U.S. FOOD & DRUG ADMINISTRATION

**VIA E-MAIL**

June 12, 2026

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Dear Xiaojun Su:

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 CCIC Huatongwei International Inspection (Suzhou) Co., Ltd. (中检华通威国际检验（苏州）有限公司 - Zhongjian Huatongwei Guoji Jianyan (Suzhou) Youxian Gongsi) (hereinafter referred to as "CCIC HTW (Suzhou)").[1]

Based on the totality of information before the agency, including FDA's data analyses communicated to you in a General Correspondence Letter (GCL) on October 30, 2025, and your subsequent response to the GCL on November 28, 2025, it is FDA's conclusion that your testing facility copied the results of one or more other studies or created falsified or otherwise invalid data that was submitted to FDA. In addition, based on the totality of information before the agency, including 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 June 25, 2025,[2] and your subsequent responses to the Warning Letter dated July 13, 2025, August 9, 2025, September 13, 2025, October 11, 2025, November 8, 2025, December 27, 2025, and February 5, 2026, FDA believes that the quality and integrity of study data generated by your firm cannot be ensured.

As described in the October 30, 2025, GCL, FDA identified multiple test reports from muscle implantation studies, Guinea Pig Maximization Test (GPMT) skin sensitization studies, and acute systemic toxicity studies conducted at your testing facility that have raised concerns,

[1] Based on information from CCIC HTW (Suzhou) test reports received in premarket submissions to FDA, as well as information gathered during the FDA inspection of your testing facility in January 2025, FDA understands that your testing facility relocated in April 2024 from Room 101, Building G, Ruoshui Road 388, Suzhou, Jiangsu Province, China, to 107 Changyang Street, Suzhou Industrial Park, Suzhou, Jiangsu Province, China.

[2] https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/ccic-huatongwei-international-inspection-co-ltd-704332-06252025.

including: (1) identical histopathological data across multiple muscle implantation studies; (2) raw data observation records across multiple muscle implantation studies without any abnormal and/or adverse clinical observations recorded; (3) GPMT skin sensitization study test reports with an improbably high number of pre- and post-treatment weight pairs that match the values reported in several other test reports generated by your testing facility; (4) GPMT skin sensitization study test reports with an improbably high number of pre-treatment weight values that are identical or extremely similar to the values in other GPMT skin sensitization study test reports generated by your testing facility; (5) GPMT skin sensitization study test reports that show highly linear body weight gains over time in guinea pigs (*Cavia porcellus*) that are biologically highly improbable; (6) abnormally low weight gains that are not reported as abnormal and/or adverse clinical observations and without any reported deviations in GPMT skin sensitization study test reports; (7) acute systemic toxicity tests with all subject mice (*Mus musculus*) consistently gaining weight at all timepoints throughout the study in a manner that is biologically highly improbable; and (8) handwritten raw data observation records that are identical across acute systemic toxicity study test reports.

As discussed more fully in the October 30, 2025, GCL, the highly linear and identical test measurements in test reports are highly improbable, and the data trends are not consistent with normal physiologic responses and variations in a healthy animal model. In rabbit muscle implantation studies, the identical histopathological data and identical animal clinical observations across multiple studies utilizing different device components are not consistent with the inherent variability of biological systems and the subjective nature of histopathological evaluation. 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 invalid. Additionally, the lack of any adverse clinical observations in such a high volume of test reports indicates that either staff are not accurately observing, recording, and/or reporting relevant findings, or the reported results are falsified or invalid. Finally, evidence of handwritten raw data observation records that are identical across acute systemic toxicity study test reports indicate that staff are not properly observing and recording relevant findings, and that there are systemic oversight failures with the Quality Assurance unit, test facility management, and study directors.[3]

As also described in our October 30, 2025, 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 one or more other studies or are falsified or otherwise invalid raise concerns about the reliability and validity of

[3] Although not discussed in the October 30, 2025, GCL, FDA has also determined that your firm used pre-filled photocopies or photocopies from one study to another of animal observation and/or scoring sensitization result study records across numerous studies for muscle implantation and skin sensitization, as discussed in more detail in this letter.

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 October 30, 2025, 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 November 28, 2025, response does 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. The data anomalies identified in our October 30, 2025, GCL are present across multiple testing methodologies involving different animal species, indicating a systemic failure within your quality assurance unit and overall test facility management. In addition, your response reaffirms FDA's concern that your testing facility copied the results of one or more other studies 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 plausible reason why the evidence of copied, falsified or otherwise invalid data discussed in FDA's October 30, 2025, GCL should not call into question the reliability and validity of all data generated by your firm and provided in past, pending, and future submissions to FDA.

**Your Response to the General Correspondence Letter**

FDA has reviewed your November 28, 2025, response to the October 30, 2025, GCL. Your overall response is that your firm has "conducted a comprehensive and in-depth investigation into the issues identified in the letter and promised to strictly comply with the regulatory requirements for data integrity" and that you "performed a thorough evaluation of the impact of data issues caused by insufficient personnel awareness." In the following sections, we address the specific topics covered in the response in the order set forth in your response.

1. Explanation for the anomalous data identified by FDA with respect to the studies discussed in the October 30, 2025, GCL.

1.1 Identical Histopathological Data Across Multiple Muscle Implantation Studies

*Summary of issues described in the October 30, 2025, GCL:*

Histopathological scoring data were identical across multiple test reports from different studies. Specifically, the Week 4 histopathological data in test report (b) (4) (Study # (b) (4) ) were identical to the Week 4 histopathological data in test report (b) (4) (Study # (b) (4) ) ("Set 1"). In addition, the Week 13 histopathological data in test report (b) (4) (Study # (b) (4) ) were identical to the Week 13 histopathological data in test report (b) (4) (Study # (b) (4) ) ("Set 2"). Finally, the Week 26 histopathological data in test report (b) (4) were identical to the Week 26 histopathological data in test report (b) (4) ("Set 3"). According to sections "3.0 Test and control articles" and "4.0 Identification of test system" of the test reports, these tests were conducted using different device component test articles and utilized test rabbits that were "not previously used in other experimental procedures." Having histopathological scoring data that are identical across multiple test reports from different studies is highly unlikely, and even more improbable given the test report protocols referenced above. According to section "8.0 The results observed" of the test reports, the cell and tissue response to the test article and control article samples were scored using the semiquantitative scoring systems per ISO 10993-6:2016 (see Table E1, E2, E3 in Annex E of ISO 10993-6:2016). This scoring system involves a subjective evaluation in which pathologists evaluate an implanted tissue section under the microscope and score histological characteristics such as polymorphonuclear cells, lymphocytes, plasma cells, macrophages, giant cells, necrosis, neovascularization, fibrosis, and fatty infiltrate, on a scale of 1 through 4 for each of the characteristics.[4] Due to the subjective nature of the evaluation of a tissue section for histological characteristics, the inherent variability of biological systems,[5] and because histopathological sections will almost certainly differ even when the tightest controls are used when manually preparing the histopathological tissue sections of tissue blocks obtained from different animals, it is biologically highly improbable that nine out of nine histopathological characteristics in all three set of studies involving different device components as test articles would all be scored with identical numbers across different studies for both test article and control article implantation sites.

*Summary of relevant discussion in the November 28, 2025, Response:*

Your response states that:

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[4] O'Brien, Maureen T., JoAnn CL Schuh, Lyn M. Wancket, Sarah D. Cramer, Kathleen A. Funk, Nicolette D. Jackson, Kamala Kannan et al. "Scientific and regulatory policy committee points to consider for medical device implant site evaluation in nonclinical studies." Toxicologic Pathology 50, no. 4 (2022): 512-530.

[5] 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. doi: 10.1038/s41583-020-0326-y. PMID: 32488205.

> SD [Study Director] believed that histopathological evaluation of tissue slides is one of the key endpoints of research, and acknowledged that a qualified pathologist must owned sufficient pathological knowledge and years of work experience. Therefore, when generating reports, SD will not confirm the pathology results through slide reading. After checked the total number of slide (ensure that the number of slides matches with the requirements of the study protocol), SD reported the histopathological evaluation results into the report based on the pathologist's data. This process is also a common practice of CRO companies. SD acknowledged that SD is a single point of GLP Study. And at the same time, she also insisted that pathologists are the main responsible personnel for the results of Histopathological data.

You also stated that you attempted to communicate with the pathologist involved in the report, but the pathologist had already resigned. Additionally, you examined the qualifications and background of the resigned pathologist and noted that the pathologist had the background and experience for a trained pathologist. You assert, "During the review of internal procedures, it is noted that although personnel completed the training on internal operating procedures in a timely manner, the training on data integrity is inadequate."

You also stated you are conducting a root cause investigation into the issue in which "standard ISO 10993-6 is re-learned in detail, it was found that there is no clear quantitative distinction in the description of pathological scoring in the standard, which may result in different scores for different personnel. And the local procedure of (b) (4) (Implantation Test for Medical Device Standard Operating Procedure) was reviewed, it is concluded that the definition of scoring such as a diagram is unclear."

Your response also states the following:

> To fix the issue, a pathology scoring manual for implant testing, which specifies typical diagrams corresponding to pathology section scores will be drafted, and the training material of pathology section scores and representative images for training to strengthen training and practical assessment will be drafted and approved (Refer ATT-001-02, CAPA-25-052).

In addition, your response states that you will take the following action:

> Re-evaluate the pathological data of the following study: (b) (4), (b) (4) (b) (4) (b) (4) If the result is in inconsistent with the report, re-open the study and amend the report.

*Discussion:*

As an initial matter, your response does not dispute that anomalous data was generated by your testing facility. Rather, you seem to be proposing actions to correct the issues with histopathological scoring with additional training for histopathological scoring, and to re-evaluate the histopathological data in the referenced studies.

Your response does not provide an adequate explanation for the cause of the anomalous data. Your response suggests that the generation of anomalous data is attributed to a single pathologist (despite being trained and qualified for the position), who you attempted to contact, but who had already resigned. However, even if this pathologist was initially responsible for generating the anomalous data, the regulatory requirements applicable to non-clinical laboratory studies that support or are intended to support applications for marketing permits for medical devices for human use establish clear systemic accountability beyond individual personnel. According to 21 CFR 58.33, "The study director has overall responsibility for the technical conduct of the study, as well as for the interpretation, analysis, documentation and reporting of results, and represents the single point of study control." Additionally, 21 CFR 58.35 states that the quality assurance unit shall "Inspect each nonclinical laboratory study at intervals adequate to assure the integrity of the study..." (§ 58.35(b)(3)). During the FDA inspection, FDA's review of the raw data records related to the muscle implantation studies identified in the GCL revealed that the study director also signed off on the histopathology records. Thus, responsibility for the generation of anomalous data to FDA cannot be placed solely on the pathologist. Moreover, we note that the pathologist's departure from your firm does not somehow relieve your testing facility from conducting an investigation into the root cause of the anomalous data. It is the study director's and quality assurance unit's responsibility to ensure that the raw data from each study contains sufficient detail and traceability to allow root cause investigation and determination when the integrity of one or more studies' data is compromised.

Your response also indicates that a root cause investigation is currently underway for the three referenced muscle implantation studies and that you are developing a pathology scoring manual for implant testing to strengthen training. In addition, your response states that the new histopathology scoring manual for implant testing will be completed on February 26, 2026, and then you will re-evaluate the histopathological data by March 30, 2026. However, you have not provided an update demonstrating that these steps have been completed.

Furthermore, you seem to assert that the subjective scoring standard in ISO 10993-6 somehow led to the data anomalies. In your response, you assert that "ISO 10993-6 is [being] re-learned in detail, it was found that there is no clear quantitative distinction in the description of pathological scoring in the standard which may result in different scores for different personnel." However, 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 whether biocompatibility testing is needed and what type(s). As stated in ISO 10993-6, the histopathological scoring systems presented in Annex E are examples. The ISO standard is not intended to provide detailed instructional descriptions for conducting histopathological scoring, as such expertise falls within the scope of the veterinary pathologists' formal education and extensive professional training. In addition, per Clause 5.5.4 of ISO 10993-6: 2016, Microscopic assessment, "The scoring system used for the histological evaluation shall take into account the extent of the area affected, either quantitatively (e.g. in micrometres) or semi-quantitatively (see Annex E). The implant orientation, number of sections and cutting geometry should be recorded." Thus, it is not clear how a non-prescriptive standard could have caused the data anomalies the Agency has identified. Your response does not provide clarity on this point as it fails to explain how identical histopathological scoring across multiple studies

could be attributed to having "no clear quantitative distinction in the description of pathological scoring in the standard."

FDA has reviewed the other attachments you included and referenced in your response: Attachment ATT-001-01 for the Pathologist Qualification Document and ATT-001-02 CAPA-25-052. FDA cannot determine the adequacy of the information provided in Attachment ATT-001-01 for the Pathologist Qualification Document because some of the language in that attachment is not in English; however, even if all of the language in the attachment were provided in English, your firm's overall response and corrective actions would still be inadequate. Specifically, your firm has not identified a root cause of the issues identified. While ATT-001-02 CAPA-25-052 is outlined and in process, FDA disagrees that it identifies the systemic root causes of the issues, as it does not examine how the identical histopathological results occurred across multiple studies. Moreover, it is unclear whether your firm plans to conduct a systemic retrospective investigation into other muscle implantation studies to determine whether they could be impacted by the issues identified. In addition, the proposed corrective actions do not address the following critical issues identified by FDA: lack of comprehensive training for muscle implantation and quantitative scoring methodology, lack of qualified personnel in pathology and pathology study oversight roles, and lack of study director and quality assurance unit oversight to ensure study data integrity.

Both the FDA 483 observations and FDA Warning Letter, issued January 14, 2025, and June 25, 2025, respectively, similarly reflect these study issues. Your July 13, 2025, August 9, 2025, September 13, 2025, October 11, 2025, November 8, 2025, December 27, 2025, and February 5, 2026, responses to the Warning Letter are inadequate to demonstrate that the GLP violations are adequately and systemically addressed and that histopathological scoring data are now being reported accurately (see the "Your Warning Letter Responses" section below).

1.2 Observation Records Across Multiple Muscle Implantation Studies Without Any Abnormal and/or Clinical Observations Recorded

*Summary of issues described in the October 30, 2025, GCL:*

In seven muscle implantation studies (Study # (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) and (b) (4) each examining a different component of a transcatheter tricuspid valve device, all observations about the animal health status and implantation sites during the studies stated: "There were no significant abnormal symptoms in all animals during the test and no rabbits was died. The skin of the implanted site was intact and there were no abnormal conditions." The test reports further document that "All the rabbits were observed *every day* after implantation" (emphasis added) and the study design calls for the technician to "[r]ecord the nature and extent of any tissue reaction observed, such as haematoma, oedema, encapsulation, and/or additional gross findings. Record the presence, form, and location of the implant, including possible remnants of degradable materials." Each of the seven test reports concludes that "There was no bleeding, suppurations, vegetations and other pathological phenomena observed around the implantation site in test period." Given the invasive nature of the implantation studies and number of animals and implantation sites involved, it is biologically

highly improbable that none of the rabbits and none of the implantation sites presented any tissue reaction, bleeding, suppurations, or any pathological findings.[6, 7]

*Summary of relevant discussion in the November 28, 2025, Response:*

You assert that you conducted an investigation, including communicating with the study director and a technician associated with one of the cited studies; reviewing SOPs and training materials; and reviewing 21 CFR Part 58 GLP regulations and the ISO 10993-10 standard. You state, "When discussing why there is no adverse clinical observation records in the records, personnel explained that because he has a good knowledge background to determine whether adverse clinical symptoms related to the test substance, if the clinical symptoms are unrelated to the test substance, normal will be recorded. It is also stated that symptoms such as scabbing that occur simultaneously in the control group animals and the treated group animals should not be considered as adverse clinical symptoms related to the test substance. This survey shows that technicians evaluated the data appropriately based on their own knowledge and recorded it."

Furthermore, you state, "Based on the above investigation, technician and SD understand that clinical symptoms related to the test substance should be recorded. When personnel determine that there is no clinically relevant test article, it will be recorded as normal. Considering that the personnel responsible for data evaluation are experienced, the results recorded in the raw data are valid for evaluating the non-clinical outcomes of the test substance." You assert that you established and implemented SOPs to address clinical observations, veterinary work and management, and updated training on clinical observations.

*Discussion:*

FDA understands your explanation to be that you reviewed the Part 58 GLP regulations and FDA-recognized standard ISO 10993-10 and may not believe they are clearly defined with respect to the need to record adverse clinical observations. Additionally, FDA understands your explanation to be that technician personnel are trained, they know what adverse clinical signs can occur, and they only record the signs if they determine the signs are directly related to the test article.

FDA disagrees with your explanations for the anomalous data. FDA also disagrees with your approach to documenting clinical observations. Recording all animal clinical observations, regardless of whether caused by the test article or not, is contemplated by both the Part 58 GLP regulations and FDA-recognized standard ISO 10993-6.[8]

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[6] *See* Saeed S, Martins-Green M. Animal models for the study of acute cutaneous wound healing. Wound Repair Regen. 2023 Jan;31(1):6-16. doi: 10.1111/wrr.13051. Epub 2022 Oct 12. PMID: 36153666.

