



**CERTIFIED MAIL
RETURN RECEIPT REQUESTED**

Reference No.: 11-HFD-45-07-02

Roger N. Hayes, Ph.D.
President, Bioanalytical
Cetero Research
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Dear Dr. Hayes:

This letter is to inform you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspections conducted at your bioanalytical facility, located in Houston, Texas, from May 3-7, 2010, by FDA investigators Mr. Patrick D. Stone, Dr. Jacqueline A. O'Shaughnessy, and Dr. Carol M. Rivera-Lopez; and from December 6-10, 2010, by FDA investigators Drs. Albert Peacock, Martin K. Yau, Sam H. Haidar, John Kadavil, and Xikui Chen. FDA investigators have identified significant violations of the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulations, Part 320. These violations include the widespread falsification of dates and times in laboratory records for subject sample extractions, and the apparent manipulation of equilibration samples to meet pre-determined acceptance criteria.

It is your firm's responsibility to ensure and confirm the reliability of your testing methods and the bioequivalence and bioavailability data collected by your firm and presented as part of any applications submitted to the FDA. The pervasiveness and egregious nature of the violative practices by your firm has led FDA to have significant concerns that the bioequivalence and bioavailability data generated at the Cetero Houston facility from April 1, 2005, to June 15, 2010, including data relied on as part of studies submitted in both New Drug Applications (NDA) and Abbreviated New Drug Applications (ANDA) to FDA, are unreliable.

As discussed below, FDA has reached this conclusion based on the following: (1) The widespread falsification of dates and times in laboratory records for subject sample extractions; (2) the apparent manipulation of equilibration or "prep" run samples to meet predetermined acceptance criteria; and (3) the lack of documentation regarding equilibration or "prep" runs that prevented you from conducting an adequate internal investigation to determine the extent and impact of these violations.

The FDA inspections included a review of various portions of the following studies:

May 2010 Inspection

- Study (b) (4) ((b) (4)), sponsored by (b) (4)
- Study (b) (4) ((b) (4)), sponsored by (b) (4)
- Study (b) (4) ((b) (4)), sponsored by (b) (4)
- Study (b) (4) ((b) (4)), sponsored by (b) (4)
- Study (b) (4) ((b) (4)), sponsored by (b) (4)

December 2010 Inspection

- Study (b) (4) ((b) (4)), sponsored by (b) (4)
- Study (b) (4) ((b) (4)), sponsored by (b) (4)
- Study (b) (4) ((b) (4)), sponsored by (b) (4)
- Study (b) (4) ((b) (4)), sponsored by (b) (4)

These inspections are part of FDA’s Bioresearch Monitoring (BIMO) Program, which includes inspections to evaluate the conduct of research, to confirm that data intended for submission to FDA are reliable as a basis for FDA approval and regulatory decisions, and to verify compliance with the bioavailability and bioequivalence requirements in 21 CFR Part 320.

In a letter dated April 22, 2009, one of your employees (the complainant) brought formal allegations of regulatory violations and other misconduct to your firm’s attention. In this letter, it was noted that as early as June 2007, the complainant “first raised certain issues in a supervisor’s meeting in which the former CEO ... attended. During such meeting, [the complainant] identified numerous Cetero Standard Operating Procedures that were not being followed within the lab by many of the chemists. [The complainant] was aware that many of the chemists were manipulating and falsifying data associated with the samples being used within various projects.”

After receipt of the April 22, 2009 letter from the complainant, your firm subsequently initiated an internal investigation regarding the complainant’s claims, as detailed in a report titled “Internal Investigation for Data Integrity Concerns Received April 22, 2009,” dated June 5, 2009. On June 5, 2009, the complainant notified the FDA Dallas District Office regarding concerns about laboratory misconduct at your Houston facility. Your firm contacted the FDA Dallas District Office on June 10, 2009, to inform FDA of the allegations, as well as to present the outcome of the internal investigation conducted by your firm. Further, your firm sought an independent third party investigation and review of the allegations that was completed July 6, 2009. In addition, your firm updated your internal investigation in a report titled “July 27, 2009 Internal Investigation Update for Data Integrity Concerns Received April 22, 2009.” We acknowledge receipt of the two reports of your firm’s internal investigation and the report from the third party investigation.

