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| **Company:** | **Year:** | **Text Of Compliance** |
| Mercy Hospital & Medical Center | 2014 | 4. Failure to retain IRB records for at least 3 years after completion of the research. [21 CFR 56.115(b)]  An IRB shall retain the records required by 21 CFR 56.115(a) for at least 3 years after completion of the research, and the records shall be accessible for inspection and copying by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner. Examples of your IRB’s failure to adhere to this regulation include, but are not limited to, the following:  a) Rosters of IRB membership prior to (b)(4) have not been retained;  b) IRB meeting minutes from meetings held (b)(4) and (b)(4), have not been retained;  c) The study “ (b)(4)” was approved on (b)(4), but the research proposal has not been retained;  d) Copies of Policies and Procedures prior to (b)(4), have not been retained.  Retaining IRB rosters, meeting minutes, and written policies and procedures is an important part of IRB activities in that it provides documentation of IRB membership and activities, including documenting the members who were present at IRB meetings and approved certain research activities. |
| Advanced Interventional Pain Ctr | 2014 | 4. Failure to prepare and maintain adequate documentation of IRB activities. [21 CFR 56.115(a)(1), (a)(2), and (a)(4)]  To fulfill the requirements of this regulation, an IRB shall prepare and maintain adequate documentation of IRB activities, including the following: copies of all research proposals reviewed, minutes of IRB meetings, and copies of all correspondence between the IRB and the investigators. You failed to maintain the following:  • copies of the original protocol that was reviewed during the convened IRB meeting held on 11/11/2009  • meeting minutes in sufficient detail to show the votes on actions including the members voting for, against, and abstaining, for convened IRB meetings held on 11/11/2009 and 10/18/2011  • documentation of a discussion held between the IRB Chairman and the Clinical Investigator pertaining to the closing of the study  It is critical that your IRB prepare and maintain adequate written procedures in order to ensure that the rights and welfare of study subjects are protected. |
| Colorado Histo-Prep | 2014 | 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 crosssectionally 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). |
| Colorado Histo-Prep | 2014 | 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.  \*Please Refer To Table In PDF FILE  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) :  \*Please Refer To Table In PDF FILE  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. |
| Colorado Histo-Prep | 2014 | 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. |
| Colorado Histo-Prep | 2014 | 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. |
| Kootenai Hospital District | 2014 | 5. Failure to prepare and maintain adequate documentation of IRB activities [21 CFR 56.115(a)(2) and (5)]  An IRB is required to prepare and maintain adequate documentation of IRB activities including, but not limited to: copies of all research proposals reviewed; IRB meeting minutes; progress reports submitted by investigators; correspondence between the IRB and the investigators; and a list of IRB members.  Your IRB failed to prepare or maintain adequate documentation. Such instances include, but are not limited to, the following:  • The IRB meeting minutes lack sufficient detail to show the votes of all attending members for the IRB meetings held on February 6, 2013, January 2, 2013, December 5, 2012, December 7, 2011, and August 3, 2011.  • Your IRB failed to maintain a copy of the roster of IRB members for changes dated February 2013, November 2012, October 2011, and June 2011.  In your IRB’s written responses, you note that the IRB policies and guidelines set appropriate terms for, among other things, documentation, complete meeting minutes, and rosters. This response is inadequate because it does not include a plan to prevent recurrence of this violation. |
| Kootenai Hospital District | 2014 | 6. Failure to prepare and maintain written procedures for IRB activities [21 CFR 56.115(a)(6)]  An IRB is required to prepare and maintain written procedures for IRB activities including, but not limited to: initial and continuing review of research; reporting its findings and actions to the investigator and the institution; determining which projects require review more often than annually; ensuring prompt reporting to the IRB of changes in research activity; and ensuring that changes in approved research may not be initiated without IRB review and approval.  Your IRB lacks written procedures for reporting its findings and actions to the investigator and the institution and for determining which projects require review more often than annually.  It is critical that your IRB prepare and maintain its written procedures for the review of research. Such procedures will help to ensure that research is reviewed in a timely manner and that the findings are adequately reported to the institution and the clinical investigator. Your IRB’s lack of written procedures for the review of research can compromise the rights, safety, and welfare of research subjects and decrease the integrity and validity of research data.  In your IRB’s written responses, you note that the IRB policies and guidelines set appropriate terms for, among other things, documentation. This response is inadequate because it fails to address written procedures for reporting IRB findings and actions to the investigator and the institution and for determining which projects require review more often than annually. |
| Ruemu Birhiray | 2014 | 2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].  As a clinical investigator, you are required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation.  For Protocols (b)(4) and (b)(4), case histories include signed and dated informed consent documents and study registration forms. You have failed to maintain adequate and accurate case histories with respect to these documents. Specifically:   a. The informed consent document for Protocol (b)(4) requires a “yes” or “no” response to six questions regarding subjects’ consent to participate in optional research studies in the future. You failed to record subjects’ consent to these optional studies adequately and accurately on the subjects’ study registration forms. Specifically:   i) Subject 214199 did not provide a “yes” or “no” response to any of the six questions regarding consent to participate in optional future studies; however, a “yes” response to each of the six questions was recorded on the subject’s registration form, indicating that the subject had provided a response to all of these questions.    ii) Subject 214632 did not provide a “yes” or “no” response to three of the six questions regarding consent to participate in optional future studies; however, a “yes” response to all six questions was recorded on the subject’s registration form, indicating that the subject had provided a response to all of these questions.   b. For Protocol (b)(4), one copy of the informed consent document for Subject 810493082 shows that the subject consented to optional future research; however, another copy of the same informed consent document shows that the subject did not consent to optional future research.  There is no documented explanation for this discrepancy, and no documentation of when this informed consent document was amended or by whom.  In your September 22, 2013, written response to the findings noted in Item 2 above, you stated that you are not currently conducting clinical research or actively recruiting subjects to any studies. You noted that, had you continued to conduct clinical research, you would have appointed designated administrative and research staff to coordinate your clinical studies, to document delegation of responsibilities, to conduct routine weekly internal monitoring, to implement a new electronic medical record system, and to use a table/flowchart to monitor laboratory results.  Your response is inadequate because you did not provide sufficient information to enable us to evaluate the adequacy of your corrective action plans for use in any future clinical research that you may conduct. For example, you did not provide details regarding how you will implement your corrective action plan to prevent protocol violations. In addition, you did not provide any details of a corrective action plan to ensure adequate training for you and your staff on protocol requirements, to prevent future violations; and you have not provided sufficient details regarding your plan to document required study data adequately. As a result, we are unable to evaluate whether the corrective actions outlined above are adequate to prevent the occurrence of similar violations in the future.  Your failure to document informed consent properly, raises concerns about the extent to which subjects’ rights were protected at your site.  This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. 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) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Failure to address the violations noted above adequately and promptly may result in regulatory action without further notice. If you believe you have complied with FDA regulations, include your reasoning and any supporting information for our consideration. |