[7] *See* Masson-Meyers DS, Andrade TAM, Caetano GF, Guimaraes FR, Leite MN, Leite SN, Frade MAC. Experimental models and methods for cutaneous wound healing assessment. Int J Exp Pathol. 2020 Feb;101(1-2):21-37. doi: 10.1111/iep.12346. Epub 2020 Mar 30. PMID: 32227524; PMCID: PMC7306904.

[8] We note that ISO 10993-10 is not applicable to muscle implantation studies, as ISO 10993-10 pertains to skin sensitization testing (including Guinea Pig Maximization Testing). Rather, the applicable ISO standard is ISO 10993-6: 2016 – Tests for local effects after implantation.

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 assure that, "[u]nforeseen 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, 21 CFR 58.185(a), Reporting of nonclinical laboratory study results, requires that "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." Any health conditions or diseases observed in test animals are important to document regardless of whether they are caused by the test article or whether they represent anticipated or unanticipated responses. Documenting these observations is essential because they may confound final study conclusions, even when unrelated to the test article. Furthermore, 21 CFR 58.90(c) requires "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. If, during the course of the study, the animals contract such a disease or condition, the diseased animals shall be isolated, if necessary. These animals may be treated for disease or signs of disease provided that such treatment does not interfere with the study. The diagnosis, authorizations of treatment, description of treatment, and each date of treatment shall be documented and shall be retained." Additionally, 21 CFR 58.43(c) requires "Separate areas shall be provided, as appropriate, for the diagnosis, treatment, and control of laboratory animal diseases. These areas shall provide effective isolation for the housing of animals either known or suspected of being diseased, or of being carriers of disease, from other animals." Without accurate identification and documentation of clinical signs, conditions or diseases, the ability to isolate, diagnose, and treat clinical conditions or, in certain circumstances, control the spread of laboratory animal diseases within animal colonies, is significantly compromised. 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, ISO 10993-6 contemplates recording all animal clinical observations, regardless of whether caused by the test article.[9] Per Clause 5.4.4 of ISO 10993-6:2016, "The health of the animals shall be observed and recorded at regular intervals during the study. Following surgery, each animal shall be observed at appropriate intervals during the test period, and any abnormal findings shall be recorded, including local, systemic, and behavioural abnormalities, and their potential influence on the results obtained described in the test reports." In addition, Clause 5.4.3 of ISO 10993-6: 2016 states, "The surgical technique may profoundly influence the result of any implantation procedure. Surgery shall be carried out under aseptic conditions and in a manner

[9] Although the ISO standards are not prescriptive, they 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 whether biocompatibility testing is needed and what types of tests.

that minimizes trauma at the implant site. Remove the hair from the surgical area by clipping, shaving, or other mechanical means. Disinfect the exposed area of skin with an appropriate antiseptic. Ensure that the implants or wound surfaces do not come in contact with the hair. After surgery close the wound using either sutures or wound clips, taking precautions to maintain aseptic conditions. Use of antibiotics should be justified." The muscle implantation studies involve surgical implantation of test and control articles into rabbit paravertebral muscles, and the clinical signs can be related to the test article, surgical technique itself, or other unanticipated events. It is not possible to definitively differentiate whether the clinical signs result from the surgical technique, reactions to test articles, or other unforeseen factors without recording the observations and then adjudicating the cause. As such, we do not agree that it is reasonable to record clinical signs as "normal" based on a determination that all clinical signs are unrelated to the test substance without any recorded adjudication.

It should be noted that each of these seven studies included study endpoints at 1, 4, 13, and 26 weeks. Each study involved 12 rabbits with 80 implantation sites, totaling 84 rabbits and 560 implantation sites across all seven studies. Each of the 84 rabbits were implanted with 3-4 test articles and 3-4 control articles. Given the invasive nature of the implantation studies and number of animals and implantation sites involved, it is biologically highly improbable that none of the rabbits and none of the implantation sites presented any tissue reaction, bleeding, suppurations, or pathological findings.[10, 11] If any of these observations occurred, they must be recorded, as it is part of the study procedure and reporting requirements. This includes evaluating and determining whether any observations are abnormal observations and/or adverse events; and adjudicating whether the observations were caused by the study article or another factor (*i.e.,* conducting a differential diagnosis by examining potential mechanisms of disease, including degenerative, anomalous, metabolic/mechanical, neoplastic/nutritional, inflammatory/infectious, traumatic/toxic, vascular, and parasitic[12]).

FDA has also reviewed the other attachments you included and referenced in your response: ATT-02-001 The procedure of clinical observation, ATT-02-002 Training evidence, ATT-02-003 Training material, and ATT-02-004 The procedure of veterinary work and veterinary management. FDA cannot determine the adequacy of the information provided because it is unclear how they address the issue of lack of abnormal and/or clinical observations recorded in the observation records across multiple implantation studies. While you provided two SOPs (ATT-02-001 and ATT-02-004) and indicated that employees received training, you did not provide evidence demonstrating how these SOPs are implemented in practice, what measures ensure observational data are accurately recorded, and you have not described what corrective actions will be taken if study personnel fail to accurately record observational data. Furthermore, the training evidence you provided contains pages that are not translated into English, preventing FDA from fully reviewing the adequacy of your training program. Additionally, the SOPs are

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[10] *See* Saeed S, Martins-Green M. Animal models for the study of acute cutaneous wound healing. Wound Repair Regen. 2023 Jan;31(1):6-16. doi: 10.1111/wrr.13051. Epub 2022 Oct 12. PMID: 36153666.

[11] *See* Masson-Meyers DS, Andrade TAM, Caetano GF, Guimaraes FR, Leite MN, Leite SN, Frade MAC. Experimental models and methods for cutaneous wound healing assessment. Int J Exp Pathol. 2020 Feb;101(1-2):21-37. doi: 10.1111/iep.12346. Epub 2020 Mar 30. PMID: 32227524; PMCID: PMC7306904.

[12] *See* Thompson. (2018). Systemic Approach to Differential Diagnosis. *Small Animal Medical Differential Diagnosis*, 87-306. doi:10.1016/B978-0-323-49830-2.00002-0.

high-level and lack specific actionable procedures ensuring consistent outcomes. For example, the SOPs do not include detailed procedures for conducting and documenting clinical observations by species, isolating, diagnosing, and treating clinical conditions and diseases, or monitoring individual animal and colony health. Without evidence of implementation controls and detailed procedural guidance, FDA cannot assess whether these SOPs and how you have implemented them adequately prevent recurrence of the observed issues identified above.

Both the FDA 483 observations and FDA Warning Letter, issued January 14, 2025, and June 25, 2025, respectively, similarly reflect these study issues. Your July 13, 2025, August 9, 2025, September 13, 2025, October 11, 2025, November 8, 2025, December 27, 2025, and February 5, 2026, responses to the Warning Letter are inadequate to demonstrate that the GLP violations are adequately and systemically addressed and that the abnormal observations and/or adverse events during studies are now being reported or reported accurately (see the "Your Warning Letter Responses" section below).

### 1.3 Identical Pre- and Post-treatment Weight Pairs Across Several GPMT Skin Sensitization Study Test Reports

*Summary of issues described in the October 30, 2025, GCL:*

For Test Report No. (b) (4) [Study # (b) (4) several of the "Pretest weight(g)" (pre-treatment) and "Finished weight(g)" (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 other skin sensitization test reports generated by CCIC HTW (Suzhou) for other devices on different dates. It is highly improbable for continuous variables[13,14] such as pre- and post-treatment weight value pairs of different animals on different dates, to be identical across test reports with such frequency, particularly given that different devices were being tested. In addition, in some instances, the animal identification number is also identical, and all of this data and information being identical is even less likely to occur across multiple independent studies conducted on different animals on different dates.

*Summary of relevant discussion in the November 28, 2025, Response:*

Your response states, in part, the following:

> "Generally, key factors that affect animal growth include: feeding, environment, feeding density, management of testing systems (age and house) and Balance (accuracy). The studies FDA mentioned in letter have been reviewed by lab management team and summarized in following tables based on the above effects [reference Table 3-1 Animal Feed Information, Table 3-2 Information Summary of Animal House Environment, Table 3-3 The Information of Test System, and Table 3-4 Instrument information for Body weight]…

[13] 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.
[14] Petrie A. and Watson P. Statistics for Veterinary and Animal Science. John Wiley & Sons, 2013.

Based on above information, following are the overall information of the experimental animals:

- According to technical standard requirements (ISO 10993) and animal must be screened before dosing which lead the initial body weight of animals is similar.
- The Species/Strain/Grade is same: health Hartley Guinea Pig (Refer to ATT-03-001, Testing report of Animal Healthy).
- The animals used in the study are all from qualified suppliers: Wuxi Hengtai experimental animal breeding co. LTD.
- Body Weights and Ages: At initiation of dosing, male and female Hartley Guinea Pig were approximately 3 months of age, and body weights ranged from 300.0 to 330.0 g.
- Animal Housing: Animals were socially housed (up to 5 animals of same sex and same dosing group together) in plastic cage cages.
- Environment: all room was controlled and monitored for humidity (targeted range 40 to 70%, actual range 49.4 to 59.0%) and temperature (targeted range 18°C to 26°C, actual range 20.0°C to 24.9°C) with 10 to 20 air changes/hour. (Refer to ATT-03-004, Testing report of Animal Environment).
- Diet and Water: Animals were supplied with Feed from full-price pellets, once daily. Nutritional components and environmental contaminants in the diet were analyzed routinely by supplier. The analysis reports and lot numbers are on file at the Testing Facility. (Refer to ATT-03-002, Testing report of Animal Feed).
- Animals were provided reverse-osmosis purified and chlorinated water ad libitum by water bottle. (ATT-03-003, Testing report of Animal drink water).

Based on the above review, the initial weights of the animals in the experiment were similar. Growing in similar environments may result in similar body weights of animals after administration. After discussing with the veterinarian, it is concluded that similar animal weights may also be due to the inadequate animal welfare provided.

*Discussion:*

Your response does not adequately explain the reason for the anomalous data. You provided evidence in Table 3-1 that in numerous test reports, the guinea pigs were fed an average of 15-30g per day, once per day, and supplied with sterile water. You claim that “growing in similar environments may result in similar body weights of animals,” while also concluding that “inadequate animal welfare” may be the cause. Neither explanation accounts for the observed data pattern. A highly controlled, consistent environment would not produce identical pre- and post-treatment weight pairs due to inherent biological variation. Moreover, inadequate welfare would likely increase, not decrease, weight variability and thus would make it even less likely that pre- and post-treatment weight values would be identical across studies. As stated in the

October 30, 2025, GCL, it is biologically highly improbable for continuous variables,[15, 16] such as pre- and post-treatment weight value pairs of different animals on different dates, to be identical across test reports with such frequency, particularly given that different devices were being tested. The improbability is further compounded by the fact that, in some of the instances, the animal identification number is also identical; the likelihood of all of this data and information being identical across multiple independent studies conducted on different animals on different dates is extremely low.

To rectify this, you propose changing animal suppliers and feed vendors. Because the data anomalies cannot reasonably be attributed to the animals "growing in similar environments," changing animal suppliers and feed vendors would not address the true cause of the issues and thus do not allay FDA concerns. Even if this were the root cause, it is not clear how changing animal suppliers or feed vendors would impact the animals "growing in similar environments" because all animals regardless of source would be expected to have biological variation inherent to living systems, as previously described.

Nor would documentation of application materials showing your attempt to obtain animal care certification provide sufficient evidence that deficient animal welfare practices in your facility have been adequately corrected. An intent to obtain animal care certification is not evidence of resolution of the animal welfare issues described above. In any event, if your firm had conducted comprehensive animal welfare practices in compliance with 21 CFR Part 58 while the animals were housed in your facility—including but not limited to intake health assessments, adequate water and feed with proper nutritional value, adequate housing and enrichment, adequate observation of clinical signs and proper diagnosis and treatment of clinical signs and diseases, not just during vendor care—the guinea pig weight gain would be expected to show both greater variability and higher values.

FDA has also reviewed the other attachments you included and referenced in your response: ATT-03-001 "Testing report of Animal Healthy," ATT-03-002 "Testing report of Animal Feed," ATT-03-003 "Testing report of Animal drink water," ATT-03-004 "Testing report of Animal Environment," ATT-03-005 "Vender audit report of test system," and ATT-03-006 "AAALAC application documents." With respect to ATT-03-002 "Testing report of Animal Feed" and ATT-03-003 "Testing report of Animal drink water," these reports do not adequately address the animal welfare concerns, as proper animal care extends beyond testing the water and feed provided to animals. With respect to ATT-03-006 "AAALAC application documents," FDA acknowledges that you applied for accreditation; however, this does not mean that you have received accreditation by AAALAC or have addressed all GLP animal care requirements. In addition, while ATT-03-001, ATT-03-004, and ATT-03-005 were not provided with English translations, the titles of these documents "Testing report of Animal Healthy," "Testing report of Animal Environment," and "Vender audit report of test system," suggest that they would not address the root cause of identical pre- and post-treatment weight pairs identified by FDA.

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[15] 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.

[16] Petrie A. and Watson P. Statistics for Veterinary and Animal Science. John Wiley & Sons, 2013.

Both the FDA 483 observations and FDA Warning Letter, issued January 14, 2025, and June 25, 2025, respectively, similarly reflect these study issues. Your July 13, 2025, August 9, 2025, September 13, 2025, October 11, 2025, November 8, 2025, December 27, 2025, and February 5, 2026, responses to the Warning Letter are inadequate to demonstrate that the GLP violations are adequately and systemically addressed and pre- and post-treatment weight pairs are now being accurately reported (see the "Your Warning Letter Responses" section below).

### 1.4 Identical and Extremely Similar Pre-treatment Weight Values Across GPMT Skin Sensitization Study Test Reports

*Summary of issues described in the October 30, 2025, GCL:*

For Test Report Nos. (b) (4) and (b) (4) the vast majority of the "Pretest weight(g)" (pre-treatment weight values) of the guinea pigs were identical or extremely similar across the non-polar extract (SO) test article groups and across the negative control groups for each study. Similarly, the vast majority of the pre-treatment weight values of the guinea pigs were identical or extremely similar across the polar extract (SC) test article groups and across the negative control groups for each study. Specifically, among the polar extract (SC) group, animal numbers 1, 7, and 10 have identical pre-treatment weights across both studies and animal numbers 2, 3, 5, 6, 8, 11, 12, 13, 14, and 15 have extremely similar pre-treatment weights (≤ 0.2 g difference). Among the non-polar extract (SO) group, animal numbers 22 and 26 have identical pre-treatment weights across both studies and animal numbers 16, 17 19, 20, 21, 23, 25, 28, and 30 have extremely similar pre-treatment weights (≤ 0.2 g difference). This very high frequency (80%) of identical or extremely similar (≤ 0.2 g difference) pre-treatment weights for animals with the same randomly assigned number across two different studies[17] is biologically highly improbable.[18] Thus, it appears the data were copied from one study to the next with a change to one or two digits across some rows to make the numbers appear like data were collected from different sets of animals.[19] Numerous other test reports for GPMT skin sensitization studies conducted at your testing facility contain a significant proportion of pre- and/or post-treatment weights that are identical or extremely similar to those of the same animal numbers in other test reports for GPMT skin sensitization studies conducted at your testing facility, including but not limited to Test Report Nos. (b) (4) (Study # (b) (4) (b) (4) (Study # (b) (4) (b) (4) (Study # (b) (4) (b) (4) (Study # (b) (4) and (b) (4) (Study # (b) (4)

[17] Section 5.0 of the study protocol requires that the test animals be "not previously used in other experimental procedures." Accordingly, we have interpreted these as independent tests conducted on two different sets of test animals.

[18] 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. doi: 10.1038/s41583-020-0326-y. PMID: 32488205.

[19] As noted in footnote 17 above, each new study must use animals not previously used in other experimental procedures. Thus, if the data were recorded accurately, it would appear that the same animals were being used across multiple studies, which is inconsistent with the study protocol.

*Summary of relevant discussion in the November 28, 2025, Response:*

You assert that you "first communicated with the operating technician (Employee ID: (b) (6) The technician denied copying the data. Then, we checked the animal purchase records of the following study. . . ." You also provided the animal purchase records for seven separate studies in Attachments ATT-004-01 Animal Health Certificate Number (b) (4) ATT-004-02 Animal Health Certificate Number (b) (4) ATT-004-03 Animal Health Certificate Number (b) (4) ATT-004-04 Animal Health Certificate Number (b) (4) and ATT-004-05 Animal Health Certificate Number (b) (4) Your response further states, in part, the following:

> Based on the information, following are the overall information of the experimental animals:
>
> - The weight of animals when they receive is very similar, the range is 300 to 330g.
> - The Species/Strain/Grade is same: Hartley Guinea Pig.
> - The animals used in the study are all from qualified suppliers: Wuxi hengtai experimental animal breeding co. LTD.
> - Animal Housing: Animals were socially housed (up to 5 animals of same sex and same dosing group together) in plastic cage cages.
> - Environment: all room was controlled and monitored for humidity (targeted range 40 to 70%, actual range 49.6 to 54.8%) and temperature (targeted range 18°C to 26°C, actual range 19.7°C to 24.3°C) with 10 to 20 air changes/hour.
> - Diet and Water: Animals were supplied with Feed from full-price pellets, 15-30 g per animal once daily. Nutritional components and environmental contaminants in the diet were analyzed routinely by supplier. The analysis reports and lot numbers are on file at the Testing Facility.
> - Animals were provided reverse-osmosis purified and chlorinated water ad libitum.
>
> According to the above investigation, the reason of "Similar Pre-Treatment Weight Values Across GPMT Skin Sensitization Study Test Reports" is due to similar weight upon arrival but being raised in the same environment.