Both the FDA inspections of your facility in May 2010 and December 2010 and the third party investigation in July 2009 identified numerous concerns regarding procedures at your facility, as well as deficiencies with your internal investigation. At the close of the May 2010 inspection, your firm was issued a Form FDA 483, and we acknowledge receipt of your firm's response, dated May 24, 2010 [hereafter referred to as May 24, 2010 483 response letter]. Despite the proposed corrective actions in your letter, FDA found continued deficiencies at your facility during the December 2010 inspection, and another Form FDA 483 was issued on December 10, 2010. We acknowledge the receipt of your December 29, 2010 response to the second Form FDA 483 [hereafter referred to as December 29, 2010 483 response letter]. However, as detailed below, your 483 response letters do not adequately address the violations which FDA discovered during its inspections.

FDA noted the following violations at your facility:

Your firm failed to demonstrate that the analytical method used in an in vivo bioavailability or bioequivalence study to measure the concentration of the active drug ingredient or therapeutic moiety, or its active metabolite(s), in body fluids or excretory products, is accurate and of sufficient sensitivity to measure, with appropriate precision, the actual concentration of the active drug ingredient or therapeutic moiety, or its active metabolite(s), achieved in the body [21 C.F.R. § 320.29(a)].

Examples include, but are not limited to, the following:

1. Instances of misconduct

a. Falsified laboratory records

FDA notes that your internal investigation identified problems related to falsified employee time/date records. You reported these issues to FDA on July 28, 2009. During the course of its inspections in May 2010 and December 2010, FDA also discovered inconsistent and/or falsified Analytical Procedure (AP) raw data sheets for several studies with respect to the times and dates of subject sample extractions.

The following are two examples of such studies:

- Study (b) (4): Analytical Runs 5 and 6 for (b) (4) and analytical Run 4 for (b) (4).
- Study (b) (4): Analytical Runs 11 through 16 for (b) (4) and Runs 13, 14, 17, and 18 for (b) (4).

In your May 24, 2010 483 response letter, you concurred with FDA's observation that the falsifications involve data from multiple studies for multiple sponsors.

As detailed below, your 483 response letters, as well as your internal investigation and the third party investigation, were inadequate to address FDA's concerns regarding the falsified laboratory records.

(1) The scope of your internal investigation was insufficient.

The scope of your internal investigation was limited to only the date/time falsifications on the AP sheets, instead of overall study conduct and other data recorded on the AP sheets; therefore, your firm has failed to determine whether other aspects of the laboratory records might be compromised. The true extent of these falsifications is thus unknown.

According to your internal investigation, electronic records of key card building entry times demonstrated approximately 1900 instances of blood/plasma samples allegedly extracted on weekends and holidays between April 15, 2005, and June 30, 2009, where the arrival times of laboratory chemists were greater than one hour after the documented start time of the sample extraction. In addition, there were approximately 875 instances where the laboratory chemists were not present in the facility at the documented sample extraction date.

In your responses to the Forms FDA 483 issued at the close of both the May 2010 and December 2010 inspections, your firm stated that chemists extracted study samples on Fridays or the day before a holiday, and documented the work as completed on the weekend or a holiday to receive financial incentives. Your firm also stated that your investigation determined that falsification of laboratory records was limited to changes to time and date of extractions.

As a result of your stated assumption that laboratory records were falsified due to chemists' incentive to receive increased compensation without the appearance of having done all the work on a single day, your firm focused initially on the weekend extraction records, and you failed to consider whether any weekday extraction records were falsified. Following the May 2010 inspection, your firm decided to investigate further, and you found that employees falsified timecards and laboratory records on both weekends and weekdays.

You stated the following in your May 24, 2010 483 response letter:

“As the reasons for the modifications to the AP were linked to the financial incentive issue ... there was no reason to doubt the validity of any other sections of the AP.”

However, you have not provided an explanation regarding why employees would have falsified the dates and times on weekday records, as there was no financial incentive for them to do so. Further, FDA disagrees both with your proposed theory that modifications of the AP sheets were linked to financial incentives for weekend extractions, and with

your assertion that there was no reason to doubt the validity of other sections of the AP sheets. Your firm has not provided any documentation to support these claims, or explained how you verified the overall reliability of your laboratory records.

(2) You failed to provide evidence for your assertion that Quality Assurance (QA) activities at your firm limited the scope of the falsification to the time and date of sample extractions.

You stated in your May 24, 2010 483 response that pre-study activities (e.g., weighing of reference standards, preparation of stock and spiking solutions, and preparation of bulk QCs) were reviewed 100% by the Quality Control/Documentation staff. In addition, you stated that all pre-study activities and 20% of the subject runs were audited by Quality Assurance (QA) staff. You claimed that these routine reviews assured the integrity of pre-study events, and by extension, verified that the alterations in laboratory records were limited to time and date of extractions. However, FDA notes that despite these audits of study runs, your QA department did not uncover the frequent alterations in laboratory records that occurred over a four-year period, from April 1, 2005 to June 15, 2009, when your firm conducted an internal investigation. These problems indicate that routine audits conducted by your QA department have been insufficient to verify or assess the reliability of your laboratory records.