| Amks Time Release Lab LLC | 2014 | 2. Failure to ensure proper monitoring of the investigations and failure to ensure that the investigations are conducted in accordance with the general investigational plan and protocols contained in the IND [21 CFR 312.50 and 312.56(a)].   FDA regulations require that sponsors ensure proper monitoring of clinical investigations and ensure that their clinical investigators conduct those investigations in accordance with the general investigational plan and protocols contained in the IND. Our investigation found that you failed to ensure proper monitoring of Protocol(b)(4) and did not ensure that a clinical investigator conducted the investigation in accordance with that protocol. Specifically:   AMKS TRL monitoring failed to identify and correct a clinical investigator’s failure to collect study subjects’ data on protocol-specific case report forms (CRFs), as required by Protocol (b)(4). We note that during the inspection, you indicated that AMKS TRL did not use any paper CRFs or electronic data capture to record study subjects’ data.   In your July 30, 2013, written response, you indicated that AMKS TRL had no written monitoring plan for Protocol (b)(4) and monitored the study’s progress through verbal discussions with the clinical investigator. We acknowledge that in that written response, you indicated that AMKS TRL has prepared a written monitoring plan and submitted that plan to FDA, along with a new protocol.   Regarding the lack of CRFs, we acknowledge that AMKS TRL has prepared and provided a copy of a CRF with your July 30, 2013, written response.   Your written response is inadequate because you did not include with it a copy of the monitoring plan or provide any details regarding the monitoring plan. As a result, we are unable to determine whether your written monitoring plan appears sufficient to prevent similar violations in the future. In addition, the CRF you provided with your July 30, 2013, written response does not appear to be related to Protocol (b)(4), because there are significant differences between the inclusion/exclusion criteria and laboratory assessments in the CRF you provided, and those for Protocol (b)(4). |
| Amks Time Release Lab LLC | 2014 | 3. Failure to maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug [21 CFR 312.57(a)].   As the sponsor of Protocol (b)(4), AMKS TRL was required to maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug (b)(4). These records were required to include, as appropriate, the name of the clinical investigator to whom the drug was shipped, and the date, quantity, and batch or code mark of each such shipment. AMKS TRL failed to maintain adequate records with respect to the investigational drug (b)(4). Specifically, AMKS TRL did not maintain any records showing the shipment or other disposition of the investigational drug.   In your July 30, 2013, written response, you do not address specifically whether AMKS TRL kept written records of the disposition of investigational drug for Protocol (b)(4). However, you do state, “We used to carry the product to the hospital in person because the hospital is close to our facility. But now in the new study we will keep accurate records for shipment as per AMKS TRL has established an S.O.P. To outline the shipment, quantity used, return or destruction of clinical drug [sic].” You also note in your response that records for use were retained in patient files at St. Joseph Hospital. |
| John M Wise MD | 2014 | This Warning Letter informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection conducted at your clinical site between March 24 and 28, 2014. Mark W. Babbitt, representing FDA, reviewed your conduct of the following clinical investigations of the investigational drug (b)(4) , (b)(4) , performed for (b)(4) .:  • Protocol (b)(4) , “(b)(4) ”;  • Protocol (b)(4) , “(b)(4) ”; and  • Protocol (b)(4) , “(b)(4) .”  This inspection is a 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, and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.  At the conclusion of the inspection, Investigator Babbitt presented and discussed with you Form FDA 483, Inspectional Observations.  From our review of the FDA Establishment Inspection Report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We wish to emphasize the following:   You failed to retain records required to be maintained under 21 CFR Part 312 for a period of two years following the date a marketing application is approved for the drug for the indication for which the drug is being investigated; or, if no application is filed or if the application is not approved for such indication, until two years after the investigation is discontinued [21 CFR 312.62(c)].  As a clinical investigator, you are required to retain records of the disposition of the drug, including dates, quantity, and use by subjects, and to retain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. You are required to retain these records for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified.  You failed to adhere to these requirements. Specifically, for Protocols (b)(4) and (b)(4) :  • You failed to retain records of the disposition of the drug, including dates, quantity, and use by subjects.  • You failed to retain adequate and accurate case histories, including signed and dated informed consent forms, case report forms, and all supporting data.  You were required to retain the study records for both protocols because a New Drug Application (NDA) had been filed for the indication under study, and the application had not yet been decided on (that is, approved or not approved) before you discarded the study records.  During the inspection, you stated that all original study records related to Protocols (b)(4) and (b)(4) were shredded on January 24, 2014. You stated that your study coordinator “mistakenly included the study files for (b)(4) and (b)(4) , along with business documents intended for shredding, and provided them to a mobile shredding company … .”  In addition, you indicated that (b)(4) notified you on February 11, 2014, that the company had filed an NDA with the FDA and had included the data from Protocol (b)(4) in this submission. You further stated that you and your staff were “well aware of regulatory record retention requirements having been involved in clinical research since 2001.  During the inspection, you stated:  “[A]ll study related records and source data pertaining to protocol (b)(4) at our site were shredded, including, but not limited to: signed informed consent forms, subject diary cards, records of screening results, documentation of assessments at additional study related visits, and laboratory test results. This data is not retrievable and was not available for inspection. Due to the destroyed study records, [the FDA investigator] was not able to verify the study data for protocol (b)(4) , or the existence of signed informed consent forms during the inspection.”  During the inspection, your study coordinator provided Investigator Babbitt with a copy of a Standard Operating Procedure (SOP), signed by you and with an effective date of October 30, 2008, for study-record retention. We are concerned that this SOP appears to be insufficiently detailed to prevent similar violations in future studies. Of note, based on the description you provided during the inspection, the boxes of study records that were shredded were labeled with pertinent identifying study information, such as sponsor, date range of the study, subject numbers, and protocol number. Your SOP for study-record retention does not address how you will ensure that boxes of study records that are appropriately labeled will not be shredded erroneously in the future.  Failure to retain study records as required by FDA regulations compromises the validity and integrity of data significantly. Because you failed to retain drug accountability records and case histories for both studies, we consider the data generated at your site for Protocols (b)(4) and (b)(4) unreliable in support of a research or marketing application. |
