

EIR: Burzynski Research Institute IRB  
9432 Old Katy Rd.  
Houston, TX. 77055

2/12-15/02  
Joel Martinez

### Summary of Findings

Present inspection of this institutional review board (IRB) was conducted per request dated 12-20-01 from HFD-47, Good Clinical Practice Branch II, Division of Scientific Investigations, CDER.

The purpose of this inspection as requested in HFD-47's assignment was:

- to determine this IRB's compliance with applicable regulations.
- to determine if research associates employed by the Burzynski Research Institute (BRI) and working on [REDACTED] clinical studies were actively involved in approving studies of patients that they were involved in the patient's medical care.
- to determine if the IRB reviewed and approved clinical studies for the drug [REDACTED]. NOTE: The [REDACTED] has not been submitted to the agency under an IND.

Inspectional observations included but were not limited to the following:

- Failure to keep a copy of the [REDACTED] study protocol and informed consent form.
- Failure to receive and/or require progress reports from the principal investigator for the [REDACTED] study.
- Failure to receive and/or require a final report from the principal investigator for the [REDACTED] study prior to removal from the IRB's active list of studies.
- Failure to assure that FDA approval was obtained by the principal investigator prior to the treatment of a patient under a special exception.
- Acceptance of special exception requests that were not signed by the principal investigator as required.
- Approval of special exceptions via expedited review. The IRB's expedited review procedure does not provide a provision for such approvals under expedited review(s).

At the conclusion of the inspection an FDA 483, Inspectional Observations, was issued to and discussed with the IRB's chairman. Voluntary corrections were indicated as well as the submission of a written response.

To illustrate current IRB procedures the following three studies were selected:

1. Phase [REDACTED] study of [REDACTED] and [REDACTED] In Patients with [REDACTED] Protocol [REDACTED].

The study protocol and informed consent form are attached as Exhibit 1. Also collected:

- IRB's approval dated 3-2-00 of a revision to the Informed Consent form (Exhibit 2).
- IRB's expedited approval of revisions to the protocol and informed consent form dated 8-24-00 (Exhibit 3).
- IRB's notice of approval to the informed consent form dated 8-31-00 (Exhibit 4).
- IRB's meeting minutes dated 10-12-00 that document review of the informed consent form. It should be noted that the protocol ([REDACTED]) is not mentioned specifically but reportedly was the approval for the expedited review (Exhibit 5).
- IRB's correspondence to Dr. Burzynski dated 12-11-00 addressing the conduct of an annual review. See Exhibit 6.
- IRB's approval to Amendments 1 and 2 to the protocol. Exhibit 7.
- IRB approval to a patient education package. Exhibit 8.

2. Phase [REDACTED] study of [REDACTED] In Patients with [REDACTED] Protocol [REDACTED].

The study protocol and informed consent form are attached as Exhibits 9 and 10 respectively. Also collected:

- IRB's annual approval and progress report. Exhibit 11.
- IRB's review and approval of the annual report to the IND. Exhibit 12.
- IRB's approval of a patient education package. Exhibit 13.

3. Treatment of [REDACTED] with [REDACTED]  
Phase [REDACTED] protocol.

The study protocol is attached as Exhibit 14. The informed consent form is attached as Exhibit 15. Also collected the following:

- IRB expedited approval to changes to the protocol and informed consent form. Exhibit 16.
- IRB approval of the protocol and progress report. Exhibit 17.
- IRB correspondence of rescheduling of annual review. Exhibit 18.
- IRB approval to the study and progress report. Exhibit 19.

Attached as Exhibit 20 are representative copies of IRB meeting minutes dated 2-6-01, 7-19-01, and 9-20-01.

#### Persons Interviewed and Individual Responsibility

During this inspection I was accompanied by Patrick D. Stone, CSO, Dallas District, Houston Resident Post.

Credentials were shown to and an FDA 482, Notice of Inspection, was issued to Carlton F. Hazlewood, Ph.D., IRB chairman. Also present were Ms. Dawn A. Bradley, BRI (Burzynski Research Institute) compliance officer, and DeEtte M. Mullins, BRI IRB administrator.