You stated the following in your May 24, 2010 483 response letter: “It is our strong belief that the reported concentration data for each of these affected studies was not compromised as only the date and time of extraction was uncertain in the extraction steps involved.” You also stated in your December 29, 2010 483 response letter: “[w]e conducted an extremely broad and thorough investigation.... As a result, we are confident that the integrity of the data generated by research chemists implicated in the day/date fraud was not affected or otherwise undermined.”

FDA does not agree with the above statements in your 483 response letters. The narrow scope of your internal investigation of the falsification of laboratory records, the lack of a consistent and credible explanation for the time and date discrepancies in timecards and sample extractions, and the failure of your QA procedures to detect the falsification, call into question the validity of all of the information documented on your AP sheets, including study results that were used as the basis for NDAs and ANDAs submitted to FDA.

In addition, the July 6, 2009 report from the independent third party investigation stated that “[t]here appears to be evidence of misconduct among lab staff that has occurred for at least several years and continued until at least April of this year. Laboratory supervisors appear to have been involved. This misconduct appears to be significant enough to cast doubt on the data generated.” Your responses have not adequately addressed these concerns raised in the third party investigation report.

The fabrication of any portion of a laboratory record casts doubt upon the reliability of the remaining portions. You failed to support your contention that fabrications of

laboratory records were limited to time and date of extractions. The extensive use of falsified laboratory records by your firm has led the FDA to question the validity of all bioanalytical data collected by your facility during the period from April 1, 2005 to June 15, 2010

b. Manipulation of Samples

FDA has determined that your firm manipulated test samples in order to meet pre-determined acceptance criteria.

According to the original complaint, equilibration or “prep” runs were allegedly used to manipulate data by “fixing” runs to meet acceptance criteria prior to inclusion of data in the official study folder.

The original complaint submitted to FDA described several examples of this practice. In one example, the complainant submitted photographs that showed that Run 38 for Study (b) (4), which was injected on January 3, 2009, failed as a result of lacking the internal standard (i.e., internal standard was not initially added to the calibration standards and quality control samples, as is standard practice). According to the notation evident in the photograph, the Run 38 samples were to be put back in the refrigerator following the failed run. The next day, the Run 38 samples were injected onto the LC/MS/MS (Liquid Chromatography with Tandem Mass Spectrometry) system, and internal standard was now present in the calibration standards and quality control samples. Your firm’s records do not explain this discrepancy, nor do they document that internal standard was added to the sample before it was reanalyzed on January 4.

As stated by the third party investigation dated July 6, 2009, “[i]t would appear the standard curve and quality controls were substituted from another run.” Quality control samples provide assurance of the accuracy and precision of the drug concentrations in subject samples. Substituting quality control samples from another run to meet acceptance criteria is not appropriate, as the drug concentration of subject samples cannot be ensured.

Your firm’s internal investigation initially failed to identify any misconduct related to Run 38, despite the complainant’s allegations. It was not until after the complainant provided photographic and other evidence, and the third party audit found that “the allegation appears to have merit,” that your firm acknowledged to FDA in the update to the internal investigation that “it is reasonable to assume that inappropriate activities surrounding run 38 standard curve and quality control samples occurred.” Your failure to recognize the improper procedures regarding Run 38 calls into question the other conclusions in your internal investigation.

2. Improper use of equilibration samples

Accurate measurement of the concentration of the active drug or active moiety is dependent on a properly validated analytical method, including calibration and

equilibration of the instrument used to perform the testing. The use of the following types of samples for equilibration of LC/MS/MS instruments is not recommended:

- Subject samples that have not yet been analyzed, and
- Calibration standards, quality controls (QCs), and blanks that are part of the official run.

The third party investigation report dated July 6, 2009 states: “If an instrument requires conditioning, only samples prepared specifically for this purpose should be used and these samples should not be part of the standards or controls for the run. There must be no manner in which these samples could be substituted for the standards and controls in another run.”

Based on the information provided by your firm and the report of the third party investigation contracted by your firm, your firm’s method of equilibrating LC/MS/MS instruments consisted of using samples such as calibration standards, quality controls, blanks, and subject samples that were part of the current run and not yet analyzed.

