Inspections, Compliance, Enforcement, and Criminal Investigations

Colorado Histo-Prep 3/11/14

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Rajan S. Bawa, Ph.D.
President
Colorado Histo-Prep
702 West Drake Road
Suite G-101
Fort Collins, CO 80526

Ref: 14-HFD-45-02-01

Dear Dr. Bawa:

This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your firm between April 10 and May 10, 2013. Ms. Theressa Smith, representing the FDA, reviewed your conduct of the following nonclinical laboratory studies performed for **(b)(4)**.:

- Study **(b)(4)**, "**(b)(4)**"; and
- Study **(b)(4)**, "**(b)(4)**."

This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of FDA-regulated research to ensure that the data are scientifically valid and accurate, in accordance with Title 21 of the Code of Federal Regulations (CFR), Part 58 – Good Laboratory Practice (GLP) regulations.

At the conclusion of the inspection, Ms. Smith presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your May 27, 2013, written response to the Form FDA 483.

From our review of the FDA establishment inspection report, the documents submitted with that report, and your May 27, 2013, written response, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of nonclinical laboratory studies. We wish to emphasize the following:

1. Your Quality Assurance Unit must determine that no deviations from approved protocols or Standard Operating Procedures were made without proper authorization and documentation [21 CFR 58.35(b)(5)].

A Quality Assurance Unit (QAU) must determine that all protocol and Standard Operating Procedure (SOP) deviations during the conduct of a nonclinical laboratory study were authorized by the study director. Specifically, your QAU failed to determine that protocol deviations, without authorization by the study director, occurred when personnel failed to follow the protocol and substituted missing protocol-defined tissue with "representative tissue," or when collected tissues were missing during the "check out" phase. Examples include the following:

a. For Study **(b)(4)**, your QAU failed to determine that protocol deviations, without authorization, occurred when your firm substituted or used nonspecific tissues samples rather than those required in the protocol for the following:

i) Animals #4004 and #4002: Your firm substituted "quadriceps muscle" with "muscle taken from chunk with sciatic nerve."

ii) Animal #1506: Your firm substituted "quadriceps muscle" with "muscle taken from the back."

iii) Animals #4506 and #1501: Your firm substituted "skin with mammary tissue" with "skin taken from ear."

b. For Study **(b)(4)**, your QAU failed to determine that protocol deviations, without authorization, occurred when your firm substituted or used nonspecific tissue samples rather than those required in the protocol. Specifically, for Animal #1507, your firm substituted "skin with mammary tissue" with a skin sample from the "peri-anal region."

c. For Study **(b)(4)**, your QAU failed to determine that protocol deviations, without authorization, occurred during tissue processing. The protocol for Study **(b)(4)** states that formalin-fixed tissue will be processed in accordance with the firm's internal procedures. Your SOP T-3, "Trimming-Large Animals,"provides instructions for the trimming of each organ during histological processing. During the conduct of Study **(b)(4)**, your firm's written "Colorado Histo-Prep Tissue Form" showed that specific tissues were present during tissue collection and the "trimming" phase; however, during the "check out" phase, the specific tissues were noted to be missing. Examples include:

i) Animals #1502 and #4004: SOP T-3 states that for submaxillary salivary glands, the technician should trim a cross-section from each of the salivary glands to expose both types of tissue. However, for these two study animals, submaxillary salivary glands were trimmed cross-sectionally and embedded, and the secondary glandular tissues were not seen on salivary glands at "check out" (i.e., slide review).

ii) Animal #1501: SOP T-3 states that for ovaries, the technician should bisect each ovary longitudinally and submit half of each ovary (total of 2). Two ovaries were recorded at "trimming," but only one ovary was received at "embedding."

In your May 27, 2013, written response, you included a draft deviation report for Study **(b)(4)** titled "Project Error Investigation and Corrective Action Form," which states that you will revise associated SOPs. Your response is inadequate because you did not include a deviation report for Study **(b)(4)**. Further, the deviation report for Study **(b)(4)** lists only missing and substituted tissue. The description of the study impact says, "… instances of missing tissues or substitutions are present in the pathology tables of the report." Your May 27, 2013, written response states that the pathology tables for Study **(b)(4)** were updated to reflect all instances of missing or substituted tissues; however, no updated tables were provided with your written response.

