U.S. FOOD & DRUG ADMINISTRATION

VIA E-MAIL

May 8, 2025

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Dear Qiming Tian:

This letter addresses significant concerns the U.S. Food and Drug Administration (FDA or the Agency) has notified you of regarding the reliability and validity of biocompatibility testing studies conducted at your testing facility (苏州苏大卫生与环境技术研究所有限公司 - Suzhou Suda Weisheng Yu Huanjing Jishu Yanjiusuo Youxian Gongsi).

Based on the totality of information before the agency, including FDA's data analyses communicated to you in a General Correspondence Letter (GCL) on December 30, 2024, and your subsequent response to the GCL on January 22, 2025, it is FDA's conclusion that your testing facility copied the results of another study or created falsified or otherwise invalid data that was submitted to FDA. In addition, based on the serious violations of Title 21, Code of Federal Regulations (CFR) Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies communicated to you in a Warning Letter on September 10, 2024,[1] and your subsequent responses to the Warning Letter dated September 29, 2024, October 30, 2024, November 28, 2024, December 18, 2024, and January 17, 2025,[2] FDA believes that the quality and integrity of study data generated by your firm cannot be ensured.

As described in the December 30, 2024, GCL, FDA identified multiple test reports from Guinea Pig Maximization Tests (GPMT)/skin sensitization studies conducted at your testing facility that have raised concerns, including: (1) several studies that show highly linear body weight changes over time in guinea pigs (*Cavia porcellus*) that are biologically highly improbable, (2) an

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[1] https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/sanitation-environmental-technology-institute-dba-sdwh-687970-09102024.

[2] FDA has received your additional responses of February 28, 2025, and March 28, 2025, and they are under review.

improbably high number of pre- and post-treatment weight pairs that are identical to the values reported in several other skin sensitization test reports generated by your testing facility, (3) weight gains over the test period that are much lower than expected based on the established growth curves for the animal strains and ages employed in the testing, and (4) a lack of adverse clinical observations in the test groups.

As discussed more fully in the December 30, 2024, GCL, the very high linearity in weight gains and identical weight pairs for the different sensitization studies is highly improbable. These data trends are not consistent with normal physiological responses and variations in a healthy animal model and support a conclusion that data was copied from the results of another study or falsified. Other issues, such as the low weight gains without any reported clinical signs, indicate that either the test animals were not well cared for (and thus the skin sensitization results may be compromised) or the weight values were falsified or otherwise invalid. Finally, the lack of any adverse clinical observations in such a high volume of test reports indicates that staff are not accurately observing, recording, and/or reporting relevant findings or the reported results are falsified or otherwise invalid.

As also described in our December 30, 2024, GCL, accurate study data in a premarket submission is necessary to enable FDA to fully and properly assess the overall safety of a device. For example, patient or user exposure to a medical device could result in adverse health effects such as cytotoxicity, allergic reactions, skin irritation or inflammation, fever, toxicity that leads to loss of tissue/organ function or failure, and anaphylaxis. These adverse health effects represent a clear risk to patients and clinical practitioners. Accurate biocompatibility data to determine the potential for such an adverse biological response resulting from direct and/or indirect contact with a medical device is important. Data that are copied from the results of another study or are falsified or otherwise invalid raise concerns about the reliability and validity of associated premarket submissions and impede FDA's ability to assess the safety and risk of a device, which may put public health and safety at risk.

In our December 30, 2024, GCL, we requested that you provide a complete response within 30 days by addressing the following:

1) explanation for the anomalous data identified by FDA with respect to the studies discussed in the GCL;
2) explanation of why your testing facility failed to identify and assess the data anomalies;
3) explanation of how your overall system of process and procedures contributed or permitted multiple studies conducted at your testing facility to have numerous instances of anomalous data;
4) whether any other studies conducted at your testing facility have similar data anomalies, and if so, an assessment of the impact of each study, if any, and a systemic root cause analysis for any identified data anomalies; and

5) any reason why the evidence of copied, falsified or otherwise invalid data discussed in the GCL should not raise questions about the reliability and validity of all data reported by your company and provided in past, pending, and future submissions to FDA.

As we explain in more detail below, your response did not resolve FDA's concerns regarding the data generated at your testing facility. It does not adequately address FDA's concerns for what caused the significant data anomalies present in your studies. In addition, your response does not alter FDA's conclusion that your testing facility copied the results of another study or created falsified or otherwise invalid data that was submitted to FDA. Further, your response does not provide adequate documentation to show that you have resolved the issues regarding the reliability and validity of biocompatibility testing studies conducted at your testing facility or provide any reason why the evidence of copied, falsified or otherwise invalid data discussed in FDA's December 30, 2024, GCL should not call into question the validity of all data generated by your firm and provided in past, pending, and future submissions to FDA.

<u>Your Response to the General Correspondence Letter</u>

FDA has reviewed your January 22, 2025, response to the December 30, 2024, GCL. Your overall response is that your firm has "reorganized and revised reports and data before and after our animal facility moved on October 2023, different space, feeding manor, environmental condition and atmosphere make quite large improvement." In the following sections, we address your specific topics covered in the response in the order set forth in your response.

1. <u>Explanation for the anomalous data identified by FDA with respect to the studies discussed in the December 30, 2024, GCL.</u>

    1.1 Linear Correlation of Weight Gains in Guinea Pigs

Summary of issues described in the December 30, 2024, GCL:
The sets of pre- and post-treatment weights of study guinea pigs in GPMT/skin sensitization studies show an extremely highly linear correlation ([redacted]) for the following studies: Report Nos. [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted]. Such a strong linear correlation is biologically highly improbable and unlikely to occur in guinea pigs with the same age, sex, and strain/stock, and given ad libitum access to plant-based food enriched with Vitamin C, fecal pellets, and water, due to inherent intra-animal physiological variations and responses to treatment. This strong linear correlation is also inconsistent with anticipated biological variation inherent to living

systems, even among age- or litter-matched animals of the same species, strain, or breed.[3, 4, 5, 6, 7, 8, 9] It is also inconsistent with weight data from your guinea pig vendor, [redacted] Therefore, it is implausible for the rate of weight gain to be nearly identical for all animals across each of these studies. Test reports containing similarly abnormally high linear correlations ([redacted]) of weight gain, similar to the examples listed above and detailed in the December 30, 2024, GCL have been observed in numerous other GPMT/skin sensitization studies conducted at your testing facility, including but not limited to Study Report Nos. [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted].