FDA is concerned that the use of extracted samples not yet analyzed for system equilibration can provide opportunities for chemists to manipulate the outcome of the official study run. A chemist would have an opportunity to determine whether the “prep” run calibration standards and quality control samples would pass or fail acceptance criteria prior to analyzing these samples as an official study run, thus creating an opportunity for manipulation of the study run, either by adding study drug or internal standard to the sample, or by substituting the sample with other samples that had previously passed.

Your May 2010 and December 2010 483 response letters, as well as your internal investigation and third party investigation, were inadequate to address FDA’s concerns regarding the improper use of equilibration samples, as detailed below.

(a) The explanation you provided for this practice in your May 24, 2010 483 response letter lacks credibility.

You claim that the purpose of an equilibration or “prep” run is to condition the system and perform any necessary troubleshooting prior to starting the subject sample run. However, this contention fails to provide an explanation for Run 20 of Study (b) (4), evaluated during FDA’s May 2010 inspection. In Run 20, the “prep” run was performed on system 95, and the actual run was performed on system 74. If the practice of “prep” runs was indeed to equilibrate and to ensure optimal performance of the LC/MS/MS System, then the same equilibrated instrument must be used.

(b) Your internal investigation regarding “prep” runs was inadequate.

Cetero’s internal investigation, including the third party investigation, has not reduced FDA’s concerns about the reliability of data generated by your firm between April 1, 2005 and June 15, 2010. The lack of sufficient documentation and SOPs regarding the

use of “prep” runs at your firm precluded your ability to conduct an adequate investigation to respond to the Forms FDA 483 issued during the May 2010 and December 2010 inspections.

Your firm instituted an investigation plan titled “Cetero Research Houston Facility Investigation Plan Revision 1,” dated July 28, 2009, to address the complainant’s allegation that runs were injected multiple times in order to obtain a passing result and that samples were somehow “fixed” in order to pass. The internal investigation evaluated approximately (b) (4) samples from your unofficial electronic “prep” run files conducted for approximately (b) (4) studies between the period of April 2005 and June 2009. The investigation identified three additional runs with misconduct similar to Run 38 of Study (b) (4), as described above.

The “Prepping Runs Decision Tree” in your internal investigation plan was intended to address the allegation by the complainant that samples were “fixed.” According to the decision tree, Cetero would evaluate whether there was an internal standard or drug response for all samples, whether all calibration standards and quality control samples had drug peaks, and whether blanks had acceptable responses. Your analysis included the assumption that the “prep” run samples were the same as those subsequently injected on the official study run. FDA does not accept this assumption as the basis for making determinations about the prep runs, because you lack documentation of the identity of samples used in the “prep” runs conducted by your firm.

The only part of your internal investigation that does not rely on sample identity is the evaluation of whether there was an internal standard or drug response for all samples. As a result, your internal investigation was more limited than planned, because it was only able to focus on “prep” runs with results that could not be explained scientifically (i.e., samples in which the drug or internal standard was initially absent but appeared in subsequent injections on the official run). The investigation was not able to evaluate whether calibrators, quality control samples, or blanks may have been spiked with drug or substituted with other samples. Further, your internal investigation could not evaluate how the prep runs were used, what was injected, and how they may have impacted the study results.

FDA’s May 2010 and December 2010 inspections revealed the fundamental lack of documentation regarding the prep runs, and as such, it became apparent that your firm’s internal investigation was insufficient to thoroughly address the allegations regarding “prep” runs. Your investigation failed to demonstrate that the use of “prep” runs did not impact the study data integrity for the period of time analyzed. The lack of documentation inhibited your ability to adequately address the actual identity of the samples used, the varying number (4 to 43) of sample injections between “prep” runs, and whether the “prep” run results were used to alter the results of the official run. This is consistent with the findings from the independent third party investigation report dated July 6, 2009, which noted that “[t]he ‘prep’ data was not always stored in the study folder and there was no documentation of what changes may have been made during the prepping process to the instrument or samples. Nor was there documentation of why

samples were injected multiple times. This process may be seen as testing into compliance since the samples were injected until a passing result was obtained and then the run was formally injected.”

In your December 29, 2010 483 response letter, you stated that chemists were “blinded” to the identity of equilibration samples to limit the possibility of misconduct, and that documentation describing the source and identity of equilibration samples was not obtained. FDA does not find this explanation credible, as you provide no evidence to demonstrate that the chemists were blinded to the identity of the samples injected in the “prep” runs. In addition, as discussed below, you had no SOPs regarding this procedure.