| Michele A Sewell MD | 2014 | 1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].   As a clinical investigator, you are required to ensure that your clinical studies are conducted in accordance with the investigational plan. The investigational plan for Protocol GLP112757 includes certain requirements related to eligibility confirmation, sulfonylurea dosing prior to screening, and pharmacokinetic (PK) blood draws, as well as criteria for increasing study-drug dose. The investigational plan for Protocol GLP112754 includes certain requirements related to Serious Adverse Event (SAE) reporting and the performance of specific assessments and procedures at certain study visits. Both protocols require that study visits occur within specified time frames. You failed to adhere to these requirements. Specifically:   a. Subject 1398757001, Protocol GLP112757:    i. Protocol GLP112757 requires that subjects receive a sulfonylurea dose that is equivalent to at least 4 mg glimepiride for at least three months prior to screening. The protocol indicates that 4 mg glimepiride is equivalent to 5 mg glyburide dosed twice daily.   Subject 1398757001 was ineligible for Protocol GLP112757 at screening on August 19, 2009, while on glyburide 5 mg daily (half of the protocol-required dose). The medication log for this subject indicates that the dose of 5 mg once daily was changed to 5 mg twice daily sometime in September 2009 (after screening), and the subject was randomized on January 6, 2010. The dose correction should have occurred at least three months before, and not after, screening.   In your September 12, 2013, written response to the Form FDA 483, you indicated that after additional review, you found that you did not have proper documentation of the required dosage of glimepiride. You also indicated that, as corrective action, your study staff would receive or had received additional training to ensure protocol compliance.   Your response is inadequate because it is not sufficiently detailed with respect to your corrective action plan. You have not provided any details or documentation regarding the training of your study staff, and you have not indicated what corrective action you personally have taken, as clinical investigator, to ensure your own compliance with study protocols. Without those details, we are unable to determine whether your corrective action is adequate to prevent similar violations in the future.    ii. Protocol GLP112757 requires that subjects who have a hemoglobinopathy that may affect determination of hemoglobin A1c (HbA1c) not be enrolled in the study.   Subject 1398757001 was ineligible for Protocol GLP 112757 at screening on August 19, 2009, with an “apparent hemoglobin variant observed during analysis of hemoglobin A1c” noted in the laboratory results. The same apparent hemoglobin variant was also observed and verified by repeat analysis in the laboratory results following the Week-4 visit on February 3, 2010. In the laboratory results following the April 22, 2011, visit, laboratory personnel noted that a hemoglobin pattern and concentration consistent with sickle-cell trait (heterozygous) was found, and suggested a clinical and hematologic correlation.   In your September 12, 2013, written response to the Form FDA 483, you indicate that no notation was made at screening because it was your professional opinion that the subject should not be excluded because of sickle-cell trait. In addition, you stated, “I felt, at the time, that there was some evidence but no definitive evidence that HbA1c could not be used for accurate glucose monitoring based on the methodology employed for accurate measurement by (b)(4).”   Your response is inadequate because Protocol GLP112757 requires exclusion of subjects who have hemoglobinopathies that may affect HbA1c determinations. Sickle-cell trait is one such exclusionary hemoglobinopathy.    iii. Protocol GLP112757 requires that all study visits occur within ±3 days, with the exception of Visit 7 (Week -1) and Visit 8 (Baseline). The protocol notes that subjects would not be considered out of compliance if visit windows extend because of extraordinary events that make it impossible for subjects to complete a visit within the visit window (e.g., holidays, vacations, personal emergencies). However, the protocol specifies that determination of the maximum visit window deviation is at the discretion of the medical monitor.   For Subject 1398757001, Visit 22 (Week 65) took place 15 days past the protocol-allowed time frame. The protocol required that Visit 22 occur 13 weeks after Visit 21 (Week 52), ±3 days. This subject’s Visit 21 occurred on January 7, 2011, and Visit 22 occurred approximately 15 weeks later, on April 26, 2011. There is no evidence of an extraordinary event or of a determination by the medical monitor.   In your September 12, 2013, written response to the Form FDA 483, you did not provide any explanation for the delay in this subject’s visit. However, you did acknowledge that problems with scheduling occurred. You noted that you have taken corrective action and that, as part of that corrective action, you hold weekly meetings with study staff and include the study staff in your weekly meetings with clinic staff. You also stated that you have Standard Operating Procedures (SOPs) on assessments, and that you, as well as the study staff, were retrained on this SOP.   Your response is inadequate because you have not provided documentation of any extraordinary events, or of any discussion with the medical monitor to determine maximum visit-window deviation in this case. In addition, you have not provided sufficient details about your corrective action plan. You have not provided a copy of the SOP on assessments, which you indicated that you have in place and on which you and your staff have been retrained, nor have you provided any details about that training. Without those details, we are unable to determine whether your corrective action is adequate to prevent similar violations in the future.   b. Subject 1398757002, Protocol GLP112757:    i. Protocol GLP112757 requires that subjects receive at least 1500 mg metformin daily for at least three months prior to screening; however, the protocol allows enrollment of subjects with a documented maximum tolerated dose of less than 1500 mg metformin daily, if the dose has been stable for at least eight weeks before randomization.   Subject 1398757002 was enrolled in the study despite the subject’s not having received at least 1500 mg metformin daily for at least three months prior to screening, and despite the subject’s not having received a documented maximum tolerated dose of less than 1500 mg daily that was stable for at least eight weeks before randomization. The concomitant medication study records show that as of August 20, 2009 (four days prior to screening), Subject 1398757002 was taking 500 mg metformin twice daily (1000 mg daily), which is 500 mg less than the requisite dose. On August 21, 2009, the dose was increased to 1000 mg metformin twice daily (2000 mg daily). This increase in the dose of metformin did not make the subject eligible for the study because the subject was not receiving at least 1500 mg metformin for a minimum of three months prior to screening. Nevertheless, Subject 1398757002 was screened for the study three days later, on August 24, 2009. Furthermore, you provided no documentation to indicate that the subject had a stable, maximum tolerated dose of less than 1500 mg metformin daily for at least eight weeks prior to randomization.   In your September 12, 2013, written response to the Form FDA 483, you stated that the subject’s maximum tolerated dose was 1000 mg metformin (daily). In your written response, you also described corrective action that you have taken to ensure that protocol-required assessments are done in a timely manner. Your response is inadequate because you provided no documentation to support your statement that the subject’s maximum tolerated dose was 1000 mg metformin daily. Of note, study records show that the subject’s metformin dose was increased to 1000 mg twice daily on August 21, 2009, for a total daily dose of 2000 mg, and we have no documentation that the subject could not tolerate that dose.   Your response is also inadequate because it is not sufficiently detailed with respect to your corrective actions. Specifically, you have not provided a copy of the SOP on assessments, which you indicated that you have in place and on which your staff has been trained, nor have you provided any details about that training. Without those details, we are unable to determine whether your corrective action is adequate to prevent similar violations in the future.    ii. Protocol GLP112757 permits you to increase the dose of study drug only when the subject meets the protocol criteria for a dose increase. The protocol requires that a subject receive a dose increase at Week 4 only if the subject has a single fasting plasma glucose of at least 250 mg/dL, as confirmed by a second sample drawn within 7 days and analyzed by the central laboratory, and if the subject’s HbA1c level is unchanged or increased from baseline. You failed to adhere to this requirement. Specifically:   Subject 1398757002 received an increased dose of study drug on December 3, 2009, even though the subject did not meet the protocol criteria for a dose increase. This subject had a fasting plasma glucose of 144 mg/dL at Week 4 on November 17, 2009. In addition to having a fasting plasma glucose below the required level, you provided no evidence that this level was confirmed by a second sample drawn within 7 days and analyzed by the central laboratory. Therefore, Subject 1398757002 should not have received a dose increase on December 3, 2009.   