adequate, then either your QMS would have identified and addressed the multiple instances of results which are unexpected based on normal physiologic variation (i.e., non-physiological data) or your response to the 2/12/2024 GCL would have explained how your site and your QMS would identify, address, and/or prevent such unexpected, non-physiological data in studies performed at your site in the future. Neither of those occurred: your QMS did not identify and address the non-physiological data in your studies and your response does not explain how your QMS will address and/or prevent future occurrences of non-physiological data. With respect to your reference to your inspection history by various agencies, we note that similar concerns to those raised in our 2/12/2024 GCL have been raised by the EMA, with the EMA CHMP recently recommending that marketing authorizations of medicines tested by Synapse be suspended or not granted after a good clinical practice inspection showed irregularities in study data and inadequacies in study documentation and in the computer systems and procedures to manage study data, which raised serious concerns about the data from bioequivalence studies conducted at your site. Thus, your response describing the adequacy of your site's QMS does not resolve FDA's concerns regarding the data generated from your site.

2. The Anomalous Pharmacokinetic Data and Unjustified Substitution of Data from Repeat Analysis in Your Studies

A. Study (b) (4) and Study (b) (4) Observations

Summary of issues described in the 2/12/2024 GCL:
(1) In both Study (b) (4) and (b) (4), a significant number of subject pairs exhibit overlapping concentration-time profiles for (b) (4) Such overlapping pharmacokinetic profiles would not be expected based on normal physiologic variation.
(2) In Study (b) (4) the Test/Reference (T/R) ratio for Cmax for subjects (b) (6) to (b) (6) ranges between 0.77- 1.26. However, for all remaining subjects (i.e., subjects (b) (6) to (b) (6) this ratio is consistently close to 1. The trend for the T/R ratio of Cmax appears to be a significant deviation from the normal population distribution of data from a group of healthy volunteers expected for a drug with low variability.

You acknowledged that there were overlapping concentration-time profiles in your data for studies (b) (4) and (b) (4) as identified by the Agency. Further, you indicated that your analyses identified additional concentration-time profile pairs (i.e., a total of 77 pairs for study #(b) (4) that you described as similar using your developed software and stated that it was not practically viable to replace so many data pairs. It is important to note that FDA's concern expressed in the GCL is regarding the presence of nearly identical 'point to point' overlapping concentration-time profiles with multiple peaks in the study conducted by Synapse and submitted to the Agency as outlined in the letter. These observations of overlapping concentration-time profiles do not appear to FDA to be possible by chance. The letter was not intended to be an exhaustive list of all similar concentration-time profile pairs. You did not dispute the presence of the nearly identical overlapping concentration-time profiles but suggested that the similar concentration-time profiles might be attributed to (b) (4) being a narrow therapeutic index (NTI) drug, for which concentration-time profiles may be similar. We disagree with your explanation. While NTI products do typically exhibit low-to-moderate within-subject variability, such variability does not explain 'point-to-point' concentration similarity across different subjects exhibiting multiple peaks.

You conducted 4 BE studies on the same test and reference formulations of (b) (4) Tablets. Two of these were conducted as two-way crossover studies under fasting (Study (b) (4) (b) (4)) and fed (Study (b) (4)) conditions and two were conducted as four-way crossover studies under fasting (Study (b) (4)) and fed (Study (b) (4)) conditions. For the two studies with four-way crossover study design, both the Agency and your in-house software identified significant numbers of similar concentration-time profiles. However, for the two-way crossover fasting study (b) (4), the Agency did not detect any similar overlapping pairs from our analysis. A visualization of the profile pairs from study (b) (4), submitted in your response dated April 13, 2024, also did not identify similar profiles between subject pairs. For the two-way crossover fed study (b) (4), only a few similar concentration-time profiles were observed. Taken together, this provides further support that overlapping pairs observed in studies (b) (4) and (b) (4) are not a result of the characteristics of the drug being studied or a chance occurrence and would not be expected based on normal physiologic variation.

Additionally, in your response, you divided the study subjects into three cohorts which you indicated was done to understand the results and flow of data trends based on your expectation of consecutive cohorts exhibiting similar pharmacokinetic characteristics, despite being dosed as one group. From this analysis, you concluded that the observed pharmacokinetic results were natural and usual across the cohorts. The shift from the failing trend to passing trend was not evident in the cohort analysis for either study.

