WARNING LETTER

Jiangsu Kerbio Medical Technology Group Co.

MARCS-CMS 705188 — JULY 11, 2025

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Product:

Medical Devices

Recipient:

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Issuing Office:

Center for Devices and Radiological Health
United States

WARNING LETTER

July 11, 2025

Dear Mr. Lin:

This Warning Letter is to inform you of objectionable conditions observed during the United States Food and Drug Administration (FDA) inspection conducted at Jiangsu Kerbio Medical Technology Group Co. from January 15, 2025, to January 24, 2025, by investigators from the FDA's Office of Bioresearch Monitoring Inspectorate (OBMI) Foreign Inspection Cadre. This inspection was conducted to determine whether activities and procedures related to your participation in Good Laboratory Practice (GLP) nonclinical studies complied with applicable federal regulations. Specifically, FDA investigators focused on the list of studies below including, but not limited to, guinea pig maximization sensitization (GPMT), acute systemic toxicity (AST), rabbit pyrogen, muscle implantation, hemolysis, and cytotoxicity tests conducted at your facility.

The list of studies below is not an all-inclusive list of studies impacted by the inspection or by the violations cited in this letter.

Study Number	Test
(b)(4)	Intracutaneous Reactivity
(b)(4)	Guinea Pig Maximization Sensitization Test (GPMT)
(b)(4)	Acute Systemic Toxicity (AST)

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(b)(4)	Rabbit Pyrogen
(b)(4)	Hemolysis
(b)(4)	Muscle Implantation Test 4 and 13 Weeks
(b)(4)	AST
(b)(4)	AST
(b)(4)	AST
(b)(4)	AST
(b)(4)	AST
(b)(4)	AST
(b)(4)	AST
(b)(4)	GPMT
(b)(4)	Intracutaneous Reactivity
(b)(4)	AST
(b)(4)	GPMT
(b)(4)	Intracutaneous Reactivity
(b)(4)	AST
(b)(4)	GPMT
(b)(4)	Intracutaneous Reactivity
(b)(4)	AST
(b)(4)	GPMT
(b)(4)	Intracutaneous Reactivity
(b)(4)	AST
(b)(4)	GPMT
(b)(4)	Intracutaneous Reactivity
(b)(4)	AST
(b)(4)	GPMT
(b)(4)	Intracutaneous Reactivity
(b)(4)	AST
(b)(4)	GPMT
(b)(4)	Intracutaneous Reactivity
(b)(4)	AST
(b)(4)	GPMT
(b)(4)	Intracutaneous Reactivity
(b)(4)	AST
(b)(4)	GPMT
(b)(4)	Intracutaneous Reactivity

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(b)(4)	AST
(b)(4)	GPMT
(b)(4)	Intracutaneous Reactivity
(b)(4)	AST
(b)(4)	AST
(b)(4)	AST
(b)(4)	AST
(b)(4)	GPMT
(b)(4)	Intracutaneous Reactivity
(b)(4)	AST
(b)(4)	GPMT
(b)(4)	MTT Cytotoxicity
(b)(4)	GPMT
(b)(4)	GPMT
(b)(4)	GPMT
(b)(4)	GPMT
(b)(4)	GPMT
(b)(4)	GPMT
(b)(4)	GPMT
(b)(4)	GPMT
(b)(4)	GPMT
(b)(4)	GPMT
(b)(4)	GPMT
(b)(4)	GPMT
(b)(4)	GPMT
(b)(4)	GPMT
(b)(4)	GPMT
(b)(4)	Intracutaneous Reactivity

These tests are used in nonclinical studies for the development of devices as that term is defined in section 201(h)(1) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. § 321(h)(1), because they are intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or to affect the structure or function of the body.

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemption, Premarket Approval applications, and Premarket Notification submissions are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

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Our review of the inspection report prepared by the OBMI revealed serious violations of Title 21, Code of Federal Regulations (CFR) Part 58 - Good Laboratory Practice for Nonclinical Laboratory Studies, which concerns, among other things, requirements prescribed under section 520(g) of the Act, 21 U.S.C. § 360j(g). Compliance with Part 58 is intended to assure the quality and integrity of the safety data filed in a premarket submission. At the close of the inspection, the FDA investigators presented the inspectional observations Form FDA-483 for your review and discussed the observations listed on the form with you.

We received a response from your firm dated February 21, 2025, concerning our investigators' observations noted on the Form FDA-483. We address this response below, in relation to each of the noted violations. This letter requests prompt corrective action to address the violations cited and discusses your written response dated February 21, 2025, to the noted violations. These violations include, but are not limited to, the following:

1. The study director failed to assure that (1) the protocol, including any change, is approved as provided by § 58.120 and is followed; (2) all experimental data, including observations of unanticipated responses of the test system are accurately recorded and verified; and (3) all applicable good laboratory practice regulations are followed [21 CFR 58.33(a), (b), and (e)].

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. The study director's responsibilities include assuring that studies are conducted in accordance with the protocol, all experimental data are accurately recorded and verified, and that applicable GLP regulations are followed. Examples of the study director's failures to adhere to these requirements include, but are not limited to, the following:

a. SOP **(b)(4)**-028 states that, "The study personnel should fill out the animal observation records in the corresponding experimental records daily." However, based on the study records reviewed by the FDA investigators for GPMT and intracutaneous reactivity studies, there were no daily animal observations raw data included in the experimental records. Documentation of animal observations in study records is necessary to allow for the reconstruction and evaluation of the final study reports. Without these records, it is not possible to confirm that these observations, which are critical to the interpretation and analysis of study results, indeed occurred, and that the final study reports accurately reflect what was observed at the time of testing.

b. The raw data for multiple studies conducted by two different study directors showed that the same person reportedly conducted two separate study related activities at the same or overlapping times. Additionally, the raw data for multiple studies showed that other study personnel were reportedly using the same equipment at the same time. This indicates that all experimental data were not accurately recorded and verified. Examples of discrepancies are as follows:

1. In two intracutaneous reactivity studies, the same study personnel, **(b)(6)**, reportedly shaved all three rabbits for study **(b)(4)** and weighed all three rabbits for study **(b)(4)** at exactly 17:19 on **(b)(4)**. It appears implausible that the same study personnel could shave and weigh multiple rabbits from two separate studies at the exact same time.

2. On **(b)(4)**, study personnel, **(b)(6)**, completed weighing **(b)(4)** guinea pigs for the GMPT study **(b)(4)** at **(b)(4)** while study personnel, **(b)(6)**, also completed weighing **(b)(4)** animals for GMPT study **(b)(4)** at 9:12 both using scale **(b)(4)**. The data suggests that either these two study activities were conducted at overlapping times using the same equipment or that **(b)(4)** animals were weighed within the span of two minutes, both of which appear implausible.

c. On January 21, 2025, one of the FDA investigators directly observed study personnel, **(b)(6)**, retroactively completing records for an ongoing subacute systemic toxicity study, **(b)(4)**, including clinical observations and animal weight data from Day 1 of the study up to Day 26 (**(b)(4)**) of the study. When asked to provide documentation that animals for this study were weighed, the records provided later that day showed that the animal weight data were incomplete as week 2 only included 5 out of 20 animal weights, and there were no weights recorded for week 3 which should have been completed on **(b)(4)**. Failure to accurately record and verify experimental data as per the study protocol undermines the integrity and reliability of the study.

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d. Raw data records for ten intracutaneous reactivity studies conducted in **(b)(4)** and two that were conducted in **(b)(4)** (refer to the table below) included an animal reuse record (document #**(b)(4)**32 Version 3.2) indicating that the studies utilized rabbits that had been previously used in other studies. This contradicts the study protocols (see protocol Section 4: Animal Care and Maintenance for each respective study) which indicate that, “Only healthy, previously unused animals were selected.”