In your September 12, 2013, written response to the Form FDA 483, you acknowledged that several required protocol procedures, physical examinations, lab assessments, and electrocardiograms (ECGs) were not done within the appropriate time frames. You indicated that you have taken corrective action to ensure that study assessments are not missed in the future. You noted that as part of that corrective action, you include your research staff in your weekly meetings with clinic staff, and you hold weekly meetings with research staff to get subject status reports. In addition, you note that you and your study staff were retrained on the SOPs for study assessments.   Your response is inadequate because you have not provided sufficient details about your corrective action plan. Specifically, you have not provided a copy of the SOP on assessments, which you indicated that you have in place and on which you and your staff have been retrained, nor have you provided any details about that training. Without those details, we are unable to determine whether your corrective action is adequate to prevent similar violations in the future.   iii. Protocol GLP112757 requires that for Week 28, subjects have their PK blood samples taken at least 2 days after they receive a dose of study drug. You failed to adhere to these requirements. Specifically:   Study drug container #2201065 was administered to Subject 1398757002 on May 4, 2010 (Visit 18/Week 28), and the subject’s PK blood sample was taken at the same visit.   In your September 12, 2013, written response to the Form FDA 483, you acknowledged that the assessments were not performed as required by the protocol, and you indicated that you have taken corrective action to ensure that study assessments are not missed in the future. You also noted that as part of that corrective action, you hold weekly meetings with study staff, and study staff were retrained on SOPs for study assessments.   Your response is inadequate because you have not provided sufficient details about the corrective action plan. Specifically, you have not provided a copy of the SOP on assessments, which you indicated that you have in place and on which your staff has been trained, nor have you provided any details about that training. Without those details, we are unable to determine whether your corrective action is adequate to prevent similar violations in the future.   c. Subject 1398754002, Protocol GLP112754:    i. Protocol GLP112754 requires that you report all SAEs to the sponsor within 24 hours. The Protocol defines SAEs as any untoward medical occurrence that results in death; is life threatening; requires hospitalization or prolongation of existing hospitalization; results in disability/incapacity; is a congenital anomaly/birth defect; or other medical event that, in the medical judgment of the clinical investigator, should be considered serious (such as an event that may require medical or surgical intervention to prevent one of the previously listed outcomes). You failed to adhere to this requirement. Specifically:   Subject 1398754002 experienced the SAE of unstable angina that resulted in hospitalization on (b)(6). However, this SAE was not reported to the sponsor until June 9, 2011, approximately 15 months later.   In your September 12, 2013, written response to the Form FDA 483, you indicated that the subject did not disclose the hospitalization to the study coordinator during five separate visits in 2010. You stated that the hospitalization was discovered on June 9, 2011, after your site received and reviewed the subject’s medical records for a separate incident.   Your response is inadequate because a printed note at the bottom of the hospital record related to the subject’s (b)(6), admission for unstable angina indicates that a copy of this record was sent to you. You have not adequately explained your failure to report the SAE experienced by Subject 1398754002, nor have you explained how you will correct this failure in the future.    ii. Protocol GLP112754 (original version dated December 8, 2008) requires that all study visits have a treatment window of ±3 days. Amendment 1 (dated August 6, 2009) of this protocol requires the same time frame for all study visits, with the exception of Visit 6 (Baseline), which will have a treatment window of ±6 days. The protocol notes that subjects will not be considered out of compliance if visit windows extend because of extraordinary events that make it impossible for subjects to complete a visit within the visit window (e.g., holidays, vacations, personal emergencies). However, determination of the maximum visit window deviation is at the discretion of the medical monitor.   Subject 1398754002 had multiple study visits that took place significantly outside of the protocol-specified time frames.   \*Please Refer To Table in PDF  In your September 12, 2013, written response to the Form FDA 483, you referred to Protocol GLP112754’s specifications for out-of-window visits (original version dated December 8, 2008): “All study visits will have a treatment window of ±3 days. Subjects will not be out of compliance if visit windows extend because of extraordinary events that make it impossible for subjects to complete a visit window within the ±3 day window (e.g., holidays, vacations, personal emergencies). However, determination of the maximum visit window deviation is at the discretion of the medical monitor.”   Your response is inadequate because you have not explained why there were significant delays in the subjects’ visits noted above, and you have not provided documentation of any extraordinary events, or of any discussion with the medical monitor to determine maximum visit-window deviations in each of these cases. Your response is also inadequate because you have not provided a corrective action plan to prevent the recurrence of similar violations in the future.   d. Subject 1398754001, Protocol 112754:    i. Protocol 112754 requires that you perform a complete physical examination at Visit 1 (Screening). You failed to adhere to this requirement. Specifically:   You failed to perform a complete physical examination on Subject 1398754001 (written incorrectly on Form FDA 483 as Subject 1398764001) at Visit 1 (Screening).   In your September 12, 2013, written response to the Form FDA 483, you acknowledged that your study staff failed to perform the required physical examination at screening. You indicated that the Visit-1 physical examination was completed at Visit 2, before other study procedures were done to determine the subject’s eligibility, and that the missed physical examination was listed on a “DVE report.” In addition, you indicated that in 2011 your study staff were provided with and instructed on a flow chart of visit events to ensure that assessments for this study are not missed in the future.   Your response is inadequate because you have not provided any documentation of the subject’s physical examination at Visit 2, or the flow chart of visit events that you provided to study staff, and you have not provided any details about how the staff were instructed on the use of the flow chart. Without those details, we are unable to determine whether your corrective action is adequate to prevent similar violations in the future.    ii. Protocol 112754 requires that you obtain triplicate ECGs and a blood sample for hematology and chemistry assessments at Visit 23 (Week 104).   Subject 1398754001 (written incorrectly on Form FDA 483 as Subject 1398764001) did not have triplicate ECG recordings or laboratory assessments at Visit 23 (Week 104). Although the subject’s study records document why the ECGs and blood draw could not be performed at this visit, there is no evidence that they were performed at a later date.   In your September 12, 2013, written response to the Form FDA 483, you acknowledged that several laboratory assessments and ECGs were not performed according to the time frames required by the protocol. You also noted that you have taken corrective action to ensure that study assessments are not missed in the future. You noted that as part of that corrective action, you include your research staff in your weekly meetings with clinic staff, and you hold weekly meetings with research staff. You and your study staff were also retrained on an SOP for study assessments, and in 2011 your study staff were provided with and instructed on a flow chart of visit events to ensure that assessments for this study are not missed in the future.   Your response is inadequate because you have not provided sufficient details about your corrective action plan. You have not provided a copy of the SOP on assessments, which you indicated that you have in place and on which you and your staff have been retrained, and you have not provided any details about that training. You also have not provided the flow chart of visit events that you provided to study staff, and you have not provided any details about how the staff were instructed on the use of the flow chart. Without those details, we are unable to determine whether your corrective action is adequate to prevent similar violations in the future.   As detailed above, you failed to conduct the investigation in accordance with the investigational plan. Specifically, enrollment of subjects who do not meet eligibility criteria, failure to report SAEs to the sponsor promptly, failure to adhere to protocol restrictions related to dose increases, failure to perform protocol-required assessments and procedures, and failure to conduct study visits within the protocol-specified time frames jeopardize subject safety and data integrity. In addition, failure to obtain blood samples for PK testing raises concern about the validity and integrity of the data collected at your site. |