As an initial matter you did not explain how your approach to create the cohorts is justified, as each cohort is significantly underpowered to draw any bioequivalence conclusion. For example, in study (b) (4), your conclusion relies on statistical analysis conducted with 8, 8 and 7 completed subjects in cohorts 1, 2 and 3, respectively.

You reasoned that the observed trend of the T/R ratio of Cmax (i.e., the ratio for subjects (b) (6) to (b) (6) close to unity) was not observed for AUCs and that this indicated there was no data manipulation. However, Cmax values represent observed concentrations at a single timepoint,

whereas AUC values are derived with respect to time and drug concentration at multiple sampling timepoints. Therefore, the trend for Cmax and AUC in the study does not need to necessarily correlate for the Cmax values to have been manipulated.

In summary, your response did not provide adequate explanations and justification for the anomalous observations of 'point-to-point' overlaps in concentration-time profiles across multiple peaks in Study #(b) (4) and (b) (4). Additionally, adequate explanations were not provided regarding the observed Cmax trend in study (b) (4).

B. Study #(b) (4) Observations:

Similar concentrations at all sampling timepoints are observed for given subjects with different treatments, specifically, Subjects (b) (6). As a result, overlapping of multiple peaks across the concentration-time profiles is observed for these subjects.

You did not provide explanations for the observed point-to-point overlaps across multiple peaks in the concentration-time profiles for the subjects receiving different treatment, specifically, *Subjects* (b) (6). Those overlapping profiles were also identified by your developed tool. Instead, you conducted statistical reanalysis by using multiple permutations and combinations of inclusion/exclusion of subjects to support your justification that there was no need to intentionally manipulate the data to generate a passing result from the study. You evaluated the following 5 scenarios:

1) A scenario in which the study results were reanalyzed after excluding the data from the identified 8 subjects with overlapping profiles; the reanalysis met the BE acceptance criteria.
2) A scenario in which the study was split into two individual cohorts (subjects (b) (6) and (b) (6)) for reanalysis; cohort 1 (subjects (b) (6)) met the BE acceptance criteria and cohort 2 (subjects (b) (6)) failed the BE acceptance criteria for Cmax only.
3) A scenario in which the data for subjects with identified overlapping profiles including subjects (b) (6) and (b) (6) that had been repeated due to batch failure due to internal standard variation was not used and instead the original values for subject (b) (6) and (b) (6) were used for statistical reanalysis with all subjects included. The reanalysis met the BE acceptance criteria.
4) A scenario in which the study results were reanalyzed after excluding the data for subject (b) (6) and (b) (6) only; the reanalysis met BE acceptance criteria.
5) A scenario in which the study results were reanalyzed after excluding the data for subjects (b) (6) and where the original values for subjects (b) (6) and (b) (6) were used; the reanalysis met the BE acceptance criteria.

Your additional analysis did not explain how the overlapping concentration-time profiles in study # (b) (4) from the same subject with different treatments (T and R) occurred. We would not expect to see such overlap for the same subject receiving two treatments due to normal physiological variations. This has raised serious concerns about data manipulation and/or mishandling of the data. This, in turn, raised serious concerns about the reliability of the overall

data generated for study #(b) (4). Therefore, your further data analysis did not alleviate our concerns regarding the observed overlapping profiles.

In summary, you did not provide explanations for the observed overlapping concentration-time profiles. Consequently, we continue to have significant concerns about the reliability of the data for study # (b) (4).

C. Study (b) (4) Observations:

Four (4) pairs of subjects showing overlapping concentration-time profiles for (b) (4) were included as examples in the GCL. Such overlapping pharmacokinetic profiles would not be expected based on normal physiologic variation.

Your analysis using the in-house software tool to detect overlapping profiles identified 3 of the 4 subject pairs referenced in the GCL. For the remaining similar pair (subject (b) (6)), you disagree with the Agency's observation and claim that the near identical profiles are considerably different. You reached this conclusion by calculating the percentage differences between concentrations at certain corresponding timepoints for the subject (b) (6) pair and noting a maximum difference of 74% for the first timepoint with measurable concentration and 183% for the last timepoint.