You assert that technicians recorded weight data "according to related SOP and principle of ALCOA (attributable, legible, contemporaneous, original, accurate)." You also state that, "Approximately [redacted] g of weight increased after the testing duration before October 2023, is [redacted]% as compared with approximately [redacted] g of weight increased now as other animal laboratory data, half range of weight increasing derived linearity double apparent."

Your response does not provide an explanation for the anomalous data. Nor does it dispute the statement in the December 30, 2024, GCL and above that "[s]uch a strong linear correlation is biologically highly improbable and unlikely to occur in guinea pigs with the same age, sex, and strain/stock, and given ad libitum access to plant-based food enriched with Vitamin C, fecal pellets, and water, due to inherent intra-animal physiological variations and responses to treatment." According to your response, guinea pigs were gaining approximately [redacted] g of weight over the testing duration. If comprehensive animal welfare was conducted, including proper feed volume and nutritional value were given over the course of the animal's life, not just the study duration, then the guinea pig weight gain would have both higher variability and higher values,

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[3] Gericke, A., Gille, U., Trautvetter, T., & Salomon, F. V. (2005). Postnatal growth in male Dunkin–Hartley guinea pigs (Cavia cutleri f. porcellus). *Journal of Experimental Animal Science*, *43*(2), 87-99.

[4] The Laboratory Rabbit, Guinea Pig, Hamster, and Other Rodents. Suckow, Stevens, and Wilson. Academic Press. 2012.

[5] Wagner, J. E. (1976). Genetics. In The biology of the guinea pig (pp. 114-115). Academic Press.

[6] Charles River Laboratories (2024). Growth chart of Hartley Guinea Pig CRL:HA outbred. Hartley Guinea Pig. https://www.criver.com/products-services/find-model/hartley-guinea-pig?region=3611

[7] Inotiv (2024). Growth curve with standard deviation of Dunkin Hartley Guinea Pig HsdDhl:DH. Dunkin Hartley Guinea Pigs. https://www.inotiv.com/model/hsddhl-dh

[8] Lu, C. J., Redmond, D., Baggs, R. B., Schecter, A., & Gasiewicz, T. A. (1986). Growth and hepatic composition in the guinea pig after long-term parenteral hyperalimentation. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 251(2), R388-R397.

[9] Voelkl B, Altman NS, Forsman A, Forstmeier W, Gurevitch J, Jaric I, Karp NA, Kas MJ, Schielzeth H, Van de Casteele T, Würbel H. Reproducibility of animal research in light of biological variation. Nat Rev Neurosci. 2020 Jul;21(7):384-393. doi: 10.1038/s41583-020-0313-3. Epub 2020 Jun 2. Erratum in: Nat Rev Neurosci. 2020 Jul;21(7):394.

per the guinea pig vendor weight-age data. Furthermore, your assertion claiming "derived linearity double apparent" appears to be a statistical assertion. However, you have not provided original raw data or any calculations demonstrating the validity of your statistical assertion.

1.2 Identical Pre- and Post-treatment Weight Pairs Across Studies

Summary of issues described in the December 30, 2024, GCL:
For GPMT/skin sensitization Study Report No. [redacted], several of the "Before Injection" (pre-treatment) and "After Experiment" (post-treatment) weight values for the test and negative control guinea pigs were identical to the pre- and post-treatment weight values of guinea pigs from numerous other skin sensitization test reports generated by SDWH for other devices on different dates. It is highly improbable for continuous variables,[10, 11] such as pre- and post-treatment weight value pairs of different animals on different dates, to be identical across test reports with such frequency. In addition, in some of the instances of matching weight pairs, the animal identification number is also identical, and all of this information being identical is even less likely to occur across multiple studies conducted on different animals on different dates.

You assert that because you are sourcing guinea pigs at weights just above [redacted]g, some initial weights are the same. You also assert that "slightly higher ratio of identical pairs post-treatment weight of Guinea Pigs was because of crowed space, limited feeding quantity. All these conditions have been making much progress currently." You also note that you had been using a scale with a digital reading that is only accurate and precise to the gram, and you assert that "the digital reading was from some other real weight that ten times precise but after rounded off."

Your response does not fully explain the reason for the anomalous data. Even though the weight values may have been rounded to the gram, that does not explain why there are so many identical pre- and post-treatment weight pairs observed in test reports generated by SDWH that have been provided to FDA in premarket submissions. Additionally, you did not provide a response as to how or why the animal number, pre-treatment weight, and post-treatment weight match across numerous studies for different medical devices. Furthermore, your assertion that the way in which the technicians were recording weights (Section 1.1 of your response) combined with the employed method of rounding (Section 1.2 of your response) makes it "twenty times more possib[le]" for paired before and after weights being identical appears to be a statistical assertion. However, you have not provided original raw data or any calculations demonstrating the validity of your statistical assertion.

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[10] Buczinski S. Reliability Associated with the Measurement of Continuous Variables in Veterinary Medicine: What the Different Possible Indicators Tell, and How to Use and Report Them. Animals (Basel). 2023 Sep 2;13(17):2793. doi: 10.3390/ani13172793. PMID: 37685057; PMCID: PMC10486732.

[11] Petrie, Aviva, and Paul Watson. Statistics for veterinary and animal science. John Wiley & Sons, 2013.

1.3 Abnormally Low Weight Gain, Lack of Other Adverse Clinical Observations, and Lack of Deviations

Summary of issues described in the December 30, 2024, GCL:
The observed weight gains of (b)(4) to (b)(4) g on average reported by SDWH during the study periods of the GPMT/skin sensitization studies cited in 1.1 above are approximately (b)(4)% to (b)(4)% lower than expected and biologically highly improbable if the study guinea pigs are properly cared for and monitored and the studies were conducted as per the protocol, considering the lack of adverse events, clinical observations, and deviations. Based on the volume of testing conducted at your facility, this pattern of consistent "normal" results with no reported deviations despite multiple reports with lower-than-normal guinea pig growth seems to indicate that either staff are not accurately observing, recording, and/or reporting skin reaction scores and other general clinical observations or the reported results are falsified or invalid.

