Inspections, Compliance, Enforcement, and Criminal Investigations

Burzynski Research Institute / IRB

Department of Health and Human Services

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

WARNING LETTER

OCT 5 2009

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref: 10-HFD-45-09-01

Carlton F. Hazlewood, Ph.D.
Chairman
Burzynski Research Institute IRB
9432 Katy Freeway #370
Houston, TX 77055-6349

Dear Dr. Hazlewood:

Between December 3 and 10, 2008, Mr. Patrick D. Stone, representing the Food and Drug Administration (FDA), inspected the Burzynski Research Institute (BRI) Institutional Review Board (IRB). The purpose of this inspection was to determine whether the IRB procedures for the protection of human subjects complied with Title 21 of the Code of Federal Regulations (CFR), Parts 50 and 56. These regulations apply to clinical studies of products regulated by FDA. We are aware that at the conclusion of the inspection, our investigator presented and discussed with you, a Form FDA 483, Inspectional Observations.

From our review of the establishment inspection report, the documents submitted with that report, and your April 2, 2009 written response to Form FDA 483, we

conclude that the IRB did not adhere to the applicable statutory requirements and FDA regulations governing the protection of human subjects. We wish to emphasize the following:

1. The IRB approved research without determining that the following criteria were met: that risks to subjects were minimized [21 CFR 56.111(a)(1)] and risks to subjects were reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result [21 CFR 56.111(a)(2)].

a. For protocol **(b)(4)** our inspection revealed the following:

On January 10, 2007, **(b)(6)**, Ph.D. (an IRB member) submitted comments to the IRB in regard to this study. The purpose of the study was to evaluate the safety and efficacy of **(b)(4)** in subjects with **(b)(4)** or **(b)(4)** Dr. **(b)(6)** reviewed the investigator's brochure, clinical protocol, and appended evaluation and had concerns related to the source of the drug, the manufacturing process, and the potential effects of the drug on human subjects. He stated more information was needed to make a risk/benefit assessment.

One year elapsed before the IRB discussed this study at a convened meeting on February 1, 2008. There was nothing in the IRB's file to indicate that the IRB received any additional information related to this study between January 2007 and February 2008. Minutes of the February 1, 2008 IRB meeting indicate that the IRB was aware that the clinical investigator had already dosed human subjects with the investigational drug. Our inspection revealed that at the February 1, 2008 meeting, the IRB was in possession of undated case reports on fifteen human subjects who had been injected with **(b)(4)**. Despite knowledge that Dr. **(b)(4)** was dosing human subjects without IRB approval, as required by 21 CFR 312.66, the IRB failed to report Dr. **(b)(4)** noncompliance to the FDA pursuant to 21 CFR 56.108(b)(2).

There is no documentation of an IRB action in regard to the **(b)(4)** study in the minutes of the February 1, 2008 IRB meeting. However, in a letter dated February 15, 2008, the IRB wrote the following to the clinical investigator, **(b)(6)** M.D.

> "... additional toxicity studies on animals will need to be completed. In the case of the human **(b)(4)** study, all adverse events are to be reported to the sponsor (**(b)(4)** and to the BRI-IRB as soon as humanly possible. Any deaths that might occur must be reported to the sponsor and our office within 24 hours. On behalf of the Committee, you may go forward with the study and we look forward to your continued success in this area".

It is unclear why the IRB allowed the study to go forward in humans when additional toxicity studies in animals were requested. In addition, it is unclear why the IRB allowed Dr. **(b)(4)** to continue **(b)(4)** the study when it appears that he initiated this research study, i.e., began dosing subjects, prior to obtaining IRB approval.

In your written response of April 2, 2009, you state that the IRB did not approve human enrollment for the **(b)(4)** study or any other related protocol. Your

response does not comport with the letter sent by the IRB to the investigator on February 15, 2008.

As a result of an IRB meeting on August 8, 2008, the IRB sent a letter to **(b)(4)** (the study sponsor) regarding the status of the animal toxicity studies. The August 18, 2008 letter to **(b)(4)** stated "At this time, I must remind you that human studies, according to the protocol, cannot proceed until your Investigative [Investigational] New Drug (IND) Application is approved by the FDA." This letter to the sponsor appears to contradict the February 15, 2008 IRB letter sent to Dr. **(b)(6)** in which the IRB permitted the study to go forward.