I began the inspection by interviewing Dr. Hazlewood. I asked him how long has he been the IRB chairman. He stated that he has been the IRB chairman since 1993. He has been on the IRB since 1983. Dr. Hazlewood stated that he was asked by Dr. Stanislaw R. Burzynski to assume the position of IRB chairman because Dr. Burzynski's previous chairman had died. Dr. Hazlewood stated that he said yes to becoming the IRB chairman. BRI's Board of Directors then approved his nomination. Dr. Hazlewood's appointment as IRB chairman is subject to annual re-approval by the IRB members. There is no term limit.

I then asked Dr. Hazlewood to state his responsibilities as IRB chairman. Dr. Hazlewood stated that it is his responsibility to have IRB meetings to review all protocols of study. He stated that he chairs the meetings, keeps control and officiates the meetings. He is kept aware of serious adverse events and reviews these adverse events. He further stated that he is responsible for bringing in the principal investigator (Dr. Burzynski) or sub-investigators periodically to inform the IRB of study protocol's progress. Dr. Hazlewood also stated that he makes sure that Dr. Burzynski or a sub-investigator is present during the IRB's discussion of compassionate exceptions (special exceptions) or serious adverse

events. Dr. Hazlewood also stated that sub-committees of a few IRB members are formed to review serious adverse events. He stated that SAE's can be problematic. He gave an example of reported SAE overdoses. He explained that it had been difficult to determine whether the reported incidents were inadvertent overdose(s), whether it was a result of patient error, or whether it was as a result of a mix up in the connection of the tubing to the pump. These sub-committees are required to report to the full board their findings and/or conclusions. Dr. Hazlewood explained that in the case of overdose problems that color coding the tubes was discussed as a possible solution to the problem.

Dr. Hazlewood stated that he along with the committee (IRB members) decide the membership and decide the future direction of the IRB.

### IRB Membership

The IRB currently has [REDACTED] members. Refer to Exhibit 21. NOTE: Also attached is a historical list of BRI IRB members for 2000. This list indicates that [REDACTED] and [REDACTED] were removed from the IRB on 10-20-00. I asked Dr. Hazlewood why were these IRB members removed. He stated that they were removed [REDACTED] and [REDACTED] are not licensed in the State of Texas, therefore, are considered to be research associates versus sub-investigators. Prior to removal from the IRB they were involved in expedited approvals of special exception requests.

Dr. Hazlewood stated that members are paid a \$ [REDACTED] honorarium for each meeting they attend. I asked Dr. Hazlewood how are IRB members selected to serve on the IRB. Dr. Hazlewood stated that he asks IRB members for recommendations or recommendations may come from his personal acquaintances. If an individual shows an interest then their nomination is voted upon by the full IRB. Dr. Hazlewood stated that he then has the final approval on an individual's IRB membership. A member serves [REDACTED] terms with no term limitations.

### IRB Operations

Dr. Hazlewood stated that the BRI IRB was established to evaluate BRI's research proposals. Dr. Hazlewood stated that the IRB meets once every [REDACTED]. The IRB's current policies and procedures are attached as Exhibit 22.

I asked Dr. Hazlewood whether Dr. Burzynski is the principal investigator for all research conducted at BRI. He said yes. He added during the last meeting it was proposed to possibly include/review research proposals from outside BRI. He asked if that would be appropriate. I stated that it would be satisfactory. That the requirement was that a principal investigator must have an IRB review and/or monitor their conduct of a clinical study.

I asked Dr. Hazlewood if the IRB has defined a quorum. He said that a quorum is defined that at least [REDACTED] IRB members be present. This is stated in the IRB's policies and procedures under SOP 2, Section 2.3.2.2.1.

I then asked Dr. Hazlewood what is distributed to IRB members prior to a meeting and when is it distributed. Dr. Hazlewood stated that the last research proposal submitted by Dr. Burzynski was in [REDACTED]. He said that the study protocol and investigator's brochure is made available to members usually about [REDACTED] prior to the scheduled meeting. Dr. Hazlewood explained that more recently what is distributed are reports of serious adverse events and copies of provisionally approved special exceptions.