Your approach for demonstrating non-similarity between PK profiles is misleading, due to the following:

- For profile comparisons, differences between the complete profiles with a full set of timepoints (16 timepoints) should have been considered rather than a few individual timepoints. For 13 of the 15 timepoints with reliable concentrations for the profile pairs for Subject (b) (6), the differences range between 0.37-19.47% (i.e., within 20%). Your approach of only looking at one or two timepoints at the early end and one or two timepoints at the tail end of the profiles with differences greater than 20% between pairs does not alter our conclusion that there is a high degree of overlap between the concentration-time profiles. Such highly similar profiles between subject pairs are not expected based on normal physiological variation.
- Your claim of 183% difference for the last sampling timepoint (timepoint #16) of the profile pair for Subject (b) (6) is also misleading. The lower limit of quantification (LLOQ) for the assay is 50.55 ng/mL. The reported concentrations at timepoint #16 (period 1: 2.12 ng/mL and period 2: 48.459 ng/mL) in Table 19 of your response are below the LLOQ and therefore are not reliable. Comparisons using unreliable data are not meaningful and therefore use of this data to support your response is misleading.

You did not provide any explanation for the observed similarities in profiles for the multiple pairs. Instead, you excluded data for the 5 subjects (subjects (b) (6)) from statistical calculations and claimed that data for the identified subject pairs did not bias the study outcome. Your response did not specifically address the concern for the observed overlapping peaks in the study. In fact, we note the profile pairs for Subjects (b) (6) (test treatment) and (b) (6)

(reference treatment) in period 1 and Subjects (b) (6) (reference treatment) and (b) (6) (test treatment) in period 2 show a two-peak and three-peak turn-by-turn overlay respectively. This would not be expected based on normal physiological variation. You provided no explanation for this observation.

Additionally, conducting statistical reanalysis by excluding data from subjects to support a lack of bias for the study outcome is not an acceptable way to address the concerns we have raised about the data generated at your site, or a valid approach for analyzing data to demonstrate bioequivalence.

We also raised concerns in the GCL regarding your approach for substituting the originally valid data of subject samples with reanalyzed data from the Incurred Sample Reproducibility (ISR) run without adequately investigating the root cause for the discrepancy between the results from the original and ISR runs. You relied on the reanalysis results of the same subjects to conclude that there was a processing error for the original runs and replaced the original concentrations for these subjects with concentrations from repeat analysis. Your substitution of the original concentrations with reanalyzed concentrations caused the study which otherwise failed to meet the BE limits to pass.

In your response, you attributed the reason for failure of the initial analysis for Subjects (b) (6) and (b) (6) to sample processing error. You made this determination only after observing the results from the ISR run and did not conduct a systematic investigation into the root cause for the large differences in concentrations between the initial analysis and ISR results. You replaced the original concentrations for these subjects with concentrations from repeat analysis.

Your rationale for attributing the differences in concentrations to a processing error is not supportable for the following reasons:

- You did not investigate why only the Cmax samples in both periods for Subjects (b) (6) and (b) (6) were impacted by the processing error. None of the samples in the elimination phase for these subjects were impacted by the alleged processing error.

- Your investigation did not explain why the processing error impacted only the study samples from Subjec (b) (6) (both periods) and not from Subject (b) (6) even though samples from both subjects were processed together in run CC015. Similarly, it does not explain why the error impacted only the samples from period 1 of Subjects (b) (6) and (b) (6) and not the samples from period 2 for both subjects, though study samples from periods 1 and 2 for both subjects were processed together in run CC019.

- Your response indicates that the processing error impacted only the study samples and not the calibration curve standards and quality control samples (QCs), possibly because the "*analyst may have processed samples of calibration curve standards and quality control samples separately in these batches (as per SOP effective during analysis period)"*[5].

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However, for the original data from runs CC015 (subjects (b) (6) and (b) (6) and CC019 (subjects (b) (6) and (b) (6)), the variations in internal standard responses for the subject samples are not observed to be significantly different from those observed for the QCs and calibration standards. Therefore, your rationale for the likely cause of the processing error is not supportable.

- You did not describe or provide the investigation report for a systematic assessment into the root cause.

Your approach for investigating the discrepancies between the results from 2 runs (original and ISR runs) by simply reanalyzing the same samples for a third time to confirm the results of the ISR run is not adequate. By substituting the original concentrations with reanalyzed concentrations you caused the study which otherwise failed to meet the BE limits to pass. In general, when individual samples are quite different from the original value (e.g., > 50%,), the Agency's expectation and industry's established practice is that it should not trigger reanalysis and replacement of the original study sample data without a systematic investigation to understand the root cause, and it is concerning that you did not conduct such an investigation. We disagree with your assessment that "*ISR evaluation is the only data that is concluded to be authentic for pharmacokinetic evaluation for this study"*[6].

