DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDINGS AND OPPORTUNITY TO EXPLAIN (NIDPOE)

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

John D. Papilion, M.D.
Advanced Orthopedics and Sports
8101 E. Lowry Blvd Suite 230
Denver, CO 80230

Dear Dr. Papilion:

Between June 27 and August 11, 2011, Ms. Linda Cherry and Ms. Carla Hinz, representing the U.S. Food and Drug Administration (FDA), conducted an inspection to review your conduct of the following clinical investigations of the investigational drug (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, Ms. Cherry and Ms. Hinz presented and discussed with you the items listed on Form FDA-483, Inspectional Observations. We acknowledge receipt of your September 1, 2011, written response to the Form FDA-483.

We have reviewed the FDA establishment inspection report, the documents submitted with that report, and your September 1, 2011, written response to the Form FDA 483. We do not find your response to be acceptable in addressing the matters under complaint, which are described below.

Based on our evaluation of information obtained by the Agency, we believe that you have repeatedly or deliberately submitted false information to the sponsor or FDA in required reports, and repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational products, as published under Title 21, Code of Federal Regulations (CFR), part 312 (copy enclosed).

This letter provides you with written notice of the matters complained of and initiates an administrative proceeding, described below, to determine whether you should be disqualified from eligibility to receive test articles, as set forth under 21 CFR 312.70, and disqualified from eligibility to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA.

A listing of the violations follows. The applicable provisions of the CFR are cited for each violation.

1. **You repeatedly or deliberately submitted to the FDA or to the sponsor false information in any required report [21 CFR 312.70(a)].**

   As a clinical investigator for Protocols (b) (4), (b) (4), and (b) (4), you were required to ensure that all study records, including source documents and case report forms (CRFs), that your site submitted to the sponsor were true and accurate. We have concluded that you repeatedly or deliberately submitted false information to the sponsor in the form of falsified study records. Specifically:

   Our investigation found that study records, including signatures of two of your sub-investigators, Dr (b) (4) and Dr. (b) (4), were falsified and submitted to the sponsor as part of an audit. In your affidavit, you state: "On February 2-4, 2009 and April 1-3, 2009 an audit was conducted my [*sic*] (b) (4) because of all the protocol deviations/violations found by the monitors. The auditors brought to my attention that they found 2 Sub-Investigators' signatures on Case Report Forms and (b) (4) source worksheets that appeared to be forged. I did nothing about this information, such as determine how wide spread [*sic*] the problem existed and/or contact the IRB or FDA with this finding." The sponsor's February and April 2009 audits covered Protocols (b) (4), (b) (4), and (b) (4).

   For Protocol (b) (4), in a letter dated June 15, 2009, (b) (4) informed you that among numerous findings identified during their audits conducted in February and April 2009, it had found that "[t]he signatures on the CRF page and the (b) (4) source worksheet for the Day 30 orthopedic examination for subject 4811 did not match the

surgeon's signature. Likewise, the handwriting for results on the (b) (4) source worksheet did not match."

Regarding questionable signatures on study records, in your September 1, 2011, written response to the Form FDA 483, you acknowledge that "the questioned documents (identified in tabulated form on pages 2 and 3 of the Form 483) were not presented to the physicians (sub-investigators) or to [the] former research coordinator (who has affirmed that she signed some study documents, without authority, in lieu of the physicians' original signatures) for verification." You also state, "... we reviewed [these] documents with the sub-investigators in order to determine their authenticity. The sub-investigators questioned the authenticity of three of the signatures, of the thirty (30) documents recorded on the Form 483, but not the remainder."

In your September 1, 2011, written response to the Form FDA 483, you describe corrective actions that include making personnel changes and scheduling regular meetings with the research coordinators to monitor their workloads, and to ensure that they have sufficient resources to oversee and maintain adherence to study protocols, including documentation requirements. You also state that you meet regularly with sub-investigators and discuss, among other topics, the nondelegation of medical staff duties and the requirement to execute necessary study documents promptly.