1.3.1 Abnormally Low Weight Gain

You assert that the abnormally low weight gain is "because of crowed space, limit feeding quantity, poor environment and atmosphere were not so well before site changed." You further assert that "[t]he environment and atmosphere have been significantly improved since being relocated to the new site in October 2023; almost all post-treatment weights of Guinea Pigs are (b)(g more than pre-treatment ones after October 2023 as environmental condition, atmosphere, and animal welfare are much better currently."

FDA understands your explanation to be that poor testing conditions led to the low weight gains, but that testing conditions improved after the animal facility relocated to a new site in October 2023. This response does not allay concerns regarding the validity of data submitted to FDA. The use of unhealthy animals, including animals with low weight gains, has the potential to confound the study outcomes due to physiological impact and may make it difficult to identify an adverse safety event related to the test article. For that reason, the relevant ISO standard referenced and relied upon in each of your sensitization test reports makes clear that healthy and acclimatized guinea pigs should be used for the Guinea Pig Maximization Test (ISO 10993-10:2021, Sec. 6.5.3).

Furthermore, this abnormally low weight gain cannot be physiologically isolated and separated from the other concerns cited – particularly the lack of other adverse clinical observations and lack of deviations – because low weight gains would be (and should have been) recorded as clinical observations and so are typically reported together. However, no deviations to the protocol have been documented or reported for these tests that might have explained the abnormally low weight gain.

1.3.2 Lack of Other Adverse Clinical Observations

You assert that animal clinical observations are defined in SDWH-302-B22a Animal Clinical Observation and Abnormal Symptoms (version 2/1). You assert, in part, "There were some non-conformity conditions should be recorded but ignored by the technicians those in charge of animal observation because of this non-conformity was supposed not worse to be a deviation. There is request of animal clinical observation defined in 21 CFR Part 58, but not clearly definition of quality and quantitative about criteria of non-conformity. This the only one regulation clearly asking all 3rd-party laboratory those who accessing FDA GLP shall implement clinical observation as if any non-conformity condition occurred, as compared with local reaction studies those requested by other requirements. ISO 10993 requirement for medical device was not definition about animal clinical observation on version of 2010, the sensitization request was defined in ISO 10993-10 till 2021, but there is neither quality nor quantitative specification defined non-conformity within."

Additionally, you assert in Attachment 01 – Analysis of the Correlation Between Clinical Symptoms Beyond Skin Reactions and Test Results in Sensitization Tests for GPMT studies, "According to the ISO 10993-10 standard, the observation indicators in this test focus primarily on the skin reactions of the test and control groups. The sensitization results are determined based on the Magnusson and Kligman grading scale, which describes and grades erythema and edema reactions on the skin. Additionally, ISO 10993-10 does not specify the need to observe or record clinical symptoms of the animals when using this method. Thus, although clinical symptoms are not recorded in this test, relying on localized reactions for GPMT result determination is acceptable and does not compromise the accuracy of the results."

FDA understands your explanation to be that the Part 58 GLP regulations and FDA-recognized standard ISO 10993-10 are not clearly defined with respect to recording adverse clinical observations. FDA disagrees. Recording all animal clinical observations is contemplated by both the Part 58 GLP regulations and FDA-recognized standard ISO 10993-10. For example, under 21 CFR 58.33(b), "[t]he study director shall assure that: . . . [a]ll experimental data, **including observations of unanticipated responses of the test system** are accurately recorded and verified" (emphasis added). The study director also has an obligation under 21 CFR 58.33(c) to ensure that, "Unforeseen circumstances that may affect the quality and integrity of the nonclinical laboratory study are noted when they occur, and corrective action is taken and documented." Additionally, 21 CFR 58.81(a) Standard operating procedures provides, "A testing facility shall have standard operating procedures in writing setting forth nonclinical laboratory study methods that management is satisfied are adequate to insure the quality and integrity of the data generated in the course of a study . . . ." In addition, per 21 CFR 58.120(a), Protocol, "Each study shall have an approved written protocol that clearly indicates the objectives and all methods for the conduct of the study…" Further, as per 21 CFR 58.185(a) Reporting of nonclinical laboratory study reports, "A final report shall be prepared for each nonclinical laboratory study and shall include, but not necessarily be limited to, the following: … (9): A description of all circumstances that may have affected the quality or integrity of the data." Thus, the GLP regulations provide the framework to design, conduct, and report any nonclinical laboratory study data intended to support safety, which includes safety data that can be extrapolated from animal clinical observation records.

Additionally, the ISO standards are not prescriptive but rather incorporate several considerations to determine the appropriate testing options based on the device's intended use and the use of risk-based approaches to determine if and/or what biocompatibility testing is needed. Your assertion that the ISO 10993-10 version 2021 does not define or prescribe "quality or quantitatively specification" for any clinical observations as a defined non-conformity, is incorrect. Per ISO 10993-10 versions 2010 and 2021, both records of observations and assessment of the results are listed per the Test Report section. Furthermore, per ISO 10993-10 version 2021 Section 7 - Key factors in interpretation of test results, "The tests included in this document are important tools for development of safe products and shall be executed in accordance with appropriate quality assurance measures (e.g. ISO/IEC 17025 or GLP) and interpreted by trained personnel. . . . Predictive test results generated by the procedures described in this document cannot stand alone and need to be interpreted alongside other information to assess the risk of a hypersensitivity reaction or other forms of immunotoxicity. A negative test result does not exclude the possibility that a product can cause allergic skin reactions. The results should be compared with other sources of information . . . ." This contradicts your assertion that adverse animal clinical observations are implemented only if study non-conformities and/or non-conformity conditions occurred.

All experimental data, which would include animal clinical observations, must be recorded and verified (21 CFR 58.33(b)) and included in the final report (*see* 21 CFR 58.185(a)(9)). These recordkeeping and reporting activities help, among other things, to determine if medical intervention is needed, to identify what steps were taken upon the observation which would be noted as a deviation, and to conduct any investigation into the cause of the clinical observation with its impact on the device study and study conclusions (*see* 21 CFR 58.31(g), 58.33(b) and (c), 58.35(b)(5) and (6), 58.185(a)(9); SOP SDWH-302-B22a V2R0 Animal Clinical Observations Abnormal Symptoms).