For all the reasons cited above, the Agency continues to have significant concerns about the integrity and reliability of the data for this study.

D. Study (b) (4) Observations:

Study subjects were dosed in 4 groups, separated by 4-6 days. The trends for the T/R ratios of the AUCt values for baseline corrected total serum iron (TI) and transferrin bound iron (TBI) appeared to deviate from the expected normal population distribution of data from a group of healthy volunteers with the same demographics.

In your response, you conclude that the trends for the T/R ratios are not unusual. Additionally, you assessed the BE criteria for each of the 4 groups and noted that the trend for the failing BE results from each group did not shift and the progress of the study with respect to the trend was not unusual.

We find your assessment for the significantly different T/R ratios between groups for the baseline corrected total serum iron (TI) and transferrin bound iron (TBI) uncompelling for the following reasons:

- You performed group wise comparison of the T/R ratios for Cmax and AUCs (AUC0-t and AUC0-∞) and concluded that in addition to AUCt, the ratios for Cmax and AUC0-∞ are also significantly different between groups 02 and 04 and the trends for the T/R ratios for all primary PK parameters Cmax, AUC0-t and AUC0-∞ for both the analytes are similar and not unusual. On the contrary, our analysis of the study data found statistically significant group-

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by-treatment interaction only for AUCt ($p < 0.0001$ for TI and $p = 0.0375$ for TBI) and AUC0-∞ ($p = 0.0376$ for TI) and not for Cmax. Furthermore, the interactions are qualitative for total iron AUCt and AUC0-∞. For example, for total iron AUCt, the analysis shows, i) the group specific geometric mean ratio (GMR) for group 04 (0.8283 < 1) is different from group 02 and in the opposite direction of those in the first 3 groups (all > 1) (table 1), and ii) the sensitivity analysis using Bayesian Shrinkage Analysis (data not shown here) continues to show the GMR for group 02 greater than 1.25 , which supports our concern that the trend for the T/R ratio for total iron AUCt between groups is unusual and should have warranted an investigation into the plausible cause, before combining the data from the 4 groups to establish BE. We concur with your premise that *"if the population is normally and randomly distributed and the pharmacokinetic analysis is free of any intervention or attempt to change the results the results should be similar in each such group"*[7]. Since our analysis shows the results are not similar in all groups, and your response did not investigate a plausible cause for the differences in the treatment effect between groups, we remain concerned about the possibility of manipulation of the PK analysis.

Table 1: Least Squares Geometric Means and Ratio of Means for Groups 1-4

	Baseline Corrected Total Iron (AUCt)		
	Test	Reference	Test/Reference Ratio
Group 1	141932	120081.93	1.18
Group 2	158215.2	116471.05	1.36
Group 3	155422.3	127245.32	1.22
Group 4	125923.8	151753.72	0.83

- Furthermore, based on the BE assessment for each of the 4 groups, you note that the trend for the failing BE results did not shift. On the contrary, we observe a notably different trend for the BE results. Based on the data from groups 1-3 alone, Study (b) (4) fails to meet the BE criteria for both the point estimate and 90% confidence interval limits for the AUCt of baseline corrected TI (T/R = 1.2542; the upper limit of the 90% CI =134.49).

As shown in Tables 2 and 3 below, the study meets the BE criteria only when the data from group 4 are considered with the cumulative data from groups 1-3.

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Table 2: Statistical Summary of Comparative Data for TI from Groups 1 - 3 (Generated by FDA)

Drug Name: (b) (4) Injection Dose: (b) (4) MG Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study No. (b) (4) TI (combined groups 1, 2, 3)							
Parameter (units)	**Test**	**N**	**Reference**	**N**	**T/R**	**Lower 90% CI**	**Upper 90% CI**
AUCt (ug*hr/mL)	152249.89	91	121390.37	91	**1.2542**	116.96	**134.49**
Cmax (ug/mL)	31069.91	91	29315.69	91	1.0598	102.42	109.67

Table 3: Statistical Summary of Comparative Data for TI from Groups 1- 4 (from ANDA submission)

Drug Name: (b) (4) Injection Dose: (b) (4) MG Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study No. (b) (4) TI (combined groups 1, 2, 3, 4)							
Parameter (units)	**Test**	**N**	**Reference**	**N**	**T/R**	**Lower 90% CI**	**Upper 90% CI**
AUCt (ug*hr/mL)	52395.53	121	54062.07	122	0.9692	87.46	107.40
Cmax (ug/mL)	2686.06	121	2719.97	122	0.9875	93.16	104.68

Therefore, your claim that "*the progress of study with respect to the change in pharmacokinetic profile /result /trend was quite natural and usual*"[8] is not valid.