The IRB has not reviewed and/or approved any protocols for a waiver of informed consent under 21 CFR 50.24.

### Objectionable conditions/Practices

The following objectionable conditions/practices were observed:

1. Protocol [REDACTED] received tentative IRB approval on 9-16-99 and then received final IRB approval on 10-28-99. The IRB has failed to keep a copy of the [REDACTED] protocol and informed consent form, FDA 483 #1.

Attached as Exhibit 23 is a copy of the meeting minutes dated 9-16-99. On page 27 it states: "Confirmation of review and official tentative approval by this IRB, of the New Protocol titled: [REDACTED] Administration of [REDACTED] to [REDACTED] Patients."

Attached as Exhibit 24 is a copy of the meeting minutes dated 10-28-99. On page 4 a discussion about the [REDACTED] protocol is documented. On page 12 it states, "Confirmation of review and official approval by this IRB, of the New Protocol titled: [REDACTED] Administration of [REDACTED] to [REDACTED] Patients."

Attached as Exhibit 25 is a S.R. Burzynski memorandum dated 7-23-99. The memo signed by Dr. Burzynski stated, "Please find attached a copy of Protocol [REDACTED] for administration of [REDACTED] to [REDACTED] patients. According to Dr. Hazlewood, this memorandum signified that the study protocol was distributed to IRB members. Exhibit 26 is a Burzynski Clinic memorandum dated 8-23-99 that addresses amendments to the [REDACTED] protocol. **NOTE:** These amendments received provisional approval from [REDACTED] on 8-23-99.

I asked Dr. Hazlewood to see the IRB's file on the [REDACTED] study protocol. He then asked Ms. Mullins to obtain the IRB binder (file). Ms. Mullins stated that the IRB had no [REDACTED] binder. Ms. Mullins stated that a [REDACTED] had taken the IRB binder. Dr. Hazlewood stated that [REDACTED] had replaced [REDACTED] but that he was no longer employed by BRI. Dr. Hazlewood stated that at the time of the [REDACTED] submission that every meeting was coordinated through [REDACTED]. According to Dr. Hazlewood, [REDACTED] was responsible for keeping the IRB updated on FDA regulations.

Ms. Bradley provided a copy of a memo dated 9-7-99 (Exhibit 27). She stated that this memo clarified that the [REDACTED] protocol was not intended to be a clinical trial/clinical study but intended to be used in Dr. Burzynski's private practice. She further stated that to be on the safe side, Dr. Burzynski had decided to submit the protocol to the IRB.

2. While the [REDACTED] study received final IRB approval on 10-28-99, it has not (to date) received any progress reports from the principal investigator, FDA 483 #2.

I asked Dr. Hazlewood to see progress reports that had been submitted to the IRB. Dr. Hazlewood stated that there were no progress reports.

3. While the [REDACTED] study protocol was removed from the IRB's list of active studies, there is no final report from the principal investigator to show that the [REDACTED] study was terminated and to assure that all reports of injuries and/or serious adverse events (SAE's) were reported during the conduct of the [REDACTED] study, FDA 483 #3.

During the previous FDA inspection a list of protocols was obtained. This list was submitted as Exhibit 4 for the EIR dated 9/11-13/00. Refer to Exhibit 28. On page 6 of the exhibit, [REDACTED] is listed as being an active protocol. At the initiation of the inspection, I asked for a list of active studies. I was provided with a listing. Refer to Exhibit 29. I noted that [REDACTED] protocol was not listed. I asked Dr. Hazlewood if the principal investigator (Dr. Burzynski) had submitted a final report. He said no.

4. The IRB issued a provisional approval for the special exception (compassionate exception) request of [REDACTED], however, it failed to assure that FDA approval was obtained by the principal investigator prior to commencement of treatment, FDA 483 #4.

Attached as Exhibit 30 is a [REDACTED] list of special exception patients and an IRB provisional approval dated 11-20-97. I asked to see documentation to demonstrate that this special exception had been submitted to CDER for review and approval. Ms. Bradley searched her files and determined that this special exception had not been submitted.