During the inspection in December 2008, you told the FDA investigator that you were unaware that this IND was on clinical hold. However, **(b)(4)** responded to the IRB in a letter dated September 4, 2008, and referenced the clinical hold placed on the IND by FDA. Minutes of the October 24, 2008 IRB meeting indicate that the IRB decided to "draft a letter to **(b)(4)** stating that their application for this IRB to act as an IRB for their study be placed on hold until such time as we receive information regarding the FDA's position on the Toxicity Studies. At that time we will also review their Toxicity Studies and consider continuing their application." The IRB conveyed this information in a letter dated November 3, 2008; however, the letter was only sent to Dr. **(b)(6)** and not to **(b)(4)**.

In your written response, you state that "[t]he IRB was informed that the sponsors were in discussion with FDA regarding their IND status. Based on this, the IRB considered its relationship to both sponsors and protocols in abeyance." As discussed above, the final piece of correspondence issued by the IRB in regard to the **(b)(4)** study was sent only to Dr. **(b)(6)** therefore, there is no documentation to demonstrate that **(b)(4)** was aware of the lRB's abeyance status of this study.

b. For the protocol" **(b)(4)** our inspection revealed the following:

As a result of the January 6,2005 IRB meeting, the IRB sent a letter on February 1, 2005 to **(b)(6)** M.D., Ph.D., sponsor-investigator, stating that the protocol, including the informed consent document, should be modified before final approval could be granted and asking him to resubmit the protocol and informed consent document to the IRB for review. In addition, the IRB informed Dr. **(b)(4)** that an Investigator's Brochure must be submitted.

At the March 17, 2005 IRB meeting, the IRB decided that if changes were made to the protocol and informed consent document, the clinical investigation could be approved. In a March 23, 2005 letter to the sponsor-investigator, the IRB agreed to approve the protocol and informed consent document contingent upon certain changes and again asked for an Investigator's Brochure.

In an April 4, 2005 letter, the IRB informed the sponsor-investigator that the revised documents had been approved. During the inspection, no Investigator's Brochure was found in the lRB's file. Therefore, it appears that the IRB approved the research without ever receiving one, which could impact an lRB's ability to determine whether risks to subjects were minimized and whether risks were reasonable in relation to anticipated benefits.

In your written response, you state that the clinical protocol for **(b)(4)** was never approved for patient enrollment. Your response does not comport with the correspondence sent by the IRB to the sponsor-investigator. During the inspection, you told the FDA investigator that this study was placed on clinical hold by the FDA. It is unclear when the IRB became aware of the clinical hold status and why the IRB informed the sponsor-investigator on April 4, 2005 that the study had been approved.

2. The IRB failed to prepare, maintain, and follow written procedures for conducting its initial and continuing review of research [21 CFR 56.108(a) and 56.115(a)(6)]. Specifically, the IRB has no written procedures for conducting reviews of device studies to determine whether they involve a significant risk device and had no evidence that it had in fact conducted such reviews [21 CFR 812.66].

Our investigation revealed that the IRE approved the "**(b)(4)** "on July 21, 2005. The protocol in the IRB's file has the following title: **(b)(4)** In correspondence with the sponsor and investigator, the study is referred to as "Protocol **(b)(4)**" and in an August 10, 2005 letter from the IRB to the sponsor, the protocol is referred to as **(b)(4)**

In reviewing a device investigation presented by the sponsor for IRB approval under 21 CFR 812.2(b)(1)(ii), an IRB must determine whether the proposed investigation involves the use of a significant risk (SR) device [21 CFR § 812.66.***1***]. If an IRB determines that an investigation presented for approval under 812.2(b)(1)(ii) involves an SR device, it shall notify the investigator and, where appropriate, the sponsor [21 CFR 812.66].