FDA has also reviewed the other attachments you included and referenced in your response: Attachment 02 for the Deviation Investigation for Lack of Other Adverse Clinical Observations, Attachment 03 for the Theory and On-site Training of Clinical Observation, and Attachment 04 for the Latest Daily Observation Record of Skin Sensitization Test. FDA cannot determine the adequacy of the information provided. FDA notes that, while routine clinical observations regarding the general health of the animals seem to now be captured on the daily observation form as demonstrated in Attachment 04, it is unclear if any action is taken once a clinical observation is made, and if these observations will be included in the study report and interpreted along with the study data. FDA also disagrees with the finding in the root cause analysis provided in Attachment 02. In part 4 of the root cause analysis provided in Attachment 02, you conclude that, "therefore, the aforementioned unrecorded reactions did not affect the final judgment of the results." It would be impossible to definitively determine that unrecorded reactions prior to April 2024 did not affect the final judgment of the results given that the findings were not recorded and, therefore, could not have been relied upon in assessing the final judgment of the results. Furthermore, it is unclear what training materials were provided to conduct the new trainings and daily observation recordings referenced in Attachments 03 and 04.

1.3.3 Lack of Deviations

1.3.3.1 "Timely protocol revisions prevented the occurrence of deviations"

Your response states the following:

> When unforeseen circumstances occur during testing, which would cause deviations if subsequent operations were carried out according to the signed study protocols, we typically negotiate with the customers to determine the appropriate measures, promptly revise the protocols, and then proceed with the subsequent operations according to the revised protocols. This has effectively reduced the occurrence of a large number of deviation events. Please see Attachment 05 for Some Case Examples of Timely Revisions of Study Protocols that Prevented Deviations from Occurring.

Your Attachment 05 includes three examples of sponsor-initiated requests to amend study protocols: one subcutaneous tissue implantation test using a rabbit test system and two pyrogen tests each using a rabbit test system.

FDA understands your response to be that the lack of deviations is explained by sponsor-initiated revision(s) to ongoing testing protocol(s). Your response appears to conflate unforeseen circumstances with deviations, and FDA notes that if a study "were carried out according to the signed study protocols" as described in your response, that action by its very nature would **not** constitute a deviation.

Your response and supporting examples do not provide an explanation for the issues raised by FDA's December 30, 2024, GCL. The December 30, 2024, GCL questioned the veracity of Guinea Pig Maximization Test skin sensitization test reports based on those reports showing abnormally low weight gains and consistently recorded "appeared normal" observations for the test guinea pigs without any documentation or reporting in the final test reports of deviations from the protocol that might have explained the low weight gains. Rather than addressing that issue, your response discusses "unforeseen circumstances" that "occur during testing" and explains that "timely" protocol amendments obviate the need for deviations to be documented. This response does not explain why the weight gains of the test guinea pigs are abnormally low while observations were consistently "normal." In addition, the examples you provided in Attachment 05 are for different types of tests (subcutaneous tissue implantation tests and pyrogen tests) conducted on a different animal model (rabbit) than the type of test at issue in FDA's December 30, 2024, GCL (GPMT/skin sensitization tests on guinea pigs). Because of the differences in the test types and animal models, FDA does not believe that these examples help explain the reason for the issues that FDA raised in the December 30, 2024, GCL as the weight changes and clinical observations for those test types and animal models vary from the test types discussed in the December 30, 2024, GCL.

FDA also notes that, if there are amendments to a protocol after the study has begun, protocol amendments should be documented and included in the final test reports. According to 21 CFR 58.120(b), "All changes in or revisions of an approved protocol and the reasons therefore shall be documented, signed by the study director, dated, and maintained with the protocol." In addition, per § 58.185(a)(2), final reports must include, "Objectives and procedures stated in the approved protocol, including any changes in the original protocol." FDA acknowledges that you have provided in Attachment 05 some examples of protocol amendment documentation. However, as noted above, these are examples of sponsor-initiated requests for protocol changes, and they are for different types of studies than the ones that FDA raised in our December 30, 2024, GCL. Additionally, in our review of final test reports generated by SDWH and submitted to FDA in premarket submissions, we have not seen any identification of protocol changes or amendments in any final test reports as would be required by § 58.185(a)(2) if protocol changes or amendments are made. Therefore, it appears that either 1) SDWH is not properly documenting protocol amendments; 2) that SDWH is not including such protocol amendments in final study reports; or 3) that there have not been any protocol amendments to GPMT/skin sensitization studies that might help explain the abnormally low weight gains. FDA emphasizes the importance of including documentation of protocol amendments in final test reports. Without that documentation, it would be impossible to definitively determine whether there are protocol amendments, which in turn raises questions about the integrity of the data in the final test reports.

In addition, your response does not adequately address the lack of reported deviations associated with proper animal monitoring and welfare during the studies, including veterinarian assessment of underweight animals or other interventions necessary to assess any animal physical reactions. As originally stated in the December 30, 2024, GCL:

> According to the experimental procedure described in your GPMT/skin sensitization reports, the duration of the experiment is 25 days. As shown in the examples below, for the same set of test reports charted above in "Linear Correlation of Weight Gains in Guinea Pigs," the guinea pigs gained the following amounts of weight over the course of the study where the guinea pigs were reported to be "Normal" and "There were no deviations…" … Based on guinea pig growth curves and animal physiology, these are lower-than-normal weights gained (b)(4) – (b)(4) g) by reportedly normal 5–7-week-old guinea pigs[12,]

[12] Gericke, A., Gille, U., Trautvetter, T., & Salomon, F. V. (2005). Postnatal growth in male Dunkin–Hartley guinea pigs (Cavia cutleri f. porcellus). *Journal of Experimental Animal Science*, *43*(2), 87-99.

> [13, 14, 15, 16, 17] over the course of the studies (i.e., through Weeks 8-10). Therefore, the much lower weight gains of [redacted] – [redacted] g on average reported by SDWH during the same period are approximately [redacted]% to [redacted]% lower than expected and biologically highly improbable if the guinea pigs are properly cared for and monitored, and the studies were conducted as per the protocol, considering the lack of adverse events, clinical observations, and deviations.

