Establishment Inspection Report	FEI:	**1000220451**
Burzynski Research Institute (BRI) / IRB	EI Start:	12/03/2008
Houston, TX 77055-6349	EI End:	12/10/2008

SUMMARY

This FY 2009-High-Priority Center for Drugs and Evaluation of Research (CDER) For-Cause Division of Scientific (DSI) Complaint #2271 was conducted pursuant to FACTS #997548 with TURBO EIR # 173134, as requested by HFD-45. The inspection was conducted in accordance with Compliance Program 7348.809, Institutional Review Board (IRB). All areas of the compliance program were covered during the course of this inspection.

The previous FDA inspection of this IRB conducted 02/12-15/2002 revealed nine objectionable observations issued on an FDA 483, Inspectional Observations form, issued at the conclusion of the inspection. The following objectionable conditions were noted: A) failing to retain copies of clinical research study records including study protocols & IRB approved Informed consent forms B) failing to retain IRB approval letters and IRB continuing review approval documentation C) the IRB granted approval to a Principal Investigator (P.I.) to begin a non FDA approved treatment. The inspection was classified as NAI. The BRI IRB was inspected by the FDA in 1994 & 2000 with a classification of VAI for Informed consent form (ICF) violations (1994), failure to follow standard operating procedures (SOPs) in conduct of IRB business (2000) and failure to review study protocols annually (2000).

The current inspection focused on current IRB operations and the DSI complaint #2271 concerning an issuance of a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) to (b) (4) Principal Investigator (P.I.). The NIDPOE letter was issued to (b) (4) for administering a investigational new drug (IND) (b) (4) to study subjects without an IND in effect, violating a clinical hold by giving study subjects (b) (4) after FDA issued an order to delay the proposed clinical investigation, and failing to obtain informed consent in accordance with the Code of Federal Regulation (CFR) statues.

I reviewed four study protocols which the BRI IRB provided medical & ethical review and oversight which are currently open. Three of the study protocols were non-BRI clinic studies and one was a BRI clinic study. I reviewed and collected copies of meeting minutes and IRB records from 2003 through the present. During this inspection I noted the following four objectionable observations issued on an FDA 483, Inspectional Observations form: 1) A clinical investigation requiring prior submission to the FDA was initiated without IRB approval 2) The IRB does not conduct continuing review of research at intervals of not less than once per year 3) Copies have not been maintained of all research proposals reviewed 4) Documentation has not been maintained of written procedures review for the IRB, as required by 21 CFR 56.108(a) and (b) for the past five years. There were no refusals during this investigation and no samples were collected. According to Dr. Hazlewood the BRI IRB is going through a period of transition and reorganization. Hurricane Ike damaged the BRI building and BRI IRB offices. The BRI clinic building is undergoing reconstructions and renovation.

ADMINISTRATIVE DATA

Inspected firm:	Burzynski Research Institute (BRI) / IRB
Location:	9432 Katy Freeway # 370 Houston, TX 77055-6349
Phone:	713-365-0222
FAX:	713-365-0879
Mailing address:	9432 Katy Freeway # 370 Houston, TX 77055-6349
Dates of inspection:	12/3-5/2008 & 12/8-10/2008
Days in the facility:	6
Participants:	Patrick D Stone, M.S., Investigator

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

My inspection was not pre-announced. On 12/03/2008,I showed my credentials and issued an FDA 482, Notice of Inspection, to Ms. Linda I. Coleman, IRB Administrator. Carlton F. Hazlewood, Ph. D., IRB Chairman, was present shortly after I started my inspection. Ms. Coleman provided me with a copy of the IRB roster (Exhibit #1). Dr. Hazlewood has served as the IRB chairman since 1994 and is the most responsible individual at the IRB. Mr. Gary L. Harvey, Second Vice-Chairman and Erich Fruchtnicht, IRB Member, were also present during my inspection and the close-out meeting. Mr. Harvey is a water treatment plant engineer by trade.

The IRB does not maintain a current copy of the studies currently under review. Ms. Coleman provided me with a copy of the Burzynski Research Institute (BRI) Annual report for a list of open studies (Exhibit #2) and did not have a list of the (b) (4) non-BRI studies currently under review. A copy of the 05/09/2002 IRB SOPs are provided with this report as Exhibit #3. Dr. Hazlewood explained that IRB SOPs have not been updated since the last FDA inspection. Meeting minutes reflect that an SOP update was tabled in 2008. The BRI IRB does not conduct monitoring audits of the studies they review or approve.

Agency correspondence regarding this inspection should be addressed to the attention of Carlton F. Hazlewood, Ph. D., IRB Chairman, at the mailing address listed above.