(b)(4)

e. SOP **(b)(4)**-030 Skin Sensitization Test (Guinea pig maximization test) requires that guinea pigs shall be acclimatized for at least 5 days. However, the study records for GPMT studies **(b)(4)** and **(b)(4)** show that this SOP was not followed. The study records documented that these studies were initiated on the guinea pigs three days after the animals were received. For example, study **(b)(4)** was started on **(b)(4)**, and according to the Animal Quality Certificate, the animal was purchased on **(b)(4)**. In addition, study **(b)(4)** was started on **(b)(4)**, and the animal was purchased on **(b)(4)**.

As the principal point of study control, the study director did not assure that studies were conducted in accordance with the protocol, that all experimental data were accurately recorded and verified, and that applicable good laboratory practice regulations were followed. When the protocol is not followed, data is erroneously recorded or analyzed, or other unforeseen circumstances occur that negatively affect the data, important findings in the study may be overlooked and the data cannot be accurately interpreted. Failure to follow the protocol impacts the quality and reliability of data contained within the final study report. This adversely impacts a manufacturer’s and FDA’s ability to assess the overall safety and risk of the subject device prior to use in humans as a marketed device or for the purposes of beginning clinical trials, as applicable. Furthermore, failure to ensure accurate data such as individual animal weights, animal preparation, observations, and results, yields questionable study results and conclusions. Based on these failures, FDA has concerns about the quality and integrity of the data generated from the nonclinical laboratory studies conducted at your testing facility. Complete and accurate study data are necessary to allow FDA to fully assess the overall safety and risk of a device with an associated premarket submission. The unreliable data raises concerns about the quality and integrity of associated premarket submissions, which may put public health and safety at risk. Additionally, lack of daily observation of individual animals directly impacts the overall study integrity, as it is unclear if the animals are malnourished or sick in any way, which would have a direct impact on the interpretation of the study results

Your written response is inadequate. The written response you provided states that the relevant standard operating procedures (SOPs) that address the concerns noted in the Form 483 will be revised and a GLP working group will be established to implement a regulatory compliance improvement plan for 21 CFR Part 58. However, the updated SOPs were not included in your response, and it is unclear whether you plan to retrain personnel on the updated SOPs.

Additionally, your firm stated that you will conduct trainings on FDA 21 CFR Part 58 regulations to ensure thorough understanding of the compliance requirements but did not provide copies of the training materials. Given the deviations and issues cited in the violations, it is necessary to review the training materials to determine their adequacy for the trained individuals to both conduct the tests per the standards being used, and to produce accurate, traceable results.

Furthermore, your response does not provide assurance that these violations will not occur again. Specifically, your response did not: (1) detail how your testing facility will assure that applicable SOPs will be followed to ensure the quality and integrity of data generated in a study; (2) address any planned preventive actions such as frequency (i.e., quarterly, annual) of audits to check for compliance or future training of new study directors, as applicable; and (3) detail how appropriate documentation/follow-up will be ensured when deviations arise in the future. Also, as your corrective action, preventative action and verification of effectiveness plans have not yet been completed, FDA cannot evaluate the adequacy of your actions in addressing this violation. Your explanation, when taken into consideration with the violations described above, which occurred in multiple studies with various study directors over many months, suggests systemic failures in study director oversight of nonclinical laboratory studies and brings into question the quality and integrity of safety data collected at your testing facility.

2. Failure to establish procedures for a system for the handling of the test and control articles to ensure that (1) proper identification is maintained throughout the distribution process and (2) the receipt and distribution of each batch is documented. Such documentation shall include the date and quantity of each batch distributed or

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returned [21 CFR 58.107(c) and (d)].

Your failures to adhere to this requirement include, but are not limited to, the following examples:

a. Verification of the lot/batch number was not found to be documented during sample receipt, preparation, or on any other source data records.

b. Your firm's Sample Information Form - **(b)(4)**052 listed the sample quantity received for study **(b)(4)** (Safety Intravenous Needles for Single Use) as "3 packs" with no record of how many needles were in each pack. The form then lists 1 and ¼ of a pack were distributed on **(b)(4)**, and **(b)(4)**, respectively. The same amounts were then listed as returned on **(b)(4)**, and **(b)(4)**, respectively. The form goes on to list that "3 packs" were disposed of on **(b)(4)**. There was no record of the number of needles used and returned.

c. Your firm's sample preparation form **(b)(4)**83 does not require verification or documentation of the lot number or quantity of needles used for extraction for GPMT testing.

d. The investigators found 12 GLP studies (refer to table below) where, after completion of the testing, the study director made changes to the test article information (indicated in bold in the table) or updated the test article photo (indicated by [1] in the table) in the final study report at the sponsor's request. These changes included revisions to the test article lot #, material, and size information, suggesting that proper identification is not maintained throughout the distribution process.

Study Number: "SSMT-S"	Test article per protocol:	Studies Completed:	Change Request date:	Test article per final study report:
(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)

1 The photo of the test article in the final report is not the same as the one in the protocol.

Failure to have established procedures for the handling of the test and control articles to ensure that proper identification of the articles is maintained and that the receipt and distribution of each batch are documented as required by the regulations creates the potential for errors to occur during handling such that the incorrect information could be attributed to the article under study. This in turn could lead to testing discrepancies and inaccurate test results and conclusions. In addition, lack of these procedures adversely impacts the traceability of the test samples, reliability of the testing, and the manufacturer's and FDA's ability to assess the overall safety and risk of the subject device prior to use in humans as a legally marketed device or for purposes of beginning clinical trials, as applicable.

Your written response is inadequate. The written response you provided states that the relevant standard operating procedures (SOPs) addressing the concerns noted in the Form 483 will be revised, and GLP experts will be invited to provide training on FDA GLP and 510(k) regulations.

However, your response did not: (1) include copies of revised SOPs **(b)(4)**-002 and **(b)(4)**-003 and (2) provide details regarding the proposed trainings, including information on the types of personnel that will undergo the trainings, training materials that will be used, and how the effectiveness of the training will be evaluated. Also, as your corrective action, preventative action and verification of effectiveness plans have not yet been completed, FDA cannot evaluate the adequacy of your actions in addressing this violation. Therefore, your response does not provide assurance that these violations will not occur again.

3. Failure of the Quality Assurance Unit (QAU) to inspect each nonclinical laboratory study at intervals adequate to assure the integrity of the study and maintain written and properly signed records of each periodic inspection and to bring any problems found during the course of an inspection which are likely to affect study integrity to the attention of the study director and management immediately [21 CFR 58.35(b)(3)].

GLP regulations require that QAU inspect each nonclinical laboratory study at intervals adequate to assure the integrity of the study and maintain written and properly signed records of each periodic inspection showing the date of the inspection, the study inspected, the phase or segment of the study inspected, the person performing the inspection, findings and problems, action recommended and taken to resolve existing problems, and any scheduled date for reinspection. Any

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problems found during the course of an inspection which are likely to affect study integrity shall be brought to the attention of the study director and management immediately. Examples of the QAU's failures include, but are not limited to, the following:

a. The QAU failed to identify any of the data irregularities, errors, and omissions that were observed by FDA, including those described in the examples of failures throughout this letter.

b. There were 67 studies reviewed during the inspection, of which 63 were conducted from 2023-2024. For these 63 studies, the final study reports include a signature attesting that the QAU audited the protocol, raw data, and final study reports. However, records did not support that all reported audits were completed at the reported times. Examples are as follows:

1. Only three (**(b)(4)**) out of the 63 covered studies had record of a raw data audit per the QA inspection summary reports.