Your response is inadequate. Although you reviewed the documents itemized on the FDA Form 483 with your subinvestigators to determine signature authenticity, you failed to investigate whether additional acts of falsification occurred in these clinical investigations. In addition, your written response is insufficiently detailed with respect to your described corrective actions. You have not provided documentation of how, and how frequently, you hold meetings with your research coordinators and subinvestigators. You also have not provided details concerning how you use these meetings to carry out the activities that you described (e.g., monitoring research coordinators' workloads, ensuring that they have sufficient resources, and discussing nondelegation of medical staff duties). Without this information, FDA cannot assess whether your corrective actions are adequate to prevent future occurrences of this type of violation.

As the clinical investigator, it is your responsibility to ensure that the data collected from study subjects are accurate and can be relied upon in any analyses of the study endpoints. When you signed the Statement of the Investigator, Form FDA 1572, you agreed to provide accurate information to the sponsor, and to ensure that you will comply with FDA regulations related to the conduct of the clinical investigations of the investigational drugs; and you agreed to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting their commitments. Furthermore, your signature constitutes both your affirmation that you are qualified to conduct the clinical investigation and your written commitment to abide by FDA regulations in the conduct of the clinical investigations. The use of false information significantly compromises the study integrity, as well as the reliability and validity of the data.

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. Adequate and accurate case histories include, among other things, source records that accurately describe events that occurred during the study and accurately reflect any changes to documents, the date of those changes, and the identity of the individual who made the changes. You failed to maintain adequate and accurate case histories. Specifically:

a. For Protocol (b) (4), the Week 3 Clinic Visit/Telephone Contact form for Subject 7805 was blank, with the exception of identifying information regarding the site and subject, contact date, and type of contact (telephone) made. The form contained no information regarding medications and adverse events that were to be asked about during the telephone contact. It is not clear whether any contact for Week 3 took place. In addition, the Week 3 Clinic Visit/Telephone Contact date was initially recorded as January 8, 2007, which was the same date as the Week 2 Clinic Visit; the date was then changed to January 4, 2007, which was before the Week 2 Clinic Visit.

   Your September 1, 2011, written response indicates that you have implemented corrective action to ensure that phone contacts with subjects are documented fully. Your response is inadequate because you did not provide details regarding how you will ensure that you obtain all study-specific information required to be obtained during telephone contacts, and how you will ensure that records accurately and clearly reflect whether such telephone contacts occur. Without this information, FDA cannot determine whether you will be able to prevent future occurrences of this type of violation.

b. For Protocol (b) (4), the Week 3 Clinic Visit/Telephone Contact form for Subject 7806 was blank, with the exception of identifying information regarding the site and subject, contact date, and type of contact (i.e., telephone) made. The form contained no information regarding medications and adverse events that were to be asked about during the telephone contact. It is not clear whether any contact for Week 3 took place.

   In your September 1, 2011, written response, you state that your phone records demonstrate that the research coordinator contacted this patient; however, you provided no explanation as to why the research coordinator failed to document information about adverse events or concomitant medications.

   Your response is inadequate. Records do not indicate that any further attempts were made to contact Subject 7806 to ensure that this subject was asked about medication and adverse events. In addition, your stated corrective action that "[p]hone contacts

with subjects are fully documented" is insufficient. You did not provide details regarding how you will ensure that you obtain all study-specific information required to be obtained during telephone contacts, and how you will ensure that records accurately and clearly reflect whether such telephone contacts occur. Without this information, FDA cannot determine whether you will be able to prevent future occurrences of this type of violation.

c. For Protocol (b) (4), two different assessments of clinical significance were made to the same laboratory results for Subject 7853 at the screening visit on December 17, 2007. Specifically, on the laboratory report dated December 20, 2007, you documented clinically significant labs for the blood and bacteria found in the urine sample. However, on the screening visit laboratory report dated December 25, 2007, showing the results of the exact same labs, you noted that there were no clinically significant labs identified.