5. The IRB accepted 2 special exception requests, one that is unsigned [REDACTED] and one signed by a research associate ([REDACTED]) instead of being signed by the principal investigator or co-investigator, FDA 483 #5.

[REDACTED] Refer to Exhibit 31 for a copy of the unsigned request for provisional approval, attachments, and subsequent IRB provisional approval.

[REDACTED] Refer to Exhibit 32 for a copy of the request for provisional approval, attachments, and subsequent IRB provisional approval. A research associate, i.e. [REDACTED] signed the request. We identified this individual through a signature log. Refer to Exhibit 33.

I asked Dr. Hazlewood if it was the IRB's policy to accept unsigned requests. He stated that no and that a request should only be submitted to the IRB either by the principal investigator (Dr. Burzynski) or a sub-investigator. Attached as Exhibit 34 is a representative FDA 1572 that lists the sub-investigators that does not include [REDACTED]

6. There is no record that the IRB reviewed and approved the following protocols: [REDACTED] and [REDACTED] FDA 483 #6.

During the inspection I inventoried all IRB binders on file. I then asked to see evidence of the IRB's initial review of the protocol and approval. Dr. Hazlewood identified a correspondence dated 6-27-96 and stated that it documented initial approval of all protocols. See Exhibit 35. Dr. Hazlewood stated that [REDACTED] and [REDACTED] were closed studies. I then asked if there had been any patient accruals in these closed studies.

We learned that for [REDACTED] there were [REDACTED] enrolled, for [REDACTED] enrolled, for [REDACTED] enrolled, and for [REDACTED] also enrolled. Refer to Exhibit 36. I explained to Dr. Hazlewood because there had been patient accruals that the IRB should have reviewed and approved these study protocols. NOTE: The meeting minutes dated 7-20-96 (Exhibit 37 page 6) state that [REDACTED] is out and not allowed by the FDA and on page 7 the

minutes state [REDACTED] is still on clinical hold therefore no need to consider. [REDACTED] and [REDACTED] were not mentioned in the IRB meeting minutes.

7. **Special Exceptions receive provisional approval via expedited review exercised by the chairperson or co-chair. The BRI's IRB SOP 3, (3.4- Expedited Review) does not provide a provision for such provisional approvals, FDA 483 #7.**

It was noted throughout this inspection that special exception requests receive provisional approval through expedited reviews exercised by the chairperson or co-chair. Refer to Exhibit 38. NOTE: [REDACTED] and [REDACTED] gave the attached provisional approvals.

Dr. Hazlewood explained that he or his co-chairs make these provisional decisions and then these decisions are presented to the full IRB. I asked Dr. Hazlewood under which SOP do these provisional approvals fall under. He stated BRI's SOP 3.4 (Exhibit 22 page 15). I reviewed this SOP and found no reference to special exceptions.

8. **A letter dated 3-30-01 states that the IRB reviewed the new pump, [REDACTED] Pump Model [REDACTED] and full board approval was granted on 3-29-01. The meeting minutes dated 3-29-01 do not document full board review and final voting results of approval, FDA 483 #8.**

Refer to Exhibit 39 for a copy of BRI IRB letter dated 3-30-01. The meeting minutes dated 3-29-01 are attached as Exhibit 40.

9. **Expedited review approval was given to a change in protocol and informed consent form for study [REDACTED]. The revised protocol and informed consent form are not on file, FDA 483 #9.**

The expedited approval letter is attached as Exhibit 41. The study protocol and informed consent form are attached as Exhibits 9 and 10. These represent the original documents. Ms. Mullins stated that the revised protocol and informed consent form were not on file.

### Discussion with Management

At the conclusion of the inspection an FDA 483, Inspectional Observations, was issued to and discussed with Dr. Carlton Hazlewood, IRB Chairman. Also present were Ms. Mullins, IRB Administrator, Ms. Bradley, BRI Compliance Officer, [REDACTED] IRB member, and [REDACTED] IRB member.