Your practice of substituting and omitting tissues without proper justification, and the lack of an appropriate response to this observation, raise concerns regarding the scientific quality and integrity of the pathology data for both Study **(b)(4)** and Study **(b)(4)**.

2. Your Quality Assurance Unit failed to be entirely separate from and independent of the personnel engaged in the conduct of that study [21 CFR 58.35(a)].

A QAU must remain entirely separate from and independent of the personnel engaged in the conduct of a nonclinical laboratory study. This separation will allow the QAU to provide an objective and unbiased assessment that each nonclinical laboratory study is conducted in accordance with the approved protocol and SOPs; that the final study report accurately reflects the raw data; that the facility is in compliance with GLP requirements; and that the findings from inspections are reported to management and the study director to allow corrective actions. You failed to maintain a QAU that is entirely separate from and independent of the personnel engaged in the conduct of nonclinical laboratory studies, which undermines the QAU from performing its required functions. Specifically, your QAU failed to maintain its independence from the actual conduct of nonclinical laboratory studies. Examples include the following:

a. Your Quality Assurance (QA) Manager received shipments of study tissues/specimens for Study **(b)(4)** on August 13, 2012 (16 animals), and on September 4, 2012 (24 animals). Your QA Manager also audited the shipments of study tissues/specimens that she received, as noted in the QA Statement for Study **(b)(4)**.

b. At the completion of Study **(b)(4)**, your QA Manager completed the slide-to-block comparison as part of the "Post-study checkout" activities on September 6, 2012.

c. Your QA Manager contacted the study director of Study **(b)(4)** via e-mail on August 30, 2012, to discuss histological processing of tissues and future evaluations of test groups.

In addition, your SOP titled "QAU Responsibilities Outline" includes "Tissue Counts/Blocking Schemes" as a QAU responsibility. The slide-to-block comparison is considered a "Post-Study" activity, a phase of Study **(b)(4)** that was also audited by the QA Manager. Therefore, it appears that management is complacent in allowing the QAU to be directly involved in the conduct of a study that is also audited by that QAU. Further, your current SOP QAU-4, "Quality Assurance Responsibilities," allows the QAU to engage the study director in the planning and conduct of GLP-compliant studies. This SOP describes specific QAU responsibilities that are considered study-related activities, including help with the inspection of materials being returned to clients, and the maintenance of client notification of arrival. Your SOP QAU-4 should be revised to ensure that the QAU's responsibilities are independent of the planning and conduct of GLP-compliant studies.

In your May 27, 2013, written response, you indicated that the QAU has been instructed not to conduct any study activities, and that these tasks will be assigned to other qualified personnel. Your response is inadequate because you do not describe specific corrective measures or changes to current procedures. Your written response offers no assurances that Colorado Histo-Prep will correct this ongoing deficient practice effectively and will adhere to GLP regulatory requirements.

3. Your Quality Assurance Unit failed to assure that the final study report accurately described the methods and Standard Operating Procedures, and that the reported results accurately reflect the raw data [21 CFR 58.35(b)(6)].

A QAU is required to review the final study report to ensure that the reported results reflect the raw data of nonclinical laboratory studies accurately. Although your QAU reviewed the final reports of Studies **(b)(4)** and **(b)(4)** in accordance with SOP QAU-4, the QAU failed to ensure that the final study reports reflect the raw data accurately. For example:

a. Your QAU audited the pathology reports for Studies **(b)(4)** and **(b)(4)**, which reported "No Significant Findings" for various tissues from 10 animals; however, those tissues were never processed and could not have been interpreted histopathologically.

