DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Institutional Review Board – Restrictions Imposed

By Certified Mail – Return Receipt Requested

Carlton F. Hazelwood, Ph.D.
Chairman
BRI Institutional Review Board
9432 Katy Freeway, Suite 105
Houston, TX 77055

Dear Dr. Hazelwood:

This letter imposing restrictions (IRB Restrictions Letter) informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection of the BRI Institutional Review Board (BRI IRB) that was conducted between January 22, 2013, and February 7, 2013. The purpose of this inspection was to determine whether the IRB's activities and procedures for the protection of human subjects comply with FDA regulations published in Title 21 of the Code of Federal Regulations (21 CFR), parts 50 and 56. These regulations govern clinical investigations of products regulated by FDA, and help ensure that human subjects are protected from undue hazard or risk during the course of clinical investigations.

At the conclusion of the inspection, a Form FDA 483, Inspectional Observations, was presented and discussed with you. We acknowledge receipt of the IRB's February 28, 2013, written response to the Form FDA 483, and a follow-up response dated March 28, 2013. We have reviewed the FDA inspection report, the Form FDA 483, and your responses. The IRB's written responses are unacceptable, as explained below. This IRB Restrictions Letter provides you with written notice describing BRI IRB's noncompliance with (violations of) applicable federal regulations governing the operation and responsibilities of IRBs under 21CFR part 56. The BRI IRB is required to respond in writing to FDA's Center for Drug Evaluation and Research (CDER), Office of Scientific Investigations (OSI) with a description of the corrective actions that will be taken by the IRB, the institution, or both, to achieve compliance with FDA regulations [21 CFR 56.120(a)]. The name and address of the person to whom you should submit your corrective action plan is provided at the end of the letter. A listing of the violations follows. The applicable provisions of the CFR are cited for each violation.

1. The IRB failed to follow FDA regulations regarding expedited review procedures [21 CFR 56.110(b)].

Under an expedited review procedure, the IRB's review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the IRB chairperson from among the members of the IRB. Further, the IRB may use the expedited review procedure to review either or both of the following: (1) some or all of the research appearing on the Federal Register list of categories of research eligible for expedited review and found by the reviewer(s) to involve no more than minimal risk; or (2) minor changes in previously approved research during the period for which approval is authorized.

Our inspection revealed that BRI IRB used expedited review inappropriately to approve Single Patient Protocols (SPPs) for patients who failed to meet enrollment criteria for open clinical investigations to receive antineoplaston therapy. Based on our review of records from the inspection, as well as statements made by Mr. Gary L. Harvey, IRB Vice-Chairman, during the inspection, the IRB would grant "provisional approval" before placing an SPP on the agenda for the next scheduled IRB meeting, and that upon granting this "provisional approval," the subject was able to receive treatment with antineoplastons. A "provisional approval" is not recognized by FDA as a valid IRB action. The IRB regulations provide for studies to be approved by either full board review or by expedited review when applicable. Because BRI IRB authorized the investigator to provide the investigational product to subjects after receiving "provisional approval" and prior to a full board review, it appears that BRI IRB uses the term "provisional approval" to mean approval via expedited review.

BRI IRB has failed to comply with the regulations for employing an expedited review procedure. Specifically, BRI IRB used expedited review to approve research that was not eligible for review under an expedited review procedure. Approval of an SPP for patients to receive antineoplaston therapy is not a minor change in previously approved research and is not a category of research eligible for expedited review as listed in the *Federal Register* notice.[1] Therefore, SPPs must be reviewed by a full board during a convened IRB meeting.

Examples of your inappropriate use of the expedited review procedure include, but are not limited, to the following:

a. On March 29, 2012, BRI IRB granted "provisional approval" (approval via expedited review) for Subject 023115. The requisite full board review did not occur until four months later, on August 3, 2012.

b. On May 2, 2012, BRI IRB granted "provisional approval" (approval via expedited review) for Subject 023320. The requisite full board review did not occur until three months later, on August 3, 2012.

[1] "Conditions for IRB Use of Expedited Review," *Federal Register*, November 9, 1998 (Volume 63, Number 216).

c. On May 3, 2012, BRI IRB granted "provisional approval" (approval via expedited review) for Subject 023410. The requisite full board review did not occur until three months later, on August 3, 2012.