| Michele A Sewell MD | 2014 | 2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. [21 CFR 312.62(b)].   As a clinical investigator, you are required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include records of adverse events that occur. You have failed to maintain adequate and accurate case histories with respect to these records. Examples of this failure include, but are not limited to, the following:   a. For Protocol GLP112754, laboratory results for Subject 1398754002 at Visit 14/Week 20 (Febraury 12, 2010) showed decreased hemoglobin, hematocrit and red blood cel count levels. The lab results were initially marked as "not clinically significant" with a signature dated February 19, 2010. However, on December 12, 2012, this determination was changed to "clinically relevant" with an additional notation that the subject had clinically significant anemia, without an explanation for the change made almost three years later.  In your September 12, 2013, written response to the Form FDA 483, you indicated that upon detailed review of the protocols definition of an adverse event, you changed your professional judgment regarding Subject 1398754002's hematology report and you documented the subjects anemia as clinically significant.  Your response is inadequate because you have failed to document your rationale for the changes you made in the clinical significance of anemia nearly three years after the anemia was noted. Without the inclusion of your rationale, these documents are inadequate to capture the adequate and accurate case history of this subject. In addition, you have not provided a corrective action plan to prevent the recurrence of similar violations in the future.   b. In addition to the adverse event noted above, Subject 1398754002 experienced other adverse events that were recorded in the Adverse Event Log, such as memory loss, cough, anemia, and pain in the right lower extremity. These adverse events were originally marked as "Yes" for "Possible IP relationship" in the Adverse Event Log. However, the same adverse events were changed to "No" for "Possible IP relationship" three years later, on February 13, 2013, without an explanation for the change.  In your September 12, 2013, written response to the Form FDA 483, you note that the change made in the Adverse Event Log for anemia was due to entry error only. Your response with regard to this change is inadequate because you failed to explain the relationship between the entry error and the changed notation. In addition, your response was inadequate because you failed to document your rationale for the changes you made in the relationship of other adverse events (specific examples provided above) to the study drug, nearly three years after the adverse events were noted. Without the inclusion of your rationale, these documents are inadequate to capture the adequate and accurate case history of this subject. In addition, your response is inadequate because you have not provided a corrective action plan to prevent the recurrence of similar violations in the future.   Your failure to maintain adequate and accurate case histories, including the failure to document a rationale for changes in adverse event classification and in the assessment of adverse events relationship to the study drug, jeopardizes subject safety and welfare and compromises the validity and integrity of data captured at your site. |
| Michele A Sewell MD | 2014 | 3. You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)].   As a clinical investigator, you are required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. According to Protocol GLP112757, the disposition of the investigational drug should be recorded in product accountability documents stating the amounts of albiglutide/matching placebo, glimepiride, and pioglitazone/matching placebo dispensed and/or administered to study subjects; the amounts returned by study subjects; and the amounts received from and returned to the sponsor, when applicable. You did not adequately maintain records of these documents. Examples of this failure include, but are not limited to, the following:   a. For Subject 1398757001, the study-drug disposition label and the Investigational Supplies Inventory Log showthat the subject received two injections on July 28, 2010: Container #2459470, administered at 10:00 a.m., and Container #2144353, administered one hour later, at 11:00 a.m.   In addition, study-drug disposition labels show that this subject received two injections (Containers #2359363 and #2565372) on August 3, 2011, at 10:00 a.m. The Investigational Supplies Inventory Log does not contain the dates and times of study-drug administration for either of these containers.  b. For Subject 1398757002:    i. The Investigational Supplies Inventory Log notes that Container #2592361 was administered on November 21, 2010, but the case report form notes that this container was administered on January 21, 2011.    ii. The Investigational Supplies Inventory Log notes that Container #2305273 was administered on March 9, 2010, and was returned to the site at an earlier date, on March 6, 2010. The case report form has no recording for the date of study-drug administration and indicates that this container was not returned to the site.    iii. The study-drug disposition label and the Investigational Supplies Inventory Log contain discrepancies regarding the injection received on July 13, 2010, at 10:02 a.m. The label indicates that the subject was administered Container #2306486 on July 13, 2010, but the log indicates that the subject was administered Container #2276486 on that date. The log indicates that Container #2306486 was administered on August 24, 2010, instead.   In addition, the study-drug disposition label shows that this subject was administered Container #2133370 on May 10, 2011, at 10:26 a.m., and was administered Container #2425379 six minutes later, at 10:32 a.m. The Investigational Supplies Inventory Log does not contain the dates and times of study-drug administration for either of these containers.   In your September 12, 2013, written response to the Form FDA 483, you acknowledged the presence of discrepancies between the recordings on the returned study-drug disposition labels and the logs. You attributed the discrepancies to the following:   - Study coordinators error in recording the information  - Study putting information in the wrong section of a form  - Mismatch between the sponsors form and study-drug disposition labels with regard to the recording of the study-drug administration information  - Long lapse in time between subjects injection/dose and return of the injection pens to the site, resulting in the subjects having difficulty in recalling the information  - Subjects filling out study-drug disposition labels improperly or not at all and  - Study coordinators failing to verify the accuracy of study-drug disposition labels before subjects left the site, resulting in lack of accurate information. |
| Rogerio Lobo MD | 2014 | 1. As the sponsor for Protocol (b)(4), your monitoring failed to identify and correct a clinical investigator’s failure to obtain informed consent from subjects, in accordance with the provisions of 21 CFR 321.60 and 50.20. Specifically:   a. Your monitoring did not identify and correct the clinical investigator’s failure to obtain informed consent from the following 26 of 50 subjects who were enrolled into Protocol (b)(4): Subjects C1, C4 through C7, C9 through C12, C17, C19, C20, C22, C26, C28, C30, C31, C33, C34, C37 through C41, C45, and A5.  b. Your monitoring did not identify and correct the clinical investigator’s failure to obtain informed consent before administering investigational drug to the following 12 subjects who were enrolled into Protocol (b)(4): Subjects C15, C16, C21, C24, C25, C32, C35, C36, C43, C44, C46, and C47. |