Study Number	Animal Number	Tissues Reported as "No Significant Findings" or "NSF"
(b)(4)	#1002	Pituitary
(b)(4)	#1504	Sternum w/marrow
(b)(4)	#4506	Sciatic nerve, skin w/mammary tissue
(b)(4)	#4006	Sternum w/marrow
(b)(4)	#1010	Pituitary
(b)(4)	#4004	Thyroid/parathyroid, esophagus, lungs
(b)(4)	#4003	Pancreas, duodenum, jejunum, stomach, mesenteric, lymph nodes, ileum, colon
(b)(4)	#1508	Sciatic nerve
(b)(4)	#1502	Urinary bladder
(b)(4)	#4509	Skin w/mammary tissue

In your May 27, 2013, written response, you explained that an amended final report will be issued with corrections, including data-entry errors (e.g., updated tables), and that the amended final report will be independently audited by another QAU. In addition, you stated that all fields in the pathology tables will be made proactive and will not have default values of "NSF" assigned. Your response is inadequate because you failed to provide either a final amended report or an estimated date by which an amended report will be issued. Although you stated that the default setting for the construction of future pathology tables will no longer be "NSF," no written procedure was provided to ensure that this observation will not be repeated in future studies.

b. Hematology parameters (i.e., WBC, RBC, HGB, HCT, MCV, MCH, MCHC, and PLT) do not correspond to the raw data for Animal #1502 in the statistical report of Study **(b)(4)**, dated March 28, 2013.

In your May 27, 2013, written response, you stated that "this error has been fixed and new tables will reflect the corrections in the amended report." However, your response is inadequate because you did not provide either the final amended report for Study **(b)(4)** or an estimated date by which an amended report will be issued.

c. Clinical chemistry serum samples from Study **(b)(4)** for three different clinical chemistry parameters (ALKP from Animal #1502, and AST and ALT from Animal #4002) were reanalyzed without any justification (i.e., no documented error codes/instrumentation flags). The following clinical chemistry samples were repeated, and the second result was reported without justification in the final report of Study **(b)(4)**:

Animal & Clinical Chemistry Parameter	Test 1 Result: 08/01/12	Test 2 Result: 08/01/12	Reported Result in Final (Statistical) Report
#1502/ALKP	289 U/L @ 14:50	266 U/L @ 16:28	266 U/L
#4002/AST	130 U/L @ 15:47	122 U/L @ 16:29	122 U/L
#4002/ALT	140 U/L @ 15:47	137 U/L @ 16:29	137 U/L

Colorado Histo-Prep's current practice of reanalyzing clinical chemistry samples is to rerun samples that "appear in error," based on the technician's knowledge of the run and review of individual animal data.

In your May 27, 2013, written response, you indicated that you "will figure out the best way to deal with this, e.g. average of 2 values, etc." Your response is inadequate because you failed to provide

a written procedure that adequately describes when it is acceptable to reanalyze study samples. Your written procedure should also define the criteria for selecting the data (i.e., original, retest, or average) that should be reported in the final study report.

In your written response, you stated that personnel have been told to perform their jobs "more diligently." However, your response offered no assurance that your firm will correct this ongoing practice effectively and will adhere to GLP regulatory requirements for reporting nonclinical safety data. Thus, the FDA is concerned that the QAU oversight at Colorado Histo-Prep is neither effective nor adequate to ensure data integrity.

4. Not all deviations from standard operating procedures in a study were authorized by the study director and documented in the raw data [21 CFR 58.81(a)].

A facility must follow SOPs in order to ensure the quality and integrity of the data generated in a nonclinical laboratory study. Your QAU failed to follow SOPs to ensure the quality of clinical pathology raw data, and the quality of all reports generated during the conduct of Studies **(b)(4)** and **(b)(4)**. For example, your SOP H-20, "Inspection of Studies," states that the QAU is required to inspect study-specific phases; and SOP QAU-4, "Quality Assurance Responsibilities," states that final project reports are reviewed by the QAU for accuracy. However, the QAU failed to follow your SOPs by not inspecting the clinical pathology raw data appropriately and by not reviewing the statistics final reports for Studies **(b)(4)** and **(b)(4)**.

In your May 27, 2013, written response, you discussed how your firm will implement the findings from audits of clinical pathology data in the future. However, you did not issue a deviation report discussing the impact of the QAU's failure to inspect the clinical pathology raw data, or their failure to review the statistics final reports for Studies **(b)(4)** and **(b)(4)**. Additionally, you failed to explain how you will ensure that the QAU will audit all clinical pathology data and final project reports in the future. As a consequence, FDA is concerned that Colorado Histo-Prep has not instituted corrective procedures to ensure proper QAU oversight.