The corrective action in your February 28, 2013, written response states that the IRB has initiated a revised IRB approval process for SPPs, to include review by a subcommittee of at least three IRB members plus the IRB Chairman or Vice-Chairman, which will review and approve any "FDA-sanctioned" SPP requests through the expedited approval method established by BRI IRB. After review by the subcommittee, the IRB Chairman or Vice-Chairman will signoff on a "provisional approval." These "provisional approvals" will then be read into the record at a subsequent IRB meeting and documented in the meeting minutes. This process is described in your Standard Operating Procedure (SOP) titled, "Emergency Exemption from Prospective IRB Approval," dated March 28, 2013 (Version 13), which was submitted in your March 28, 2013, written response. Your corrective action is unacceptable. Under FDA regulations, SPPs are not eligible for review via the expedited review procedure. Therefore, your corrective action documenting an expedited review procedure for SPPs fails to comply with FDA's regulatory requirements.

We note that the SOP submitted with your March 28, 2013, response appears to confuse the requirements under 21 CFR 56.104(c) regarding emergency use of a test article, with the requirements under 21 CFR 56.110 for expedited review. Emergency use of a test article is exempt from IRB review, whereas expedited review, as its name suggests, is an expedited process for IRB review. FDA does not consider these SPPs to qualify as an emergency use of a test article. BRI IRB was in possession of e-mails from FDA to the clinical site, dated March 29, 2012; May 2, 2012; and May 3, 2012, stating that "each special exception patient must be approved, prior to treatment, by the IRB that is responsible for review of these clinical investigations (21 CFR part 56)." Thus, BRI IRB was aware that FDA considered these SPPs (referred to in the e-mails as "special exceptions") to require IRB review and approval.

FDA facilitates access to investigational drugs for treatment use for patients with serious or immediately life-threatening diseases or conditions who lack therapeutic alternatives through its expanded access program under 21 USC 360bbb. Individual patient protocols (also referred to as single patient protocols) are part of this program. Prospective IRB review and approval is a critical regulatory requirement for expanded access, in order to provide ethical oversight for this inherently vulnerable population. The absence of prospective full board IRB review and approval of SPPs at a convened meeting at which a majority of the members of the IRB are present [21 CFR 56.108(c)] raises concerns about the level of oversight given to patients whose treatments are overseen by BRI IRB.

Please submit a corrective and preventive action (CAPA) plan to address the violations cited above. With your CAPA plan, submit a copy of your written procedures, or any draft procedures in development, and a timeline for the implementation of any new procedures. Please provide a description of any training provided or to be provided to IRB members on the new procedures and a list of attendees, or a projected timeline of planned training.

2. The IRB approved research without determining that the following criteria were met: risks to subjects were minimized [21 CFR 56.111(a)(1)]; 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)].

In order to approve research, an IRB must determine that all of the requirements as defined in 21 CFR 56.111 are satisfied. Specifically, an IRB must determine that risks to subjects are minimized and reasonable in relationship to the anticipated benefit. An IRB makes such a determination by reviewing sufficient information to assess anticipated benefits to subjects.

Our inspection revealed that BRI IRB failed to ensure that the risks to subjects were minimized and reasonable in relation to the anticipated benefits, because BRI IRB did not review the subjects' medical records and other pertinent information prior to granting approval. In addition, the IRB member who granted the majority of these approvals, IRB Vice-Chairman Gary L. Harvey, was a community (i.e., nonscientific) member of the IRB with a Master's degree in Business Administration. According to the IRB roster submitted with your February 28, 2013, written response, Mr. Harvey is self-employed in water rehabilitation services; therefore, he does not have the clinical expertise necessary to make the required informed evaluation of the risks to subjects and their reasonableness in relation to anticipated benefits.

For example:

a. On June 21, 2012, IRB Vice-Chairman Gary Harvey, on behalf of BRI IRB, granted approval for Subject 022056 to receive antineoplastons. However, the only document in the IRB's possession at the time of approval was the Informed Consent Document (ICD). The ICD is a written summary of the information that should be provided to the subject. Many clinical investigators use the consent document as a guide for the verbal explanation of the study when obtaining consent from a potential subject; however, it alone is insufficient information for an IRB to determine the approvability of a proposed protocol.