In your written response, you state that the IRB reviewed the FDA's Information Sheet for Significant Risk and Nonsignificant Risk Device Studies and made the determination that the study could be approved for human accrual as a nonsignificant risk (NSR) device. There is no documentation in the IRB's records (minutes of the September 23, 2004, January 6, 2005, May 26, 2005, and July 21, 2005 IRB meetings or IRB correspondence) that the IRB considered the use of the device in the clinical investigation, reviewed a description of the device, and the sponsor's explanation as to why the device is NSR, and then made an SR/NSR determination based on this review. In addition, we note that the IRB's Standard Operating Procedures (SOP) do not contain a procedure for the review of investigational device studies.

3. The IRB failed to ensure that informed consent would be sought from each prospective subject or the subject's legally authorized representative in accordance with and to the extent required by 21 CFR Part 50 [21 CFR 56.111(a)(4)] and that informed consent would be appropriately documented in accordance with and to the extent required by 21 CFR 50.27 [21 CFR 56.111(a)(5)].

a. For the **(b)(4)** study, our inspection revealed that there was no discussion about the informed consent document at the February 1, 2008 IRB meeting or at subsequent meetings held on August 8, 2008 and October 24, 2008 in which this study was discussed. There was no mention of the informed consent document in IRB correspondence dated February 15, 2008, August 18, 2008, and November 3,

2008 and there was no IRE-approved informed consent document in the IRB's file. Therefore, it appears that the IRB approved the clinical investigation without ensuring that informed consent would be obtained and documented in accordance with 21 CFR Part 50.

We note that this observation was not listed on Form FDA 483, and therefore, was not addressed in your written response.

b. For the **(b)(4)** Study, the informed consent document approved by the IRB on July 21, 2005 does not contain all of the elements required by 21 CFR 50.25 and therefore is not in compliance with Part 50. The following required elements are inaccurate or missing:

i) A description of the procedures to be followed, and identification of any procedures which are experimental [21 CFR 50.25(a)(1)]. The "Study Procedures" section of the informed consent document does not describe the study procedures outlined in the protocol. The informed consent document states "We will ask you to fill out brief patient assessment form every time you receive therapy"; however, there is no description of the therapy or the assessment forms. In addition, there are no descriptions of the lab work and the clinical, neurological, and functional testing required by the protocol.

ii) A description of any benefits to the subject or to others, which may reasonably be expected from the research [21 CFR 50.25(a)(3)]. The version of the informed consent document approved by the IRB is inaccurate in that it states "There may be direct benefits to you associated with participating in this research study: Relief of **(b)(4)**." This statement is not supported by the protocol which contains the following statements: "Poorly documented reports on the usefulness of **(b)(4)** in **(b)(4)** have been published... a search of the literature does not show any reports of scientific trials. To our knowledge, the use of **(b)(4)** has not been tried on **(b)(4)** patients." In addition, a version of an informed consent document included in the protocol states that "there is no guarantee that **(b)(4)** will help me and that the exact mechanism of action of these fields to produce possible benefits is not known to the investigators at the present time".

iii) A statement that notes the possibility that the Food and Drug Administration may inspect the records [21 CFR 50.25(a)(5)]. There was no such statement in the informed consent document.

iv) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject [21 CFR 50.25(a)(7)]. This explanation is missing from the informed consent document. In addition, **(b)(6)**, M.D., is incorrectly identified as the study coordinator; Dr. **(b)(4)** is the clinical investigator.

v) A statement that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled [21 CFR 50.25(a)(8)]. There was no such statement in the informed consent document.

4. The IRB failed to ensure that no member participated in the initial or continuing review of a project in which the member had a conflicting interest, except to provide information requested by the IRB [21 CFR 56.107(e)].

a. For the **(b)(4)** study, you (IRB Chairman, Carlton F. Hazlewood, Ph.D.) are listed as a clinical investigator on the "Certification: Financial Interests and Arrangements of Clinical Investigators"; you are also listed as being an ex-officio advisor to the **(b)(4)/**IBR Central Registry Control Committee/Data Monitoring Committee. Therefore, you had a conflict of interest.