2. Thirty out of the 63 covered studies did not have the reported final study report audits included on the QA inspection summary reports.

3. Study **(b)(4)**, completed on **(b)(4)**, was observed to have an error within the printed cassette labels; however, there was no deviation or record of when this error was discovered or that it had been reported to the study director. The FDA investigators found the final report for this study was still in draft form but included the quality assurance statement reporting QAU inspections of the study protocol on **(b)(4)**, and the raw data and final study report on **(b)(4)**. However, when asked to provide copies of those QA audit reports, your firm only provided a copy of a QAU inspection report for the study protocol which was dated **(b)(4)**. This audit report was not recorded on the QA Summary Report of Inspections. These discrepancies, including differences between the protocol audit date recorded in the quality assurance statement of the draft study report versus in the QAU inspection report, along with the missing audit report for the final study report and raw data, and lack of related audits mentioned in the QA Summary Report of Inspections, indicate a lack of adequate monitoring by the QAU.

A reliable QAU is integral to the successful understanding and completion of any GLP study. Without appropriate QAU oversight, neither the sponsor nor FDA reviewers have assurance that the data in the final study report are accurate and valid. Failure to perform QAU functions, such as monitoring studies to ensure protocols were followed and data are accurately recorded, over the course of multiple studies also calls into question the quality and integrity of studies conducted at your testing facility.

Your written response is inadequate. Your written response included a document that outlines your QAU's review of QA statements, corresponding QA inspection reports, and Summary of Inspection Report for the final study reports reviewed by the FDA investigators. You also indicated in your response that the relevant SOPs addressing the concerns noted in the Form 483 will be revised along with Form QAU-F002 "Summary of Inspection Report", interviews will be conducted with QA personnel to clarify responsibilities, a gap analysis of the existing quality management system will be conducted, and a working group will be established to identify existing problems and make improvements. Additionally, you stated plans to have training provided by an external GLP expert. However, your response did not: (1) include copies of the revised SOPs and form such that the adequacy of the revisions can be assessed and (2) provide details regarding the proposed trainings, including the training materials that will be used and how the effectiveness of the training will be evaluated. Also, as your corrective action, preventative action and verification of effectiveness plans have not yet been completed, FDA cannot evaluate the adequacy of your actions in addressing this violation. Therefore, your response does not provide reasonable assurance that QAU failures will be avoided in the future.

4. Failure of a testing facility to have standard operating procedures in writing setting forth nonclinical laboratory study methods that management is satisfied are adequate to ensure the quality and integrity of the data generated in the course of a study. The study director failed to authorize all deviations in the study from standard operating procedures and ensure the deviations were documented in the raw data [21 CFR 58.81(a)].

SOPs should be adequate to ensure the quality and integrity of data generated in a study. However, not all SOPs appear to be adequate. The study director also must authorize all deviations from SOPs in a study and document all study deviations in the raw data. However, the study directors at your testing facility did not adhere to these requirements.

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Deviations from standard operating procedures in a study also were not authorized by the study director and documented in the raw data. Examples of these issues include the following:

a. Your firm was found to be operating under two sets of SOPs for conducting the same types of tests. One was originated for conducting testing per domestic standards and the more recent set is referred to as your GLP SOPs. There were no instructions directing which SOPs were to be used for any given study. FDA investigators found conflicting instructions between your firm's "domestic" study procedures and your "GLP" procedures. For example, the domestic SOP, SOP-**(b)(4)**02 Animal Clinical Observation requires the use of four separate forms (**(b)(4)**: General clinical observation during study, **(b)(4)**: Detailed clinical observation during study, **(b)(4)**: General clinical observation during quarantine, and **(b)(4)**: Detailed clinical observation during quarantine) to record clinical observations separately while animals are in quarantine versus on study. However, the corresponding GLP SOP **(b)(4)**-028 only requires one form to document clinical observations while animals are in quarantine (**(b)(4)**: Animal Reception, Animal Receipt, Distribution and Quarantine Records) and does not have any requirement to use certain forms for documenting observations while on study. The lack of appropriate forms to document observations in your "GLP" procedures indicates the inadequacy of your SOPs to ensure the quality and integrity of data generated. Additionally, the GLP SOP states that, "The study personnel should fill out the animal observation records in the corresponding experimental records daily." However, as described under violation 1 of this letter, it does not appear that daily animal observations were being recorded in accordance with this SOP. This deviation from the SOP does not appear to be authorized by the study directors nor documented in the raw data.

b. SOP **(b)(4)**-028: "Animal clinical observation and management of abnormal conditions" does not include any information on signs of abnormal conditions based on species, though GLP studies were conducted on mice, rats, and rabbits. Lack of sufficient detail within this SOP could lead to errors in identifying abnormal conditions exhibited by study animals which in turn could directly impact the quality and integrity of the data generated in the course of the studies.

c. SOP **(b)(4)**-030: "Skin Sensitization Test (Guinea Pig Maximization Test)" does not include adequate instructions for clinical observation of the animals during the studies, such as assuring that their breathing is not restricted when wrapping them with the occlusive dressings during the challenge and induction phases and that animals undergo observation daily to ensure isolation and treatment of any wounds or illness throughout the study. Additionally, the SOP and training materials for the GPMT test lacked photos to demonstrate how to use the Magnusson Kligman scores. Clinical observations are essential to the quality and integrity of the data generated from this testing, and this SOP was found to lack sufficient detail to ensure that tests can be conducted reliably and consistently.

Failure of a testing facility to have adequate SOPs, or follow established SOPs if adequate, in multiple studies with multiple study directors over many months suggests systemic failures in the operation of your nonclinical laboratory. This failure raises questions about the reliability and accuracy of the data and does not ensure the quality and integrity of data generated in a study. Failing to follow SOPs and having inadequate SOPs yield inadequate protocols that introduce ambiguity and uncertainty as to how study requirements are to be followed, as well as inconsistent execution of studies and unreliable study results. Any deviations from the SOPs must be authorized by the study director and documented in the raw data. Failure to properly document any authorized deviations could result in study data with a high level of variability that challenges the ability to effectively interpret the study results associated with a device. This in turn adversely impacts a manufacturer's and FDA's ability to assess the overall safety and risk of the subject device prior to use in humans as a legally marketed device or for purposes of beginning clinical trials, if applicable.

Your written response is inadequate. Your written response acknowledged the observations cited and indicated that the relevant SOPs addressing the concerns noted in the Form 483 will be revised, a gap analysis of the existing quality management system will be conducted, and an external GLP expert will be engaged to perform an audit. However, the response did not: (1) include copies of the revised SOPs such that the adequacy of the revisions can be assessed (2) describe plans for retraining personnel on revised SOPs (3) detail how your testing facility will ensure that applicable SOPs will be followed to ensure the quality and integrity of data generated in a study; (4) address any planned preventive actions such as frequency (i.e., quarterly, annual) of audits to check for compliance or future training of new study directors, as applicable; and (5) detail how appropriate documentation/follow-up will be ensured when deviations arise in the future. Also, as your corrective action, preventative action and verification of effectiveness plans have not yet been completed, FDA cannot evaluate the adequacy of your actions in addressing this violation. Therefore, your written response does not provide assurance that similar violations would not occur again.

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5. Failure of the testing facility to ensure that all newly received animals from outside sources were isolated and their health status evaluated in accordance with acceptable veterinary medical practice [21 CFR 58.90(b)].