| Rogerio Lobo MD | 2014 | 3. Your monitoring failed to ensure that the investigation was conducted in accordance with the investigational plan.   Protocol (b)(4) contained two study treatment arms: (1) a “traditional” or “standard” (b)(4) treatment arm, and (2) a “stair-step” arm. The “traditional” treatment arm required that the subject receive 50 mg of (b)(4) daily for 5 days on Day 5 - 9 of the first menstrual cycle during the study. If the subject did not develop a positive response (i.e., follicles of at least 17 mm in size) after the first menstrual cycle, the protocol required that the dose be increased to 100 mg on the second menstrual cycle. If the subject did not develop a positive response after the second cycle, the protocol required that the dose be increased to 150 mg on the third cycle. The “stair-step” arm required that the subject receive the same dosing of (b)(4) (i.e., 50 mg, 100 mg, and 150 mg) in an attempt to induce a positive response, but within a shorter time frame and without waiting for the next menstrual cycle before increasing the (b)(4) dose from 50 mg to 100 mg or from 100 mg to 150 mg.   Your monitoring did not identify and correct a clinical investigator’s failure to administer the correct dose of study drug to 4 subjects. Specifically:   a. Subject C4 was enrolled in Protocol (b)(4) on October 10, 2010, and was assigned to the “traditional” or “standard” dosing arm. The subject’s dosing log shows that Subject C4 received the protocol-required (b)(4) doses of 50 mg and 100 mg during Cycles 1 and 2, respectively. However, the dosing log shows that for Cycle 3, the subject again received 100 mg daily for 5 days, rather than 150 mg daily for 5 days, as required by the protocol. The Progress Note Addendum for Subject C4 states that the subject responded to 50 mg of (b)(4), and no further assessment was needed; however, this statement is not supported by the dosing log.   b. Subject C6 was enrolled in Protocol (b)(4) on December 17, 2010, and was assigned to the “stair-step” dosing arm. The subject’s dosing log shows that Subject C6 received (b)(4) 50 mg daily from January 11 to 15, 2011, and the same dose again from March 31 to April 6, 2011; the subject then received 75 mg from April 7 to 14, 2011, rather than the protocol-required stair-step dosing. The Progress Note Addendum for Subject C6 states that the subject responded to 50 mg of (b)(4) and became pregnant. Thus, the Progress Note Addendum conflicts with the dosing log.   c. Subject C19 was enrolled in Protocol (b)(4) on December 13, 2010, and was assigned to the “stair-step” dosing arm. The subject’s dosing log shows that Subject C19 received (b)(4) 25 mg daily from December 13 to 17, 2010, and the same dose again from February 15 to 19, 2011, rather that the protocol-required stair-step dosing. The Progress Note Addendum notes that the subject had, in the past, had a strong response to a dose of 50 mg of (b)(4).   d. Subject C35 was enrolled in Protocol (b)(4) on January, 21, 2011, and was assigned to the “traditional" or "standard" treatment arm. According to the subjects dosing log, Subject C35 received 100 mg daily for 5 days during Cycles 1, 2 and 3, rather than starting with the protocol required dose of 50 mg in Cycle 1 and progressing to 100 mg in Cycle 2 and 150 mg in Cycle 3. The Progress Note Addendum indicates that the subjects first treatment of cycle was for 50 mg, followed monthly by three 100-mg cycles. Thus the Progress Note Addendum conflicts with the dosing log. |
| Gilbert R Weiner | 2014 | 2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].   As a clinical investigator, you are required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories for Protocol (b)(4) include the hypersensitivity assessment forms, telemetry, and electrocardiograms. You have failed to maintain adequate and accurate case histories. Specifically:   a. Signs and symptoms of hypersensitivity were not recorded on the hypersensitivity assessment forms for the following subjects:    i. For Subject 032, tachycardia, a sign of hypersensitivity, was reported on the adverse event form for Day 36, but was not reported on the hypersensitivity assessment form for Day 36.    ii. For Subject 057, nausea, a symptom of hypersensitivity, was reported on the adverse event form for Day 8, but was not reported on the hypersensitivity assessment form for Day 8.    iii. For Subject 227, tachycardia was reported on the adverse event form for Day 78, but was not reported on the hypersensitivity assessment form for Day 78.   In your December 3, 2013, written response, you indicated that subjects who experienced some tachycardia manifested this sign prior to dosing, and that their heart rates later returned to normal. However, you did not provide documentation to show that Subjects 032 and 227 experienced tachycardia prior to dosing, and you did not explain why nausea was not documented in the hypersensitivity assessment form for Subject 057. Your response is also inadequate because you have not provided a corrective action plan to prevent the recurrence of similar violations in the future.   b. Records corresponding to the listed subjects’ dosing periods indicated that hypersensitivity assessment forms were completed, but those forms were missing, as follows:    i. Subject 002 – Periods 2 (Week1) and 4 (Week 11)    ii. Subject 004 – Period 2 (Week 1)    iii. Subject 013 – Periods 1, 2, and 3 (Weeks 0, 1, and 5, respectively)    iv. Subject 014 – Periods 1 (Week 0) and 2 (Week 1)    v. Subject 015 – Periods 1 (Week 0) and 2 (Week 1)    vi. Subject 021 – Period 1 (Week 0)    vii. Subject 031 – Period 2 (Week 1)     viii. Subject 201 – Period 2 (Week 1)    ix. Subject 210 – Periods 2 (Week 1) and 3 (Week 5)    x. Subject 213 – Periods 1 (Week 0) and 2 (Week 1)    xi. Subject 214 – Periods 1 (Week 0) and 2 (Week 1)    xii. Subject 215 – Periods 1 (Week 0) and 2 (Week 1)   In your December 3, 2013, written response, you indicated that you were unable to review the above findings because you did not have access to the study records. You also indicated that it “does not appear logical to conduct the [hypersensitivity] assessments on some of the patients and only part or none on others.” Your response is inadequate because you did not provide an explanation for the missing study records, and because you did not provide a corrective action plan to prevent the recurrence of similar violations in the future.   c. Study records contained hypersensitivity assessment forms that were signed and dated but that did not contain any subject identification or any other information with regard to hypersensitivity signs and symptoms. For example, study records contained hypersensitivity assessment forms with your dated signature but no other information for Days 36 and 78. In addition, for Subject 210, the hypersensitivity assessment form for Day 36 contained your dated signature but was otherwise blank.   On September 9, 2013, you sent an e-mail to the sponsor noting that due to the large number of subjects, you signed and stamped the blank forms “just prior to filling them out.”  In your December 3, 2013, written response, you indicated that you would stamp a block of hypersensitivity forms and indicated that you should have drawn a line across the signed, unused forms and initialed and dated them. You also stated that you plan to avoid this type of practice in future clinical trials. Please note, we expect that you will not pre-sign blank forms in FDA-regulated studies in the future.   d. Telemetry records were missing for at least 27 of the 38 subjects whose records were reviewed for inclusion of this record during the inspection.   e. Electrocardiograms were missing for Subjects 004 and 201.   We acknowledge that Items 2.d. and 2.e. above were not listed on the Form FDA 483 that was issued to you and, therefore, your written response to the Form FDA 483 did not address these violations. |
| Moussa C. Mansour, MD | 2014 | 2. Failure to maintain accurate, complete and current records regarding correspondence with the IRB [21 CFR 812.140 (a)(1)]   A clinical investigator must maintain an accurate, complete, and current record of all correspondence with the IRB. Listed below are examples where you have failed to meet this requirement. For example:   a. For the PROTECT-AF and CAP Registry studies,the study records indicate that subjects (b)(4), (b)(6) and (b)(4), (b)(6) had successfully completed the study. However, your staff reported to the IRB on September 6, 2005 and August 16, 2006 that the subjects (b)(4), (b)(6).   Your failure to accurately report to the IRB the (b)(4) of study subjects under your care is a serious violation of your responsibility as a clinical investigator. Proper reporting of study related events, especially subject (b)(4), to the IRB is an important part in ensuring the safety and welfare of all study subjects as these reports provide vital information on the study’s progress to the reviewing IRB. This information helps the IRB evaluate and decide whether changes need to be made to the study to continue to ensure subject safety.   Your CAP is inadequate because it does not specifically address the issue of how you will verify information on items of correspondence to the IRB before signing them. Also, you explained in your written response dated November 4, 2013, that your study coordinator had (b)(4), (b)(6). Your written response is inadequate because it does not propose corrective or preventative actions to address how the deficiencies will be avoided in the future.    Please provide a preventative action plan detailing how you will review and verify study data to ensure that information reported to the IRB is accurate, complete, and current. Also, please provide new and/or revised SOPs/checklists to address the above violations.    