The lack of documentation regarding “prep” runs prevents your firm from undertaking a thorough internal investigation and determining the impact of your “prep” run practices. The lack of documentation also prevents the Agency from undertaking an informed evaluation of your actual testing practices. As a result, we are unable to support the conclusion of your internal investigation that the use of “prep” runs had no impact on the data integrity of studies conducted at your facility.

(c) Your firm lacked SOPs for equilibration of LC/MS/MS instruments.

In your May 24, 2010 483 response, you acknowledge that the historical practice of conditioning LC/MS/MS instruments at your facility was to utilize a subset of samples that were to be analyzed on the current run. As noted above, the complainant sent a letter to Cetero on April 22, 2009. In May 2009, Cetero management provided instructions to immediately stop the practice of using samples not yet analyzed to condition/equilibrate the LC/MS/MS instrument, and to use only previously analyzed samples for conditioning/equilibration purposes. However, your firm did not implement written guidance on conditioning LC/MS/MS instruments until December 14, 2009 (CET_SOP_04_INS-006, Equilibration of LC/MS/MS, Version 1). This SOP stated that a pooled sample of previously injected calibration standards, quality controls samples, and subject samples should be used to equilibrate LC/MS/MS instruments. FDA notes that this first version of the SOP did not require documentation of the identification and source of equilibration samples, and therefore, it was not acceptable.

The third party independent investigation report dated July 6, 2009 provided the following recommendation regarding the use of “prep” runs and equilibration of LC/MS/MS instruments: “The practice of “prepping” using standards and controls for any run should be discontinued immediately. If an instrument requires conditioning, only samples prepared specifically for this purpose should be used and these samples should not be part of the standards or controls for the run. There must be no manner in which these samples could be substituted for the standards and controls in another run. Every injection made, every sample prepared and every action taken from the initiation of a study should be documented. Data should only be acquired in the official study folder and it must be traceable to the documentation.”

Despite this recommendation, it was not until June 15, 2010 that your firm implemented an acceptable SOP designed to ensure an unbiased and consistent approach to equilibrate or “prep” LC/MS/MS instruments at your Houston facility. Therefore, the development and implementation of your SOP does not remedy FDA’s concerns about the data generated at your Houston facility prior to June 15, 2010.

3. Concerns about data reliability at Cetero Houston

As discussed above, FDA has significant concerns that all data relevant to FDA-regulated research conducted at your Houston, Texas, facility from April 1, 2005 to June 15, 2010 are unreliable, based on the following reasons:

- (1) The widespread falsification of dates and times in laboratory records for subject sample extractions,
- (2) The apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and
- (3) The lack of documentation regarding “prep” runs that prevented you from conducting an adequate internal investigation to determine the extent and impact of these violations.

The independent third party investigation shared FDA’s concerns, and stated the following with respect to the general impact on data reliability:

“[C]hromatography may have been acceptable, QCs may have passed and ISR [Incurred Sample Reanalysis] data (recent) may be very good, but doubt remains regarding the integrity of the basic elements of the analytical process due to the documentation irregularities. If the foundation of the laboratory is corrupt, then the data generated will be also. The investigation has uncovered practices that are clearly unacceptable. The major concern is the impact they may have had on the data generated. It is not possible to know the extent of the improprieties or their ultimate impact.”

We remind you that it is your firm’s responsibility to ensure the integrity of all data generated at your firm that is submitted to the FDA in ANDAs or NDAs. Given the scope and the egregious nature of both the fabrications associated with your extraction records and the practice of “prep” runs, we have significant concerns that the data generated between April 2005 and the implementation of CET_SOP_04_INS-006, Version 2, on June 15, 2010, are unreliable.

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above. You must also implement appropriate corrective actions for preventing their recurrence and the occurrence of other violations.

Within fifteen working days of receipt of this letter, please respond in writing and provide FDA with a list of all studies conducted at Cetero Houston between April 1, 2005 and June 15, 2010 that are relevant to FDA-regulated research, so that the Agency can assess the impact of studies submitted in support of NDAs and ANDAs. For each study, we request that you provide the drug name, the study number, and the name of the sponsor.

You should also include an explanation of steps being taken to both correct the violations noted in this letter and to prevent the recurrence of violations. Please provide copies of supporting documentation.

If you have any questions or wish to meet with the Office of Scientific Investigations, please contact Sam H. Haidar, Ph.D., R.Ph., at 301-796-3150. Your written response and any pertinent documentation should be addressed to:

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Sincerely,

{See appended electronic signature page}

Leslie K. Ball, M.D.
Director (Acting)
Office of Scientific Investigations
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/s/

SAM H HAIDAR
07/26/2011

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07/26/2011