   We recognize that the Form FDA 483 issued to you does not list this violation, so that your written response did not directly address this violation.

Your failure to maintain adequate and accurate case histories raises concerns about both the validity and integrity of data captured at your site, and the adequacy of your protection of study subjects enrolled at your site.

3. 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 requires, among other things, that you enroll eligible subjects and perform study-related procedures based on the protocol schedule. You failed to adhere to these requirements for Protocols (b) (4) and (b) (4). Specifically:

a. For Protocol (b) (4), four subjects were enrolled in the trial despite their not meeting eligibility requirements.

   i. For inclusion in Protocol (b) (4), a subject must be at minimal risk from anesthesia and classified according to the American Society of Anesthesiologists (ASA) as Physical Status (PS)-1 (a normal healthy patient) or PS-2 (a patient with mild systemic disease that results in no functional limitation). Subject 7865 had a PS-3 rating. Despite not meeting this inclusion criterion, Subject 7865 was randomized and treated with study drug.

      In your September 1, 2011 response, you indicated that the PS rating was not obtained and reviewed prior to surgery, and that the source documents showing administration of study drug to the subject were accurate. However, study records indicated that the PS rating was obtained prior to surgery, and that the subject was

ineligible for the study based on the PS-3 rating recorded on the Preoperative Eligibility Assessment form.

In your September 1, 2011, written response, you note that you have implemented corrective action of personally training subinvestigators on study protocol and documentation. Your response is inadequate because you did not provide details regarding how you will train study staff to ensure that all study-specific eligibility criteria are appropriately reviewed prior to subject enrollment in a study, and how you will ensure that subjects who do not meet eligibility criteria are not enrolled in future studies.

ii. Subjects undergoing bilateral knee surgery were to be excluded from Protocol (b) (4). Subject 7863 underwent bilateral knee surgery. Despite meeting this exclusion criterion, Subject 7863 was randomized and treated with study drug.

In your September 1, 2011, written response, you note that you have implemented corrective action of personally training subinvestigators on study protocol and documentation. Your response is inadequate because you did not provide details regarding how you will train study staff to ensure that all study-specific eligibility criteria are appropriately reviewed prior to subject enrollment in a study, and how you will ensure that subjects who do not meet eligibility criteria are not enrolled in future studies.

iii. Inclusion criteria for Protocol (b) (4) state that subjects were to have laboratory test results that were within normal limits or that were clinically nonsignificant. The protocol also stated that blood and urine samples for laboratory testing were to be taken at the screening visit, and that eligibility was to be confirmed preoperatively (i.e., during the 24 hours before surgery) at the baseline visit.

Records indicate that Subjects 7809 and 7839 were ineligible for the study based on your determination that these subjects had clinically significant screening laboratory results. Specifically, we note the following:

Subject #	Date Screening lab collected	Date of Screening lab report	Date of Documented review of lab	Date of Surgery
7809	2/12/07	2/14/07	2/15/07	(b) (6)
		2/14/07	2/19/07*	
		2/18/07	3/15/07*	
7839	9/12/07	9/13/07	9/17/07*	(b) (6)
		9/18/07	9/27/07*	

* Documentation of clinically significant labs.

We note that Subjects 7809 and 7839 had clinically significant liver-function test results, with Subject 7809 having an ALT (SGPT) level of 93 IU/L (reference range 6-48 IU/L), and Subject 7839 having an AST (SGOT) level of 124 IU/L (reference range 10-36 IU/L) and an ALT (SGPT) level of 234 IU/L (reference range 6-36 IU/L). Results for clinically significant liver-function tests in laboratory reports for both subjects were annotated with the words "will repeat." We have no evidence that these tests were repeated.

In your September 1, 2011, response, you stated that additional laboratory tests were ordered for Subject 7839 but were not taken due to error, and that this subject subsequently demonstrated normal lab results. Thus, you indicated that subject safety was not compromised for this subject. You also stated the "PI and Sub-Investigators did obtain lab results, verbally, prior to all surgeries."