In response to FDA's request that you explain how your overall system of process and procedures contributed or permitted multiple studies conducted at your test facility to have numerous instances of anomalous data, your response states, in part, the following:

> QA staff lacking related animal testing education background, experience, and without well-training, so that QA staff to conduct review and inspection must be a gap away from what GLP request, before September 2024.
>
> All these abnormal linearity about Guinea Pigs weight increasing found compared with data generated migrate into new site, and animal clinical observation request in 21 CFR Part 58 were closely re-study and frequently internal self-retraining and opinion exchanging to complete observation description, to promote alertness about potential deviations.

FDA understands your explanation to be that your facility did not have a functional quality assurance unit to observe deviations prior to September 2024. FDA acknowledges that these systemic inadequacies may address how deviations could have occurred without being documented or reported. However, your response reaffirms FDA's concerns that your testing facility was not in compliance with GLP regulations, including 21 CFR 58.29(a), (c) (Personnel), 21 CFR 58.31(c), (f), (g) (Testing facility management), 21 CFR 58.33(a), (b), (c), (e), (f) (study director), 21 CFR 58.35(a), (b) (Quality assurance unit), 21 CFR 58.81 (Standard operating procedures), and 21 CFR 58.120 (Protocol). Moreover, and as referenced further below, your response does not provide sufficient assurances that such systematic inadequacies will not persist.

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[13] The Laboratory Rabbit, Guinea Pig, Hamster, and Other Rodents. Suckow, Stevens, and Wilson. Academic Press. 2012.

[14] Wagner, J. E. (1976). Genetics. In The biology of the guinea pig (pp. 114-115). Academic Press.

[15] Charles River Laboratories (2024). Growth chart of Hartley Guinea Pig CRL:HA outbred. Hartley Guinea Pig. https://www.criver.com/products-services/find-model/hartley-guinea-pig?region=3611

[16] Inotiv (2024). Growth curve with standard deviation of Dunkin Hartley Guinea Pig HsdDhl:DH. Dunkin Hartley Guinea Pigs. https://www.inotiv.com/model/hsddhl-dh.

[17] Lu, C. J., Redmond, D., Baggs, R. B., Schecter, A. & Gasiewicz, T. A. (1986). Growth and hepatic composition in the guinea pig after long-term parenteral hyperalimentation. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 251(2), R388-R397.

Both the FDA 483 observations and FDA Warning Letter, issued March 15, 2024, and September 10, 2024, respectively, similarly reflect these animal welfare and study observations. Your September 29, 2024, October 30, 2024, November 28, 2024, December 18, 2024, and January 17, 2025, responses to the Warning Letter are inadequate to demonstrate that protocol deviations and adverse events during studies are now being reported or reported accurately (see the "Your Warning Letter Responses" section below).

1.3.3.2 "Reports with abnormal situations may not be submitted to the FDA by the customers."

Your response states the following:

> Deviation report indeed has been initiated as if occurred during testing, because of deviation had been found so that the testing was always being asked to pause by customer, all such deviation reports were total within the final reports to customer. Customers had never issued application to FDA within failure testing report those deviations were contained. Thus, such deviation reports will not be reported to FDA as if without permission from customer. All these reports to customer those abnormal condition occurred within deviation reports.
>
> Some other cases without issuing deviation, even those occurred, all were because of these testings were asked to be directly terminated according to customers' decision. Discontinued reports had been issued and provided for the customers. Customers will not use such discontinued reports to issue application to FDA, so that FDA has never received such discontinued reports. Examples for those discontinued reports.
>
> There were some critical testings cause obvious symptoms occurred, such as pyrogen test, acute toxicity test, and intracutaneous reactivity even cause death cases. Customers will not deliver all these failure testing reports, especial cause death cases, to FDA for registration application. Please kindly refer some cases as your references. The abnormal condition, those caused testing terminated suddenly, have been happened almost every week in the past years as hardcopy report and record kept and storage as requirements requested.
>
> All these reports with abnormal situations have been issued and provided to the customers, but they are typically not submitted to the FDA for registration applications. Please see Attachment 06 for Some Case Examples of Reports on The Discontinued Studies, and Attachment 07 for Some Case Examples of Reports with Unsatisfactory Results.

FDA understands your explanation to be that it is the customers choosing not to submit any reports to FDA where either the study was terminated, the report contained deviation(s), or where critical tests contained obvious symptoms. However, your response is unrelated to the originally identified problem of a lack of adverse clinical observations and/or deviations being observed, documented, and reported, considering the low weight gains of the study animals. As previously stated, per 21 CFR 58.120(b), "All changes in or revisions of an approved protocol and the reasons therefore shall be documented, signed by the study director, dated, and maintained with the protocol." In addition, per 58.185(a)(2), final reports must include, "Objectives and procedures stated in the approved protocol, including any changes in the original protocol." As noted above, FDA acknowledges that you have provided in Attachment 05 examples of protocol amendment documentation. However, in our review of final test reports generated by SDWH and submitted to FDA in premarket submissions, we have not seen any identification of such protocol changes or amendments in final test reports for GPMT/skin sensitization tests. It would be impossible to definitively determine whether there are protocol amendments if they are not included or otherwise identified in the final test reports, which raises questions about the integrity of the data in final test reports. Additionally, as per your Attachment 02, routine clinical observations were not identified and reported. All experimental data, which would include animal clinical observations, must be recorded and verified (21 CFR 58.33(b)). This recordkeeping activity helps to, among other things, determine if medical intervention is needed and conduct any investigation into the cause of the clinical observation with its impact on the device study and study conclusions (see 21 CFR 58.31(g), 58.33(b) and (c), 58.35(b)(5) and (6), 58.185(a)(9); SOP SDWH-302-B22a V2R0 Animal Clinical Observations Abnormal Symptoms). While SOP SDWH-302-B22a V2R0 Animal Clinical Observations Abnormal Symptoms requires diagnosis, authorizations of treatment, description of treatment, and each date of treatment to be documented and retained, it is also important to note any medical intervention as a deviation within the raw data of the relevant section(s) of the test report and amendments as deemed necessary for additional information and support. While the customer is submitting the final report to the FDA, it is the test lab's requirement to properly observe, record, and report all deviations and interventions during the study where such occurred (see 21 CFR 58.35(b)(5) and (b)(7), 58.185(a)(14), and Attachment 09, Deviation Control SOP).