b. For the CAP-AF study, you inaccurately reported adverse events to the IRB in Continuing Review reports. According to reports dated (b)(4) and (b)(4), you stated that (b)(4).” However, the study records indicate that adverse events had been reported to you throughout the course of the study. Despite this, no adverse events were reported to the IRB until the (b)(4) Continuing Review report (b)(4).   Not accurately reporting adverse events can compromise the integrity of the data in this study. Your CAP states that you will be monitoring adverse events and that you provided training to your research staff on adverse event reporting. This is incomplete because it does not specify how monitoring of AEs will occur.    Additionally, in your written response dated November 4, 2013, you stated, “I delegated tasks to the research coordinator, (b)(4). whom I believed had the experience to perform these tasks.” Your written response is inadequate because it does not propose corrective or preventative actions to address how the deficiencies will be avoided in the future.    Please provide a preventative action plan detailing further measures that you will take to ensure that you and your staff will be adequately trained, so AEs and SAEs are appropriately reported in future studies.   We also note that, for the PREVAIL study, you signed neurological assessment worksheets that appear to have been completed by the study coordinator (b)(4) but (b)(4) was not employed at the hospital at the time of the subject visits. Handwritten notes on monitor reports from later dates, which appear to be from this study coordinator, state that no documentation for the neurologist exam could be found; however, the signed worksheets did exist and were found in a separate folder outside of the subject records. Examples of subject files that are questionable include the (b)(4) neurology assessments for Subjects (b)(4), (b)(6) and (b)(4), (b)(6).   We request that you provide a preventative action plan detailing additional measures beyond the CAP that you will take to ensure proper oversight and accurate documentation of current and future research studies under your purview. In addition, please provide new and/or revised SOPs/checklists to address the above violations. |
| Pattanam D. Srinivasan, MD | 2014 | 3. Failure to maintain accurate, complete, and current records related to the investigation [21 CFR 812.140(a)(2), 21 CFR 812.140(b)(3), and 21 CFR 812.140(d)].   CIs are responsible for maintaining accurate, complete, and current records of study-related matters, including receipt and use of a device. Sponsors are responsible for maintaining financial disclosure information. CIs and sponsors must maintain these records during the investigation and for two years after the latter of the following two dates: the date the investigation is terminated or completed, or the date that the records are no longer required to support a PMA application. Examples of your violations include the following:   Original ICFs and subjects’ source documents, including PRI-assessment results, were not maintained for a period of 2 years after the date on which the investigation was completed.  Device use and disposition documentation was not maintained to indicate which device or lot codes were used for each subject. This is a serious violation, as accurate device accountability records are important for the control of devices and adequate follow-up should any device related adverse events occur. Accurate device records also help to confirm that the investigational device is used only by qualified investigators on subjects appropriately enrolled in the study. As the sponsor, you did not maintain financial disclosure forms for each sub-investigator or other physicians who performed study procedures. Examples include (b)(4).   Your written responses state that you implemented a new electronic patient record (EPR) system to prevent treatment and included a patient records SOP to maintain original source documents and device accountability records.   Your response is not adequate because you did not provide complete financial disclosure forms for all sub-investigators and you also did not provide documentation of training for all research staff. We recommend that you implement time-stamped audit trail of your EPR system to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Please refer to FDA’s Guidance for Industry: Part 11, Electronic Records; Electronic Signatures — Scope and Application, which is available online at http://www.fda.gov/regulatoryinformation/guidances/ucm125067.htm. |
| Advanced Magnetic Research Institute International LLC | 2014 | 3. Failure to maintain required records under § 812.140(b)(4) and make the reports required under § 812.150(b)(1) through (3) and (5) through (10) [21 CFR 812.2(b)(1)(v].   As sponsor of an investigation you are responsible for maintaining specific records that are accurate, complete, and current, and preparing and submitting specific reports that are complete, accurate, and timely.   You failed to adhere to the above-stated regulation. Examples of your failure to adhere to these requirements include, but are not limited to, the following: Records concerning many adverse device effects were not available for FDA inspection, nor were the unanticipated adverse device effects submitted to FDA as specified by this regulation. Specifically, you failed to report several serious adverse events including:  o breast cancer (6 months after MME),  o a death related to an undiagnosed cancer (4 months after MME),  o a death of unknown etiology (possible TIA 30 days after MME), and  o a subject who withdrew from the study and was also newly diagnosed with cancer.   Proper reporting of adverse effects according to FDA regulations is a critical step in ensuring the safety and welfare of study subjects.    You failed to provide records to indicate the name and address of the IRB that reviewed the above-stated studies, as required by 21 CFR 812.140(b)(4)(iv). Additionally, there were no records to indicate the extent to which the good manufacturing practice regulations in 21 CFR Part 820 were followed to manufacture the MME device, as required by 21 CFR 812.140(b)(4)(v). |
| Taber, Louise A,. MD | 2014 | 1. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational rug or employed as a control in the investigation [21 CFR 312.62(b)].  As a clinical investigator, you are required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories for Protocol (b)(4) included pure-tone air- conduction audiometry reports. You failed to maintain adequate and accurate case histories with respect to these reports.  Specifically, for 4 of the 19 subjects whose records were reviewed during the inspection, pure-tone air-conduction audiometry reports that were represented as reports for these subjects were originally reports for other subjects. The original subject identification numbers and visit dates on audiometry reports were obscured with black marks, and handwritten subject identification numbers and visit dates that do not correspond with the original subject identification numbers were subsequently added to these reports.  a. For Subject 3045003, audiometry reports that were represented as reports for this subject at Visit 2 (August 31, 2011) and Visit 3 (September 22, 2011) are obscured audiometry reports that were originally for other subjects.  The audiometry report for Visit 2 (August 31, 2011) was originally a report for Subject 3045026. Also of note, the audiometry results entered into Subject 3045003’s electronic case report form (eCRF) for Visit 2 are identical to the results in Subject 3045026’s eCRF for Visit 2.  The audiometry report for Visit 3 (September 22, 2011) was originally a report for Subject 3045040. Also of note, the audiometry results entered into Subject 3045003’s eCRF for Visit 3 are identical to the results in Subject 3045040’s eCRF for Visit 2.  b. For Subject 3045005, audiometry reports that were represented as reports for this subject at Visit 2 (September 6, 2011) and Visit 3 (September 21, 2011) are obscured audiometry reports that were originally for other subjects.  The audiometry report for Visit 2 (September 6, 2011) was originally a report for Subject 3045012. Also of note, the audiometry results entered into Subject 3045005’s eCRF for Visit 2 are identical to the results in Subject 3045012’s eCRF for Visit 3.  The audiometry report for Visit 3 (September 21, 2011) was originally a report for Subject 3045016. Also of note, the audiometry results entered into Subject 3045005’s eCRF for Visit 3 are identical to the results in Subject 3045016’s eCRF for Visit 2.  c. For Subject 3045011, audiometry reports that were represented as reports for this subject at Visit 2 (September 20, 2011) and Visit 3 (October 13, 2011) are obscured audiometry reports that were originally for other subjects.  The audiometry report for Visit 2 (September 20, 2011) was originally a report for Subject 3045012. Also of note, the audiometry results entered into Subject 3045011’s eCRF for Visit 2 are identical to the results in Subject 3045012’s eCRF for Visit 3, except that Subject 3045011’s eCRF contains a transcription error.  