All newly received animals should be isolated and evaluated to determine health status. This can allow for early detection of potential health issues. Your failures to adhere to this requirement include, but are not limited to, the following examples:

a. The FDA investigators reviewed guinea pig receiving and quarantine records totaling five months during 2023 and 2024. The records documented that the firm received over **(b)(4)** guinea pigs in these five months and all these guinea pigs were recorded as "normal" or "okay" with no deaths reported while in quarantine. This seems highly implausible as there were six deaths among 903 animals in the guinea pig quarantine room **(b)(4)** over a two-day period that occurred during the inspection.

b. Your firm's records indicate on at least one occasion while still conducting GLP rabbit studies, you received more rabbits than you have the capacity to isolate for the required time. For example, 180 New Zealand White Rabbits were received on **(b)(4)**, and these rabbits were reportedly held under quarantine from **(b)(4)**. However, according to your firm, the capacity across all designated rabbit quarantine rooms in your **(b)(4)** building (**(b)(4)** in the **(b)(4)** building) is 141 rabbits.

Your records raise significant concerns regarding your isolation procedures as well as your evaluation of the status of test animals. Failure to isolate newly received animals or evaluate the animal's health status can raise serious concerns about the validity of study data. Animals may be sick upon arrival. If transferred to housing with other test animals already enrolled in another study, the newly received test animal could make the other test animals sick and impact study results. Further, test animals must be free of any disease or condition that might interfere at the beginning of a study or may significantly impact study data and/or results.

Your firm's failure to have adequate intake and isolation procedures for test animals arriving at your facility suggests systemic failures in your firm's nonclinical laboratory practices. Further, failures that relate to test animals used in numerous studies raises questions about the quality and integrity of data collected at your facility.

Your written response is inadequate. Your written response includes revising SOP **(b)(4)**-002, issuing death reports for the six guinea pig deaths identified during the inspection, and converting Room **(b)(4)** in Building **(b)(4)** into a rabbit quarantine room, adding **(b)(4)** cages to comply with company standards. However, your response does not include: (1) copies of the revised SOP such that the adequacy of the revisions can be assessed, (2) documentation that addresses the changes to the rabbit quarantine room by adding additional cages to accommodate the animals more efficiently, and (3) documentation that demonstrates the special training for QAU personnel on SOP **(b)(4)**-002 procedures was conducted and Quality Assurance Manager roles and responsibilities have been established. Also, as your corrective action, preventative action and verification of effectiveness plans have not yet been completed, FDA cannot evaluate the adequacy of your actions in addressing this violation. Your explanation, when taken into consideration with the violations described above, which occurred over many months, suggests systemic failure in study director and veterinarian oversight of nonclinical laboratory studies and brings into question data integrity and animal care and welfare at your testing facility.

6. Failure of the testing facility to ensure warm-blooded animals, excluding suckling rodents, used in laboratory procedures that require manipulations and observations over an extended period of time or in studies that require the animals to be removed from and returned to their home cages for any reason (e.g., cage cleaning, treatment, etc.) received appropriate identification [21 CFR 58.90(d)].

Your failures to adhere to this requirement include, but are not limited to, the following example:

a. Your firm does not use unique or study-specific animal identification numbers to prevent mix-ups during studies that require animals be removed from their cages for study related procedures including weighing and assessments. For example, for 11 GPMT studies started on **(b)(4)**, and completed **(b)(4)**, and 14 GPMT studies started on **(b)(4)**, and completed **(b)(4)**, the polar negative control group animals for each study are all identified as "**(b)(4)**" to "**(b)(4)**" and the non-polar vehicle controls are "**(b)(4)**" to "**(b)(4)**." All the test animals for each study are numbered "**(b)(4)**" to "**(b)(4)**" for the polar and "**(b)(4)**" to "**(b)(4)**" for the non-polar. The records the FDA investigators reviewed indicated your firm has assessed and weighed guinea pigs with identical IDs from multiple studies concurrently, in the same room, and on the same scale.

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Failure to appropriately identify each animal by ensuring that they are identified with unique, study-specific identification numbers raises concerns about lack of traceability of the specific animal in the cage to the test and/or to the results of the testing presented in the reports. The inability to distinguish the test animals and control animals across different studies raises serious concerns about the validity of the test results. Since the ability to identify specific animals is foundational to being able to draw scientifically valid conclusions from the studies, the accuracy of study results cannot be verified.

Your written response does not adequately address the issue of misidentification. Your written response includes revising the SOP (**(b)(4)**-002) to enforce unique animal identification numbers. It also includes revising test records for guinea pig studies to add unique ID numbers to ensure data traceability and the recruitment of external GLP experts to train staff on FDA 21 CFR Part 58. However, your response does not include copies of the revised SOP such that the adequacy of the revisions can be assessed, written documentation of the GLP training information, nor does it discuss the specific personnel that will undergo the future GLP training and/or newly implemented procedures as applicable. Given the deviations and issues cited in the violations above, it is necessary to review the training materials to determine their adequacy for the trained individuals to both conduct the tests per the standards being used, and to produce accurate, traceable results. Also, as your corrective action, preventative action and verification of effectiveness plans have not yet been completed, FDA cannot evaluate the adequacy of your actions in addressing this violation. Therefore, your written response does not provide assurance that misidentification of animals would not reoccur.

7. Failure to provide a separate laboratory space, as needed, for the performance of the routine and specialized procedures required by nonclinical laboratory studies [21 CFR 58.49].

A testing facility must provide separate laboratory space for routine and specialized procedures required by nonclinical laboratory studies, as needed. This requirement ensures that studies are conducted in a controlled environment and that potentially hazardous materials or procedures are isolated from other operations. Your failures to adhere to this requirement include, but are not limited to, the following examples:

a. According to your firm's floor plan for Building **(b)(4)**, rooms **(b)(4)** and **(b)(4)** are listed as a "Procedure Room" and "Anteroom" respectively, with **(b)(4)** connecting to Guinea Pig Room **(b)(4)**, and **(b)(4)** connecting to Guinea Pig Room **(b)(4)**. During the inspection, study director **(b)(6)** indicated that Rooms **(b)(4)** and **(b)(4)** are shared as the procedure rooms for both rabbits and guinea pigs for rabbit intracutaneous reactivity studies and for guinea pig sensitization studies, respectively. Not only are they shared space for different species, according to your firm's floor plan, these two rooms are connected, not separate. Maintaining proper separation of species or test systems is a requirement per 21 CFR 58.43(a)(1).

b. During the inspection, it was found that scale **(b)(4)**-494 located in one of the rabbit pyrogen rooms, is shared for measuring weights of both rabbits and guinea pig species. It was also found that your firm does not have procedures for cleaning the room or equipment between studies of different species, as required per 21 CFR 58.81(b)(11).

c. There is inadequate space in both rabbit pyrogen test rooms **(b)(4)** and **(b)(4)** to conduct the procedures that are required for this test. Per the United States Pharmacopeia (USP) <151> Pyrogenicity Test standard for the rabbit pyrogen test, it should be conducted in a separate area designated solely for pyrogen testing and under environmental conditions that are free from disturbances likely to excite the rabbits. According to study director **(b)(6)**, due to the limited space in the rooms, rabbits are transferred one at a time from the rabbit feeding rooms and put on the restrainers. This opening and closing the doors causes repeated disturbances to the rabbits already transferred to the pyrogen room as they await testing. In addition, there is extremely limited space for personnel to move around or to conduct procedures on the rabbits without disturbing the others.

Separation of animal species during biomedical testing is important to prevent interspecies disease transmission, minimize potential anxiety and behavioral changes due to conflict, and ensure the reliability of experimental results. The presence of multiple intermixed species can introduce confounding factors into in vivo testing, making it difficult to isolate the effects of a specific treatment or intervention, which impacts data integrity. Minimizing additional stress in terms of designating adequate laboratory space for procedures and housing is also important for the health and welfare of the study animals.