NOTE: Prior to the discussion Dr. Hazlewood asked if it was possible to record the discussion. I stated that it would be acceptable if a duplicate copy of the recorded discussion was provided to me. Attached as Exhibit 42 is a cassette tape.

We read each FDA 483 observation. In response to FDA 483 #1, 2 and 3, Dr. Hazlewood acknowledged the minutes contained the word "study." He stated that it was never considered to be a clinical study of any IND. He said the IRB did not consider it to be a study associated with an IND. He mentioned that Dr. Burzynski submitted the study protocol and consent form because he wanted to see if the IRB had a problem.

Dr. Hazlewood stated that it was considered to be a procedure in Dr. Burzynski's private practice and that the submission to the IRB was to see if there were any clinical issues. [REDACTED] stated that it was (protocol and consent form) for the IRB's information only.

Dr. Hazlewood stated that it was not a study protocol. I explained that without reviewing the study protocol and informed consent form I could not conclude that it was not intended to be a study. I asked again for a copy of the study protocol and informed consent form. Dr. Hazlewood stated that they did not have a copy. [REDACTED] stated that it was part of Dr. Burzynski's clinical practice. He then asked others present if the study protocol and consent form were on a CD. Those present did not answer with an acknowledgement that the study protocol and consent form were on CD.

In response to FDA 483 #4 and #5, Dr. Hazlewood stated that he could not comment on the observations at this time. That he would have to look into it.

In response to FDA 483 #6, Dr. Hazlewood stated that the protocols were not submitted because these studies had been closed by the FDA. I acknowledged this action but explained that because patients had been enrolled into these protocols that the IRB should have reviewed and approved the study protocols.

In response to FDA 483 #7, I explained that in my opinion that expedited approvals for special exceptions did not fall under the conditions as set forth under 21 CFR 56.110. But because CDER in their letter dated 8-14-97 (Exhibit 43) had specified a procedure for granting exceptions to protocols that this procedure should be addressed in the IRB's SOP's. Dr. Hazlewood stated that the SOP would be revised.

In response to FDA 483 #8, Dr. Hazlewood asked Ms. Mullins if the minutes mentioned the pump. She said no.

In response to FDA 483 #9, Dr. Hazlewood stated that he would get that changed, i.e. obtain the revised documents.

To conclude Dr. Hazlewood stated that they would respond to the inspectional observations in writing.



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Investigator  
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**Exhibits:**

- 1- Protocol [REDACTED] and informed consent form
- 2- IRB correspondence dated 3-2-00
- 3- IRB correspondence dated 8-24-00
- 4- IRB correspondence
- 5- IRB meeting minutes dated 10-12-00
- 6- IRB correspondence dated 12-11-00
- 7- IRB approval to amendments
- 8- IRB approval to patient education package
- 9- Protocol [REDACTED]
- 10- Informed consent form
- 11- IRB's annual approval and progress report
- 12- IRB correspondence
- 13- IRB approval to patient education package
- 14- Protocol [REDACTED]
- 15- Informed consent form
- 16- IRB expedited approval
- 17- IRB correspondence
- 18- IRB correspondence
- 19- IRB correspondence and progress report
- 20- IRB meeting minutes
- 21- IRB roster
- 22- IRB policies and procedures
- 23- IRB meeting minutes
- 24- IRB meeting minutes
- 25- Dr. Burzynski memo
- 26- Burzynski clinic memo dated 8-23-99
- 27- Burzynski clinic memo dated 9-7-99
- 28- List of study protocols obtained during the previous FDA inspection
- 29- Current list of study protocols
- 30- [REDACTED] list of special exceptions
- 31- [REDACTED] request
- 32- [REDACTED] request

- 33- Signature log
- 34- FDA 1572
- 35- IRB correspondence
- 36- [REDACTED] enrollment
- 37- Meeting minutes dated 7-20-96
- 38- Special exception requests and provisional approvals
- 39- BRI IRB letter dated 3-30-01
- 40- Meeting minutes dated 3-29-01
- 41- IRB expedited approval
- 42- Cassette tape of discussion with management
- 43- CDER letter dated 8-14-97