Minutes of the August 8, 2008 IRB meeting indicate that you attended this meeting and participated in the discussion of the **(b)(4)** study. At this meeting, the IRB voted to draft a letter to **(b)(4)** to inquire about the status of the animal toxicity studies. According to the minutes, all members were in favor, none were opposed, and none abstained. Minutes of the October 24, 2008 IRB meeting indicate that you attended the meeting and participated in the discussion of the **(b)(4)** study. At this meeting, the IRB voted to draft a letter to **(b)(4)** informing them that their application was on hold. The vote on this action is recorded as unanimous; therefore, according to the minutes of these two IRB meetings, you participated in the review of this study and voted on it even though you had a conflict of interest. We also note that you signed off on all correspondence sent by the IRB to Dr. **(b)(6)** and the sponsor in regard to this study.

We note that this observation was not listed on Form FDA 483, and therefore, was not addressed in your written response.

b. For the **(b)(4)** study, **(b)(6)** is listed on the protocol as a co-investigator. Minutes of the March 17, 2005 IRB meeting indicate that ten IRB members attended the meeting including **(b)(6)** and **(b)(6)**, M.D. was present as an invited guest and as an IRB member for the **(b)(4)** study only. The minutes indicate that "Dr. **(b)(6)** is present for **(b)(4)** discussion and Mr. **(b)(6)** leaves." At this meeting the IRE voted to generate a letter requesting changes to the protocol and informed consent document. The vote is recorded as "nine for and zero against." Nothing in the minutes indicates that **(b)(6)** left the meeting or abstained from voting. Therefore, it appears that **(b)(6)** participated in the review of this study even though he had a conflict of interest.

We note that this observation was not listed on Form FDA 483, and therefore, was not addressed in your written response.

5. The IRB failed to conduct continuing reviews for the following IRB approved studies [21 CFR 56.109(1)]:

Our inspection revealed no documentation in the IRB's files to indicate that the IRB conducted continuing review of the following studies:

a. "**(b)(4)**", approved by the IRB on March 17, 2005.

In your written response of April 2, 2009, you state that the **(b)(4)** study was never approved for patient enrollment. Your explanation is contradicted by evidence obtained during the inspection. As stated earlier in this letter, our

inspection revealed that the IRB approved the **(b)(4)** study on March 17, 2005 contingent on changes to the protocol and informed consent document and informed the investigator in an April 4, 2005 letter that the revised documents had been approved. The April 4, 2005 letter states that the protocol (including informed consent documents) has a BRI IRB date stamp of approval.

b. Protocol #**(b)(4)**, also known as the **(b)(4)** Study, approved by the IRB on July 21, 2005.

In your written response of April 2, 2009, you state that protocol **(b)(4)** has been approved for patient enrollment, but no subjects have been enrolled because of funding problems. Your response fails to discuss the lack of continuing review and is inadequate.

In addition, your written response states that the IRB failed to formally request a report or review the progress of these two proposed studies, but did obtain verbal reports from the investigators and/or sponsor. We note that verbal reports from the investigator and/or sponsor are not an acceptable means of conducting continuing review. You state this oversight will be corrected and that the IRB planned to request these reports in April 2009.

6. The IRB failed to maintain copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators and reports of injuries to subjects, and correspondence with investigators [21 CFR 56.115(a)(1) and 56.115(a)(4)].

a. For the **(b)(4)** study, our inspection revealed that the Investigator's Brochure. (IB) was reviewed by the IRB, but was not in the IRB's file. In your written response you state that the IB was misfiled at the time of the FDA inspection and that the IB has been located and placed in the file; however, you did not attach the IB to your response.

b. For the **(b)(4)** study, an April 4, 2005 IRB letter to the sponsor-investigator refers to a copy of the protocol (which includes an informed consent document) with a BRI IRB date stamp of approval. The copy of the protocol and informed consent document with the date stamp of approval was not maintained by the IRB.

c. For the **(b)(4)** study our investigation found the following:

i) At the January 6,2005 IRB meeting the IRB requested that a letter be drafted to address several issues, including the evaluation of the device by an engineer. The IRB's file contained a May 14, 2005 letter from an engineer; however, the IRB's letter requesting the engineer's evaluation was not maintained.

ii) The protocol in the IRB's file is entitled **(b)(4)** Therefore, it appears there was either another version of the protocol (with a different title) that was not maintained by the IRB or the IRB has confused these two studies and misfiled documents.

iii) The minutes of the July 21, 2005 IRB meeting, refer to a board discussion and disapproval of a "Tri-Fold Brochure" and a July 28, 2005 memorandum from

the IRB administrator, **(b)(4)** to **(b)(4)**, refers to a letter of denial for tri-fold flyer. The IRB did not maintain the brochure/flyer and the IRB letter denying approval of the flyer.