*Discussion:*

FDA understands your explanation to be that animals weigh the same pre-treatment because when the animals arrived, they were similar weights, and continued to stay similar weights because they were raised in the same environment.

Your response does not fully explain the reason for the anomalous data. Your response does not explain how or why the animal number and pre-treatment weights are identical or extremely similar among matching test article groups across numerous studies. Furthermore, your response offers two different explanations without adequately addressing the core issues. You previously

stated in Response 1.3 regarding identical pre- and post-treatment weights that "[g]rowing in similar environments may result in similar body weights of animals after administration," while also concluding "inadequate animal welfare" may be the cause. Neither explanation accounts for the observed data pattern. In addition, as noted above, you have not provided sufficient new or updated animal welfare SOPs, trainings, and evidence to demonstrate that the "inadequate animal welfare" issue has been rectified at your testing facility.

Your response states that you "have taken multiple measures, such as introducing computerized systems and strengthening data integrity training, to enhance FDA's trust in the CCIC HTW data." However, it is unclear what computerized systems you are referring to and it is also not clear what you have done to strengthen your data integrity training. In the absence of additional information about what these measures entail, FDA cannot determine the adequacy of the proposed solutions provided. Furthermore, it does not appear that a retrospective review of GPMT studies (other than those referenced) and systemic root cause investigation into animal welfare and GPMT study records were conducted.

Both the FDA 483 observations and FDA Warning Letter, issued January 14, 2025, and June 25, 2025, respectively, similarly reflect these study issues. Your July 13, 2025, August 9, 2025, September 13, 2025, October 11, 2025, November 8, 2025, December 27, 2025, and February 5, 2026, responses to the Warning Letter are inadequate to demonstrate that the GLP violations are adequately and systemically addressed and that pre-treatment weight values are now being accurately reported (see the "Your Warning Letter Responses" section below).

1.5 Linear Correlation of Weight Gains in GPMT Skin Sensitization Study Test Reports

*Summary of issues described in the October 30, 2025, GCL:*

The sets of pre- and post-treatment weights of study guinea pigs in GPMT skin sensitization studies show an extremely linear correlation ($R^2 \geq 0.99$) in which the body weight of each guinea pig increased in an extremely similar proportion with minimal variability between guinea pigs for the following studies: Report Nos. (b) (4) (Study # (b) (4) and (b) (4) (Study # (b) (4) 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.[20, 21, 22, 23, 24, 25, 26] Therefore, it is implausible for the rate of weight gain to be nearly identical for all animals across each of these studies because of the inherent individual variation.

As noted in the October 30, 2025, GCL, test reports containing similarly abnormally high linear correlations ($R^2 \geq 0.99$) of weight gain, similar to the examples listed above and detailed in the October 30, 2025, GCL have been observed in numerous other GPMT skin sensitization studies conducted at your testing facility, including but not limited to Study Report Nos (b) (4) (Study # (b) (4) (b) (4) (Study # (b) (4) (b) (4) (Study # (b) (4) (b) (4) (Study # (b) (4) (b) (4) (Study # (b) (4) (b) (4) (Study # (b) (4) (b) (4) (Study # (b) (4) (b) (4) (Study # (b) (4) and (b) (4) (Study # (b) (4)

*Summary of relevant discussion in the November 28, 2025, Response:*

You state that you conducted an investigation and checked the training of technical personnel on data integrity and reviewed the logbook and calibration records of the instruments used in the studies. You provided the qualifications of the suppliers providing the study animals. You also state that, according to your investigation, "the experimental data was obtained by qualified personnel on calibrated instruments" and that "the supplier is also qualified by the company." You then assert that "Per above description, data can be reliable. The similarity in weight growth curves may be due to their similar growth environments."

*Discussion:*

Your response does not fully provide an explanation for the anomalous data. Nor does it dispute the statement in the October 30, 2025, 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." While your response asserts that all employees have received training on data

[20] 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.
[21] The Laboratory Rabbit, Guinea Pig, Hamster, and Other Rodents. Suckow, Stevens, and Wilson. Academic Press. 2012.
[22] Wagner, J. E. (1976). Genetics. In The biology of the guinea pig (pp. 114-115). Academic Press.
[23] 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.
[24] 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.
[25] 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.
[26] 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.

integrity, your response does not provide sufficient detail about the training to permit an evaluation of its adequacy. For example, it cannot be determined what the "Data Integrity Training" is, how it is defined, the extent of training, and the adequacy of the training, including the comprehensiveness of the training material. Your response also fails to describe what systemic measures and corrective actions are being implemented to ensure that GLP study data integrity is not compromised. In addition, FDA finds the statement of "similar growth environments" scientifically inadequate to account for the extremely linear GPMT study results. This rationale does not provide evidence or explanation of a plausible physiological basis for these data patterns.

As previously stated in the October 30, 2025, GCL Letter, guinea pigs, like other animals, exhibit a wide range of individual phenotypic variations due in part to physiological status, biological characteristics, food and water intake, handling, husbandry, and environmental factors. These factors would be expected to result in variable weight gain among study animals even if all the guinea pigs in each study were of similar age, sex, strain/stock and growing rapidly.

FDA has also reviewed the other attachments you included and referenced in your response: ATT-05-001 Equipment certification and ATT-05-002 Vendor certification of test system. FDA cannot determine the adequacy of ATT-05-002 Vendor certification of test system because it is not in English; however, even if the document were provided in English, based on the document title and the certificates in the attachment, it would not explain how the linear correlation of weight gain issue has been addressed because of expected inherent intra-animal physiological variations regardless of the type of vendor chosen. You provided ATT-05-001 Equipment certification to demonstrate properly calibrated equipment. While equipment calibration helps to ensure accurate measurements, it does not explain the lack of normal biological variability in weight gain data, which would be expected with properly calibrated equipment.

Both the FDA 483 observations and FDA Warning Letter, issued January 14, 2025, and June 25, 2025, respectively, similarly reflect these study issues. Your July 13, 2025, August 9, 2025, September 13, 2025, October 11, 2025, November 8, 2025, December 27, 2025, and February 5, 2026, responses to the Warning Letter fail to adequately demonstrate that the GLP violations concerning animal welfare, SOPs, and GPMT studies are fully and systemically addressed (see the "Your Warning Letter Responses" section below).

1.6 Abnormally Low Weight Gains That Are Not Reported as Abnormal and/or Adverse Clinical Observations and Without Any Deviations Reported in GPMT Skin Sensitization Study Test Reports

*Summary of issues described in the October 30, 2025, GCL:*

The observed weight gains of 64.0 to 64.7 g on average reported by CCIC HTW (Suzhou) during the study periods of the GPMT skin sensitization studies are approximately 36% to 68% lower than expected and biologically highly improbable if the study guinea pigs were properly cared for and monitored and the studies were conducted as per the protocol, considering the lack of abnormal and/or adverse clinical observations and the lack of deviations noted in the test reports. Based on the volume of testing conducted at the facility, the consistent pattern of results with "no

abnormal signs" and "no visible change" as demonstrated by a consistent score of zero in the "Guinea pig Sensitization Dermal Reactions" chart, and no reported protocol 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 otherwise invalid.

*Summary of relevant discussion in the November 28, 2025, Response:*

Your response states, in part, the following:

> Communicated with the veterinarian (Employee ID: (b) (6)), abnormal clinical symptoms include emaciation, discoloration, weakness, or vomiting in animals. If an animal is in good condition with a low body weight, the low body weight will not be considered as an adverse clinical symptom. We acknowledged that the procedure of clinal observation is inadequate.
>
> … As described earlier, due to the procedure inadequate, some deviation was note be triggered such as low bodyweight, but this is a situation (low body weight) recorded in the test records. And Data can be tracked; there is no DI issue. And after checked the background of technician, refer to Obs 02 and Obs 03), the personnel are qualified and experienced.
>
> We agreed that if any deviation from SOP and protocol was noted, the deviation (including procedure and protocol) should be triggered and it should be reported in final report. However, Per SOP ((b) (4) Clinical observation) and protocol, the requirement that low body weight (Even animal is in good condition) should be reported as deviation did not be defined. So, there is no deviation is trigger. As noted by the FDA, even if low body weight is not reported, conclusions about low body weight can still be drawn from the data. Therefore, the impact of this issue on the overall data conclusion is low.
>
> We fully agree with the FDA's statement that accurate research data submitted before market launch is necessary for the US Food and Drug Administration to fully and accurately evaluate the overall safety of the device, CCIC HTW are constantly improving our software and hardware facilities to accurately record the experimental process as much as possible, so that we can reconstruct this study in the future (if necessary).

*Discussion:*

FDA understands your explanation to be that if an animal is in good condition with a low body weight, the low body weight will not be considered as an adverse clinical sign; that your firm's procedure for noting clinical evaluation deviations is inadequate because it does not define low body weight as a deviation trigger; that the impact of low body weight on the overall data is low; that your technicians are qualified and experienced; and that data integrity is not an issue.

Your response does not fully explain the reason for the anomalous data. Importantly, your response does not address the issue of low body weight *gain*, and it instead addresses a different topic—low body weight. As previously stated in the October 30, 2025, GCL regarding guinea pig physiology and growth rates:

> Based on Hartley guinea pig growth curves and animal physiology, these are lower-than-normal average weights gained (64.0 g minimum to 64.7 g maximum) by reportedly healthy 2.5-to-3.5 week-old male and 4-to-5-week-old female Hartley guinea pigs[27, 28, 29, 30, 31, 32] over the course of the studies (i.e., through Weeks 5–10). More specifically, as seen in Figures 1 and 2 below, growth curves from two example guinea pig suppliers, Charles River Laboratories and Inotiv, illustrate that healthy Hartley guinea pigs at juvenile stages are expected to gain around 100 to 200 g in a 25-day period. Therefore, the much lower average weight gains of 64.0 to 64.7 g on average reported by CCIC HTW (Suzhou) during the same period are approximately 36% to 68% lower than expected.

[27] 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.

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

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

[30] 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.

[31] 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.

[32] 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.

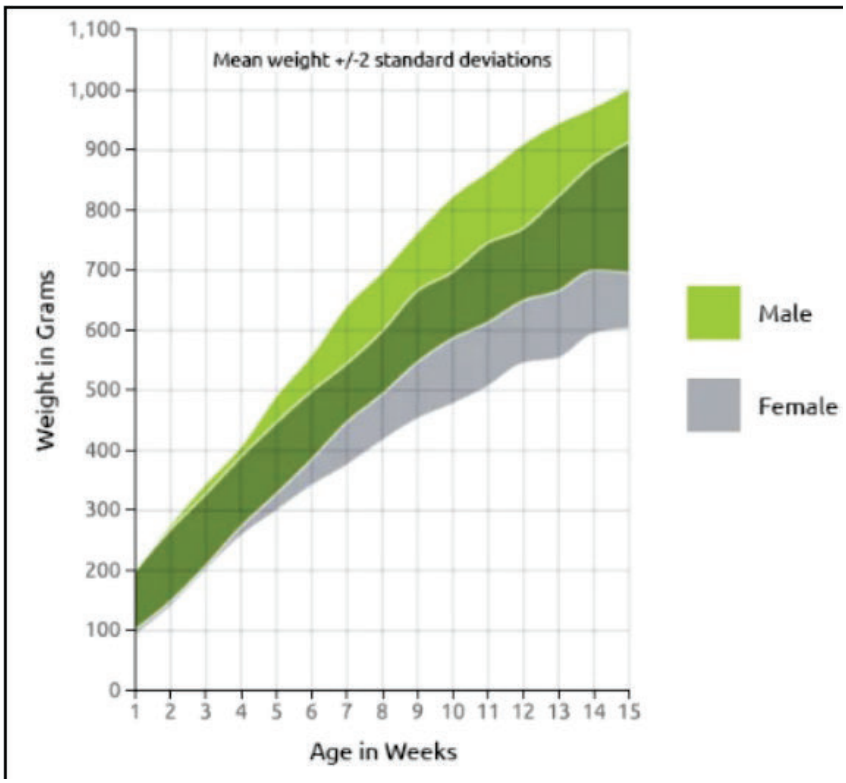


*Figure 1. Charles River Laboratories Hartley Guinea Pig Growth Curve*

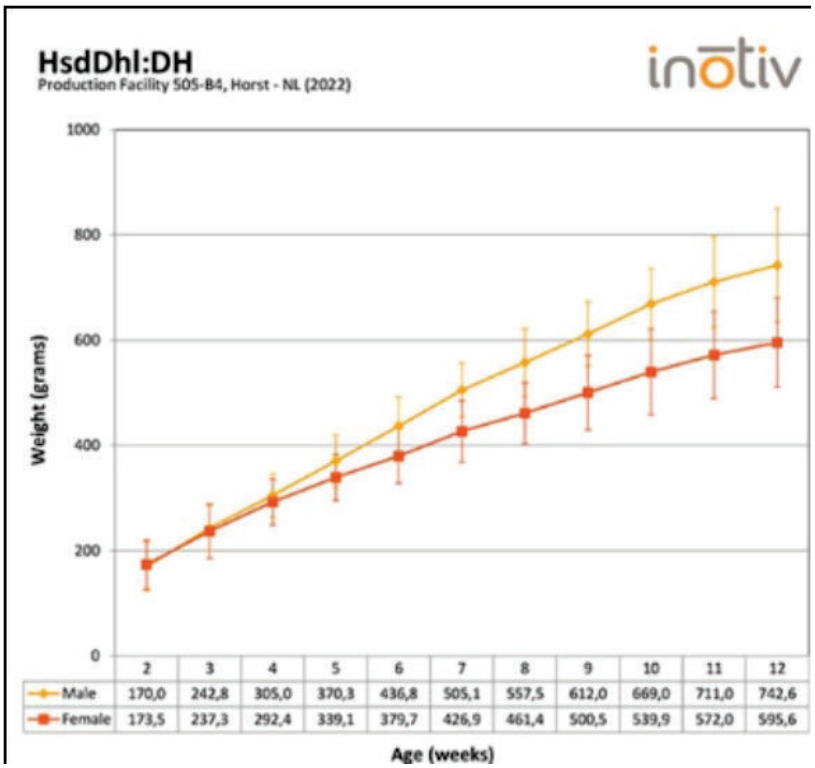


*Figure 2. Inotiv Dunkin-Hartley Guinea Pig Growth Curve*

. . . .

> Given the volume of GPMT skin sensitization study test reports generated by your testing facility and received by FDA in premarket submissions (more than one hundred), the "no abnormal signs" observation occurring in such a significant number of animals (more than one thousand) is biologically improbable. Due to the nature of the study, the adjuvant used (Complete Freund's Adjuvant or CFA) can have systemic effects and elicit pain[33] and can cause focal and coalescing wounds in the dorsum area where the CFA is intradermally injected, which is away from the flank where the skin reaction is observed and scored. The sodium dodecyl sulfate applied on the skin during the topical induction phase can also be generally irritating to some guinea pigs.

As noted above and previously, the low weight gains should have been noted in the study reports as an abnormal and/or adverse clinical observation for each applicable animal. Based on the physiological explanation above and previously provided in the October 30, 2025 GCL, FDA disagrees with your statement, "If an animal is in good condition with a low body weight, the low body weight will not be considered as an adverse clinical symptom."

Specifically, FDA disagrees with your assessment that the impact of low body weight on the overall data conclusion is low. Your response suggests that "inadequate animal welfare" may be a cause for data anomalies. The abnormally low weight gain you recorded is a clear clinical indicator of poor animal health. Using unhealthy animals in a study violates the principles of the standard upon which your GPMT skin sensitization studies rely (ISO 10993-10:2021) and renders the data unreliable, as it becomes impossible to distinguish device-related effects from pre-existing health conditions in the test animals. FDA also disagrees that low body weight should be documented as a "deviation." Instances of low body weight or low body weight gain should instead be characterized as an abnormal and/or adverse clinical observation, depending on the situation. Therefore, the consistent pattern of results with "no abnormal signs" and "no visible change" indicates 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 otherwise invalid.