1.3.3.3 "Gaps in the perception and management of deviations."

You assert, in part, that, "before October 2024, the SOP for deviation investigations had defects, and the QAU (Quality Assurance Unit) did not participate in deviation investigations and tracking. This resulted in deficiencies in the identification, investigation, assessment, and tracking of deviations."

FDA understands your explanation to be that you did not have an adequate system for identifying, investigating, assessing, and tracking deviations prior to October 2024. FDA acknowledges that this lack of procedure addresses how deviations can occur without being reported. However, your response also reaffirms FDA's concerns that your testing facility has not been in compliance with GLP regulations, including 21 CFR 58.35(b)(5)–(6) (Quality assurance unit), and 21 CFR 58.81 (Standard operating procedures).

You also provided updated SOPs that "outline the QAU's management functions for deviations" and "clarif[y] the entire process of deviation management, including identification, classification, investigation, impact assessment, corrective and preventive actions, and closure…" among other things (Attachments 08 and 09). However, the changes made to the SOPs do not appear to be adequate corrective actions, as described below in the section titled, "Your Warning Letter Responses."

2. <u>Explanation of why your testing facility failed to identify and assess the data anomalies.</u>

Your response states the following:

> Animal testing, since quarantine, testing, till euthanasia, all performed and recorded according to SOPs those based upon related requirements, being strictly followed by technicians, reviewed by QAs, and custody by SDs. There were no apparently fluctuation and data deviate, so that no abnormal or non-conformity was taken notice.
>
> Even though all routine operation had been reviewed by quality assurance unit (QAU), but for the little knowledge and few experiences on animal studies neither seldom training, it is hard to produce review and custody function from QAU on the only little technical background before September 2024.
>
> Quality management system (QMS) re-construction based upon 21 CFR part 58 and all GLP related requirements since received warning letter (CTS# GEN2300489/E001) September 2024, (b)(4) trainings to all colleagues especially QAU and SDs, more than 100 needed SOPs new created and updated, validation & qualification introducing and related protocols deployed and report generated, data integrity deployed onto all kinds testings including animal treatment and instrument analysis, and VMP monthly protocol renew, review and updating; all these above promised conducting actions, within evidence documents have been

> kept reporting to FDA. to make FDA real-time well know current corrective and preventive actions condition every month.
>
> GLP internal audit, data integrity self-inspection, and monthly VMP updating, full scope reviewing QMS and each individual testings to minimize risk of ignorance of deviation without taking alert.

FDA understands your explanation for the data anomalies to be that your facility did not have adequate SOPs, training, quality assurance, and study oversight prior to September 2024.

FDA acknowledges that these systemic inadequacies address how deviations can occur without being reported. However, your response also reaffirms FDA's concerns that your testing facility was not in compliance with GLP regulations, including 21 CFR 58.29(a), (c) (Personnel), 21 CFR 58.31(c), (f), (g) (Testing facility management), 21 CFR 58.33(a), (b), (c), (e), (f) (study director), 21 CFR 58.35(a), (b) (Quality assurance unit), 21 CFR 58.81 (Standard operating procedures), and 21 CFR 58.120 (Protocol). Likewise, your September 29, 2024, October 30, 2024, November 28, 2024, December 18, 2024, and January 17, 2025, responses to the Warning Letter are inadequate to demonstrate that data anomalies are now being reported or reported accurately (see the "Your Warning Letter Responses" section below).

3. <u>Explanation of how your overall system of process and procedures contributed or permitted multiple studies conducted at your test facility to have numerous instances of anomalous data.</u>

Your response states the following:

> Certainly, system not allowed all deviation keep occurring, but for all these abnormal conditions has not been clearly defined in clinical observation requirements, this nonconformity was kept before October 2023.
>
> QA staff lacking related animal testing education background, experience, and without well-training, so that QA staff to conduct review and inspection must be a gap away from what GLP request, before September 2024.
>
> All these abnormal linearity about Guinea Pigs weight increasing found compared with data generated migrate into new site, and animal clinical observation request in 21 CFR Part 58 were closely re-study and frequently internal self-retraining and opinion exchanging to complete observation description, to promote alertness about potential deviations.

> QAU are well functioning after regulation defined the QMS installation, validation & qualification construction, data integrity deployment, certain SOPs implementation, and training & qualified, and QMS is more completeness and confidence, so that risks are minimized and well controlled since September 2024.

FDA understands your explanation to be that your facility did not have a functional quality assurance unit prior to September 2024.

FDA acknowledges that the QAU failure, in addition to the previously stated systemic inadequacies, explain how deviations and data anomalies can occur without being reported. However, your response also reaffirms FDA's concern that your testing facility has not been in compliance with GLP regulations, including 21 CFR 58.29(a), (c) (Personnel), 21 CFR 58.31(c), (f), (g) (Testing facility management), 21 CFR 58.33(a), (b), (c), (e), (f) (study director), 21 CFR 58.35(a),(b) (Quality assurance unit), 21 CFR 58.81 (Standard operating procedures), and 21 CFR 58.120 (Protocol). Likewise, your October 30, 2024, November 28, 2024, and December 18, 2024, responses to the Warning Letter are inadequate to demonstrate that your QAU is now functioning in accordance with GLP regulations (see the "Your Warning Letter Responses" section below).

4. Whether any other studies conducted at your testing facility have similar data anomalies, and if so, an assessment of the impact of each study, if any, and a system root cause analysis for any identified data anomalies.

Your response states, in part, the following:

> No, there is no data approaches as similar situation on less weight growth, data of weight coincide, nor linearity of weight growth curve, after reviewed other testings, data and records. QAU have been well trained and qualified to implement all testing data after GLP QMS reinstallation since September 2024.
>
> Not only the anomalies coincide of Guinea Pigs' weight pre & post-treatment weight increasing linearity but also acute toxicity, pyrogen testing, and skin irritation etc. have been tracebacked to investigate whether deviation or non-conformity was ignored during testing, according to more needed SOP new created and modified, introducing data integrity construction from raw data those of clinical observation, treatment, sampling, and instrument analysis, install validation & qualification and VMP to minimize potential deviation be ignored and occurred. Data integrity self-inspection scrutinized take alert on animal testing procedures to enforce and complete testing quality.