The audiometry report for Visit 3 (October 13, 2011) was originally a report for Subject 3045015. Also of note, the audiometry results entered into Subject 3045011’s eCRF for Visit 3 are identical to the audiometry report results for Subject 3045015 for Visit 2.  d. For Subject 3045013, audiometry reports that were represented as reports for this subject at Visit 2 (September 21, 2011) and Visit 3 (October 7, 2011) are obscured audiometry reports that were originally for other subjects.  The audiometry report for Visit 2 (September 21, 2011) was originally a report for Subject 3045026. Also of note, the audiometry results entered into Subject 3045013’s eCRF for Visit 2 are identical to the results in Subject 3045026’s eCRF for Visit 2.  The audiometry report for Visit 3 (October 7, 2011) was originally a report for Subject 3045026. Also of note, the audiometry results entered into Subject 3045013’s eCRF for Visit 3 are identical to the results in Subject 3045026’s eCRF for Visit 2.  In your August 1, 2014, written response to the Form FDA 483, you indicated that (b)(4), the clinical research organization (CRO) site monitor, instructed your study coordinator to obscure identifying subject information. In addition, you acknowledged that your study coordinator made errors in transcribing the subject information. You indicated that the errors in transcribing the subject information were not intentional and involved only 5% of all audiograms that your site generated for Protocol (b)(4).  You further indicated that, where applicable, you have instituted additional measures and procedures to address the inspection findings.  Your response is inadequate, because you did not provide sufficient information to enable us to evaluate the adequacy of your corrective action plans for use in any future clinical research that you may conduct. You did not provide any details of a corrective action plan to prevent similar violations from occurring in the future, nor have you provided sufficient details regarding your plan to implement additional measures and procedures to address the inspection findings. Without these details, we are unable to determine whether your corrective action plan appears sufficient to prevent similar violations in the future.  Your failure to maintain adequate and accurate case histories with respect to audiology reports raises concerns about the validity and integrity of the data captured at your site. |
| Howard M Gross M.D. Dayton Clinical Oncology Program | 2015 | 2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].  As a clinical investigator, you are required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. For Protocol (b)(4), these case histories include source documents recording serious adverse events. For Protocol (b)(4), a serious adverse event was defined as an adverse event requiring inpatient hospitalization. You failed to maintain adequate and accurate case histories with respect to these study records.  Specifically, a telephone record shows that on June 6, 2012, your study coordinator was made aware that Subject 001 had been hospitalized. However, a progress note shows that the study coordinator was notified on June 13, 2012, of Subject 001’s hospitalization. There is no documented explanation for this discrepancy.  This is particularly concerning to us because Protocol (b)(4) required that serious adverse events be reported to the sponsor within 24 hours of your becoming aware of the event. The sponsor was notified of this serious adverse event on June 15, 2012. However, because of the discrepancy in the date of your awareness of the event, we were unable to evaluate whether you adhered to this protocol requirement.  We acknowledge that this violation, as written, was not included on the Form FDA 483 that you received.  Your failure to maintain adequate and accurate case histories, including the aforementioned discrepancies in the dates on documentation related to serious adverse events, raises concerns about the validity and integrity of data captured at your site. |
| Thomas S Tooma | 2015 | 3. You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)].  As a clinical investigator, you are required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. You failed to comply with this requirement. Specifically, you failed to maintain drug disposition records for any of the subjects at the seven study sites who underwent corneal cross-linking and received riboflavin ophthalmic solution in one or both eyes. |
| Monmouth Medical Center IRB | 2015 | 1. The IRB failed to determine at the time of initial review that studies involving children are in compliance with 21 CFR part 50, subpart D, Additional Safeguards for Children in Clinical Investigations [21 CFR 56.109(h)].  Under 21 CFR 56.109(h), when some or all of the subjects in a clinical investigation are children, the IRB must determine that the clinical investigation is in compliance with 21 CFR part 50, subpart D (Additional Safeguards for Children in Clinical Investigations) at the time of the initial review of the research. Under 21 CFR 50.50, the IRB must review the clinical investigation and approve only those clinical investigations that satisfy the criteria described in 21 CFR 50.51 (clinical investigations not involving greater than minimal risk), 21 CFR 50.52 (clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects), or 21 CFR 50.53 (clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject’s disorder or condition).  Under 21 CFR part 50, subpart D (Additional Safeguards for Children in Clinical Investigations), the IRB must make certain findings with respect to clinical investigations involving children. In addition, under 21 CFR 56.115, the IRB is required to document its activities, including actions taken during IRB meetings.  However, there is no documentation, either in the meeting minutes or in any other materials reviewed during the inspection, of the IRB’s requisite determination at the time of the initial review that the following clinical investigations involving pediatric subjects were in compliance with subpart D:  a) IRB Study (b)(4), “(b)(4)  b) IRB Study (b)(4), “(b)(4)  In the May 1, 2015, written response, you indicate that the IRB will implement the following corrective or preventive actions:  a) The IRB will place Protocol (b)(4), which was closed to enrollment in February 2014, on an IRB agenda within the next fiscal quarter.  b) An IRB meeting supplement form will be drafted to identify the type of vulnerable subjects, if any, and the risk category.  c) The IRB will review and revise, as needed, its policy to include a reference to a standard operating procedure (SOP) for reviewing research involving children and other vulnerable subjects.  d) The IRB will review and revise, as needed, an IRB checklist used for evaluating pediatric studies.  We acknowledge that your written response contains documentation of the IRB’s review of Protocol (b)(4) and subpart D determination on April 13, 2015. However, we are unable to undertake an informed evaluation of your written response because you did not provide documentation for the following items:  a) The IRB’s subpart D determination for Protocol (b)(4)  b) A finalized copy of the IRB meeting supplemental form  c) A finalized copy of the IRB checklist used for evaluating pediatric studies  d) Any relevant SOPs that have been revised  e) A description of any training provided to the IRB staff and members on the new SOPs, and a list of staff and members trained, or a projected timeline of planned training  Please submit any corrective or preventive actions the IRB plans to take to ensure that the pediatric risk determinations are appropriately completed for all ongoing and future FDA-regulated pediatric studies in order to avoid the recurrence of the violations. Please include items a) through e) listed above.  Failure to determine that the additional safeguards for children in research are met may expose this vulnerable population to unnecessary risks, and may result in the child’s parent(s) or guardian(s) not being fully informed about the proposed research. |
| Monmouth Medical Center IRB | 2015 | 3. The IRB failed to prepare and maintain adequate documentation of IRB activities, including minutes of IRB meetings [21 CFR 56.115(a)(2)].  The IRB is required to prepare and maintain adequate documentation of IRB activities, including minutes of IRB meetings, which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions, including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution. The IRB failed to adhere to this requirement. Specifically:   The minutes of the IRB’s February 11, 2013, meeting indicate that Dr. (b)(6), who was either a principal investigator or a subinvestigator for three FDA-regulated studies ((b)(4)), attended the meeting and voted to approve these studies during the meeting. However, in letters dated April 6 and April 30, 2015, which were included in the IRB’s response to the Form FDA 483, Dr. (b)(6) stated he had abstained from voting on these studies. |