As noted in Section 1.2 above, FDA cannot determine the complete adequacy of the information provided in ATT-02-001. FDA notes that, while routine clinical observations regarding the general health of the animals now seem to be captured on the daily observation form as demonstrated in ATT-02-001, it is unclear if any action is taken once a clinical observation is made, other than "immediately notify the veterinarian and the project leader to take appropriate measures in a timely manner." It is also unclear whether these observations will be included in the study report and interpreted along with the study data. Furthermore, it is unclear how the procedure will define "low weight gain." All experimental data, which would include animal clinical observations, must be recorded and verified (21 CFR 58.33(b)) and a description of all circumstances that may have affected the quality or integrity of the data shall be included in the final report (21 CFR 58.185(a)(9)). These recordkeeping and reporting activities help, among

[33] Billiau, Alfons, and Patrick Matthys. "Modes of action of Freund's adjuvants in experimental models of autoimmune diseases." *Journal of leukocyte biology* 70, no. 6 (2001): 849-860.

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)).

As noted in Sections 1.3 and 1.4 above, you previously stated in Response 1.3 with regard to identical pre- and post-treatment weights, "Based on the above review, the initial weights of the animals in the experiment were similar. Growing in similar environments may result in similar body weights of animals after administration. After discussing with the veterinarian, it is concluded that similar animal weights may also be due to the inadequate animal welfare provided." This acknowledgment is directly relevant to the current issue– GMPT studies demonstrated identical weight gains across numerous studies, in which all animals in those studies had low weight gains with no abnormal and/or adverse clinical observations and without any deviations reported; if comprehensive animal welfare was conducted, then under normal conditions, the growth rate at this juvenile stage is expected to be fast. In addition, like other animals, guinea pigs exhibit a wide range of individual phenotypic variations due in part to physiological status, biological characteristics, food and water intake, handling, husbandry, and environmental factors. These factors would be expected to result in variable weight gain among study animals even if all the guinea pigs in each study were of similar age, sex, strain/stock and growing rapidly. Therefore, it is implausible for the rate of weight gain to be nearly identical and extremely low without any abnormal and/or adverse clinical observations and without any deviations reported.

Additionally, FDA disagrees with your conclusion that not reporting low body weight gain has a low impact on the overall data conclusion. 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 shall be used for the Guinea Pig Maximization Test (ISO 10993-10:2021, Clause 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.

Additionally, considering that you have not provided any evidence or explanation of your proposed solutions for improving the software and hardware facilities to accurately record the experimental process as much as possible, FDA is unable to determine the adequacy of your proposed solutions.

Both the FDA 483 observations and FDA Warning Letter, issued January 14, 2025, and June 25, 2025, respectively, similarly reflect these study issues. Your July 13, 2025, August 9, 2025, September 13, 2025, October 11, 2025, November 8, 2025, December 27, 2025, and February 5,

2026, responses to the Warning Letter are inadequate to demonstrate that the GLP violations are adequately and systemically addressed and that animal weights and clinical observations are now being accurately reported (see the "Your Warning Letter Responses" section below).

### 1.7 Abnormally Consistent Weight Gains in Acute Systemic Toxicity Studies

*Summary of issues described in the October 30, 2025, GCL:*

For Test Report Nos. (b) (4) (Study # (b) (4) (b) (4) (Study # (b) (4) and (b) (4) (Study # (b) (4) the rate of weight gain of the test and control animals are consistently linear. However, the animal model in this acute systemic toxicity test, the ICR mouse, like other laboratory inbred and outbred mouse strains, exhibits a wide range of individual phenotypic variations based on physiological status, biological characteristics, food and water intake, fecal and urine excretion, level of activities, handling, husbandry, and environmental factors, such as cohort pressure in group housing. Depending on the strain, a mouse can eat up to 25% of its body weight and drink up to 30% of body weight per day[34, 35] and will defecate, urinate, and metabolize at different rates. These factors are expected to result in variable weight changes among study animals, even if all the mice in each study were of similar age, sex, and strain/genotype.[36, 37, 38] Moreover, weight changes would be expected to include weight loss or slow to no weight gain as the mice in these studies are exposed to stress, which can reduce food intake, and thus, weight.[34, 35] Stress and adverse responses especially occur at study initiation due to removing the mice from their cages, restraining the mice to immobilize them, and administering an intravenous or intraperitoneal injection. [39] The consistent rate of weight gain of all mice in these test reports, without any indication of plateau or weight loss, is inconsistent with anticipated individual variability. Therefore, the weights reported for the test and control mice in these studies are biologically highly improbable.

Test reports containing similarly abnormally consistent weight gains in test and control mice, similar to the examples above, have been observed in numerous other acute systemic toxicity studies conducted at your testing facility, including but not limited to Study Report Nos. (b) (4) (Study # (b) (4) (b) (4) (Study #

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[34] Bachmanov, A. A., Reed, D. R., Beauchamp, G. K., & Tordoff, M. G. (2002). Food intake, water intake, and drinking spout side preference of 28 mouse strains. Behavior genetics, 32, 435-443.

[35] Benevenga, N. J., Calvert, C., Eckhert, C. D., Fahey, G. C., Greger, J. L., & Kee, C. L. (1995). Nutritional requirements of laboratory animals.

[36] Yang, Y., Smith Jr, D. L., Keating, K. D., Allison, D. B., & Nagy, T. R. (2014). Variations in body weight, food intake and body composition after long-term high-fat diet feeding in C57BL/6J mice. Obesity, 22(10), 2147-2155.

[37] The Jackson Laboratory. Body weights for selected strains, by age (MPD 36) Mouse phenome database web site. 2000 http://phenome.jax.org/pub-cgi/phenome/mpdcgi?rtn=projects/details&sym=Jax1.

[38] Reed, D. R., Bachmanov, A. A., & Tordoff, M. G. (2007). Forty mouse strain survey of body composition. Physiology & behavior, 91(5), 593-600.

[39] Talbot, Steven R., Svenja Biernot, Andre Bleich, Roelof Maarten van Dijk, Lisa Ernst, Christine Häger, Simeon Oscar Arnulfo Helgers et al. "Defining body-weight reduction as a humane endpoint: a critical appraisal." Laboratory animals 54, no. 1 (2020): 99-110.

(b) (4) (b) (4) (Study # (b) (4)
(b) (4) (Study # (b) (4) (b) (4) (Study #
(b) (4) and (b) (4) (Study # (b) (4)

*Summary of relevant discussion in the November 28, 2025, Response:*

You assert that you checked the raw data of Test Report No. (b) (4) and found that the raw data was not accurately reflected in the report. You included a report amendment of (b) (4) in ATT-07-002. You also state that you reviewed the housing conditions of the testing system and suppliers and "found that the feeding and welfare environment of animals in study with similar animal weights are very similar."

Your response also states the following:

- According to technical standard requirement (ISO10993) and animal should be screening before dosing, which lead the initial body weight of animals is similar.
- The Species/Strain/Grade is same: ICR healthy mouse. (Refer to ATT-07-003, Testing report of animal from 2023-2024).
- The animals used in the study are all from qualified suppliers: Wuxi Hengtai experimental animal breeding co. LTD.
- Body Weights and Ages: At initiation of dosing, male and female ICR mouse were approximately 6 weeks of age, and body weights ranged from 17.0 to 23.0 g.
- Animal Housing: Animals were socially housed (up to 5 animals of same sex and same dosing group together) in plastic cage cages.
- Environment: all room was controlled and monitored for humidity (targeted range 30 to 70%, actual range 49.4 to 59.0%) and temperature (targeted range 20°C to 25°C, actual range 20.0°C to 24.9°C) with 10 to 20 air changes/hour.
- Diet and Water: Animals were supplied with Feed from full-price pellets, once daily. Nutritional components and environmental contaminants in the diet were analyzed routinely by supplier. The analysis reports and lot numbers are kept at the Testing Facility. (Refer to ATT-07-004, Test report of animal Feed from 2023- 2024).
- All animals were given qualified bedding (Refer to ATT-07-005, Test report of animal bedding from 2022-2024).

Based on the above information, it is found that the feeding and welfare environment of animals in study with similar animal weights are very similar. Similar weight before and after treatment is reliable.

*Discussion:*

Your response admits that raw data was not accurately reflected in the final report for study (b) (4) You provided new raw data in ATT-07-001 Raw data of (b) (4) however, your amended report does not provide an explanation for why the

data does not match and what exactly was amended; it simply states, “One report amendment was implemented to reopen the study. No deviations occurred during this study.” Notably, in your plot of the corrected data, the mice still exhibit abnormally consistent weight gains, with apparent linear growth. Overall, it does not appear that a retrospective review of acute systemic toxicity studies (other than those referenced) and systemic root cause investigation into animal welfare and acute systemic toxicity study records were conducted. It also fails to explain how your quality system allowed it to occur Furthermore, this error was only identified in response to FDA’s inquiry, which demonstrates a fundamental failure of your internal data review and quality assurance processes.

Notably, the new raw data you provided continues to demonstrate abnormally consistent weight gains in this acute systemic toxicity study and therefore does not address FDA’s concerns. FDA understands your explanation to be that you followed ISO 10993 in which the animal is screened before dosing and that is what led to the similar initial body weights, and that animals raised in a similar environment will have similar growth rates.

FDA disagrees with your suggestion that consistently linear weight gains in acute systemic toxicity studies is not anomalous under the circumstances here. Notably, you previously stated in Response 1.3 with regard to identical pre- and post-treatment weights in GPMT studies, “Based on the above review, the initial weights of the animals in the experiment were similar. Growing in similar environments may result in similar body weights of animals after administration. After discussing with the veterinarian, it is concluded that similar animal weights may also be due to the inadequate animal welfare provided.” However, this does not explain abnormally consistent weight gains in acute systemic toxicity studies. This is biologically highly improbable considering the wide range of individual phenotypic variations of the ICR mouse used in this acute systemic toxicity test, as described above and in the October 30, 2025 GCL, even where animals grow in similar environments or inadequate animal welfare is provided.

Furthermore, as noted above, even if the anomalous data was caused, at least in part, by inadequate animal welfare, your response has not adequately addressed such animal welfare concerns. You have not provided sufficient new and/or updated animal welfare protocols, trainings, and evidence that the “inadequate animal welfare” has been rectified at your testing facility.

Your firm provided ATT-07-005 Test report of animal bedding from 2022-2024, describing the physical and scientific properties of your animal bedding. However, bedding quality alone does not account for the abnormally consistent weight gain observed in study animals, which are inconsistent with the inherent biological variability of living systems.

Your firm also provided the following other attachments with your response: ATT-07-003 Testing report of animal from 2023-2024 and ATT-07-004 Test report of animal Feed from 2023-2024. FDA cannot determine the adequacy of the information provided in these attachments because much of the documentation is not in English. Even if full English translations were provided, these reports are merely two factors that could contribute to the systemic root causes of the issues and do not fully address the concerns previously outlined with respect to the abnormally consistent weight gains and the lack of normal biological variability in weight gain data, which would be expected with proper GLP-compliant animal welfare.

Both the FDA 483 observations and FDA Warning Letter, issued January 14, 2025, and June 25, 2025, respectively, similarly reflect these animal welfare and study issues. Your July 13, 2025, August 9, 2025, September 13, 2025, October 11, 2025, November 8, 2025, December 27, 2025, and February 5, 2026, responses to the Warning Letter are inadequate to demonstrate that the GLP violations are adequately and systemically addressed and that animal weights are now being accurately reported (see the "Your Warning Letter Responses" section below).

1.8 Handwritten Raw Data Observation Records Are Identical Across Acute Systemic Toxicity Study Test Reports

*Summary of issues described in the October 30, 2025, GCL:*

In two out of three study records FDA has obtained for acute systemic toxicity studies conducted by CCIC HTW (Test Report Nos. (b) (4) (Study # (b) (4) and (b) (4) (Study # (b) (4) certain portions of the handwritten raw data observations recorded for the study animals are identical across the two studies. Specifically, there are identical handwritten slash marks in the columns labeled "abnormal symptoms" for all test and control animals between Test Report Nos. (b) (4) and (b) (4) There are also identical handwritten signatures and dates at each time point. These identical handwritten markings, signatures, and dates suggest that the observations for each animal were either pre-filled photocopies for both studies or were photocopied from one study to the other.

*Summary of relevant discussion in the November 28, 2025, Response:*

Your response asserts, in part, the following:

> Two technicians (Employee ID: (b) (6) Employee ID: (b) (6) were interviewed, per the personnel's description, it is found that in order to improve operational efficiency, staff signed and record the date in blank experimental record form per study schedule before activity start. After copying, the blank form will be brought to the site, and technician recorded the clinical observations and body weight per the actual animal status.
>
> The QA [Quality Assurance] staff (Employee ID: (b) (6) was interviewed and QA acknowledges that testing records were not controlled well before 2025. And QA also noted that personnel carried blank forms with pre signed date during on-site audits. Considering that the experimental data are recorded and filled out on site (means data was contemporaneous), it was not recorded as observation in the QA audit report.
>
> Regarding this issue, The SD (Employee ID: (b) (6) was interviewed. SD explained that SD mainly focused on the status of the instruments and animals' status during the on-site inspection, QA should check the timeliness of records.
>
> Test Facility Management [TFM] (Employee ID: (b) (6) were interviewed. TFM checked the audit report of the relative studies ((b) (4) (b) (4) and explained that he did not receive a description of the

> relevant observation (copies of the records). And TFM knowing raw data should comply with the requirements of data integrity (attributable, legible, contemporaneous, original, accurate). Meanwhile, TFM emphasizes that the CCIC HTW has established some procedure to prevent similar situations from happening.

Your response also states:

> It is noted that the US Food and Drug Administration cited some international (not-domestic) literature as judgment, we still need to consider the differences in animal husbandry and growth between domestic and foreign animals. Therefore, while improve employees' requirements for data integrity, we will also continue to strengthen the animal management of suppliers and feeding.

*Discussion:*

Your explanation that staff pre-signed, pre-dated, and photocopied blank record forms "to improve operational efficiency" is an admission of violating the fundamental GLP requirement for contemporaneous data recording [21 CFR 58.130(e)], which requires that all data generated during the study be "recorded directly, promptly, and legibly in ink" and that all data entries be "dated on the date of entry and signed or initialed by the person entering the data." This practice makes it impossible to verify that the observations were made as stated or that the data are original and accurate. Your assertion that technicians subsequently filled in the data on-site lacks adequate supporting documentation. This practice, combined with the identical handwritten slash marks across studies, which your response failed to address, indicates that records were falsified. The interactions between technicians, QA, and management described in your response demonstrate significant deficiencies in your quality system and insufficient accountability across organizational levels.

FDA finds your explanation inadequate, as it does not fully address or explain the reason for the referenced anomalous data or demonstrate that the issue has been systemically investigated across all acute systemic toxicity studies. Nor does it dispute the statement in the October 30, 2025, GCL, where FDA specifically cited the identical handwritten slash marks in the columns labeled "abnormal symptoms" in addition to the identical handwritten signatures and dates. While your response acknowledged the lack of document control, it did not provide documented evidence that the clinical observations were actually observed during the studies. It should be noted that the identical portions of the study records include study director signatures (as the reviewers of raw data record). This indicates that the study directors at CCIC HTW (Suzhou) are aware of this practice but failed in their overall responsibilities to ensure study data integrity. Furthermore, your explanation does not demonstrate that a systemic root cause investigation was conducted into the issues; it appears that only some employees with different responsibilities and oversight were interviewed, without a complete retrospective review of your test protocols, completed acute systemic toxicity studies, QA and TFM units and requirements, and Study Director responsibilities.

Additionally, FDA disagrees with your statement, "…the raw data reflects the status of the animals (such as weight, clinical observations)." As discussed further above, the explanations

you provided regarding the data anomalies identified are inadequate and the corrective actions taken and proposed to address the anomalies also are inadequate.

All experimental data, which would include animal clinical observations, must be recorded and verified (21 CFR 58.33(b)) and a description of all circumstances that may have affected the quality or integrity of the data shall be 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)).

Additionally, as noted in the FDA 483 observation from the inspection, FDA found multiple examples where entries on animal clinical observation tables and the signatures of the persons completing them and the study director's signature appeared to be photocopies of the same document, with only changes to the week number and date. Upon review of the source data records for animal and implantation site observations, FDA identified evidence that indicates the records were photocopied. Specifically, portions of the handwritten raw data observation records for the study animals are identical across multiple weeks. For example, during the 13-week implantation period for test report (b) (4) (Study #(b) (4) the animal observation records, which are marked with slashes to indicate that observations of animals and implantation sites have been conducted, show identical slash marks from weeks 2-9, accompanied by identical signatures. Representative examples of these animal observation records are provided below, illustrating that for test report (b) (4) week 2 daily observation records of 3 animals with 10 implantation sites have identical slashes to the week 3 daily observation records and week 4 daily observation records.