FDA understands your response to be that you have not identified any other studies conducted at your testing facility with similar data anomalies. However, this response is inadequate, as per your previous assertions:

> There were some non-conformity conditions should be recorded but ignored by the technicians those in charge of animal observation because of this non-conformity was supposed not worse to be a deviation…
> When unforeseen circumstances occur during testing, which would cause deviations if subsequent operations were carried out according to the signed study protocols, we typically negotiate with the customers to determine the appropriate measures, promptly revise the protocols, and then proceed with the subsequent operations according to the revised protocols. This has effectively reduced the occurrence of a large number of deviation events.

It is FDA's view that any departure from the originally approved protocol, including but not limited to those triggered by an "unforeseen circumstance," should be recorded within the relevant section as a protocol amendment or deviation, as applicable; this includes all clinical observations or adverse events that require veterinarian intervention, with the veterinarian attributing each clinical observation / adverse event to either the test article and/or other outside factor. Therefore, the retrospective investigations you conducted and reported as having no other traces of anomalous data cannot be verified, as the records would not accurately reflect all protocol amendments, deviations, clinical observations, and/or adverse events.

5. <u>Any reason why the evidence of copied, falsified or otherwise invalid data discussed in the December 30, 2024, GCL should not raise questions about the reliability and validity of all data reported by your company and provided in past, pending, and future submissions to FDA.</u>

Your response states the following:

> We have implemented all testing according to SOPs those based upon related requirements since the very first, even though our awareness was little deviated from regulation asked while the regulation has few clearly definition before, for example as animal clinical observation. Formats for animal clinical observation record have been modified to easily record, legible, traceable, thus, the quality management and data integrity is conformed and robustness. Abnormal condition of sensitization and Guinea Pigs weight are always less impact to final results. Please see <u>Attachment 01 for Analysis of the Correlation Between Clinical Symptoms Beyond Skin Reactions and Test Results in Sensitization Tests</u>. This will not affect the authenticity of the reports we have issued in the past, nor the accuracy of our data.

> An FDA safety and compliance experienced expert was invited to assist in re-establishing the GLP QMS, introduce validation & qualification requirements and all equipment/instrument qualification & process/analytical test method validation protocol deployment, SOPs for calibration, operation, cleaning and maintenance fully covering all scopes from each individual testing through instrument analysis to those of technical management, deviation investigation, change control, VMP issuance, periodic GLP internal audit & frequent data integrity self-inspection, to practically, effectively and efficiently promote Sanitation & Environment Technology Institute of Soochow University Ltd in a short period of time.
>
> Of course, after more than half a year of effective and substantial improvements, our routine operations should be approaching completeness. On the basis of already genuine reports, we invite FDA more trust on the authenticity of the reports we have issued, and in the future, have even more confidence in our ongoing efforts to strengthen the introduction of improvements, including clinical observations, data integrity, validation and qualification, etc., to make our QMS more comprehensive advanced.
>
> We are implementing daily routine work and record keeping as certain SOPs defined those based upon 21 CFR Part 58. and we would like to keep reporting to FDA all solidified documents to support our authentication and integrity. Certainly, we will appreciate all articles requested from FDA to enforce trust and confidence to us. Reassessing and keeping FDA GLP accreditation, is not only about positive financial feedback from marketing revenue, but also about the honesty, mentality, and integrity those what Sanitation & Environment Technology Institute of Soochow University Ltd most concerns.

FDA understands your response to be that steps taken and being implemented by your firm will correct all gaps, observations, and violations previously outlined in the FDA 483 observations, FDA Warning Letter, and FDA General Correspondence Letter. However as noted above, it is FDA's view that any departure from the originally approved protocol, including but not limited to those triggered by an "unforeseen circumstance," should be recorded within the relevant section as a protocol amendment or deviation, as applicable; this includes all clinical observations or adverse events that require veterinarian intervention, with the veterinarian attributing each clinical observation / adverse event to either the test article and/or other outside factor. Therefore, the retrospective investigations you conducted and reported as having no other traces of anomalous data cannot be verified, as the records would not accurately reflect all protocol amendments, deviations, clinical observations, and/or adverse events.

Additionally, FDA does not agree with your assertion, "Abnormal condition of sensitization and Guinea Pigs weight are always less impact to final results." FDA understands your response to be that abnormal conditions and weights of guinea pigs observed during skin sensitization studies have a minimal impact on the final study results. You do not cite to any information in support of such a statement, and we are not aware of any such support. Rather, the GLP regulations and ISO 10993-10 version 2021 emphasize the need for healthy and well cared for animals. Per 21 CFR 58.90, "At the initiation of a nonclinical laboratory study, animals shall be free of any disease or condition that might interfere with the purpose or conduct of the study." Additionally, per ISO 10993-10 version 2021, upon which your sensitization studies rely, "Animals and husbandry – Healthy young adult albino guinea pigs of either sex from a single outbred strain, weighing 300 g to 500 g at the start of the test, shall be used. If female animals are used, they shall be nulliparous and not pregnant. The animals shall be acclimatized and cared for as specified in ISO 10993-2. Preliminary tests, when necessary, should be carried out on one set of animals to determine the optimal test concentrations (*see* 6.5.4.2)." Clinical observations (which you refer to as "abnormal conditions"), including any unanticipated responses of the test system such as weight concerns, must be recorded and verified, and corrective action taken and documented on a case-by-case basis when unforeseen circumstances could affect the quality and integrity of the study (*see* 21 CFR 58.33(b) and (c); *see also* 21 CFR 58.35(b)(5) and (7)). Any such necessary recording verification, and corrective actions could be in the context of the device materials, general animal health, other observations during the study (e.g., color change or particulates in extract materials), and/or deviations from the protocol to determine the impact and root cause of the clinical observation(s) and whether the test device was a contributing factor.

Furthermore, it cannot be determined if you are in compliance with GLP regulations based on your responses to the FDA 483 observations, FDA Warning Letter, and FDA General Correspondence Letter (see the "Your Warning Letter Responses" section below). Therefore, FDA does not agree with your response as to whether past, pending, and future submissions will not raise questions about the reliability and validity of all data reported by your company.