Your response is inadequate because you did not provide any documentation to support your statements that Subject 7839 subsequently demonstrated normal laboratory results, and that you and your subinvestigators obtained verbal laboratory results before all surgeries. You did not address Subject 7809 specifically in your response.

In your written response, you also state that you will "schedule in-office, routine review of all screening labs prior to subject randomization." Your response is inadequate because it fails to provide documentation of how you have implemented these corrective actions. Without this information, FDA cannot assess whether these corrective actions are adequate to prevent future occurrences of this type of violation.

Your enrollment of Subjects 7865, 7863, 7809, and 7839 in Protocol (b) (4) raises concerns about subject safety.

b. For Protocol (b) (4):

For 6 of 10 subjects whose records were reviewed, you permitted administration of medications for postoperative nausea that were not permitted by the protocol. Administration of these medications could interfere with the interpretation and validity of investigational endpoints, because in addition to nausea, these medications are also indicated to treat pain. In addition, two instances were found in which laboratory reports were not reviewed before surgery, as required by the protocol, and one instance was found in which a subject was ineligible for enrollment. Specifically:

i. The protocol permitted serotonin- $5HT_3$ receptor antagonists (for example, ondansetron, dolasetron, and granisetron), perphenazine, or metoclopramide to be used in the recovery room, if necessary, to treat postoperative nausea. Six subjects (1004, 1005, 1007, 1012, 1057, and 1058) were given Decadron, a medication not permitted under the protocol, to treat postoperative nausea. Subject 1007 was also administered Phenergan, another medication not permitted under the protocol.

The validity and interpretation of investigational endpoints related to pain intensity were compromised by permitting the use of Decadron and Phenergan for postoperative nausea, because in addition to alleviating nausea, Decadron and Phenergan may also alleviate pain.

Your September 1, 2011, written response states that your research coordinators will follow subjects to postoperative care to ensure adherence to study protocol. Your response is inadequate because it fails to provide documentation of how you have implemented these corrective actions. Without this information, FDA cannot assess whether these corrective actions are adequate to prevent future occurrences of this type of violation.

ii. For inclusion in the study, the subjects' screening evaluation laboratory results must be within normal limits or must be determined by the investigator to be clinically nonsignificant. The protocol also specified that evaluation of eligibility criteria was to be confirmed preoperatively (i.e., during the 48 hours before surgery) at the baseline visit. Records indicate that surgery was performed on Subjects 1004 and 1057 before their screening laboratory results were available. Specifically, for Subject 1004, the laboratory report was dated February 8, 2008, the date of surgery; however, the laboratory results were not faxed to your site until approximately 5 ½ hours after the subject's surgery began. For Subject 1057, surgery was performed on (b) (6), but the screening laboratory report was dated March 18, 2008, (b) (6) days after surgery.

Your September 1, 2011, written response states that you will ensure that study activities are scheduled with appropriate spacing – for example, surgeries will be scheduled to permit the completion of the initial laboratory tests and confirmatory tests, with time for review, well in advance. Your response is inadequate because it fails to provide documentation of how you have implemented these corrective actions. Without this information, FDA cannot assess whether these corrective actions will be adequate to prevent future occurrences of this type of violation.

Furthermore, your failure to ensure that screening laboratory results were reviewed before surgery raises concern about subject safety.

iii. Subjects who received more than two doses of Ketoprofen or any other nonsteroidal anti-inflammatory drug (NSAID) during the 7 days before screening were to be excluded from the study. The protocol also stated that each subject's compliance with eligibility criteria was to be confirmed preoperatively (i.e., during the 48 hours before surgery) and again on the scheduled day of surgery (Day 0).

Records titled "Source Notes – Prior and Concomitant Medications" indicate that at the January 6, 2009, screening visit, Subject 1067 had taken an NSAID (Celebrex) daily for pain from January 3 through January 6, 2009. The subject underwent surgery on (b) (6). The Medication Reconciliation Record dated January 9, 2009, notes that Subject 1067 last took Celebrex on January 5,

2009. Based on the use of more than two doses of an NSAID during the 7 days before screening, this subject was ineligible for enrollment into the study.