(b) (4) (Study #(b) (4) week 2

(b) (4)

试验动物与植入点观察（2 周）

| 编号 | 分组 | 植入点 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 试验组 | 1 | √ | √ | √ | √ | √ | √ | √ |
| | | 2 | √ | √ | √ | √ | √ | √ | √ |
| | | 3 | √ | √ | √ | √ | √ | √ | √ |
| | | 4 | √ | √ | √ | √ | √ | √ | √ |
| | 对照组 | 1 | √ | √ | √ | √ | √ | √ | √ |
| | | 2 | √ | √ | √ | √ | √ | √ | √ |
| | | 3 | √ | √ | √ | √ | √ | √ | √ |
| | | 4 | √ | √ | √ | √ | √ | √ | √ |
| 2 | 试验组 | 5 | √ | √ | √ | √ | √ | √ | √ |
| | | 6 | √ | √ | √ | √ | √ | √ | √ |
| | | 7 | √ | √ | √ | √ | √ | √ | √ |
| | 对照组 | 5 | √ | √ | √ | √ | √ | √ | √ |
| | | 6 | √ | √ | √ | √ | √ | √ | √ |
| | | 7 | √ | √ | √ | √ | √ | √ | √ |
| 3 | 试验组 | 8 | √ | √ | √ | √ | √ | √ | √ |
| | | 9 | √ | √ | √ | √ | √ | √ | √ |
| | | 10 | √ | √ | √ | √ | √ | √ | √ |
| | 对照组 | 8 | √ | √ | √ | √ | √ | √ | √ |
| | | 9 | √ | √ | √ | √ | √ | √ | √ |
| | | 10 | √ | √ | √ | √ | √ | √ | √ |
| 操作人签名 | | | (b) (6) | | | | | | |
| 操作日期 | | | 2024.02.08 | | | | | | |

若出现异常情况，详细记录动物情况，必要时将动物解剖，进行大体检查与其他检查。
√：表示已进行观察。

审核人签名/日期：(b) (6)

(b) (4) (Study #(b) (4) week 3

(b) (4)

试验动物与植入点观察（3 周）

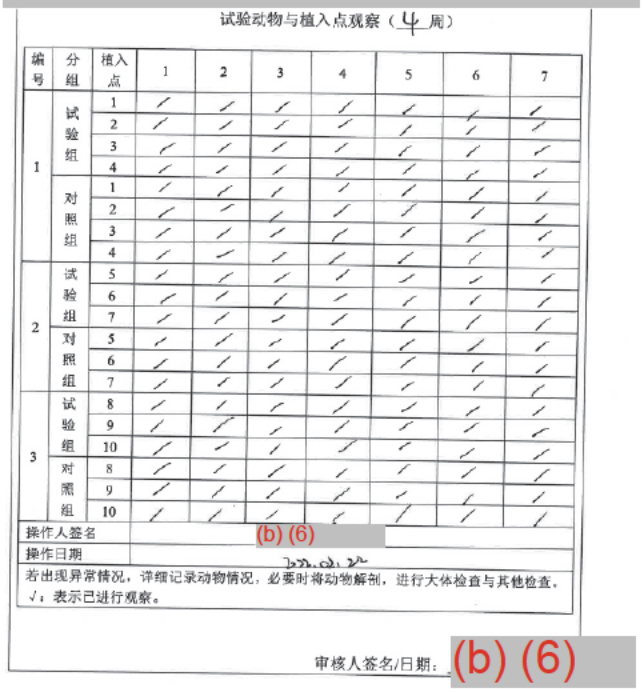
| 编号 | 分组 | 植入点 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 试验组 | 1 | √ | √ | √ | √ | √ | √ | √ |
| | | 2 | √ | √ | √ | √ | √ | √ | √ |
| | | 3 | √ | √ | √ | √ | √ | √ | √ |
| | | 4 | √ | √ | √ | √ | √ | √ | √ |
| | 对照组 | 1 | √ | √ | √ | √ | √ | √ | √ |
| | | 2 | √ | √ | √ | √ | √ | √ | √ |
| | | 3 | √ | √ | √ | √ | √ | √ | √ |
| | | 4 | √ | √ | √ | √ | √ | √ | √ |
| 2 | 试验组 | 5 | √ | √ | √ | √ | √ | √ | √ |
| | | 6 | √ | √ | √ | √ | √ | √ | √ |
| | | 7 | √ | √ | √ | √ | √ | √ | √ |
| | 对照组 | 5 | √ | √ | √ | √ | √ | √ | √ |
| | | 6 | √ | √ | √ | √ | √ | √ | √ |
| | | 7 | √ | √ | √ | √ | √ | √ | √ |
| 3 | 试验组 | 8 | √ | √ | √ | √ | √ | √ | √ |
| | | 9 | √ | √ | √ | √ | √ | √ | √ |
| | | 10 | √ | √ | √ | √ | √ | √ | √ |
| | 对照组 | 8 | √ | √ | √ | √ | √ | √ | √ |
| | | 9 | √ | √ | √ | √ | √ | √ | √ |
| | | 10 | √ | √ | √ | √ | √ | √ | √ |
| 操作人签名 | | | (b) (6) | | | | | | |
| 操作日期 | | | 2024.02.15 | | | | | | |

若出现异常情况，详细记录动物情况，必要时将动物解剖，进行大体检查与其他检查。
√：表示已进行观察。

审核人签名/日期：(b) (6)

(b) (4) (Study #(b) (4) week 4

(b) (4)



试验动物与植入点观察（4 周）

| 编号 | 分组 | 植入点 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 试验组 | 1 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 2 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 3 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 4 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | 对照组 | 1 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 2 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 3 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 4 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 2 | 试验组 | 5 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 6 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 7 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | 对照组 | 5 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 6 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 7 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 3 | 试验组 | 8 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 9 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 10 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | 对照组 | 8 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 9 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 10 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

操作人签名 (b) (6)

操作日期 2021.07.26

若出现异常情况，详细记录动物情况，必要时将动物解剖，进行大体检查与其他检查。

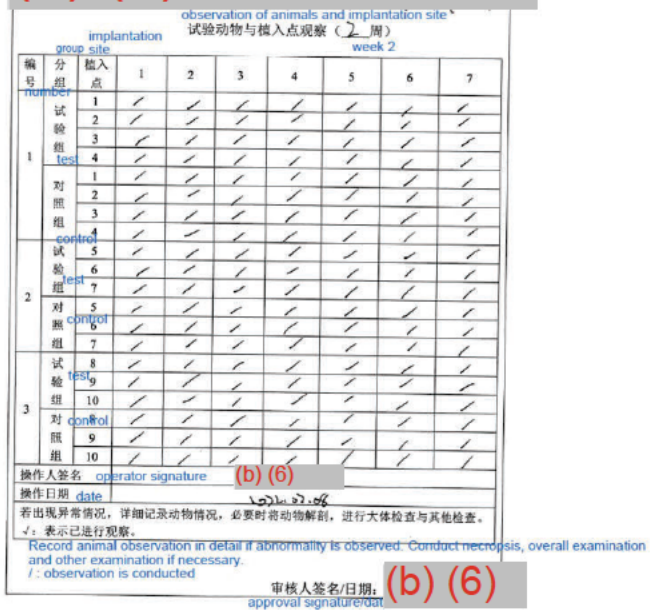
√：表示已进行观察。

审核人签名/日期：(b) (6)

English translations are added below in blue:

(b) (4) (Study #(b) (4) week 2

(b) (4)



observation of animals and implantation site

试验动物与植入点观察（2 周）

implantation site

week 2

| 编号 number | 分组 | 植入点 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 试验组 test | 1 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 2 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 3 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 4 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | 对照组 control | 1 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 2 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 3 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 4 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 2 | 试验组 test | 5 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 6 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 7 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | 对照组 control | 5 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 6 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 7 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 3 | 试验组 test | 8 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 9 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 10 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | 对照组 control | 8 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 9 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 10 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

操作人签名 operator signature (b) (6)

操作日期 date 2021.07.26

若出现异常情况，详细记录动物情况，必要时将动物解剖，进行大体检查与其他检查。

√：表示已进行观察。

Record animal observation in detail if abnormality is observed. Conduct necropsis, overall examination and other examination if necessary.

√: observation is conducted

审核人签名/日期：(b) (6)

approval signature/date

This evidence includes identical slash marks appearing across multiple pages of records (ultimately indicating no abnormal signs) for multiple animals and timepoints within individual studies and across multiple study reports.

Importantly, both the FDA 483 observations and FDA Warning Letter noted that in multiple GPMT studies conducted by three different study directors and three different technicians, there were six pages of source data in each study where the results and the technicians' signatures were photocopied from prior studies and reused by adding new dates and animal weights. The photocopied data include both animal observation and final skin sensitization scores. In addition to the animal weight-related anomalies for Report Nos. (b) (4) (Study # (b) (4) and (b) (4) (Study # (b) (4) described above, certain portions of the handwritten raw data observations recorded for the study animals were identical across the two studies, as shown below (English translations added in blue):

(b) (4) Study # (b) (4) ori inal/not translated, art 1

试验过程

| 分组 | 编号 | 体重 | 被毛 | 皮内诱导阶段 | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 皮内注射部位、溶剂及剂量（0.1mL） | | | | | | 皮内诱导后刺激反应观察 | | | | | | |
| | | | | 左上 | 右上 | 左中 | 右中 | 左下 | 右下 | 第一天 | 第二天 | 第三天 | 第四天 | 第五天 | 第六天 | 第七天 |
| 试验组 | 1 | 318.1 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 2 | 307. | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 3 | 318.0 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 4 | 306.8 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 5 | 307.4 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 6 | 318.5 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 7 | 308.8 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 8 | 317.1 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 9 | 304.1 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 10 | 316.8 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| 阴性对照组 | 11 | 306.0 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 12 | 310.4 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 13 | 308.2 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 14 | 307.2 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 15 | 312.5 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| 操作人 | (b) (6) | | | | | | | | | | | | | | | |
| 日 期 | 09.13 | | | 09.14 | | | | | | 09.14 | 09.15 | 09.16 | 09.17 | 09.18 | 09.19 | 09.20 |

注："/" 代表已执行

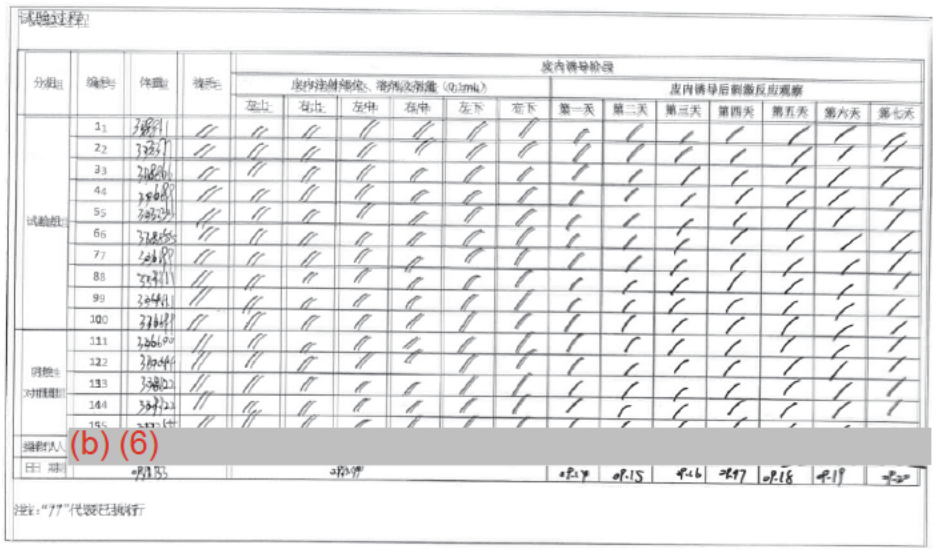
(b) (4) (Study # (b) (4) (original/not translated, part 1)

试验过程

| 分组 | 编号 | 体重 | 被毛 | 皮内诱导阶段 | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 皮内注射部位、溶剂及剂量（0.1mL） | | | | | | 皮内诱导后刺激反应观察 | | | | | | |
| | | | | 左上 | 右上 | 左中 | 右中 | 左下 | 右下 | 第一天 | 第二天 | 第三天 | 第四天 | 第五天 | 第六天 | 第七天 |
| 试验组 | 1 | 318.1 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 2 | 333.2 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 3 | 318.4 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 4 | 306.8 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 5 | 333.3 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 6 | 318.5 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 7 | 308.8 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 8 | 319.1 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 9 | 304.1 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 10 | 316.8 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| 阴性对照组 | 11 | 306.0 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 12 | 310.4 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 13 | 308.2 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 14 | 309.2 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 15 | 312.5 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| 操作人 | (b) (6) | | | | | | | | | | | | | | | |
| 日 期 | 07.15 | | | 07.17 | | | | | | 07.19 | 07.15 | 07.16 | 07.17 | 07.18 | 07.19 | 07.20 |

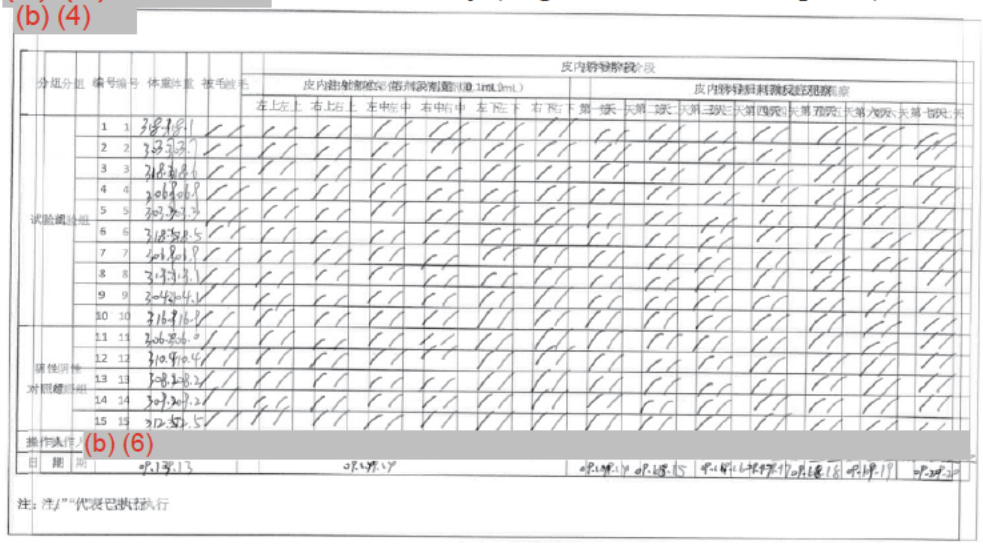
注："/" 代表已执行

(b) (4) (Study # (b) (4) and (b) (4) (Study # (b) (4) Direct Overlay (original/not translated, part 1)



In the above image, the (b) (4) table is set to 60% transparency and overlaid onto the (b) (4) table. Column 3 shows weight values from both tables but the slash marks for each animal are exactly on top of each other (*i.e.,* identical).

(b) (4) (Study # (b) (4) and (b) (4) (Study # (b) (4) Off-set Overlay (original/not translated, part 1)



In the above image, the (b) (4) (Study # (b) (4) table is set to 60% transparency, overlaid onto the (b) (4) (Study # (b) (4) table, and shifted to the side for easier side-by-side comparisons of each slash mark. Each slash mark has identical characteristics (*e.g.,* same length, same shape, same relative box positioning).