Your Warning Letter Responses

You provided responses to the FDA Warning Letter on September 29, 2024, October 30, 2024, November 28, 2024, December 18, 2024, and January 17, 2025.[18] Your responses do not demonstrate that all GLP concerns identified in the September 10, 2024, Warning Letter have been adequately addressed. FDA's review of those responses have raised additional questions and concerns. FDA's outstanding concerns include the following:

[18] As described in note 2 above, FDA has received your additional responses of February 28, 2025, and March 28, 2025, and they are under review.

You significantly revised a QAU SOP to address the observations in the Warning Letter relating to 21 CFR 58.35 (identified as violation 3 in the Warning Letter). However, based upon our review of the completed inspection forms, which you provided as evidence of the new QAU inspection procedures, FDA cannot determine the adequacy of your responses. For the most part, the information contained in those forms indicated "no findings" were reported. When a "finding" was identified, a simple statement says "[a]ll problems found have been rectified" without identification of steps taken to rectify the problems. Further, when test documents were modified (after finding a deviation), there is no indication that the test documents were modified (amended) and signed by the study director as required by 21 CFR 58.33(c). This indicates that changes made in the revised QAU SOP have not resulted in appropriate corrective action(s).

In addition, many of the "audits" to assess the performance of your QAU were for routine test facility management procedures such as receipt of animals, verifying a veterinarian examined animals upon receipt, room lighting requirements, calibration of equipment, etc. The QAU should be performing daily audits of the multiple GLP animal studies in progress in the facility, as opposed to routine test facility management procedures. Documentation describing how the QAU audits animal studies in progress for GLP compliance was not provided.

Further, SDWH-QAU-006-05 audit report SDWH-QAP202400048 states with respect to QAU personnel, "Analysis of the guinea pig body weight for the sensitization test, and no linear relationship" – which relates to the observation noted in the December 30, 2024, GCL that raised questions regarding data integrity. This statement from the audit report is concerning because it suggests that QAU personnel are being instructed to specifically verify that animal weights are not linear, and implies that technicians should ensure there is sufficient variability in weights, as opposed to ensuring they are recording the actual weights of animals.

In addition, you have not provided documentation that your test facility management understands that the QAU is not responsible for correcting deviations, but that when a deviation from a protocol or SOP is observed by the QAU, that deviation should be promptly reported to the study director and test facility management. The QAU must be separate and independent from personnel engaged in the direction and conduct of the GLP studies (21 CFR 58.35(a)). Your revised SOP in response to violation 5.a. of the Warning Letter indicates that the QAU will supervise implementation of the blood collection process, which implies that the QAU is not separate from personnel engaged in the direction and conduct of the study. Such a lack of separation would be in violation of 21 CFR 58.35(a). Your responses raise concerns that your test facility management does not understand that the study director has overall responsibility for the technical conduct of GLP studies, as well as the interpretation, analysis, documentation, and reporting of results (21 CFR 58.33). The study director must assure that the protocol is followed correctly and that unforeseen circumstances that may affect the quality and integrity of the nonclinical laboratory study are noted when they occur, and corrective action is taken and documented (21 CFR 58.33(a) and (c)).

With respect to the Warning Letter violation relating to 21 CFR 58.33 (identified as violation 1 in the Warning Letter), you provided a revised cytotoxicity protocol, but it does not adequately address the data integrity issues because it does not indicate the individuals who maintain access to the data or address any potential limitations on sharing the collected data with other experiments in the future to prevent copying of such data.

Overall, you have not provided an in-depth evaluation of the impact of the issues identified by the Agency. There is no mention or indication of any retrospective or prospective evaluations of the impact of the identified nonconformances on the studies that were conducted or are being conducted specifically related to the data integrity issues identified in the September 10, 2024, Warning Letter. While you opened and conducted several CAPA investigations and internal audits addressing the specific data integrity issues (identified in the Warning Letter as violation1), you have not indicated whether you have completed any other investigations or internal audits to address systemic issues regarding any additional data integrity concerns. Additionally, adequate documentation of implementation and completion of CAPA activities has not been provided and effectiveness of the CAPA activities has not been demonstrated.

Further, you did not provide information as to whether or how data integrity concerns were investigated and addressed relating to already conducted studies. You have indicated you are looking into using (b)(4) to review and assess all firm activities. We note, that for third party audits to be most effective, it is important that the auditors are properly trained and qualified and do not have conflicts of interest with the site being audited. Until such review and assessments are concluded, and this information is provided to FDA, the Agency in unable to evaluate the effectiveness of your CAPAs and training activities.

<u>FDA's Conclusions</u>

Your response to FDA's December 30, 2024, GCL is inadequate because you failed to adequately address (1) FDA's concerns for what caused the anomalous data, (2) whether any other studies conducted at your testing facility may have similar data anomalies, and (3) any 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.

SDWH's management of the studies cited in the December 30, 2024, GCL 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 copying of results of another study or creation of falsified or otherwise invalid data that was submitted to FDA in the studies discussed in the December 30, 2024, GCL and here, we have no reason to believe that any data that you have produced are reliable or valid. In addition, as noted above, FDA considers your responses to the September 10, 2024, Warning Letter, which advised you of numerous violations of the GLP regulations under 21 CFR Part 58, to be inadequate. Thus, based on the totality of information before the agency, FDA has determined that all study data from all studies conducted at your firm will be rejected until you have demonstrated that the issues described in the December 30, 2024, GCL and herein have been adequately addressed.

You are responsible for ensuring that your testing facility 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, your firm's documentation of your implementation and adherence to procedures that are sufficient to prevent the use of copied, falsified or otherwise invalid data – similar to those identified by FDA in studies conducted at your firm. 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 the Office of Product Evaluation and Quality (OPEQ) Regulation, Policy, and Guidance (RPG) Team at RPG@fda.hhs.gov.

Sincerely,

ANGELA C. KRUEGER -S

Digitally signed by ANGELA C. KRUEGER -S
Date: 2025.05.08 15:30:28 -04'00'

Angela C. Krueger
Deputy Director for Regulatory Policy
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