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Your written response is inadequate. Your written response included an explanation of the planned corrections, including: (1) dedicating rooms **(b)(4)** to performing guinea pig studies only, (2) reducing the number of rabbit pyrogen tests in rooms **(b)(4)** and **(b)(4)** to ensure the number of test items matches the facility's capacity, (3) transferring of some pyrogen testing to the backup laboratory to comply with USP <151>, and (4) revising SOPs **(b)(4)**-014 and **(b)(4)**-002.

However, the response did not provide the following: (1) objective evidence that the appropriate SOPs have been revised, and (2) documentation that addresses the changes to the designation of different testing rooms to accommodate the animals more efficiently. Also, as your corrective action, preventative action and verification of effectiveness plans have not yet been completed, FDA cannot evaluate the adequacy of your actions in addressing this violation. In addition, your response stated that priority was given to completing a volume of studies over GLP compliance, which resulted in insufficient space to assure proper adherence to regulatory requirements. This suggests that these issues are systemic and brings into question the quality and integrity of the laboratory operation areas and data collected at your testing facility. Therefore, your response does not provide assurance that these violations will not occur again.

8. Failure of the Quality Assurance Unit (QAU) to maintain a copy of a master schedule sheet of all nonclinical laboratory studies conducted at the testing facility indexed by test article and containing the test system, nature of study, date study was initiated, current status of each study, identity of the sponsor, and name of the study director [21 CFR 58.35(b)(1)].

Your failures to adhere to this requirement include, but are not limited, to the following examples:

a. There was no master schedule (MS) prior to February 12, 2022, but your firm has been conducting GLP studies since at least April 2020. Moreover, the MS does not include the sponsor or test system.

b. Per your SOP **(b)(4)**-014, the test facility manager is responsible for maintaining the master schedule, not the QAU.

c. In addition, the FDA investigators found the following completed GLP studies were archived but were not included on the master schedule: **(b)(4)**.

Without a complete and accurate MS, the study director and QAU would not know which studies are underway, at which stages and when inspections or audits are indicated. Without appropriate QAU oversight, neither the sponsor nor FDA reviewers have assurance that the data in the final study report are accurate and valid. Failure to perform QAU functions can have a negative impact on a study because it indicates a lack of oversight to ensure compliance with all applicable GLP regulations and calls into question the quality and integrity of studies conducted.

Your written response is inadequate. Your written response attributes these failures to inadequate planning and insufficient training to ensure that GLP requirements are fully understood. You propose to correct the MS to include all GLP studies conducted from **(b)(4)** to present. Your corrective action includes revising "SOP **(b)(4)**-013 Project Acceptance, Distribution of Project Numbers, Assignment of Project Leaders, and Management of Master Plan Forms," among other actions. However, it does not provide documentation that the appropriate SOPs have been revised. Also, as your corrective action, preventative action and verification of effectiveness plans have not yet been completed, FDA cannot evaluate the adequacy of your actions in addressing this violation. Therefore, your response does not provide assurances that QAU failures will be avoided in the future.

The violations described above are not intended to be an all-inclusive list of problems that may exist with your facility. It is your responsibility as a non-clinical laboratory to ensure compliance with the Act and applicable regulations.

FDA acknowledges that your written response dated February 21, 2025, included a signed letter stating that "…due to the increasingly intense price competition within the domestic market, our institution has become unsustainable to support the basic costs associated with full system compliance. This presents significant long-term challenges and risks to our institution, as well as potential product quality risks for our customers. As a result, we hereby affirm that, effective immediately, we will suspend all FDA-related non-clinical testing for a minimum period of three years, until December 31, 2027." Furthermore, you state that, "In the event that our company decides to resume FDA-related non-clinical testing services after January 1, 2028, we commit to the following:

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- Submitting a formal notification to the FDA at least six (6) months prior to any planned resumption of services, detailing our operational readiness and compliance measures.
- Resuming services only after obtaining written authorization from the FDA and ensuring alignment with current regulatory expectations.
- Ensuring that all activities are conducted in full compliance with the FDA's most recent regulatory requirements, quality standards, and inspection protocols in effect at the time of resumption."

Within 15 working days of receiving this letter, please provide documentation of the additional corrective and preventive actions that you have taken or will take to correct these violations and to prevent the recurrence of similar violations in current or future studies for which you are the testing facility. Any submitted corrective action plan should include projected completion dates for each action to be accomplished as well as a plan for monitoring the effectiveness of your corrective actions. In addition, please provide a complete list of all nonclinical laboratory studies of FDA-regulated devices for the last five years, including the name of the study, the test article, the name of the study director and sponsor, and the current status of the study. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. In addition, FDA could initiate disqualification proceedings against you in accordance with 21 CFR 58.202. If you believe that you have complied with the FD&C Act and FDA regulations, please include your reasoning and any supporting information for our consideration.

Your response should reference "CTS# EC250079/E001" and be sent via email to: Irfan.Khan@fda.hhs.gov.

A copy of this letter has been sent to FDA's OBMI Foreign Inspection Cadre via email FDAInternationalBIMO@fda.hhs.gov. Please send a copy of your response to that office.

If you have any questions, please contact Angela Dixon-Allamby, by phone at (301) 796-5548 or email at Angela.Dixon-Allamby@fda.hhs.gov.

Sincerely yours,
/S/

Soma Kalb, PhD
Director
DCEA1: Division of Clinical Policy and Quality
Office of Clinical Evidence & Analysis
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

WARNING LETTER

CCIC Huatongwei International Inspection Co., Ltd.

MARCS-CMS 704332 — JUNE 25, 2025

More Warning Letters (/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters)

Product:
Medical Devices

Recipient:
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Issuing Office:
Center for Devices and Radiological Health
United States

WARNING LETTER

June 25, 2025

Dear Mr. Su:

This Warning Letter is to inform you of objectionable conditions observed during the United States Food and Drug Administration (FDA) inspection conducted at CCIC Huatongwei International Inspection (Suzhou) Co., Ltd. from January 6, 2025, to January 14, 2025, by investigators from the FDA's Office of Bioresearch Monitoring Inspectorate (OBMI) Foreign Inspection Cadre. This inspection was conducted to determine whether activities and procedures related to your participation in Good Laboratory Practice (GLP) nonclinical studies complied with applicable federal regulations. Specifically, FDA investigators focused on the list of studies below including, but not limited to guinea pig maximization, rabbit muscle implantation, acute systemic toxicity, MTT cytotoxicity, rabbit pyrogen, intracutaneous reactivity, and hemolysis studies conducted at your facility.

The list of studies below is not an all-inclusive list of studies impacted by the inspection or by the violations cited in this letter:

Study number	Test
(b)(4)	Rabbit Muscle Implantation
(b)(4)	Rabbit Muscle Implantation
(b)(4)	Rabbit Muscle Implantation
(b)(4)	Rabbit Muscle Implantation

(b)(4)	Rabbit Muscle Implantation
(b)(4)	Rabbit Muscle Implantation
(b)(4)	Rabbit Muscle Implantation
(b)(4)	Guinea Pig Maximization Test (GPMT)
(b)(4)	GPMT
(b)(4)	GPMT
(b)(4)	GPMT
(b)(4)	GPMT
(b)(4)	GPMT
(b)(4)	GPMT
(b)(4)	GPMT
(b)(4)	GPMT
(b)(4)	GPMT
(b)(4)	Acute Systemic Toxicity (AST)
(b)(4)	AST
(b)(4)	AST
(b)(4)	MTT Cytotoxicity
(b)(4)	Rabbit Pyrogen Test

These tests are used in nonclinical studies for the development of devices as that term is defined in section 201(h)(1) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. § 321(h)(1), because they are intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or to affect the structure or function of the body.