In your written response, you stated that this subject was advised during screening to refrain from taking excluded medications, and that the subject did not inform study staff of the medication use. You further stated that this was not discovered until after the surgery chart was reviewed.

Your response is inadequate. Medication records dated January 6, 2009, and that appear to have been signed by you, indicate that on the date of screening (January 6, 2009), this subject received more than two doses of an NSAID (Celebrex) during the week before screening, in violation of eligibility criteria.

In your September 1, 2011, written response, you stated that you understood that adhering to the protocol was a critical condition of executing an effective study and generating reliable data. To correct the findings, you stated that the addition of two individuals to the study staff has allowed you to implement a series of improvements and corrective actions to your site's procedures, including but not limited to the following: (1) Ensuring that study activities are scheduled with appropriate spacing – for example, ensuring that surgeries are scheduled to permit the completion of initial laboratory tests and confirmatory tests, with time for review, well in advance; (2) your training subinvestigators personally on study protocol and documentation; (3) research coordinators' attending study surgeries and ensuring that complete information appears in the operative reports and other related documents; (4) research coordinators' following subjects to postoperative care to ensure adherence to study protocols; (5) research staff's obtaining and reviewing medication logs to ensure adherence to protocol; (6) your scheduling in-office, routine review of all laboratory screening results before subject randomization; (7) Source documents, including electronic documents, being retained in archival hard copy in subjects' records; (8) developing agreements (supported by necessary subject consents and approvals) with facilities' medical records departments, thus providing complete access to and copying of subjects' medical records for study documentation; (9) study coordinators' contacting each subject before office visits with a reminder to bring all study-related documents for documentation; and (10) study coordinators' attending preoperative subject visits to determine whether subjects remain eligible for participation (for example, to ensure that no excluded medications have been used).

You noted having implemented the above measures, and you indicated that the errors or omissions identified in these previous studies between 2005 and 2008 have not occurred again. In addition, you noted that one of your current study coordinators is thoroughly versed in all clinical protocols and has completed training regarding clinical study protocol adherence as recently as April 2010.

Your response is inadequate. You provide a large number of corrective actions for future studies in order to prevent future occurrences of these types of violations, but you have provided no documentation to show how and whether these corrective actions have been

implemented. Without this information, FDA cannot assess whether these corrective actions are adequate to prevent future occurrences of these types of violations. We wish to remind you again that as the clinical investigator, it is your ultimate responsibility to ensure that the studies are conducted properly and in compliance with FDA regulations.

4. You failed to obtain informed consent in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60; 21 CFR 50.20; 21 CFR 50.25(a)].

As a clinical investigator, it is your responsibility to obtain informed consent in accordance with 21 CFR part 50. FDA's regulations at 21 CFR 50.20 state that except as provided in 21 CFR 50.23 and 21 CFR 50.24, no investigator may involve a human being as a subject in research covered by the regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. In addition, FDA's regulations at 21 CFR 50.25(a) require that subjects be provided with, among other things, a description of the procedures to be followed.

You failed to obtain legally effective informed consent before involving subjects in research covered by FDA regulations. You also failed to provide subjects with a description of the procedures to be followed. Specifically:

a. For Protocol (b) (4), you failed to obtain informed consent from Subject 7810 for entry into the study. Records indicate that Subject 7810 had the following procedures done on the respective dates.

   i. February 8, 2007: Screening and eligibility assessments, orthopedic examination, and medical history

   ii. February 14, 2007: Collection of blood and urine samples

   iii. February 16, 2007: Physical examination, surgery, and injection of study medication

   In a report to the IRB dated October 6, 2010, your site noted that Subject 7810 had been consented on February 8, 2007, to (b) (4) Protocol (b) (4); that the subject's screening failed for that protocol; and that the subject was put into Protocol (b) (4) without being consented. Thus, you failed to obtain informed consent from Subject 7810 for entry into Protocol (b) (4).