   Your February 28, 2013, written response states that the IRB Vice-Chairman reviewed the history and physical exam for this subject prior to granting approval. Your response contradicts an IRB letter sent to the Burzynski Clinic on December 7, 2012 (after the IRB had already granted approval), requesting medical records for Subject 022056.

b. On June 21, 2012, Vice-Chairman Gary Harvey, on behalf of BRI IRB, granted approval for Subject 023356 to receive antineoplastons. However, the only document in the IRB's possession at the time of approval was the ICD. As discussed above, an ICD alone is insufficient information for an IRB to determine the approvability of a proposed protocol.

Your February 28, 2013, written response states that the IRB Vice-Chairman reviewed the history and physical exam for this subject prior to granting approval. Your response contradicts an IRB letter sent to the Burzynski Clinic on December 7, 2012 (after the IRB had already granted approval), requesting medical records for Subject 023356.

c. On June 21, 2012, Vice-Chairman Gary Harvey, on behalf of BRI IRB, granted approval for Subject 023520 to receive antineoplastons. However, it appears from the evidence reviewed during the inspection that the only document in the IRB's possession at the time of approval was the ICD. As discussed above, an ICD alone is insufficient information for an IRB to determine the approvability of a proposed protocol.

   Your February 28, 2013, written response states that a detailed history and physical exam for this subject were reviewed by the IRB. However, your response fails to include any documentation (i.e., history and physical exam) to support your statement.

d. On July 28, 2011, Chairman Carlton Hazelwood, on behalf of BRI IRB, granted approval for Subject 021237 to receive antineoplastons. However, the approval form sought clarity as to why a Karnofsky score of 50 had been assigned, as evidenced by Dr. Hazelwood's handwritten comment: "[P]lease clarify history and physical for assigning KPS 50 – not evident at present." BRI IRB did not receive a corrected medical history and physical exam for this subject until August 2, 2011.

   Your February 28, 2013, written response states that "the IRB did not feel it necessary to clarify the rating, since the history and physical supported the rating." Your response, however, contradicts the handwritten comment on the approval form which questioned the Karnofsky score of 50, but still granted the approval.

The corrective action as described in your February 28, 2013, written response states that an SOP was being prepared to ensure that the risks to subjects are reasonable in relation to the anticipated benefits, and that it will be finalized no later than April 1, 2013. You included two SOPs in your March 28, 2013, written response, neither of which appears to address this violation.

BRI IRB cannot meet the regulatory requirements for approval of SPPs (i.e., ensuring that risks to subjects are minimized and reasonable) without (1) reviewing the subject's medical records (history and physical exam), and (2) clarifying any outstanding issues with respect to the suitability of treating the subject with antineoplastons (for example, the Karnofsky score) prior to granting IRB approval. BRI IRB's approval without reviewing necessary information raises concerns about the level of oversight given to patients who received antineoplaston therapy.

Please submit a CAPA plan to address the violations cited above. With your CAPA plan, submit a copy of your written procedures, or any draft procedures in development, and a

timeline for the implementation of any new procedures. Please provide a description of any training provided or to be provided to IRB members on the new procedures and a list of attendees, or a projected timeline of planned training.

3. **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)].**

   This is a repeat violation from our 2010 inspection.

   Under 21 CFR 56.109(h), when some or all of the subjects in a study are children, the IRB must determine that the research study is in compliance with 21 CFR part 50, subpart D (Additional Safeguards for Children in Clinical Investigations) at the time of initial review. Under 21 CFR 50.50, an IRB must review the clinical investigation and approve only those clinical investigations that satisfy the criteria described in section 50.51 (clinical investigations not involving greater than minimal risk), section 50.52 (clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects), or section 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. Under 21 CFR 56.115, the IRB is required to document its activities, including actions taken. Our inspection revealed that in its review and approval of research involving pediatric subjects, BRI IRB failed to document adequately that the research satisfied the criteria of subpart D. Specifically, the following SPPs were reviewed and approved by the IRB, but the IRB records fail to specify that the IRB had determined that the study satisfied the criteria under subpart D.

   a. On May 2, 2012, BRI IRB granted "provisional approval" for Subject 023320 (5-year-old child) to receive antineoplastons, followed by a full board approval on August 3, 2012. There is no documentation, as required by 21 CFR 56.115, of the IRB's requisite determination under subpart D.

   b. On May 3, 2012, BRI IRB granted "provisional approval" for Subject 023410 (4-year-old child) to receive antineoplastons, followed by a full board approval on August 3, 2012. There is no documentation, as required by 21 CFR 56.115, of the IRB's requisite determination under subpart D.

   c. On March 29, 2012, BRI IRB granted provisional approval for Subject 023115 (3-year-old child) to receive antineoplastons, followed by a full board approval on August 3, 2012. There is no documentation, as required by 21 CFR 56.115, of the IRB's requisite determination under subpart D.