(b) (4) (Study # (b) (4) (original/not translated, part 2)

| 分组 | 被毛 | 局部诱导前24h是否出现刺激反应 | | 局部诱导阶段 | | | | | 激发阶段 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 左 | 右 | 10%SDS预处理 | 贴敷部位 | 剂量 | 贴敷 | 去除贴敷 | 被毛 | 贴敷部位与剂量 | 贴敷 | 去除贴敷 |
| 试验组 | √ | 0 | 0 | √ | 肩胛骨内侧部位，覆盖诱导注射点 | 浸透样品浸提液（面积约8cm²的吸水性纱布块） | √ | √ | √ | 左侧腹部：浸透样品浸提液（约0.4mL）的吸水性纱布（2.5cm×2.5cm）；右侧腹部：浸透对照液（约0.4mL）的吸水性纱布（2.5cm×2.5cm）。 | √ | √ |
| 阴性对照组 | √ | 0 | 0 | √ | | 浸透对照液 | √ | √ | √ | | √ | √ |
| 操作人 | (b) (6) | | | | | | | | | | | |
| 日 期 | 3月20 | | | 3月21 | | | 3月23 | | 10.24 | 10.25 | 11.06 | |

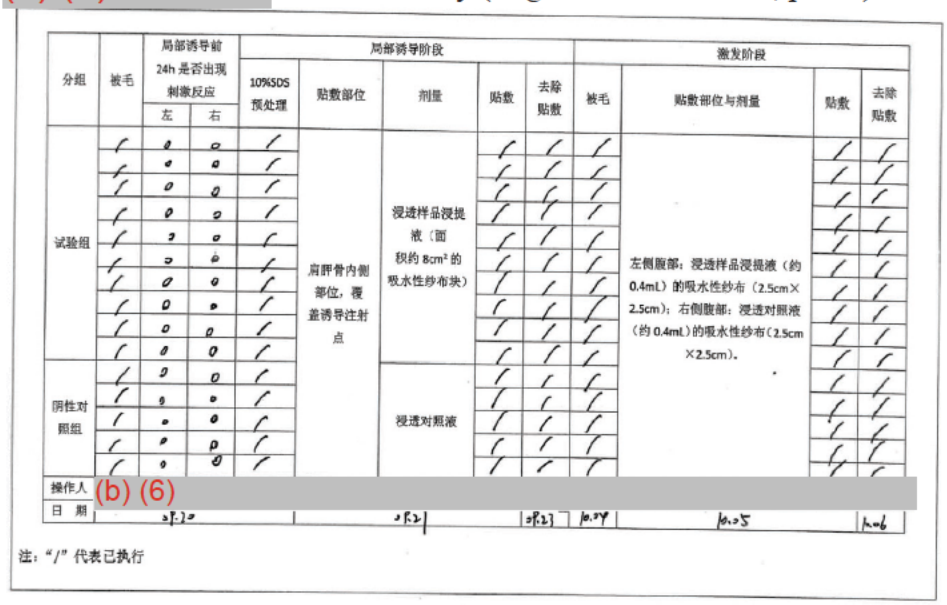
注："/"代表已执行

(b) (4) (Study # (b) (4) (original/not translated, part 2)

| 分组 | 被毛 | 局部诱导前24h是否出现刺激反应 | | 局部诱导阶段 | | | | | 激发阶段 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 左 | 右 | 10%SDS预处理 | 贴敷部位 | 剂量 | 贴敷 | 去除贴敷 | 被毛 | 贴敷部位与剂量 | 贴敷 | 去除贴敷 |
| 试验组 | √ | 0 | 0 | √ | 肩胛骨内侧部位，覆盖诱导注射点 | 浸透样品浸提液（面积约8cm²的吸水性纱布块） | √ | √ | √ | 左侧腹部：浸透样品浸提液（约0.4mL）的吸水性纱布（2.5cm×2.5cm）；右侧腹部：浸透对照液（约0.4mL）的吸水性纱布（2.5cm×2.5cm）。 | √ | √ |
| 阴性对照组 | √ | 0 | 0 | √ | | 浸透对照液 | √ | √ | √ | | √ | √ |
| 操作人 | (b) (6) | | | | | | | | | | | |
| 日 期 | 3月20 | | | 3月21 | | | 3月23 | | 10.24 | 10.25 | 11.06 | |

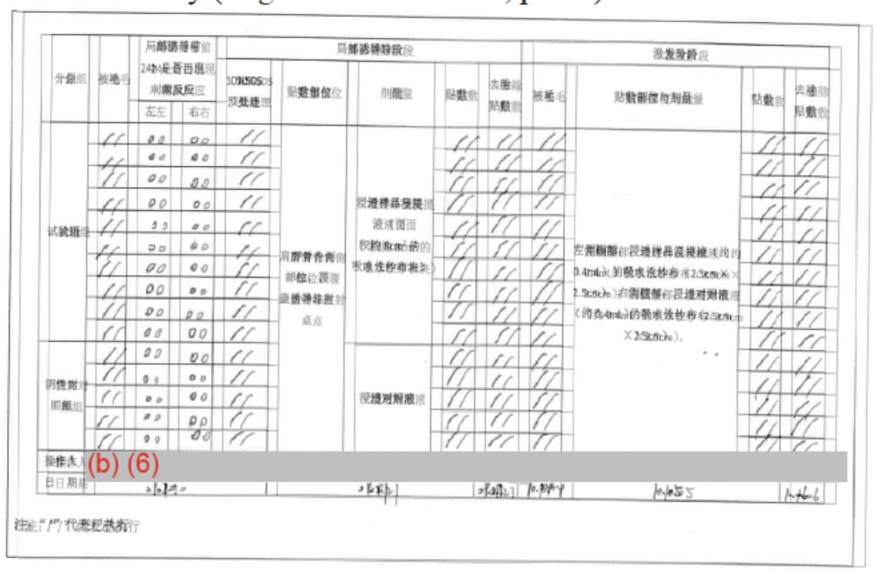
注："/"代表已执行

(b) (4) (Study # (b) (4) and (b) (4) (Study # (b) (4) Direct Overlay (original/not translated, part 2)




In the above image, the (b) (4) table is set to 60% transparency and overlaid onto the (b) (4) (Study # (b) (4) table. The entire table is exactly on top of the other (*i.e.,* identical).

(b) (4) (Study # (b) (4) and (b) (4) (Study # (b) (4)
Off-set Overlay (original/not translated, part 2)




In the above image, the (b) (4) table is set to 60% transparency, overlaid onto the (b) (4) (Study # (b) (4) table, and shifted to the side for easier side-by-side comparisons of each slash mark. Each slash mark has identical characteristics (*e.g.,* same length, same shape, same relative box positioning).

(b) (4) (Study # (b) (4) (original/not translated, part 3)

试验结果观察

| 分组 | 编号 | 体重（g） | 去除贴敷后 Magnusson 和 Kligman 分级评分 | | | | 皮肤反应外的临床表现 |
|---|---|---|---|---|---|---|---|
| | | | 24±2h 结果 | | 48±2h 结果 | | |
| | | | 红斑 | 水肿 | 红斑 | 水肿 | |
| 试验组 | 1 | 383.0 | 0 | 0 | 0 | 0 | / |
| | 2 | 367.7 | 0 | 0 | 0 | 0 | / |
| | 3 | 382.7 | 0 | 0 | 0 | 0 | / |
| | 4 | 371.2 | 0 | 0 | 0 | 0 | / |
| | 5 | 387.3 | 0 | 0 | 0 | 0 | / |
| | 6 | 383.5 | 0 | 0 | 0 | 0 | / |
| | 7 | 371.8 | 0 | 0 | 0 | 0 | / |
| | 8 | 383.1 | 0 | 0 | 0 | 0 | / |
| | 9 | 368.9 | 0 | 0 | 0 | 0 | / |
| | 10 | 382.4 | 0 | 0 | 0 | 0 | / |
| 阴性对照组 | 11 | 370.4 | 0 | 0 | 0 | 0 | / |
| | 12 | 375.2 | 0 | 0 | 0 | 0 | / |
| | 13 | 371.9 | 0 | 0 | 0 | 0 | / |
| | 14 | 379.3 | 0 | 0 | 0 | 0 | / |
| | 15 | 376.5 | 0 | 0 | 0 | 0 | / |
| 操作人 | | (b) (6) | | | | | |
| 日 期 | | 10.08 | 10.07 | | 10.08 | | 10.08 |

注：Magnusson 和 Kligman 分级评分：0 分：无明显改变；1 分：散发性或斑点状红斑；2 分：中度融合性红斑；3 分：重度红斑和水肿。

操作人签名/日期：(b) (6) 2021.10.08

审核人签名/日期：(b) (6) 2021.10.08

(b) (4) (Study # (b) (4) (original/not translated, part 3)

试验结果观察

| 分组 | 编号 | 体重（g） | 去除贴敷后 Magnusson 和 Kligman 分级评分 | | | | 皮肤反应外的临床表现 |
|---|---|---|---|---|---|---|---|
| | | | 24±2h 结果 | | 48±2h 结果 | | |
| | | | 红斑 | 水肿 | 红斑 | 水肿 | |
| 试验组 | 1 | 383.3 | 0 | 0 | 0 | 0 | / |
| | 2 | 367.6 | 0 | 0 | 0 | 0 | / |
| | 3 | 383.6 | 0 | 0 | 0 | 0 | / |
| | 4 | 372.0 | 0 | 0 | 0 | 0 | / |
| | 5 | 367.5 | 0 | 0 | 0 | 0 | / |
| | 6 | 383.0 | 0 | 0 | 0 | 0 | / |
| | 7 | 371.2 | 0 | 0 | 0 | 0 | / |
| | 8 | 382.6 | 0 | 0 | 0 | 0 | / |
| | 9 | 367.8 | 0 | 0 | 0 | 0 | / |
| | 10 | 381.6 | 0 | 0 | 0 | 0 | / |
| 阴性对照组 | 11 | 369.6 | 0 | 0 | 0 | 0 | / |
| | 12 | 374.7 | 0 | 0 | 0 | 0 | / |
| | 13 | 371.6 | 0 | 0 | 0 | 0 | / |
| | 14 | 372.8 | 0 | 0 | 0 | 0 | / |
| | 15 | 376.0 | 0 | 0 | 0 | 0 | / |
| 操作人 | | (b) (6) | | | | | |
| 日 期 | | 10.08 | 10.07 | | 10.08 | | 10.08 |

注：Magnusson 和 Kligman 分级评分：0 分：无明显改变；1 分：散发性或斑点状红斑；2 分：中度融合性红斑；3 分：重度红斑和水肿。

操作人签名/日期：(b) (6) 2021.10.08

审核人签名/日期：(b) (6) 2021.10.08

(b) (4) (Study # (b) (4) and (b) (4) (Study # (b) (4) Direct Overlay (original/not translated, part 3)

试验结果观察

| 分组 | 编号 | 体重（g） | 去除贴敷后 Magnusson 和 Kligman 分级评分 | | | | 皮肤反应外的临床表现 |
|---|---|---|---|---|---|---|---|
| | | | 24±2h 结果 | | 48±2h 结果 | | |
| | | | 红斑 | 水肿 | 红斑 | 水肿 | |
| 试验组 | 1 | 3283.0 | 0 | 0 | 0 | 0 | / |
| | 2 | 2670.7 | 0 | 0 | 0 | 0 | / |
| | 3 | 2738.7 | 0 | 0 | 0 | 0 | / |
| | 4 | 3732.2 | 0 | 0 | 0 | 0 | / |
| | 5 | 2670.3 | 0 | 0 | 0 | 0 | / |
| | 6 | 2885.5 | 0 | 0 | 0 | 0 | / |
| | 7 | 3717.8 | 0 | 0 | 0 | 0 | / |
| | 8 | 3802.6 | 0 | 0 | 0 | 0 | / |
| | 9 | 3807.9 | 0 | 0 | 0 | 0 | / |
| | 10 | 3816.1 | 0 | 0 | 0 | 0 | / |
| 阴性对照组 | 11 | 3689.6 | 0 | 0 | 0 | 0 | / |
| | 12 | 3718.3 | 0 | 0 | 0 | 0 | / |
| | 13 | 3721.8 | 0 | 0 | 0 | 0 | / |
| | 14 | 3722.3 | 0 | 0 | 0 | 0 | / |
| | 15 | 3716.5 | 0 | 0 | 0 | 0 | / |
| 操作人 | | (b) (6) | | | | | |
| 日 期 | | 10.08 | 10.07 | | 10.08 | | 10.08 |

注：Magnusson 和 Kligman 分级评分：0 分：无明显改变；1 分：散发性或斑点状红斑；2 分：中度融合性红斑；3 分：重度红斑和水肿。

操作人签名/日期：(b) (6) 2021.10.08

审核人签名/日期：(b) (6) 2021.10.08

In the above image, the (b) (4) table is set to 60% transparency and overlaid onto the (b) (4) (Study # (b) (4) table. Column 3 shows weight values from both tables but the "0" scores for every animal and slash marks are exactly on top of each other (*i.e.,* identical).

(b) (4) (Study # (b) (4) and (b) (4) (Study # (b) (4)

Off-set Overlay (original/not translated, part 3)

In the above image, the (b) (4) table is set to 60% transparency, overlaid onto the (b) (4) (Study # (b) (4) table, and shifted to the side for easier side-by-side comparisons of each "0" score and slash mark. Each "0" and slash mark has the identical characteristics (*e.g.,* same incomplete "0"s, same length, same shape, same relative box positioning) (English translations added in blue).

(b) (4) (Study # (b) (4)

Test Procedures

试验过程

| Group 分组 | No 编号 | Weight 体重 | Back Fur 被毛 | Intradermal Injection Site, solution and dosage (0.1mL) 皮内注射部位、溶剂及剂量（0.1mL） | | | | | | Intradermal Induction Phase 皮内诱导阶段 | | | | | | Post Induction Observation for Irritation 皮内诱导后刺激反应观察 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 左上 Upper Left | 右上 Upper Right | 左中 Center Left | 右中 Center Right | 左下 Bottom Left | 右下 Bottom Right | 第一天 Day 1 | 第二天 Day 2 | 第三天 Day 3 | 第四天 Day 4 | 第五天 Day 5 | 第六天 Day 6 | 第七天 Day 7 |
| Test Article 试验组 | 1 | 318.1 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 2 | 303.6 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 3 | 318.9 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 4 | 308.2 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 5 | 303.9 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 6 | 318.6 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 7 | 306.7 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 8 | 319.2 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 9 | 304.5 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 10 | 316.8 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| Negative Control 阴性对照组 | 11 | 298.8 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 12 | 310.3 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 13 | 308.0 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 14 | 304.0 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 15 | 312.7 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| Operator 操作人 | | (b) (6) | | (b) (6) in all | | | | | | (b) (6) | | | | | | |
| Date 日 期 | | 09.13 | | signatures on this page | | | | | | 09.14 | 09.15 | 09.16 | 09.17 | 09.18 | 09.19 | 09.20 |

注："/" 代表已执行

Note (b) (6) n all signatures on this page

(b) (4) (Study # (b) (4)

Test Procedures

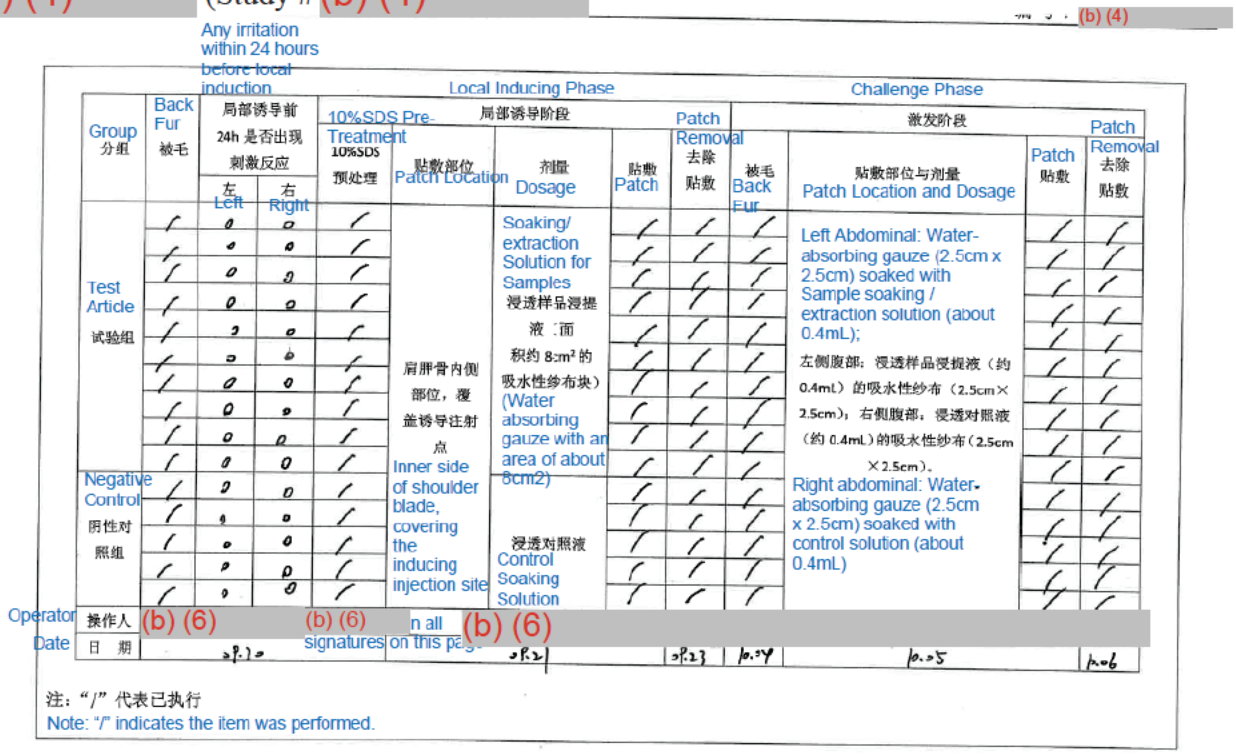
试验过程

| Group 分组 | No. 编号 | Weight 体重 | Back Fur 被毛 | Intradermal Injection Site, solution and dosage (0.1mL) 皮内注射部位、溶剂及剂量（0.1mL） | | | | | | Intradermal Induction Phase 皮内诱导阶段 | | | | | | Post Induction Observation for Irritation 皮内诱导后刺激反应观察 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 左上 Upper Left | 右上 Upper Right | 左中 Center Left | 右中 Center Right | 左下 Bottom Left | 右下 Bottom Right | 第一天 Day 1 | 第二天 Day 2 | 第三天 Day 3 | 第四天 Day 4 | 第五天 Day 5 | 第六天 Day 6 | 第七天 Day 7 |
| Test Article 试验组 | 1 | 318.1 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 2 | 303.7 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 3 | 318.9 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 4 | 308.8 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 5 | 303.3 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 6 | 318.5 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 7 | 308.8 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 8 | 319.1 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 9 | 304.1 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 10 | 318.8 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| Negative Control 阴性对照组 | 11 | 306.0 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 12 | 310.4 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 13 | 308.2 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 14 | 307.2 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| | 15 | 312.5 | / | / | / | / | / | / | / | / | / | / | / | / | / | / |
| Operator 操作人 | | (b) (6) | | (b) (6) n all | | | | | | (b) (6) | | | | | | |
| Date 日 期 | | 09.13 | | signatures on this page | | | | | | 09.14 | 09.15 | 09.16 | 09.17 | 09.18 | 09.19 | 09.20 |

注："/" 代表已执行

Note: "/" indicates the item was performed.