   Your failure to obtain the informed consent of Subject 7810 before enrolling the subject in the study jeopardized the safety and welfare of the subject by denying the subject an opportunity to assess the risks and benefits of participation in the clinical investigation.

   In your September 1, 2011, written response, you stated that this violation occurred several years ago, and that the study was completed in 2009. You also indicated that

you currently have two new research coordinators with years of experience, who are well-prepared to manage and document the completion of studies that you conduct. You noted further that you have instituted controls that will better ensure that all documents, and especially consent documents, are properly administered, filed, and retained among the relevant study's documents in a secure location. These controls include (1) your reviewing all subjects' consents personally, including verifying that the consents are appropriate for the study activities to be conducted; (2) the research coordinators' retaining hard copies of any new study documents, including consent forms; (3) ensuring that previous consent forms are replaced on your server with revised/updated forms; (4) placing new versions of consent forms in each subject's chart, so that they will be reviewed at the next visit; and (5) retaining copies of all previous versions of executed consent forms.

Your response is inadequate. Specifically, your response does not indicate whether you informed Subject 7810 about your failure to obtain Subject 7810's informed consent before Subject 7810's enrollment into Protocol (b) (4), nor does it indicate how you will ensure that study-related activities occur only after informed consent is properly obtained and documented. In addition, you provided no documentation to show how and whether your corrective actions have been implemented. Without this information, FDA cannot assess whether these corrective actions are adequate to prevent future occurrences of these types of violations.

b. For Protocol (b) (4), Subjects 4803, 4813, and 4815 met a protocol-specified exclusion criterion and were to be followed for safety evaluations only; however, the approved informed consent form signed by these subjects did not describe the changes in the study for subjects who entered into the safety-only population.

In your September 1, 2011, written response, you agreed that the consent documents signed by these subjects did not accurately reflect the protocols applicable to the subjects. You also stated that subjects were verbally advised of the exact nature of their participation and treatment changes, but you acknowledged that this is not reflected in the documentation. Your corrective actions include auditing consent forms routinely to ensure that the consent form accurately reflects the study protocol.

Your response is inadequate. Verbally advising subjects of treatment changes is not an appropriate means to obtain informed consent. In your response, you failed to provide documentation that these three subjects were properly consented, with a consent form that included a complete and accurate description of the procedures to be followed, including changes in the study for subjects in the safety-only population. In addition, you failed to provide documentation of your proposed audit process so that FDA can make an assessment as to whether this corrective action is adequate to prevent future occurrences of this type of violation.

Your failure to provide subjects with a description of all study procedures jeopardizes the safety and welfare of enrolled subjects by denying them an opportunity to assess the risks and benefits of their participation in the clinical investigation.

5. 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 did not maintain adequate drug dispensation records. Specifically:

a. Protocol (b) (4) specified that during arthroscopic surgery, study drug or vehicle irrigation solution was to be perfused through the joint via inflow and outflow cannulas. The protocol also stated that at the end of the procedure, following routine removal of all fluid from the joint, 30 mL of irrigation solution (study drug or vehicle) was to be administered by intra-articular injection through a previously closed portal site. In reviewing the records of 27 subjects, it could not be verified in either the surgeon's operative reports or the nursing records that 30 mL of study drug or vehicle was injected into 13 subjects (Subjects 7801, 7809, 7812, 7829, 7840, 7852, 7853, 7854, 7859, 7863, 7865, 7871, and 7878), as required by the protocol.

b. Protocol (b) (4) specified that at the end of the operation, approximately 30 mL of assigned (b) (4) or vehicle irrigation solution would be administered by intra-articular injection through a closed portal site. The protocol also stated that no intra-articular injections other than the (b) (4) or vehicle solution were to be injected into the previously closed portal site. In reviewing the records of 10 subjects, there was no mention in either the surgeons' operative reports or the nursing records that 3 subjects (Subjects 1007, 1011, and 1057) were injected with 30 mL of study drug or vehicle, as required by the protocol.