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemption, Premarket Approval applications, and Premarket Notification submissions are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

Our review of the inspection report prepared by the OBMI revealed serious violations of Title 21, Code of Federal Regulations (CFR) Part 58 - Good Laboratory Practice for Nonclinical Laboratory Studies, which concerns, among other things, requirements prescribed under section 520(g) of the Act, 21 U.S.C. § 360j(g). Compliance with Part 58 is intended to assure the quality and integrity of the safety data filed in a premarket submission. At the close of the inspection, the FDA investigators presented the inspectional observations Form FDA-483 for your review and discussed the observations listed on the form with you. We received a response from your firm dated February 4, 2025, concerning our investigators' observations noted on the Form FDA-483. We address this response below, in relation to each of the noted violations. These violations include, but are not limited to, the following:

1. The study director failed to assure that all experimental data, including observations of unanticipated responses of the test system are accurately recorded and verified and that all raw data, documentation, protocols, specimens, and final reports are transferred to the archives during or at the close of the study [21 CFR 58.33(b), and 58.33(f)].

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. The study director's responsibilities include ensuring that all experimental data are accurately recorded and verified. Additionally, the study

director is responsible for assuring that all raw data, documentation, protocols, specimens, and final reports are transferred to the archives as required by the regulations. Examples of the study director's failures to adhere to these requirements include, but are not limited to, the following:

a. Study records for nine GPMT studies (**(b)(4)**) conducted by four different study directors throughout **(b)(4)** to **(b)(4)** contained six pages of source data that were photocopied and reused across different studies. The copied data included documentation of all animal preparation, administration of test and control articles, observations, and results. Additionally, the technicians' signatures included within the source data were photocopied and reused across different studies. The experimental data was therefore not accurately recorded and verified.

b. In all of the seven significant risk device muscle implantation studies reviewed, for the Weeks 4, 13, and 26 datasets, multiple examples were found where the entries on the animal observation tables and the signature of the person completing them appeared to have been photocopies of the same document with only a change to the week number and the date. These studies all started on **(b)(4)** and ended on **(b)(4)**. The bolded numbers in the chart below indicate records that are also copied across the data sets within the same study. For example, in **(b)(4)**, the observation data for the weeks bolded in the 13-week study (weeks 2-9) and the observation data for the weeks bolded in the 26-week study (weeks 2-12) are all identical. The experimental data was therefore not accurately recorded and verified. Some examples are as follows:

Study Protocol	Interval	Weeks with photocopied animal observation data
(b)(4)	4 Weeks	2-4
	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
	26 Weeks	2-12 and 14-26
(b)(4)	4 Weeks	2-4
	13 Weeks	2-9 and 11-13
	26 Weeks	2-12 and 14-26

c. The study director used templates with pre-completed information to generate study final reports that included pre-completed study observations and results. As confirmed by the study director during the inspection, these templates utilized red font and/or brackets to indicate where new information is to be populated within the documents. However, several sections of the template reports which should have been study-specific were pre-completed and not identified in red font and/or brackets as requiring updates (i.e., the template reports did not indicate that the template should be revised to incorporate the study-specific observations and results), including:

1. Muscle Implant Test Report Template: statements regarding animal observations, macroscopic assessments, the microscopic semiquantitative score for the tests, and overall conclusions.
2. Acute Systemic Toxicity Test Report Template: pre- and post-extraction conditions of the test article and control, statements regarding the results of the test article and negative controls and overall conclusions.
3. Guinea Pig Maximization/Skin Sensitization Test Report Template: pre- and post-extraction conditions of the test article and control, skin reaction results and clinical observations for the test article and control, and overall conclusions.

The use of templates such as these indicates a failure of the study director to assure that all experimental data, including observations of unintended responses of the test system are accurately recorded and verified. Each test article is nuanced in its combination of materials, construction, intended use, and duration of use. Use of templates that contain pre-completed observations, results, and overall conclusions indicates lack of proper scientific assessment and calls into question whether the experimental data was accurately recorded and verified in the final reports.

d. During the inspection it was observed that all study folders on the GLP archivist's portable hard drive had been modified on or about January 5, 2025, shortly prior to the inspection. According to the Quality Assurance Unit Manager and GLP archivist, prior to the pre-announcement of this inspection on December 27, 2024, they had not archived any study protocols or sample submission forms, and so they added them to the archive index ahead of the inspection. The required records were therefore not transferred to the archives during or at the close of each study. In addition, the following deficiencies regarding the archival practices were found:

1. Of the 21 study records initially requested for review, only seven were found in the dedicated GLP archive room.[1]
2. The tissue slides from Muscle Implantation study **(b)(4)** were not retained.
3. There were no tissue blocks and cassettes for any studies stored in the GLP archive room.
4. For both Muscle Implantation studies **(b)(4)** and **(b)(4)**, tissue slide "20" of the 20 tissue slides was missing from the archives.
5. The electronic source data for the rabbit pyrogen tests is not maintained. Only the hand-transcribed data is included in the study records. The rabbit pyrogen test is conducted using a pyrogen meter that provides machine-generated results, which are then transcribed by hand to a paper record.

As the principal point of study control, the study director did not assure that all experimental data were accurately recorded and verified, that applicable good laboratory practice regulations were followed and that all raw data, documentation, protocols, specimens, and final reports were transferred to the archives during or at the close of the study. Failure to ensure accurate data such as individual animal weights, animal preparation, the administration of test and control articles, observations, and results, yields questionable study results and conclusions. Furthermore, failure to ensure all data is retained and timely transferred to the archives can result in incomplete documentation of the study in the archives and could limit reconstruction and evaluation of the study. Based on these failures, FDA has concerns about the quality and integrity of the data generated from the nonclinical laboratory studies conducted at your testing facility. Complete and accurate study data are necessary to allow FDA to fully assess the overall safety and risk of a device with an associated premarket submission. The unreliable data raises concerns about the quality and integrity of associated premarket submissions, which may put public health and safety at risk.

Your written response is inadequate. You acknowledge in your response that “there are issues with personnel's understanding of 21CFR Part 58 and the implementation of standard operating procedures,” including that “It was found during the inspection that QA was unfamiliar with GLP regulations” and that “[d]uring the investigation, it was shown that SD cannot clearly understand the responsibilities required in 21CFR part 58.” The response provided indicates that certain standard operating procedures (SOPs) relevant to the concerns noted in the Form 483 were revised, new procedures related to data integrity were developed, and some related staff training was conducted. Additionally, the response stated that new electronic systems for document management and training will be implemented and additional training provided. However, your response does not provide: (1) documentation of actions that have been or will be taken to fully address and correct the specific violations observed during the studies, including the conditions which allowed them to occur; (2) detail regarding how your testing facility will ensure that GLP regulations and applicable SOPs will be followed to ensure the quality and integrity of data generated in a study; (3) detail regarding how appropriate documentation/follow-up will be ensured when deviations arise in the future; (4) detail regarding planned preventive actions such as frequency (e.g., quarterly, annual) of audits to check for compliance or future training of new study directors, as applicable; and (5) detail regarding how the effectiveness of proposed preventative actions such as the implementation of electronic systems (which have not yet been implemented) will be assessed. Thus, your response does not provide assurance that similar violations would not occur again. Your explanation, when taken into consideration with the violations described above, which

occurred in multiple studies with various study directors over many months, suggests systemic failures in study director oversight of nonclinical laboratory studies and brings into question the quality and integrity of safety data collected at your testing facility.

2. Failure to properly identify specimens used in nonclinical laboratory studies by test system, study, nature, and date of collection [21 CFR 58.130(c)].