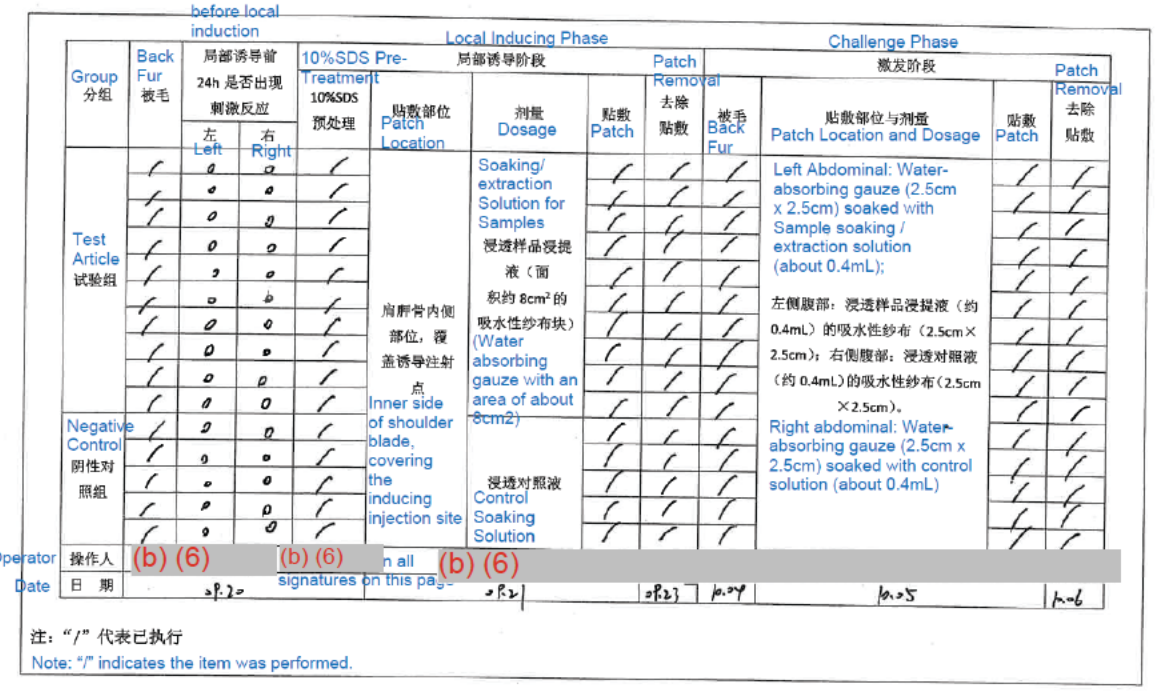
(b) (4) (Study # (b) (4)



| Group 分组 | Back Fur 被毛 | 局部诱导前 24h 是否出现刺激反应 Any irritation within 24 hours before local induction 左 Left | 右 Right | Local Inducing Phase 局部诱导阶段 10%SDS Pre-Treatment 10%SDS 预处理 | 贴敷部位 Patch Location | 剂量 Dosage | 贴敷 Patch | Patch Removal 去除贴敷 | Challenge Phase 激发阶段 被毛 Back Fur | 贴敷部位与剂量 Patch Location and Dosage | 贴敷 Patch | Patch Removal 去除贴敷 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Test Article 试验组 | | | | | 肩胛骨内侧部位，覆盖诱导注射点 Inner side of shoulder blade, covering the inducing injection site | Soaking/extraction Solution for Samples 浸透样品浸提液（面积约 8cm² 的吸水性纱布块）(Water absorbing gauze with an area of about 8cm2) | | | | Left Abdominal: Water-absorbing gauze (2.5cm x 2.5cm) soaked with Sample soaking / extraction solution (about 0.4mL); 左侧腹部：浸透样品浸提液（约 0.4mL）的吸水性纱布（2.5cm×2.5cm）；右侧腹部：浸透对照液（约 0.4mL）的吸水性纱布（2.5cm×2.5cm）。 Right abdominal: Water-absorbing gauze (2.5cm x 2.5cm) soaked with control solution (about 0.4mL) | | |
| Negative Control 阴性对照组 | | | | | | 浸透对照液 Control Soaking Solution | | | | | | |
| Operator 操作人 | (b) (6) | | | (b) (6) n all signatures on this page | | | | | | | | |
| Date 日 期 | | 9月20 | | | | 9月22 | 9月23 | 10.24 | | 10.25 | | 10.26 |

注："/" 代表已执行
Note: "/" indicates the item was performed.

(b) (4) (Study # (b) (4)



| Group 分组 | Back Fur 被毛 | 局部诱导前 24h 是否出现刺激反应 Any irritation within 24 hours before local induction 左 Left | 右 Right | Local Inducing Phase 局部诱导阶段 10%SDS Pre-Treatment 10%SDS 预处理 | 贴敷部位 Patch Location | 剂量 Dosage | 贴敷 Patch | Patch Removal 去除贴敷 | Challenge Phase 激发阶段 被毛 Back Fur | 贴敷部位与剂量 Patch Location and Dosage | 贴敷 Patch | Patch Removal 去除贴敷 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Test Article 试验组 | | | | | 肩胛骨内侧部位，覆盖诱导注射点 Inner side of shoulder blade, covering the inducing injection site | Soaking/extraction Solution for Samples 浸透样品浸提液（面积约 8cm² 的吸水性纱布块）(Water absorbing gauze with an area of about 8cm2) | | | | Left Abdominal: Water-absorbing gauze (2.5cm x 2.5cm) soaked with Sample soaking / extraction solution (about 0.4mL); 左侧腹部：浸透样品浸提液（约 0.4mL）的吸水性纱布（2.5cm×2.5cm）；右侧腹部：浸透对照液（约 0.4mL）的吸水性纱布（2.5cm×2.5cm）。 Right abdominal: Water-absorbing gauze (2.5cm x 2.5cm) soaked with control solution (about 0.4mL) | | |
| Negative Control 阴性对照组 | | | | | | 浸透对照液 Control Soaking Solution | | | | | | |
| Operator 操作人 | (b) (6) | | | (b) (6) n all signatures on this page | | | | | | | | |
| Date 日 期 | | 9月20 | | | | 9月22 | 9月23 | 10.24 | | 10.25 | | 10.26 |

注："/" 代表已执行
Note: "/" indicates the item was performed.

(b) (4) (Study # (b) (4)

Observation of Test Results

试验结果观察

Scoring by Magnusson and Kligman Scale after the patch removal

| Group 分組 | No. 编号 | Weight (g) 体重（g） | 去除贴敷后 Magnusson 和 Kligman 分级评分 24±2h 结果result 红斑 Erythema | 水肿 Swelling | 48±2h 结果result 红斑 Erythema | 水肿 Swelling | 皮肤反应 外的临床表现 Clinical Manifestation other than skin reactions |
|---|---|---|---|---|---|---|---|
| Test Article 试验组 | 1 | 383.0 | 0 | 0 | 0 | 0 | / |
| | 2 | 387.7 | 0 | 0 | 0 | 0 | / |
| | 3 | 382.7 | 0 | 0 | 0 | 0 | / |
| | 4 | 377.2 | 0 | 0 | 0 | 0 | / |
| | 5 | 387.3 | 0 | 0 | 0 | 0 | / |
| | 6 | 387.5 | 0 | 0 | 0 | 0 | / |
| | 7 | 377.8 | 0 | 0 | 0 | 0 | / |
| | 8 | 383.1 | 0 | 0 | 0 | 0 | / |
| | 9 | 388.4 | 0 | 0 | 0 | 0 | / |
| | 10 | 382.4 | 0 | 0 | 0 | 0 | / |
| Negative Control 阴性对照组 | 11 | 377.4 | 0 | 0 | 0 | 0 | / |
| | 12 | 375.2 | 0 | 0 | 0 | 0 | / |
| | 13 | 377.9 | 0 | 0 | 0 | 0 | / |
| | 14 | 377.3 | 0 | 0 | 0 | 0 | / |
| | 15 | 376.5 | 0 | 0 | 0 | 0 | / |
| Operator 操作人 | | (b) (6) | | | | | (b) (6) in all 4 signatures here |
| Date 日 期 | | 10.08 | 10.07 | | 10.08 | | 10.08 |

注：Magnusson 和 Kligman 分级评分：0 分：无明显改变；1 分：散发性或斑点状红斑；2 分：中度融合性红斑；3 分：重度红斑和水肿。

操作人签名/日期：(b) (6) 2021.10.08

审核人签名/日期：(b) (6) 2021.10.08

Note: Scoring reference by Magnusson & Kligman Scale - 0: No visible change; 1: discrete or patchy erythema; 2: Moderate or confluent erythema; 3: Intense erythema and swelling

Operator Signature/Date: (b) (6) 2021.10.08
Approval Signature/Date: (b) (6) 2021.10.08

(b) (4) (Study # (b) (4)

Observation of Test Results

试验结果观察

Scoring by Magnusson and Kligman Scale after the patch removal

| Group 分組 | No. 编号 | Weight (g) 体重（g） | 去除贴敷后 Magnusson 和 Kligman 分级评分 24±2h 结果result 红斑 Erythema | 水肿 Swelling | 48±2h 结果result 红斑 Erythema | 水肿 Swelling | 皮肤反应 外的临床表现 Clinical Manifestation other than skin reactions |
|---|---|---|---|---|---|---|---|
| Test Article 试验组 | 1 | 385.3 | 0 | 0 | 0 | 0 | / |
| | 2 | 367.6 | 0 | 0 | 0 | 0 | / |
| | 3 | 387.6 | 0 | 0 | 0 | 0 | / |
| | 4 | 372.0 | 0 | 0 | 0 | 0 | / |
| | 5 | 367.5 | 0 | 0 | 0 | 0 | / |
| | 6 | 383.0 | 0 | 0 | 0 | 0 | / |
| | 7 | 371.2 | 0 | 0 | 0 | 0 | / |
| | 8 | 382.6 | 0 | 0 | 0 | 0 | / |
| | 9 | 367.8 | 0 | 0 | 0 | 0 | / |
| | 10 | 381.6 | 0 | 0 | 0 | 0 | / |
| Negative Control 阴性对照组 | 11 | 368.6 | 0 | 0 | 0 | 0 | / |
| | 12 | 374.7 | 0 | 0 | 0 | 0 | / |
| | 13 | 371.6 | 0 | 0 | 0 | 0 | / |
| | 14 | 372.8 | 0 | 0 | 0 | 0 | / |
| | 15 | 376.0 | 0 | 0 | 0 | 0 | / |
| Operator 操作人 | | (b) (6) | | | | | (b) (6) in all 4 signatures here |
| Date 日 期 | | 10.08 | 10.07 | | 10.08 | | 10.08 |

注：Magnusson 和 KHgman 分级评分：0 分：无明显改变；1 分：散发性或斑点状红斑；2 分：中度融合性红斑；3 分：重度红斑和水肿。

操作人签名/日期：(b) (6) 2021.10.08

审核人签名/日期：(b) (6) 2021.10.08

Note: Scoring reference by Magnusson & Kligman Scale - 0: No visible change; 1: discrete or patchy erythema; 2: Moderate or confluent erythema; 3: Intense erythema and swelling

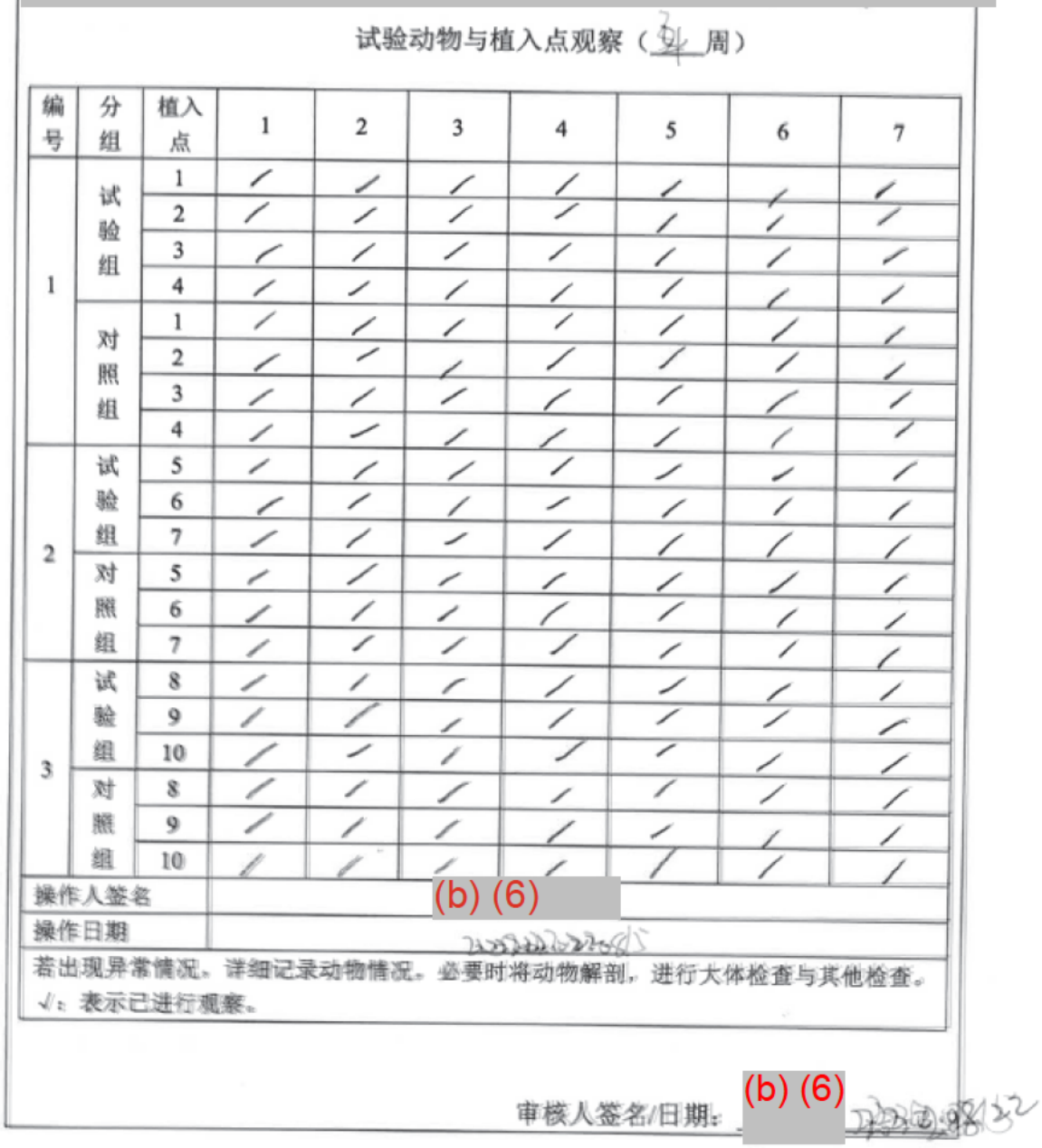
Operator Signature/Date: (b) (6) 2021.10.08
Approval Signature/Date: (b) (6) 2021.10.08

As can be seen in the copies of the raw data records above, there are identical handwritten slash marks and identical handwritten zero "0" scores for all test articles and control animals between Report Nos. (b) (4) (Study # (b) (4) and (b) (4) (Study # (b) (4) These identical handwritten markings and scores indicate that the observations for each animal were either pre-filled photocopies for both studies or were photocopied from one study to the other. A total of six pages have photocopied data in each study. The two studies discussed here are examples, as FDA found multiple GPMT skin sensitization studies with photocopied raw data records during the inspection.