Four (4) pairs of subjects showing overlapping concentration-time profiles for TI were included as examples in the GCL. Such overlapping pharmacokinetic profiles would not be expected based on normal physiologic variation.

You did not provide any valid explanation for the observed similarity in profiles. You claim that the similar profile pairs for TI included in the GCL are considerably different. You made this determination by calculating the percentage differences for the baseline corrected TI concentrations[9] at each corresponding timepoint and noting differences that exceeded 30%. As highlighted in your response, we note that such differences are especially prominent in the elimination phase for the profile pair of Subjects (b) (6) and (b) (6) and your in-house software tool

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[9] The Agency's analysis for profile comparisons used the baseline uncorrected data.

did not identify this subject pair as showing overlapping profiles.

Your approach for demonstrating non-similarity between PK profiles based on differences in individual timepoints rather than complete profiles is misleading and not acceptable.

- You used baseline corrected data for the calculation. To detect data anomalies, it is more appropriate to use the raw (un-corrected concentrations) data rather than derived data like the baseline corrected concentration which is created from 2 individually measured concentrations. Since the measured baseline concentrations differ considerably between the subject pairs as is the case for the Subject pair (b) (6) and (b) (6) (baseline TI concentrations differ by 34%), the derived data tends to exaggerate the actual differences between measured TI concentrations. Using the uncorrected TI data, the differences in concentrations for the 4 profile pairs collapse, e.g., from the highest difference of 600% for subject pairs (b) (6) vs. (b) (6) to 18%. Similarly, the highest difference of 400% for subject pairs (b) (6) vs. (b) (6) collapses to 0.4%. Contrary to your analysis, we note that the concentration values for the full set of timepoints for these subject pairs are highly similar and do not support your claim that the profiles are not overlapping. Such highly similar profiles between subject pairs are not expected based on normal physiological variation.
- Furthermore, for profile comparisons, differences between the complete profiles with a full set of timepoints (20 timepoints) should be considered rather than individual timepoints as explained above for Study (b) (4). Your approach does not alter our conclusions for the observed overlap between the concentration-time profiles.

Lastly, you indicate that "*the flow of bioanalytical activity was uninterrupted which supports that there was …[not] any irrelevant activity performed/reported"*[10]. We note that intervention to influence study outcome may not be limited to bioanalytical activity. Intervention is plausible at multiple stages of the study. You did not provide real-time documentation and study logs for all stages of the study activities to rule out intervention with certainty. Your argument is uncompelling and does not allow the Agency to conclude with certainty that your site did not create and cause the submission of falsified data for this study.

In summary, your response did not provide adequate explanation for the concerning study observations and is inadequate to assure the Agency of the reliability of the entire dataset from this study.

3. Your Site's Failure to Identify and Assess the Data Anomalies, and How Your Overall System Contributed or Permitted Multiple Studies to have Numerous Instances of Overlapping Subject Sample Concentrations

The FDA's 2/12/2024 GCL specifically requested that you explain the following:

2) why your site failed to identify and assess the data anomalies.

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3) how your overall system of process and procedures contributed to or permitted multiple studies conducted at your site to have numerous instances of overlapping subject sample concentrations.

You combined your response to these two inquiries, indicating that you have had multiple inspections by multiple regulatory agencies, including FDA, and noting that these falsified data were not detected previously. Additionally, you note your QMS has been audited by various independent monitors and sponsors and that no critical observations were reported. Further, you note that you have had some studies that had similar profiles that were not submitted to any agency. However, this does not explain why you failed to identify these anomalies or why numerous instances of these anomalous data occurred in multiple studies. Furthermore, as noted above and described in more detail in the following section, similar concerns to those raised in our 2/12/2024 GCL have been raised by the EMA, with the EMA CHMP recently recommending that marketing authorizations of medicines tested by Synapse be suspended or not granted after a good clinical practice inspection showed irregularities in study data and inadequacies in study documentation and in the computer systems and procedures to manage study data, which raised serious concerns about the data from bioequivalence studies conducted at your site. FDA must conclude your systems were insufficient to prevent and/or identify these anomalies, and therefore these failures undermine the reliability and validity of all the studies generated by your site.