Not all specimens were identified by test system, study, nature, and date of collection. This information was not located on the specimen container or did not accompany the specimen in a manner that precluded error in the recording and storage of data. Your failures to adhere to this requirement include, but are not limited to, the following examples:

a. Six muscle implantation studies (**(b)(4)**) conducted on a high-risk device had the following deficiencies regarding the histopathology slides that contained the study specimens:

1. The slides did not have a study ID and were only identified by the numbers 1-20 written in pencil. There was also no information provided about the test system, nature, or the date of collection. Additionally, the animal identification numbers in the related source records for all six studies do not correspond to the labels on the slides. The animal and implant site identification in the source records only included numbers 1-10, and therefore, the slides are not attributable. In addition, the animal identification numbers in the source records were the same for both the tests and controls (both were labelled 1-10), such that test and control samples cannot be distinguished.
2. Some of the numbers written on the slides were no longer legible and it appeared some numbers had been wiped off and/or written over, including the complete set of slides for study **(b)(4)** Week 4 and **(b)(4)** Week 13. These slides therefore have no identification at all.

Failure to properly label specimens in a manner that precludes error in the recording and storage of data can attribute to evaluating specimens for the wrong animal, wrong implant site, and wrong study. Therefore, the reliability and quality of data of these studies are in question. This in turn adversely impacts a manufacturer’s and FDA’s ability to assess the overall safety and risk of the subject device prior to use in humans as a legally marketed device or for purposes of beginning clinical trials.

Your written response is inadequate. You acknowledge that the procedure lacks some instructions for the study ID requirements and that correct identification was not included on the specimens. The new procedure has details regarding how to identify the slides, blocks, etc. However, your response does not address the issue of providing a unique animal identification system that would allow adequate traceability of specimens to prevent attribution of incorrect or invalid histopathology data to the test articles under study. Therefore, your written response does not provide assurance that similar violations would not reoccur.

3. Failure to ensure that warm-blooded animals, excluding suckling rodents, receive appropriate identification [21 CFR Part 58.90(d)].

Warm-blooded animals, excluding suckling rodents, used in laboratory procedures that require manipulations and observations over an extended period of time or in studies that require the animals to be removed from and returned to their home cages for any reason, shall receive appropriate identification. Your failures to adhere to this requirement include, but are not limited to, the following examples:

a. Some source records do not include unique animal ID numbers. For example:

1. In the AST study, **(b)(4)**, both the test and control animals are only identified as numbers 1 through 5, which is not consistent with SOP **(b)(4)**: Animal Marking Method.
2. In muscle implantation studies, rabbits implanted with control and test articles are both named only “1”, “2”, or “3,” without identifiers to indicate the study numbers for these animals or to distinguish between control and test.

Identifying multiple animals in a particular study with the same number, as noted above, indicates that the animals did not receive appropriate identification. Failure to properly identify each animal within an animal-housing unit raises concerns about the potential for animals to be incorrectly assigned to studies or study groups. The accuracy of study results cannot

be verified since the ability to identify specific animals is foundational to being able to draw scientifically valid conclusions from the studies.

Your written response is inadequate. You acknowledge the observation and have identified the root cause as being due to inadequate procedures and have acknowledged that the non-traceability of animal identification numbers can lead to the loss of tracking of testing systems, which can affect the reconstruction of experiments and data integrity. Proposed corrective actions include the revision of procedures, creation of new procedures and creation of guidelines for electronic data management. Your response indicates that your corrective and preventive action plan has been initiated to track animal numbers for testing for high-risk products. However, this does not appear to be adequate. This action should include all animals received and used at the facility to address the overall system and not isolated practices or only for certain products. Also, as not all of the corrective actions have been implemented at this time, the adequacy cannot be evaluated. Therefore, your written response does not provide assurance that misidentification of animals would not reoccur.

4. Failure to conduct nonclinical laboratory studies in accordance with the protocols [21 CFR 58.130(a)].

Nonclinical laboratory studies shall be conducted in accordance with the study protocol(s). Your failures to adhere to this requirement include, but are not limited to, the following examples:

a. Regarding the ongoing GPMT studies (**(b)(4)** and **(b)(4)**, both started on **(b)(4)**), on **(b)(4)** none of the guinea pigs' cages contained water bottles. Study protocols **(b)(4)** and **(b)(4)** Animal management, states “Water: Drinking water met the Standards for Drinking Water Quality **(b)(4)** 5749-2022.” However, no water was observed to be provided to the guinea pigs, and when asked, the veterinarian stated they used cabbage as the water source. Additionally, it was observed that feed pellets were intermixed with bedding/excreta. Per the aforementioned protocol, feed should consist of “Full-price pellets, **(b)(4)**.” and there should be “no known contaminants present in the feed, water, or bedding expected to interfere with the test data.” Additionally, in multiple cages, the feed box was empty and feed pellets fell into the beddings through the spacings between metal wires of the feed box. Due to the large gaps between the wires of the feed box, the feed box could not provide “reliable and easy” access for guinea pigs to eat the feed pellets. Per the SOP **(b)(4)**-SOP-IAC-001 Animal welfare, Section 3.2, “Drinking and feeding devices for animals should be safe, reliable and easy to eat, and should be kept clean and in normal use.”

b. Within the aforementioned studies, on **(b)(4)**, it was observed that the recorded weights for multiple guinea pigs were less than 300 grams (22 of 30 in the **(b)(4)** study and 24 of 30 in the **(b)(4)** study). Per study protocols **(b)(4)** and **(b)(4)**, section 7.2 Test Animal, all animals should weigh 300-500 grams at the initiation of the study. Per the study protocols and internal procedure **(b)(4)**-SOP-BIO-003, all animals should weigh 300 - 500 grams at the initiation of the study.

Failure to follow the protocol impacts the reliability and quality of data contained within the final study report. This in turn adversely impacts a manufacturer’s and FDA’s ability to assess the overall safety and risk of the subject device prior to use in humans as a legally marketed device or for purposes of beginning clinical trials. Deprivation of food and water is inhumane, and can have adverse effects on animal growth, the immune system, and metabolic state, as well as impact how the body responds to the extract (i.e., device) that is being tested, thus impacting the reliability of the data generated from the nonclinical laboratory studies conducted at your testing facility. Likewise, utilizing animals that do not meet the protocol-specified weight requirements can impact the interpretation and validity of the test results.

Your written response is inadequate. You acknowledge the concern raised by the investigator that not all nonclinical laboratory studies were conducted in accordance with the protocol. Your response indicates that certain SOPs relevant to the concerns noted in the Form 483 were revised, protocol amendments and deviations for certain studies were documented, training for the laboratory supplier was conducted, and a plan was developed for inviting a third-party consultant to audit the animal tracking process. However, your response does not: (1) demonstrate how you will ensure that all personnel will follow study protocols; (2) provide documentation of deviation incidents for all impacted studies; and (3) address any planned preventive actions, such as frequency (e.g., quarterly, annual) of audits to check for compliance following completion of the submitted audit plan or future training for new staff and/or new procedures, as appropriate. Therefore, your written response does not provide assurance that similar violations would not occur again.

5. Failure of the Quality Assurance Unit (QAU) to maintain a copy of a master schedule sheet of all nonclinical laboratory studies conducted at the testing facility indexed by test article and containing the test system, nature of study, date study was initiated, current status of each study, identity of the sponsor, and name of the study director [21 CFR 58.35(b)(1)].

Your failures to adhere to this requirement include, but are not limited to, the following examples:

a. Of the 26 studies requested, 14 of them listed below were not found on the master schedule (MS):

(b)(4)

b. The MS has not been updated since September 30, 2024. However, studies **(b)(4)** and **(b)(4)**, which were not included in the MS, were observed to be ongoing on **(b)(4)**.

c. The MS does not include the name of the study director, the test system, or the sponsor.