Similar issues were observed in the studies referenced in Section 1.2 above. The table below identifies certain weeks that show where animal observation data has been photocopied, along with examples of records demonstrating identical observation entries. In the 7 muscle implantation studies listed for this cardiovascular implant that was being studied, over 200 pages of handwritten observation data, which record the daily health status of the studied animals and implantation sites, are identical from one week to the other within individual studies and across different study timepoints.

| Report # / Study # | Study endpoint weeks | Weeks with photocopied animal observation data |
|---|---|---|
| (b) (4) | 4 Weeks | 2-4 |
| | 13 Weeks | 2-9 and 11-13 |
| Study # (b) (4) | 26 Weeks | 2-12 and 14-26 |
| (b) (4) | 4 Weeks | 2-4 |
| | 13 Weeks | 2-9 and 11-13 |
| Study# (b) (4) | 26 Weeks | 2-12 and 14-26 |
| (b) (4) | 4 Weeks | 2-4 |
| | 13 Weeks | 2-9 and 11-13 |
| Study # (b) (4) | 26 Weeks | 2-12 and 14-26 |
| (b) (4) | 4 Weeks | 2-4 |
| Study# (b) (4) | 13 Weeks | 2-9 and 11-13 |
| | 26 Weeks | 2-12 and 14-26 |
| (b) (4) | 4 Weeks | 2-4 |
| | 13 Weeks | 2-9 and 11-13 |
| Study# (b) (4) | 26 Weeks | 2-12 and 14-26 |
| (b) (4) | 4 Weeks | 2-4 |
| | 13 Weeks | 2-9 and 11-13 |
| Study# (b) (4) | 26 Weeks | 2-12 and 14-26 |
| (b) (4) | 4 Weeks | 2-4 |
| | 13 Weeks | 2-9 and 11-13 |
| Study # (b) (4) | 26 Weeks | 2,9-10; 16-26 |

(b) (4)



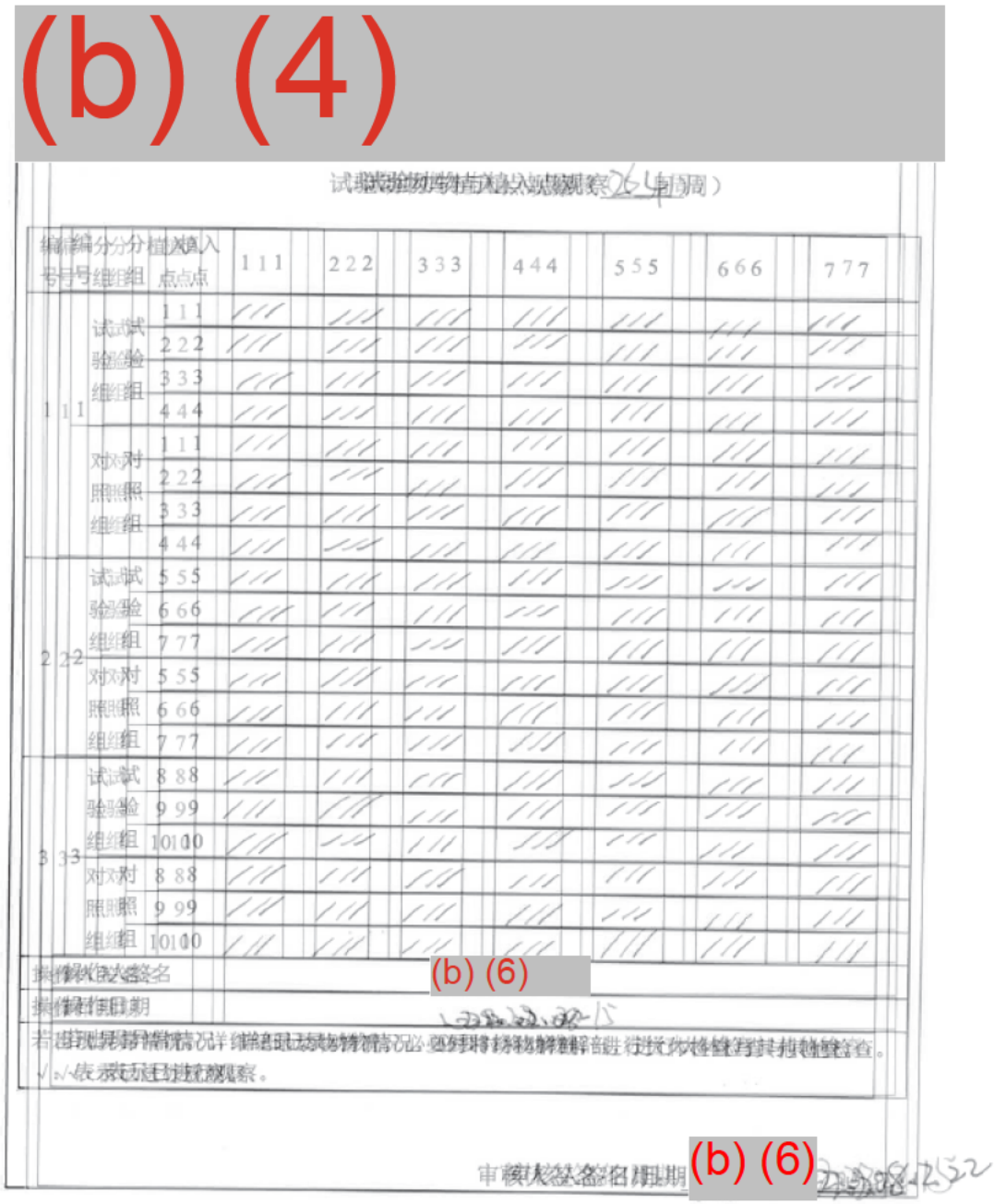
试验动物与植入点观察（3 周）

| 编号 | 分组 | 植入点 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 试验组 | 1 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 2 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 3 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 4 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | 对照组 | 1 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 2 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 3 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 4 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 2 | 试验组 | 5 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 6 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 7 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | 对照组 | 5 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 6 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 7 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 3 | 试验组 | 8 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 9 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 10 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | 对照组 | 8 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 9 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 10 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 操作人签名 | | | (b) (6) | | | | | | |
| 操作日期 | | | | | | | | | |

若出现异常情况，详细记录动物情况，必要时将动物解剖，进行大体检查与其他检查。
√：表示已进行观察。

审核人签名/日期：(b) (6)

In the above image, the (b) (4) (Study #(b) (4) tables for Weeks 2, 3, and 4 are set to 60% transparency and overlaid each other. The slash marks for every animal are exactly on top of each other (*i.e.,* identical). The differences can be seen in the handwritten week numbers and dates.




In the above image, the (b) (4) (Study #(b) (4) tables for Weeks 2, 3, and 4 are set to 60% transparency, overlaid each other, and shifted to the side for easier side-by-side comparisons of each slash mark. Each slash mark has identical characteristics (*e.g.,* same length, same shape, same relative box positioning).

For all of the above cited studies, each slash mark has identical characteristics (*e.g.,* same length, same shape, same relative box positioning). These identical handwritten markings indicate that the observations for each animal and implantation site were either pre-filled photocopies or were photocopied from one study to the other, and thus actual observations do not appear to have been made of the animals involved in the study.

FDA acknowledges the responses that your firm submitted following issuance of the FDA Form 483 and the subsequent Warning Letter. Your firm described a range of immediate and longer-term corrective actions, including the development of new SOPs, training, electronic system controls, and retrospective data reviews. However, these corrective actions appear reactive in nature rather than systemic. They address only the observations cited in the Form 483 and subsequent Warning Letter, without adequately remediating the underlying root cause(s) of the deficiencies. Furthermore, the photocopied data issue represents a critical data integrity failure: it spans multiple study types, multiple personnel, and multiple years, demonstrating that this is a systemic problem rather than an isolated occurrence. Your firm has not demonstrated that the proposed corrective actions are effective or sufficient to prevent recurrence of these issues.

Additionally, your November 28, 2025 response to the GCL 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 systemic inadequacies will not persist.

You also provided ATT-08-001 Data Integrity SOP, ATT-08-002 Data Integrity Training Material, and ATT-08-003 Training Assessment Results. However, FDA cannot determine the adequacy of your response for the following reasons. First, FDA cannot evaluate the nature or extent of the "Data Integrity Training" because the submitted documents were not provided in English. Second, even if the documents had been provided in English, they would not directly address the fundamental issue identified in this observation and the observations cited above. The core issue is that handwritten raw data records are identical across multiple studies—a pattern that cannot be attributed to coincidence and that indicates a systemic data integrity problem spanning multiple study types. Training materials alone are insufficient to address a problem of this nature and scope. Additionally, the limited list of personnel that were identified in ATT-08-003 Training Assessment Results indicates that the training was not implemented facility-wide and did not include all study personnel and study oversight levels. Furthermore, you have not conducted a complete retrospective review of your facility's studies to determine the full scope and extent of the identical handwritten raw data observation records across multiple studies. Such a review should encompass test protocols, completed acute systemic toxicity studies, Quality Assurance and Test Facility Management units and requirements, and Study Director responsibilities.

You also stated, "It is noted that the US Food and Drug Administration cited some international (not-domestic) literature as judgment, we still need to consider the differences in animal husbandry and growth between domestic and foreign animals. Therefore, while improve employees' requirements for data integrity, we will also continue to strengthen the animal management of suppliers and feeding." Your assertion that it is appropriate to "consider the differences in animal husbandry and growth between domestic and foreign animals" lacks supporting scientific evidence and does not address the fundamental concerns identified above. The principles of biological variation apply to all living systems, and your response lacks supporting data to demonstrate that the animal strains used in your studies would be exempt from such variation. The observed patterns of identical values and linear data trends cannot be

adequately explained by established biological mechanisms or standard animal husbandry practices.

Both the FDA 483 observations and FDA Warning Letter, issued January 14, 2025, and June 25, 2025, respectively, similarly reflect these and study issues. Your July 13, 2025, August 9, 2025, September 13, 2025, October 11, 2025, November 8, 2025, December 27, 2025, and February 5, 2026, responses to the Warning Letter are inadequate to demonstrate that the GLP violations are adequately and systemically addressed and that study observations are now being reported or reported accurately (see the "Your Warning Letter Responses" section below).

2. Other items requested by FDA in the October 30, 2025, GCL.

As stated above, in our October 30, 2025, 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.

Throughout Observations 1-8 of your response, you provided some responses to FDA-requested items 2-5.

You provided some explanations regarding why your testing facility failed to identify and assess the data anomalies. Specifically, you asserted that training on data integrity is inadequate, that abnormal clinical observations of animals need to be recorded and the clinical observation procedure is inadequate, that raw data was not accurately reflected in a report/study, that inadequate animal welfare may have been the cause of data anomalies, that animal weights are similar upon arrival and animals are raised in the same environment, that there was a lack of testing record controls, that certain staff are responsible for the results of data and are qualified to do the testing, and that similar animal weights before and after treatment is reliable. However, these data anomaly incidents are not isolated instances, as the volume and breadth of instances demonstrate a systemic failure of study conduct, training, and oversight by the study directors, quality assurance unit, and test facility management. Furthermore, these data anomaly identification failures demonstrate that they cannot be evaluated in isolation from the broader system of process and procedures.

You also provided a partial explanation of how your overall system of procedures contributed or permitted multiple studies conducted at your testing facility to have numerous instances of anomalous data. In addition, you provided and/or described corrective actions you are taking to

address specific gaps and issues as described in Sections 1.1 – 1.8 above. FDA notes that, while you provided ATT-02-001 The procedure of clinical observation, it is unclear how animal study observations will be recorded as part of the raw data records, what actions will be taken once a clinical observation is made beyond "immediately notify the veterinarian and the project leader to take appropriate measures in a timely manner," and whether these observations will be included in the study report and interpreted along with the study data. Furthermore, it is unclear what training materials were provided to conduct the new trainings and daily observation recordings referenced in Attachment ATT-02-003 Training material, as the documents were not in English, preventing FDA from fully reviewing the adequacy of your training program. Additionally, and importantly, you provided updated "Data Integrity" documents, specifically ATT-08-001 Data Integrity SOP, ATT-08-002 Data Integrity Training Material, and ATT-08-003 Training Assessment Results; however, FDA cannot determine the adequacy of these materials, as they were not provided in English. Furthermore, it should be noted that study data integrity is mandated by the GLP regulations and is not simply a matter of internal SOP compliance.

Your response lacks critical information regarding whether any other studies conducted at your testing facility exhibit 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. The CAPA investigations provided represent surface-level investigations limited to the specific studies that FDA cited in the original October 30, 2025 GCL, rather than systemic retrospective root cause investigations. In addition, your response stated that "[g]rowing in similar environments may result in similar body weights of animals after administration," while also concluding "inadequate animal welfare" may be the cause, as previously described above in Sections 1.3, 1.4, 1.6, 1.7, and 1.8. While you provided documentation regarding animal housing, feed, water, health status, environment, and vendor audits, several documents were not in English and could not be evaluated. Even if these documents were provided in English, based on the document titles and the descriptions you provided in your November 28, 2025 response to the GCL, they do not appear to be relevant to the explanations and assessment requested by FDA in items 2-5 above. Furthermore, while many of the attachments were not in English, it is apparent that attachments ATT-03-001, ATT-03-004, and ATT-07-003 were generated by SDWH. We note that FDA previously determined that Sanitation & Environment Technology Institute of Soochow University dba SDWH (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) has in several instances copied the results of another study or created falsified or otherwise invalid data that was submitted to the FDA. See https://www.fda.gov/medical-devices/industry-medical-devices/notifications-data-integrity-medical-devices. Until SDWH adequately addresses these issues, all study data from all studies conducted at this testing facility will be rejected. SDWH has not yet adequately addressed these issues; therefore, FDA remains concerned with the quality of data and other information provided by SDWH. As such, even if they had been provided in English, FDA does not consider those particular attachments to be reliable sources in adequately addressing FDA's concerns.

Additionally, during the FDA inspection, FDA investigators observed that the animals in the CCIC HTW (Suzhou) facility were not given proper animal care. For example, during the inspection, FDA investigators found that guinea pigs were deprived of food and water, as

documented in the FDA 483 observations and FDA Warning Letter. Adequate veterinary care is essential for study validity, as only healthy animals can serve as reliable subjects for detecting and characterizing abnormal observations and adverse events.

FDA requested that you explain why the evidence of copied or otherwise falsified or invalid data discussed in the October 30, 2025, 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. However, as also discussed with each observation above, the documents and explanations you provided do not systematically address these data integrity issues.

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**

FDA has reviewed your responses to the June 25, 2025, Warning Letter[40] dated July 13, 2025, August 9, 2025, September 13, 2025, October 11, 2025, November 8, 2025, December 27, 2025, and February 5, 2026. Your responses do not demonstrate that all GLP concerns identified in the Warning Letter have been adequately addressed. FDA's review of those responses has raised additional questions and concerns. FDA's outstanding concerns include, in part, the following:

In reviewing your responses to the FDA Warning Letter, there is an overarching concern that you fail to recognize the systemic nature of the violations, and that corrective and preventative actions are needed to address the impact on all GLP studies conducted at your facility, rather than just those specific to high-risk products or studies mentioned in FDA's correspondence.

For example, one of the corrective actions taken to address the violation related to 21 CFR 58.33(b) (identified as violation 1 in the FDA Warning Letter) included an evaluation of the specific studies referenced in the FDA Warning Letter as having used pre-filled study report templates. The studies were re-opened for review against source data. However, your response did not mention any plans to evaluate other study reports that were also generated using pre-filled templates beyond those specifically cited in the Warning Letter or a justification for why this is not needed. Furthermore, your response did not address the accuracy and validity of the source data itself which is critical to ensuring the reliability of the study data.

In response to multiple violations cited in the FDA Warning Letter, you conducted retraining to address personnel's lack of understanding of procedures and regulations. However, you have not indicated whether any systematic reviews of your training program will be conducted to identify and correct any gaps in personnel training. Furthermore, while you have provided training records containing personnel's signatures, you have not adequately described how the effectiveness of the training will be measured, including how personnel's ability to perform the

[40] https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/ccic-huatongwei-international-inspection-co-ltd-704332-06252025.

tasks in question will be assessed to ensure that the training achieves its intended goal. Therefore, your response is inadequate to ensure that the violations cited do not recur.

In response to multiple violations cited in the FDA Warning Letter, you also proposed conducting quarterly external audits. While external audits can be helpful in identifying noncompliance, internal controls and ongoing monitoring mechanisms, including robust Quality Assurance Unit, Testing Facility Management, and Study Director oversight consistent with the requirements of 21 CFR 58, are also needed to identify any potential issues in a timely manner and provide assurance that similar violations would not occur again. For example, one of the corrective actions proposed to address the violation related to 21 CFR 58.90(d) (identified as violation 3 in the FDA Warning Letter) was employing an external third-party team to conduct quarterly inspections of animal activities; however, you have not adequately described the "activities" that will be audited or provided a rationale for why this frequency of audit is sufficient.

Additionally, your responses mentioned several corrective and preventative actions which have yet to be completed, and therefore, their adequacy cannot be determined at this time. For example, regarding your response to the violation related to 21 CFR 58.130(c) (identified as violation 2 in the FDA Warning Letter), there are still pending actions relating to the e-animal management system which you have indicated will help ensure proper identification of animals. It is unclear from your responses whether this system has been fully implemented, and no evaluation of the system's effectiveness has been provided. Further, with respect to your responses to this violation and violation 3 in the FDA Warning Letter, you have not adequately addressed how lack of traceability of specimens and possible reuse of animals due to the inadequacy of the animal identification system may have impacted the reliability of study data.

**FDA's Conclusions**

Your response to FDA's October 30, 2025, GCL is inadequate because you failed to adequately address (1) FDA's concerns for what caused the anomalous data, (2) 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, (3) whether any other studies conducted at your testing facility may have similar data anomalies, and (4) 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 testing facility and provided in past, pending, and future submissions to FDA. Therefore, your response does not resolve FDA's concerns regarding the data generated at your testing facility.

CCIC HTW (Suzhou)'s management of the studies cited in the October 30, 2025, 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 one or more other studies or creation of falsified or otherwise invalid data that was submitted to FDA in the studies discussed in the October 30, 2025, GCL and here, and in light of your inadequate response to the concerns raised, 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 June 25, 2025, 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 October 30, 2025, 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: 2026.06.12 09:55:32 -04'00'

Angela C. Krueger
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Office of Product Evaluation and Quality
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