IRB RECORDS REVIEWED

The first study protocol (b) (4) I reviewed was entitled (b) (4) (b) (4) I collected a copy of the (b) (4) initial FDA 1571, IND form, for phase 3 human trials (Exhibit #4) found in the IRB records. A copy of the FDA 1572, Statement of Investigator, form for (b) (4) is included with this report as Exhibit #5. I also collected a copy of the FDA 3454, Financial Interests and Arrangements of Clinical Investigators (Exhibits #6) which lists Carlton Hazlewood, Ph. D. as a

Clinical Investigator for (b) (4) A copy of the (b) (4) protocol is provided with this report as Exhibit #7. A copy of an email and review from 01/10/2007 are included with this report as Exhibit #8. On 02/15/2008 the BRI IRB sent a letter to (b) (4) stating that "you may go forward with the study and we look forward to your continued success in this area" (Exhibit #9). According to Dr. Hazlewood and the meeting minutes, he excused himself as the IRB Chairman and presented the (b) (4) study protocol with (b) (4) On August 18, 2008 the BRI IRB sent a letter to (b) (4) requesting additional animal toxicity studies and reminded them that human studies cannot proceed until an IND number is granted by the FDA (Exhibit #10). (b) (4) submitted a response to the IRB on 09/04/2008 stating that safety and toxicity studies in animals have not begun (Exhibit #11). The IRB sent a letter on 11/03/2008 to (b) (4) stating that his project was on hold until toxicity studies were performed or the FDA approved the IND to continue (Exhibit #12). An Investigator Brochure was not found on file for this test article. In January of 2007 (b) (4) study subjects were entered into this trial prior to FDA and IRB approval. The BRI IRB was presented with these pilot case reports during the 02/01/08 meeting when it was approved by the board. On page 11 of the official approved meeting minutes it states near the bottom of the page (b) (4) (misspelled) The drug is made____ ____(b) (4) ' as the way the test article is derived. The board approved this protocol to continue without further explanation. See Exhibit #23 for a full copy of the February 01, 2008 meeting minutes.

The second protocol I reviewed clinical device protocol (b) (4) was entitled (b) (4) (b) (4) (b) (4) Carlton F. Hazlewood, Ph.D., was the Co-P.I. for this protocol. A copy of the study protocol and supporting documentation is included with this report as Exhibit #13. I collected copies of correspondence from the BRI IRB requesting additional FDA device regulation information and administrative changes to the protocol (Exhibit #14). The BRI IRB requested that a State of Texas certified engineer conduct a safety test of the (b) (4) device. A copy of the certified letter from the engineer detailing the specifications and safety of the (b) (4) device is provided as Exhibit #15. Copies of the BRI IRB approval letter for the ICF and protocol are included with this report as Exhibit #16. The BRI IRB stamped approved ICF makes therapeutic device claims on line number "9. Benefits Associated with Study Participation. There may be direct benefits to you associated with participation in this research study: (b) (4)
Annual review and approval was not conducted from 2006-present. I did not observe a device description or see a picture and information regarding the (b) (4) device in the study file. A copy of the September 23, 2004 IRB meeting minutes when the protocol was approved may be found in Exhibit #23. The BRI SOPs do not have significant or non-significant risk device determinations nor do they describe the IRB procedures for reviewing or approving medical device studies. According to Dr. Hazlewood, no subjects were treated with this device and the project is hold because the funding ran out.

The third study protocol I reviewed was entitled (b) (4) (b) (4) A copy of the study protocol and supporting documentation is included with this report as Exhibit #17. An Investigator

Brochure was not found on file in the study documentation. On February 01, 2005 The BRI IRB sent a protocol modification letter to the P.I. (Exhibit #18). I also collected copies of two approval letters for this protocol dated March and April of 2005 (Exhibit #19). There were no progress reports, continuing approvals, or close-out documentation found in the PME file. A copy of the January 06, 2005 meeting minutes when the IRB approved this protocol may be found in Exhibit #23. According to Dr. Hazlewood, this protocol did not have an FDA approved IND number. Dr. Hazlewood also stated that no patients were treated with this test article and the project is on hold and the BRI IRB should have kept up with these files. Dr. Hazlewood took full responsibility for the missing information in the files.

The fourth study I reviewed for this audit as a BRI in-house clinic study (b) (4). Protocol (b) (4) is entitled (b) (4) (b) (4). Copies of progress reports (2003-2008) and BRI IRB continuing review approvals are provided with this report as Exhibit #20. I did not observe any missing information from the BRI IRB records. Exhibit #23 contains numerous examples of IRB meeting minutes with annual report and special exemptions approvals by the BRI IRB.