A reliable QAU is integral to the successful completion of any nonclinical laboratory study. Without appropriate QAU oversight, neither the sponsor nor FDA reviewers have assurance that the data in the final study report is accurate and valid. Failure to perform QAU functions can have a negative impact on a study because it indicates a lack of monitoring and oversight of each study to ensure compliance with all applicable GLP regulations, and calls into question the quality and integrity of studies conducted.

Your written response is inadequate. You acknowledged in your response the concern that the quality assurance unit failed to maintain a copy of a MS sheet that contained all required elements for all nonclinical laboratory studies, and you indicated that this was likely due to an inadequate MS procedure, as well as QA personnel having overlooked their responsibilities. Your response indicates that SOP **(b)(4)**-SOP-GEN-008 Master Schedule will be revised, QA personnel will be trained on responsibilities, and the FDA GLP studies in the past three years will be sorted out and “a complete GLP master plan” will be submitted to FDA. However, your response does not address how missing studies will be systematically identified and included in the MS. In addition, your response does not discuss whether there will be preventative actions implemented such as audits to check for compliance to the SOPs, nor does it discuss future training for new staff and/or new implemented procedures as applicable. Therefore, your response does not provide assurances that QAU failures will be avoided in the future.

6. Failure to prepare final reports that were signed and dated by each of the individual scientists or other professionals involved in the studies [21 CFR 58.185(a)(12)].

Nonclinical laboratory study results are to be documented in a final study report that must include the signed and dated reports of each of the individual scientists or other professionals involved in the study. Your failures to adhere to this requirement include, but are not limited to, the following example:

The final reports of all of the seven muscle implantation studies for significant risk devices that were reviewed (**(b)(4)** through **(b)(4)**) did not include the signature of the responsible pathologist that provided the histopathology assessment. The pathologist’s signature and date were also missing on the source records where the tissue reaction scores were reported.

Inclusion of the dates and signatures ensures that the findings of the study results can be attributed to the individual scientist completing the study and helps to provide confirmation that the findings are accurately reflected. Without this documentation, it is unknown if the pathologist was involved in the generation of these reports, and whether the data truly reflect the pathologist’s findings. These failures raise questions about the quality and integrity of data collected at your facility.

Your response is inadequate. Your response indicates that SOP **(b)(4)**-SOP-ORG-003 Study Director Duties and Responsibilities was revised, personnel training was conducted, and a plan was developed for inviting a third-party consultant to audit the pathological report management process. Additionally, you indicated that the final reports of high-risk products from 2020-2024 would be reopened to supplement pathological report and evaluate the impact. However, you have not detailed how you intend to assess and supplement these reports. Additionally, while you have revised the

aforementioned SOP, the revisions made do not address the fact that a final report should include the signed and dated reports of each of the individual scientists or other professionals involved in the study. Your response also does not discuss whether there will be preventative actions implemented such as frequency (e.g., quarterly, annual) of audits to check for compliance following completion of the submitted audit plan or future training for new staff and/or new procedures, as appropriate. Therefore, your response does not provide assurances that these failures will not reoccur.

7. Failure to provide for orderly storage and expedient retrieval of all raw data, documentation, protocols, specimens and interim and final reports [21 CFR 58.190(b)].

GLP regulations require that archives are maintained in a way that allows for orderly storage and expedient retrieval of all raw data, documentation, protocols, specimens, and interim and final reports. Your failures to adhere to this requirement include, but are not limited to, the following examples:

a. Your study archives are not organized to permit expedient retrieval. It was observed that records from multiple different studies were stored together in at least 30 boxes without any labels, and GLP study records could not be readily located. On **(b)(4)**, it took up to eight employees over two hours to locate records from eight studies that should have been in the GLP archive room. Two sets of study data were found in the GLP archive room and the remaining six were in the non-GLP storage room.

b. The original final study report for GPMT study **(b)(4)** was amended on 10/12/22; however, a copy of the original report was not retained in the GLP archive portable hard drive. It was stored in the non-GLP public folder.

Inadequate archiving practices could result in the loss or destruction of study material, prevent, or reduce the ability to confirm or amend study results, and puts the archive data at risk of being attributed to the incorrect study. Further, having the raw data readily accessible to the FDA reviewer enables the study to be verified as needed to facilitate review and helps to ensure patient safety. Based on these failures, FDA has concerns about the quality and integrity of the data generated from the nonclinical laboratory studies conducted at your testing facility.

Your response is inadequate. Your response indicates that SOP **(b)(4)**-SOP-ORG-005 Archival, Maintenance and Retrieval, Disposal and Transfer of Records and Materials has been revised, and that you intend to take additional actions, including expansion of the archiving area, adding personnel, and verifying and recovering the completed studies. However, your response does not provide complete documentation of actions that have been or will be taken to fully address and correct the specific violations observed during the inspection, including the conditions that allowed them to occur or detail regarding planned preventive actions such as frequency (e.g., quarterly, annual) of audits to check for compliance or future training of new personnel, as applicable. Therefore, your response does not provide assurance that these failures have been corrected and will not reoccur.

In addition to the violations described above, we have concerns about the records generated during GLP studies that were not maintained in a manner to prevent unauthorized access, changes, or deletions, which further calls into question the reliability and integrity of the data. The histopathology results were transferred between the current pathologist and study director on a portable USB device with a shared password and stored in an unlocked cabinet in the pathologist’s reading room. In addition, for 14 of the 24 studies inspected, the study director has her username and password **(b)(4)**, which would allow anyone to log in.

The study director’s workstation is an open cubicle within a large office that did not have controlled access. The combination of shared password access and unsecured physical storage increases the vulnerability of critical data to be altered or deleted by unauthorized individuals. The absence of physical security measures increases the likelihood of unauthorized individuals accessing not only the study director’s laptop but also any sensitive data saved in the laptop.

The violations described above are not intended to be an all-inclusive list of problems that may exist with your facility. It is your responsibility as a non-clinical laboratory to ensure compliance with the Act and applicable regulations.

Within 15 working days of receiving this letter, please provide documentation of the additional corrective and preventative actions that you have taken or will take to correct these violations and to prevent the recurrence of similar violations in current or future studies for which you are the testing facility. Any submitted corrective action plan should include projected

completion dates for each action to be accomplished as well as a plan for monitoring the effectiveness of your corrective actions. In addition, please provide a complete list of all nonclinical laboratory studies of FDA-regulated devices for the last five years, including the name of the study, the test article, the name of the study director and sponsor, and the current status of the study. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. In addition, FDA could initiate disqualification proceedings against you in accordance with 21 CFR 58.202. If you believe that you have complied with the FD&C Act and FDA regulations, please include your reasoning and any supporting information for our consideration.

Your response should reference “CTS# EC250057/E001” and be sent via email to: Irfan.khan@fda.hhs.gov.

A copy of this letter has been sent to FDA’s OBMI Foreign Inspection Cadre via email FDAInternationalBIMO@fda.hhs.gov. Please send a copy of your response to that office.

If you have any questions, please contact Adaliz Santaliz-Cruz by phone at (787) 729-9024 or email at Adaliz.Santaliz-Cruz@fda.hhs.gov.

Sincerely yours,
/S/

Soma Kalb, PhD
Director
DCEA1: Division of Clinical Policy and Quality
Office of Clinical Evidence & Analysis
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

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1 Facilities must have space provided for archives that is “limited to access by authorized personnel only, for the storage and retrieval of all raw data and specimens from completed studies.” 21 CFR 58.51; see also 21 CFR 58.190(d).