In your written response of April 2, 2009, you state that the description of the **(b)(4)** unit (Protocol #**(b)(4)** was misfiled at the time of the FDA inspection and the complete file, including the Investigator's Brochure, has been found; however, you did not attach any documents to your response to support that all documents pertaining to this study are currently in the IRB's file.

7. The IRB failed to prepare and maintain the minutes of IRB meetings 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 [21 CFR 56.115(a)(2)].

a. It appears that the IRB tape records its meetings, which are then transcribed into a hard copy format. It is difficult to discern what studies are being discussed because the minutes do not reference the exact study titles or study numbers. In addition, it appears that when the transcriptionist does not understand certain words, they are transcribed as either blanks or question marks. Due to the numerous blanks, it is difficult to determine whether controverted issues were discussed.

b. For the **(b)(4)** study that was discussed at the February 1, 2008 IRB meeting, there is no IRB action recorded in the minutes; however, an approval letter, dated February 15, 2008 was sent to the clinical investigator.

In your written response, you state that the IRB did not approve this or any other related protocol to begin human accrual and that investigators were directed to complete adequate animal toxicity studies. This does not comport with the IRB's February 15, 2008 letter to Dr. **(b)(6)** in which the IRB refers to the human CIDP study and instructs Dr. **(b)(6)** to report all adverse events and deaths to the sponsor and BRI-IRB. The letter goes on to state that on behalf of the Committee, "you may go forward with the study".

8. Each IRB is required to have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution [21 CFR 56.107(a)].

Our inspection revealed that, in some instances, when an IRB member had a conflict of interest for a particular study, another person, who was not an IRB member, was allowed to take the place of the conflicted member and participate in the IRB's action. There is no provision in FDA regulations for this type of action.

For example:

- Minutes of the March 17, 2005 IRB meeting indicate that nine members were present for this meeting, in addition to **(b)(6)**, M.D. a non-member who was present for the **(b)(4)** study only. Dr. **(b)(6)** is listed as an invited guest. The

minutes indicate that "Dr. **(b)(6)** is present for **(b)(4)** discussion and Mr. **(b)(6)** leaves." The vote on the **(b)(4)** study is recorded as nine for and zero against; therefore, it appears that Dr. **(b)(6)** participated in the action on this study.

• Minutes of the May 26, 2005 and July 21, 2005 IRB meetings indicate that nine members were present for these meetings, in addition to, **(b)(6)** M.D. who was present for the **(b)(4)** and **(b)(4)** studies only. Dr. **(b)(6)** is listed as an invited guest. The minutes indicate that "Dr. **(b)(6)** was present as a member for the **(b)(4)** Study. Mr. **(b)(6)** took over as chairman for the study. Dr. Hazlewood and Dr. **(b)(6)** abstain from voting regarding any matter in this study and are only present for discussions." The **(b)(4)** study was discussed at each of these meetings and actions were taken with a vote of eight for, zero against, and two abstained; therefore, it appears that Dr. **(b)(6)** participated in the actions on this study.

This letter is not intended to be an all-inclusive list of deficiencies for the protocols reviewed and approved by BRI IRB. It is the IRB's responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. The IRB should address these deficiencies and establish procedures to ensure that any on-going 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 or will be taking to prevent similar violations in the future. Your response should include an update on the status of the **(b)(4)** and **(b)(4)** studies. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Kevin A. Prohaska, D.O., M.P.H., at 301-796-3707; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

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Sincerely yours,
/S/

Leslie K. Ball, M.D.
Director
Division of Scientific Investigations
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For more information on this determination, see "Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies," available at http://www.fda.gov/oc/ohrt/irbs/devrisk.pdf.