The BRI Clinic continues to enroll Special Exception subjects into its research protocols with BRI IRB approval. According to Dr. Hazlewood, as the BRI clinic protocols close-out they are receiving less special exception requests. I collected copies of two lists of Special Exceptions from 2005 to 2007 (Exhibit #21). I also collected copies of three complete special exception requests that were approved by the BRI IRB (Exhibit #22).

Copies of eight BRI IRB meeting minutes from 09/23/2004 through 10/24/2008 are provided with this report as Exhibit #23. I have kept the meeting minutes all together showing the chronology of meeting minutes and BRI IRB approvals as they occurred. I observed that on March 09, 2006 the BRI IRB approved the annual report for IND (b) (4) with numerous protocols via email vote. Copies of the meeting minutes for 03/09/06 are provided with this report as Exhibit #24.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

Observations listed on form FDA 483

OBSERVATION 1

A clinical investigation requiring prior submission to the FDA was initiated without IRB approval.

Specifically, On February 01, 2008 The BRI IRB was presented with study protocol # (b) (4) entitled (b) (4) (b) (4) Principal Investigator (P.I.) and Carlton F. Hazlewood, Ph.D., Co-P.I. (b) (4) human subjects' were entered into protocol (b) (4) under pilot

case reports between January and February 2007 without an effective FDA Investigational New Drug number. On February 15, 2008 the BRI IRB approved the protocol to begin human accrual.
Reference: 21 CFR 56.103(a)

Supporting Evidence and Relevance: A copy of the (b) (4) Pilot Case Reports is included with this report as Exhibit #25. The BRI IRB was presented this patient information on 02/01/2008. A full copy of the IRB meeting minutes for February 01, 2008 may be found in Exhibit #23. According to Dr. Hazlewood and the meeting minutes, he excused himself as the IRB Chairman and presented the (b) (4) study protocol (b) (4) with (b) (4) As a sub-investigator for this clinical protocol Dr. Hazlewood had very little knowledge or written information (Investigator Brochure) regarding the test article. No subjects were seen by Dr. Hazlewood. The BRI IRB and Dr. Hazlewood knew this protocol did not have an authorized FDA IND as discussed in numerous meetings. The IRB sent a letter on 11/03/2008 to (b) (4) stating that his project was on hold until toxicity studies were performed or the FDA approved the IND to continue (Exhibit #12).

Discussion with Management: Dr. Hazlewood took full responsibility for the BRI IRB's actions for this CFR violation despite not voting for the approval of this treatment on clinical hold by the FDA. Dr. Hazlewood explained that he was unaware of the NIDPOE letter or the FDA hold on the IND. Dr. Hazlewood stated that this IND did not go through phase one human trials or sufficient animal toxicity studies as request twice by the BRI IRB.

OBSERVATION 2

The IRB does not conduct continuing review of research at intervals of not less than once per year.

Specifically,

A) Clinical protocol entitled (b) (4) (b) (4) was not reviewed & approved by the IRB annually from 2006 through 2008. In addition there are no continuing review reports on file from the P.I. to the IRB.

B) Clinical Device Protocol (b) (4) entitled (b) (4) (b) (4) (b) (4) conducted by Carlton F. Hazlewood, Ph.D., Co-P.I. was not reviewed & approved by the IRB annually from 2005 through 2008. In addition there are no continuing review reports on file from the P.I. to the IRB.

Reference: 21 CFR 56.109(f)

Supporting Evidence and Relevance: A copy of the January 06, 2005 meeting minutes when the IRB approved the (b) (4) protocol may be found in Exhibit #23. According to Dr. Hazlewood, this

protocol did not have an FDA approved IND number. Dr. Hazlewood also stated that no patients were treated with this test article and the project is on FDA hold and the BRI IRB should have kept up with these files.

The BRI IRB stamped approved ICF for the (b) (4) device makes therapeutic device claims on line number "9. Benefits Associated with Study Participation. There may be direct benefits to you associated with participation in this research study: (b) (4) (b) (4) The BRI IRB should have requested changes to the ICF before it approved this device protocol. A device description, (b) (4) picture, and information regarding the (b) (4) device should have been present in the study file before the BRI IRB approved this protocol. Annual review and approval was not conducted from 2006-present for the (b) (4) device. According to Dr. Hazlewood, no subjects were treated with this device and the project is hold because the funding ran out.

Discussion with Management: Dr. Hazlewood took full responsibility for the missing BRI IRB continuing review and approval or termination letters.

OBSERVATION 3

Copies have not been maintained of all research proposals reviewed.

Specifically,
A) The Investigators Brochure for study protocol (b) (4) was not found in the BRI IRB study records.

B) The device description or detailed information regarding the (b) (4) device (Protocol (b) (4) was not found in the BRI IRB study records.