In your September 1, 2011, written response, you listed corrective actions you have taken to prevent recurrence of violations such as those listed in Items 5.a. and 5.b. above. Your corrective actions include, among other things, training subinvestigators personally on study protocol and documentation, and having research coordinators attend surgeries to ensure that complete information appears in the operative reports and other related documents.

Your response is inadequate because you did not provide documentation of how you have implemented the described corrective actions. Without this information, FDA cannot assess whether these corrective actions are adequate to prevent future occurrences of this type of violation. In addition, your response is inadequate because you appear to be relying on research coordinators to ensure that complete information appears in operative reports and other related documents, rather than taking direct responsibility. As clinical investigator, you are responsible for ensuring that study records, including drug accountability records, are accurate and complete.

Failure to maintain adequate and accurate drug accountability records in Protocols (b) (4) and (b) (4) raises concerns about both the validity and integrity of the data at your site, and the adequacy of your protection of the study subjects enrolled at your site.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational products. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations.

On the basis of the above-listed violations, FDA asserts that you have failed to protect the rights, safety, and welfare of subjects under your care; repeatedly or deliberately submitted false information to the sponsor; and repeatedly or deliberately failed to comply with the cited regulations, which placed unnecessary risks on human subjects and jeopardized the integrity of data, and the FDA proposes that you be disqualified as a clinical investigator. You may reply to the above-stated findings, including an explanation of why you should not be disqualified as a clinical investigator, either in a written response or at an informal conference in my office. This procedure is provided for by regulation 21 CFR 312.70.

Within fifteen (15) days of your receipt of this letter, write or call me at 301-796-3865 to arrange a conference time or to indicate your intent to respond in writing.

Should you choose to respond in writing, your written response should be forwarded within thirty (30) days of your receipt of this letter.

Your reply should be sent to:

Sean Y. Kassim, Ph.D.
Acting Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5346
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Should you request an informal conference, we ask that you provide us with a full and complete explanation of the above-listed violations. You should bring with you all pertinent documents, and a representative of your choice may accompany you. Although the conference is informal, a transcript of the conference will be prepared. If you choose to proceed in this manner, we plan to hold such a conference within 30 days of your request.

At any time during this administrative process, you may enter into a consent agreement with FDA regarding your future use of investigational products. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement between you and FDA.

The FDA's Center for Drug Evaluation and Research (the Center) will carefully consider any oral or written response. If your explanation is accepted by the Center, the disqualification process will be terminated. If your written or oral responses to our allegations are unsatisfactory, or we cannot come to terms on a consent agreement, or you do not respond to

this notice, you will be offered a regulatory hearing before FDA, pursuant to 21 CFR 16 (enclosed) and 21 CFR 312.70. Before such a hearing, FDA will provide you with notice of the matters to be considered, including a comprehensive statement of the basis for the decision or action taken or proposed, and a general summary of the information that will be presented by FDA in support of the decision or action. A presiding officer who has not participated in this matter will conduct the hearing. After such hearing, the Commissioner will determine whether you will remain entitled to receive test articles and to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA.

You should be aware that neither entry into a consent agreement nor pursuit of a hearing precludes the possibility of a corollary judicial proceeding or administrative remedy concerning these violations.

To enter into the enclosed consent agreement with FDA, thereby terminating this disqualification process, you must:

(1) Initial and date each page of this Agreement;
(2) Sign and date the last page of this Agreement; and
(3) Return this Agreement initialed, signed, and dated to the signer below.

A copy of the fully executed Agreement will be mailed to you.

Sincerely yours,

{See appended electronic signature page}

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

Enclosures:
#1 - Consent Agreement
#2 - 21 CFR 16
#3 - 21 CFR 312.70

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

/s/

SEAN Y KASSIM
04/11/2014