In your February 28, 2013, written response, you state that a pediatric risk assessment form for potentially terminally ill patients had been created, and that your new procedure for review of research involving children includes the following:

- The clinical investigator is asked to provide his/her risk/benefit assessment;
- All determinations about the degree of risk will be made in accordance with the regulatory definition of greater than minimal risk;
- The IRB will review and determine whether there is concurrence with the clinical investigator's determination; and
- The IRB's risk/benefit determination will be documented in the meeting minutes.

In addition, you stated that the IRB will formally specify the justification of risk in its SOPs, which will be completed by April 1, 2013.

Your written response dated March 28, 2013, includes the following: SOP #13, "Emergency Exemption from Prospective IRB Approval," and SOP #35, "Research Involving Children." Your responses, however, are unacceptable, because the IRB's review of SPPs involving children as subjects must be performed during a convened IRB meeting [21 CFR 56.108(c)] and not under an expedited review procedure, as described by your SOP #13.

Failure to determine that the additional safeguards for children in research are met may expose this vulnerable population to unnecessary risks and result in the child's parent(s) or guardian(s) not being fully informed about the proposed research. The absence of prospective IRB review and approval of SPPs involving children raises concerns about the level of oversight given to pediatric patients whose treatments are overseen by BRI IRB.

Please submit a CAPA plan to address the violations cited above. With your CAPA plan, submit a copy of your written procedures, or any draft procedures in development, and a timeline for the implementation of any new procedures. Please provide a description of any training provided or to be provided to IRB members on the new procedures and a list of attendees, or a projected timeline of planned training.

4. **The IRB failed to prepare, maintain, and follow written procedures and maintain adequate documentation governing the functions and operations of the IRB [21 CFR 56.108(a), 21 CFR 56.108(b), and 21 CFR 56.115(a)(6)].**

   In order to fulfill the requirements of an IRB that reviews clinical investigations regulated by FDA, each IRB must prepare, maintain, and follow written procedures describing IRB functions and operations specified in the regulations. Your IRB failed to adhere to these requirements. Compliance with these requirements is intended to protect the rights and welfare of research subjects involved in such investigations. Specifically:

a. BRI IRB failed to follow its written procedures when it granted "provisional approvals," because the IRB's written procedures in "SOP 4 Application to the IRB," section 4.4, "IRB Review of Application," subsection 4.4.1, "BRI IRB Decision," state: "BRI IRB will consider the application at a convened meeting." The IRB had no written procedures for the process that it used to review and approve SPPs, i.e., using expedited review (which it refers to as "provisional approval"). The written procedures for conducting initial review do not contain any provision for conducting IRB review through an expedited mechanism. Expedited review is only discussed under "SOP 5 Continuing Review of Research."

b. BRI IRB failed to prepare written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of (1) any unanticipated problems involving risks to human subjects or others, and (2) any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB.

In your February 28, 2013, written response addressing your failure to follow written procedures for conducting initial review of research, you explain that the IRB had been using the expedited review procedure "for cases that have been pre-approved by the FDA." We wish to emphasize that an FDA determination that the criteria in 21 CFR 312.305 and 312.310 are met is a distinct and completely separate action from IRB review and approval. The IRB must make its own determinations and comply with the regulations in 21 CFR parts 50 and 56 for FDA-regulated clinical investigations. Specifically, the IRB must ensure that all of the criteria specified in 21 CFR 56.111 have been met prior to IRB approval. Your corrective action is unacceptable, because it appears that the IRB intends to continue to use the expedited review procedure to approve SPPs. Specifically, your response states, "The procedure we have immediately initiated is described in Observation #1, which requires a sub-committee of at least 3 IRB members plus the IRB Chairman or Vice-Chairman to review and approve any FDA-sanctioned single patient protocol requests." As stated earlier, under FDA regulations, SPPs are not eligible for review via the expedited review procedure. Therefore, your corrective action documenting an expedited review procedure for SPPs fails to comply with FDA's regulatory requirements.