Reference: 21 CFR 56.115(a)(1)

Supporting Evidence and Relevance: As a sub-investigator for clinical protocol (b) (4) Dr. Hazlewood had very little knowledge or written information (Investigator Brochure) regarding the test article. This IND did not go through phase one human trials or sufficient animal toxicity studies as request twice by the BRI IRB. According to the February 01, 2008 and protocol (b) (4) an Investigator Brochure was submitted to the BRI IRB.

A device description, (b) (4) picture, and information regarding the (b) (4) device should have been present in the study file before the BRI IRB approved this protocol.

Discussion with Management: Dr. Hazlewood took full responsibility for the BRI IRB's missing records.

OBSERVATION 4

Documentation has not been maintained of written procedures for the IRB, as required by 21 CFR 56.108(a) and (b).

Specifically, The BRI IRB written procedures section 4.2.2.1 states that "These policies and Procedures (SOPs) will be reviewed annually". The SOPs were not reviewed from 2003 through 2008.

Reference: 21 CFR 56.115(a)(6)

Supporting Evidence and Relevance: A copy of the 05/09/2002 IRB SOPs are provided with this report as Exhibit #3. Dr. Hazlewood explained that IRB SOPs have not been updated since the last FDA inspection in 2002. Meeting minutes reflect that an SOP update was tabled in 2005 & 2008.

Discussion with Management: Dr. Hazlewood took full responsibility for the BRI IRB's actions and promised corrections for all of the listed CFR violations. The BRI IRB will respond in writing to all of the listed observations.

GENERAL DISCUSSION WITH MANAGEMENT

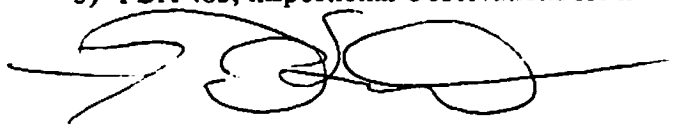
On 12/10/2008 I issued and read an FDA 483, Inspectional Observations form to Carlton F. Hazlewood, Ph. D., IRB Chairman. Mr. Gary L. Harvey, Second Vice-Chairman and Erich Fruchtnicht, IRB Member, were also present during my close-out meeting. We discussed the New Drug Application Regulations and "off the shelf" (off label) use of prescription drugs. The BRI will implement Device SOP's and follow the current ones. The BRI will also start requiring confidentiality agreements with new P.I.'s. I stated to the IRB that they needed to start monitoring and auditing the studies they review. I explained that I had discussed the need to monitor IRB reviewed studies with them in 2002. I explained to them that email voting is not the best way to approve any IRB business. Dr. Hazlewood explained that this was an isolated incident and it would not happen again. I also stated that persons at CDER would further review my report and the documents I collected. I thanked them for their cooperation & closed the inspection.

EXHIBITS COLLECTED

1) A copy of the IRB roster
2) A copy of the BRI Annual report for a list of open studies
3) A copy of the 05/09/2002 IRB SOPs
4) A copy of the (b) (4) initial FDA 1571, IND form, for phase 3 trial
5) A copy of the FDA 1572, Statement of Investigator, form for (b) (4)
6) A copy of the FDA 3454, Financial Interests and Arrangements of Clinical Investigators
7) A copy of the (b) (4) protocol
8) A copy of an email and review from 01/10/2007
9) A copy of the letter the BRI IRB sent 02/15/2008 to approve (b) (4)
10) A copy of an August 18, 2008 letter the BRI IRB sent to (b) (4) requesting additional animal toxicity studies and putting study on hold
11) A copy of (b) (4) response to the IRB dated 09/04/2008
12) A copy of IRB a letter sent on 11/03/2008 to (b) (4) stating his project was on hold
13) A copy of the (b) (4) study protocol and supporting documentation
14) Copies of correspondence from the BRI IRB requesting additional FDA device regulation information
15) A copy of the certified letter from the engineer detailing the specifications and safety of the (b) (4) device
16) Copies of the BRI IRB approval letter for the ICF and protocol
17) A copy of the (b) (4) study protocol and supporting documentation
18) A copy of the February 01, 2005 (b) (4) protocol modification letter the BRI IRB sent to the P.I.
19) Copies of two approval letters for the (b) (4) protocol dated March and April of 2005
20) Copies of (b) (4) progress reports (2003-2008) and BRI IRB continuing review approvals
21) Copies of two lists of Special Exceptions from 2005 to 2007
22) copies of three complete special exception requests
23) Copies of BRI IRB meeting minutes from 09/23/2004 through 10/24/2008
24) Copies of the meeting minutes for 03/09/06
25) A copy of the (b) (4) Pilot Case Reports

ATTACHMENTS

1) FDA 482, Notice of Inspection form
2) CDER assignment memo FY09'
3) FDA 483, Inspectional Observations form



Patrick D Stone, M.S., Investigator