5. Your testing facility failed to establish standard operating procedures for data handling, storage, and retrieval [21 CFR 58.81(b)(10)].

A testing facility is required to have written SOPs for nonclinical laboratory studies that ensure consistency of procedures from study to study and from technician to technician. Without such procedures, the quality and integrity of data generated in nonclinical laboratory studies cannot be ensured.

Your firm failed to establish SOPs describing the handling and retrieval of electronic data. Handling of electronic data includes the security (e.g., audit trails) and statistical analysis of raw data. Specifically, the SOP for handling electronic data should describe a procedure for the archiving of multiple statistical analyses of the clinical pathology raw data with the study records. For Study **(b)(4)**, multiple sets of statistical analyses were maintained on the firm's electronic server, and were not archived appropriately.

During the inspection, you failed to provide the FDA Investigator with any procedures related to raw data received for statistical analysis. Furthermore, your facility does not have a defined process for saving and archiving electronic data. Although you provided the FDA Investigator with SOP H-31, "Server" and "Data Storage and Disaster Recovery," which describes the physical storage of electronic data in a central file server, your SOP lacks details concerning how you ensure the security of data, and how changes to the files are managed and documented. Furthermore, you failed to monitor access and record changes (via an audit trail) of electronic statistical data and statistical analyses. Thus, the quality and integrity of your data and analyses cannot be ensured.

In your May 27, 2013, written response, you stated that SOPs will be written and implemented to address the issue. Your response is inadequate, however, because you failed to provide the new or

revised SOPs to support your corrective actions, and a timeline for their anticipated implementation.

6. You failed to ensure that all equipment used in the generation, measurement, or assessment of data is adequately tested, calibrated, and/or standardized [21 CFR 58.63 (a)].

Equipment used to generate raw data in a nonclinical laboratory study is required to be tested, calibrated and/or standardized, based on the manufacturer's recommendations.

You failed to replace reagents in the Tissue Tek processor in accordance with the manufacturer's recommendations when you processed tissues for Studies **(b)(4)** and **(b)(4)**. According to the manufacturer's guide for the Tissue Tek processor, reagents (i.e., xylene, alcohol and water) used in the "Clean Cycle" should be replaced after every five runs to avoid paraffin contamination. Between April 2012 and October 2012, there were five instances when the reagents were changed after more than 5 runs (i.e., after 11, 8, 6, 15, and 19 runs). By using suboptimal instrumentation conditions to process tissues for nonclinical laboratory studies, you failed to ensure the integrity of the data generated by the Tissue Tek processor.

During the inspection, you stated that this equipment is not used in a clinical setting, and therefore, there is no need to perform the maintenance as described in the maintenance guide. However, in your May 27, 2013, written response, you stated that the technician had changed the reagents at appropriate intervals, but neglected to properly document the reagent changes. In addition, you provided a form used to record reagent changes and stated that you revised the corresponding SOP to address this deficiency. Your response is inadequate, however, because you failed to provide a copy of the revised SOP and an anticipated date for its implementation. Thus, we are unable to assess the adequacy of your response and corrective action for this violation.

This letter is not intended to be an all–inclusive list of deficiencies at your facility. Your written responses, dated May 27, 2013, are severely inadequate, and it is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any ongoing or future studies will be in compliance with FDA regulations.

Within fifteen (15) business days of your receipt of this letter, you should notify OSI in writing of the actions you have taken or will take to prevent similar violations in the future. Your written response should include any documentation necessary to show that full and adequate correction has been or will be achieved. Please include the projected completion dates for each action to be accomplished. Failure to address the violations noted above adequately and promptly may result in regulatory action without further notice.

If you have any questions, please contact Charles R. Bonapace, Pharm.D., at 301-796-1507; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

Charles R. Bonapace, Pharm.D.
Acting Branch Chief, Good Laboratory Practice Branch
Division of Bioequivalence and Good Laboratory Practice Compliance
Office of Scientific Investigations
Office of Compliance
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Sincerely yours,

{See appended electronic signature page}

Sean Y. Kassim, Ph.D.
Acting Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SEAN Y KASSIM
03/11/2014

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