In your February 28, 2013, written response addressing your failure to prepare a written procedure for ensuring prompt reporting to the IRB, appropriate institutional officials, and FDA of any unanticipated problems involving risks to human subjects or others, you explain that you will institute guidelines and procedures to ensure that investigators promptly report any unanticipated problems involving risk to subjects or others, and referred to the SOP titled "Reporting of Unanticipated Problems Involving Risks to Participants and Others." Your corrective action is unacceptable, because the SOP does not explicitly provide a procedure for reporting to FDA.

In your February 28, 2013, written response addressing your failure to prepare a written procedure for ensuring prompt reporting to the IRB, appropriate institutional officials, and FDA of any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB, you refer to the SOP titled "Reporting

of Unanticipated Problems Involving Risks to Participants and Others." The SOP indicates only that the suspension or termination of IRB approval will be reported. This SOP is unacceptable, because it fails to include a procedure for reporting serious or continuing noncompliance.

Written procedures are important because they describe how an IRB operates and conducts its major functions. Failure of an IRB to prepare, maintain, and follow written procedures may have an adverse impact on the rights and welfare of research subjects, because it may lead to violations of regulations (such as those observed during our inspection) that were put in place to protect the rights and welfare of these subjects.

Please submit a CAPA plan to address the violations cited above. With your CAPA plan, submit a copy of your written procedures, or any draft procedures in development, and a timeline for the implementation of any new procedures. Please provide a description of any training provided or to be provided to IRB members on the new procedures and a list of attendees, or a projected timeline of planned training.

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

Based on the continuing pattern of deficiencies found during the last three inspections, BRI IRB does not meet the requirements of 21 CFR part 56. We have no assurance that the IRB procedures are adequately protecting the rights and welfare of the human subjects involved in research. For this reason, and effective immediately:

(1) No new studies subject to the requirements of 21 CFR parts 50 and 56 are to be approved by BRI IRB [21 CFR 56.103(a) and 56.120(b)(1)];

(2) No new subjects are to be added to ongoing studies subject to 21 CFR part 56 [21 CFR 56.120(b)(2)]; and

(3) FDA is suspending the IRB's use of the expedited review procedure to protect the rights or welfare of subjects [21 CFR 56.110(d)].

These restrictions will remain in effect until such time as FDA has evidence of adequate corrective actions, and notifies you in writing that the IRB's corrective actions are satisfactory. You are responsible for notifying the affected sponsors and clinical investigators about these restrictions (see 21 CFR 312.66). These restrictions do not relieve the IRB of its responsibilities for receiving and reacting to reports of unanticipated problems involving risks to human subjects or others, and routine progress reports from ongoing studies. The restrictions state that no new subjects are to be enrolled in SPPs or in any active Phase 2 or 3 studies; however, this restriction would not affect any subjects already enrolled in ongoing SPPs or Phase 2 or 3 studies, as long as it is in the best interest and safety of individual subjects to remain enrolled.

Within 30 working days of receipt of this letter, you should respond in writing with a description of the corrective actions that will be taken or that have been implemented to achieve compliance with the regulations.

Your response should address each item of noncompliance listed above. If you do not believe your IRB is in violation of FDA requirements, include your reasoning and any supporting information for our consideration. If you assert that full and adequate correction has been achieved, you should include any documentation necessary that affirms your corrective actions. For each action to be accomplished, include the projected completion dates.

Include with your response a copy of the IRB's written communication to each of the affected sponsors and clinical investigators, notifying them of the current FDA-imposed restrictions. In addition, please provide a list of all studies being reviewed by your IRB that are subject to 21 CFR part 56, and list all studies that are affected by the above restrictions.

Your failure to adequately respond to this letter may result in further administrative actions, as authorized by 21 CFR 56.120 and 56.121.

Your written reply should be sent to:

Catherine Parker, R.N.
Team Lead, Human Subject Protection Branch
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5247
10903 New Hampshire Avenue
Silver Spring, MD 20993

FDA's Center for Drug Evaluation and Research will carefully consider your written response. Additionally, your corrective actions will be verified during a future inspection.

Sincerely yours,

{See appended electronic signature page}

Thomas N. Moreno, M.S.
Acting Office Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

THOMAS N MORENO
09/23/2013