4. The EMA CHMP's Findings

In our 2/12/2024 GCL, we requested an explanation for whether and to what extent the findings of the EMA CHMP should affect our assessment of the data generated by your site in support of FDA applications.

You indicated in your response that you replied to the EMA CHMP with a point-by-point response to all the observations made by the Spanish regulatory agency Agencia Espanola de Medicamentos y Productos Sanitarios (AEMPS) inspection (which the EMA CHMP based their findings on). AEMPS had 6 observations and you shared the responses you provided to AEMPS and discussed how you think the AEMPS observations should affect the data generated at your site in support of applications submitted to FDA. Overall, you concluded the observations of the AEMPS inspection have no impact, except for the PK Profiling Analysis observation, which is similar to the overlapping profile analysis which you performed on studies submitted to FDA and which you indicate confirmed overlapping profiles only in the 5 studies that FDA noted in the 2/12/24 GCL.

The EMA CHMP found that "for the majority of the medicines tested by Synapse Labs on behalf of EU companies…supporting data were lacking or insufficient to show bioequivalence and therefore recommended suspending the marketing authorisations of these medicines."[11] We do not find your explanation regarding this finding responsive to our request. Your response focused on your conclusions that the AEMPS observations were not relevant or even qualified as

[11] https://www.ema.europa.eu/en/documents/referral/synapse-article-31-referral-synapse-labs-pvt-ltd-re-examination-confirms-suspension-medicines-over-flawed-studies_en.pdf

observations, suggesting they were opinions or aggregated assumptions. However, we consider your response to the conclusions of our regulatory partners regarding data integrity concerns to be inappropriately dismissive. Your response mostly dismissed any relevance of AEMPS' conclusions and did not address the significant concerns of overlapping PK profiles and data concerns observed by AEMPS. Thus, the absence of a meaningful response to the EMA CHMP findings further undermines our confidence in the studies conducted at your site.

5. Any Other Bioequivalence or Bioavailability Studies Conducted at Your Site that Have Similar Pharmacokinetic Data Anomalies

In the 2/12/2024 GCL, FDA requested you provide information regarding any other bioequivalence or bioavailability studies conducted at your site that have similar pharmacokinetic data anomalies, and an assessment of the impact of any such data anomalies on each study, if any, and the root cause for any identified data anomalies.

You indicated in your response that all other studies conducted at your site in support of applications submitted to FDA did not contain similar pharmacokinetic profiles and provided those reports in your second response (received 4/13/2024). However, your response does not mitigate our concerns with the overall reliability of the data generated by your site, as you have also insisted your conduct and processes were in line with applicable regulatory guidelines, policies, manuals, etc., for the 5 studies identified by FDA and the 18 studies discussed with AEMPS where concerns about non-physiological overlapping subject profiles were raised. As discussed in detail above, you have indicated that you have no concerns regarding the integrity of those studies while failing to provide any rational explanation for the anomalous results observed. This undermines confidence in all study data generated at your site.

6. Your Explanation for 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.

You indicate in your response that you have not found any additional overlapping profiles apart from those identified by FDA and that you have conducted all your studies according to all applicable guidelines. However, you have not addressed the source of the non-physiologic data that indicates falsification of data in several studies you have conducted in support of submissions to the Agency.

FDA's Conclusions

Your response to FDA's 2/12/2024 GCL 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 if data were not being manipulated, and (3) any legitimate, scientifically valid reason why the evidence of falsification of data discussed in the GCL 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 time-concentration profiles and/or anomalous PK trends raises significant concerns about the bioavailability and bioequivalence data generated at your firm and 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.

Again, 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 all legal and regulatory requirements and to ensure the integrity of all data generated at your firm that are submitted to the FDA.

Based on the foregoing, FDA cannot ensure the reliability and validity of study data generated by your firm. 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 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, documenting your implementation of and adherence to processes and procedures that are sufficient to promptly identify, assess, and resolve any aberrant 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.

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

Sean Kassim, Director
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Sincerely,

/s/
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Office of Translational Sciences
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/s/
Partha Roy, Director
Office of Bioequivalence
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