

EIR: Stanislaw R. Burzynski, M.D., Ph.D.
Burzynski Research Institute
9432 Old Katy Rd.
Houston, TX. 77055

8/6-10/01
Joel Martinez

Summary of Findings

Present directed inspection of this clinical investigator was conducted per request, dated June 7, 2001, from HFD-47, Good Clinical Practice Branch II, Division of Scientific Investigations, CDER (FACTS #213702). The purpose of this inspection was to determine this clinical investigator's compliance with applicable regulations. The inspection was conducted under CP7348.811, Clinical Investigators.

Inspectional coverage was given to study protocols under IND (b) (4) (Antineoplastons AS2-1 & A10 injections) and IND (b) (4) (Antineoplaston AS2-A10 capsules). Specific coverage was given to patients reported as complete responders (CR) and partial responders (PR) in the firm's annual report(s).

Significant objectionable conditions/practices included but were not limited to the following:

- Enrollment of subjects into antineoplaston study protocols prior to the protocol-specified interval following prior chemotherapy and/or radiation therapy.
- Failure to report all serious adverse events (SAE's) and adverse events (AE's) to the agency and/or IRB.
- Failure to follow proper informed consent procedures.
- Failure to maintain adequate drug accountability records.
- Discrepancies between the case report forms and source documents.

At the conclusion of the inspection an FDA 483, Inspectional observations, was issued to and discussed with the clinical investigator.

No samples were collected.

History of Business

Burzynski Research Institute (BRI), Inc., 9432 Old Katy Rd., Houston, TX. 77055 is under the direction of Stanislaw R. Burzynski, M.D., Ph.D. Dr. Burzynski is a holder of two IND's.

1. IND (b) (4) Antineoplaston A10 and AS2-1 intravenous injections.
2. IND (b) (4) Antineoplaston A10 & AS2-1 capsules.

Dr. Burzynski has (b) (4) phase II studies under IND (b) (4) and approximately (b) (4) clinical studies under IND (b) (4)

In May 1984 a Permanent Injunction was ordered on the Burzynski Cancer Research Institute and Dr. Burzynski. Refer to Exhibit 1 for a copy of the final judgment.

In 1993 the National Institutes of Health (NIH) filed an IND but was withdrawn in July 1995. Reportedly, Dr. Burzynski declined to supply antineoplastons.

In February 1996 in response to FDA inquiries about patients being treated off protocol without the agency's knowledge and following a federal judge's order (that no patient may be treated outside a protocol), Dr. Burzynski began to file the first of (b) (4) study protocols. Patients (b) (4) antineoplaston treatment were entered into a special protocol called CAN-01.

In August 1997 Dr. Burzynski's annual reports noted (b) (4) in (b) (4) patients on the breast cancer study (Protocol BR-12) and (b) (4) in (b) (4) patients on (b) (4). For non-small cell lung cancer (Protocols LA-3, LA-4, LA-5, and LA-6), Dr. Burzynski's annual report noted (b) (4) in (b) (4) patients on protocol and (b) (4) patients entered under a (b) (4). Because of these (b) (4) reported responses in these two groups of individuals, (b) (4) for patients with breast and non-small cell lung cancer. Refer to Exhibit 2.

Persons Interviewed and Individual Responsibility

It should be noted that on 7-30-01, I called the BRI and asked to speak with Dr. Burzynski to notify him of our intent to conduct a data audit inspection. His secretary (b) (7)(C) stated that he was with a patient but that she would leave a message with him. I explained to her that we would like to begin the inspection Monday (8-6-01) on/about 9:00am. She said OK. On that same day (b) (7)(C) called to ask if we could postpone the audit until 8-20-01. I explained to her that because of travel arrangements that had already been made that would not be possible. She asked if that meant "NO." I said yes.

On 7-31-01 I received a message from Barbara Tomaszewski, Business Manager for BRI. Her phone message stated that the person in charge of clinical trial documentation is out of the country and would not return until 8-20-01. I returned her telephone call and left two messages. She then telephoned Dwight Herd, SCSO, SA-RP. Dwight Herd, SCSO and I then had a telephone

conversation with Ms. Tomaszewski. As a result of the telephone conversation and consultation with Dr. U of DSI, we decided to fax a list (**Exhibit 3**) of those patients that had been reported as PR's (partial responders) and CR's (complete responders). The list was then faxed to BRI prior to the inspection. This was done to facilitate BRI's compilation of the patient files, source documents, and related study records and to facilitate the absence of this individual that was out of the country.

On the first day of the inspection, the FDA inspection team consisted of myself, Patrick D. Stone, Investigator, Hou-RP, and Khin Maung U, M.D., Medical Officer, Good Clinical Practice Branch II (HFD-47).

Credentials were shown to and an FDA 482, Notice of Inspection, was issued to Dr. Stanislaw R. Burzynski, Principal Investigator. Refer to **Exhibit 4** for a list of individuals also present at the initiation of the inspection.

Dr. Burzynski is the principal investigator for all clinical studies and most responsible individual. His CV is attached as **Exhibit 5**. He provided organizational charts (**Exhibit 6**) for the following:

1. Organization of Medical Departments.
2. Organization of the Department of Medical Documentation and Clinical Trials Supervision.
3. Organization of the Department of Medical Data Processing Management, Statistics and Clinical Trials

Dr. Burzynski has three licensed physicians. They include:

- Robert I. Lewy, M.D.- Refer to **Exhibit 7** for his CV.
- Marc Bestak, M.D.- See **Exhibit 8** for his CV.
- Robert A. Weaver, M.D.- See **Exhibit 9**.

All other M.D.'s listed in the organizational charts are not licensed. Their CV's/resumes are attached as **Exhibit 10**.

Dr. Burzynski stated that he currently has (b) (4) active protocols. He also mentioned that one protocol (CAN-01) has been terminated/closed.

I first asked Dr. Burzynski for the source of his patients. He stated that the majority of prospective patients that present to the clinic do not qualify for entry into a study protocol, therefore, are treated with traditional FDA approved drugs/treatments, i.e. radiation or chemotherapy. Dr. Burzynski then added that approximately (b) (4) of his patients are treated with antineoplastons. He stated that prospective patients learn of his clinic by word of mouth or are referred by

other patients. Dr. Burzynski stated that he currently has (b) (4) patients. Dr. Burzynski stated that he does not advertise for patients to participate in his clinical trials.

I asked Dr. Burzynski to describe an individual's qualification into a clinical study. He stated that a selected patient is asked to provide medical records to include previous oncology reports, tissue slides, scans/films, and a description of previous treatments. Dr. Burzynski stated that an "associate M.D." conducts the telephone interview and performs the initial review of the medical records. Dr. Burzynski stated that he has approximately (b) (4) associate M.D.'s on staff. These associate M.D.'s are listed in the organizational charts. If the patient appears to qualify after the initial review, the patient is asked to come to the BRI for a physical examination and further evaluation by 3 physicians that include a research physician, a senior physician, and Dr. Burzynski. Dr. Burzynski stated that he makes the final decision with respect to one's participation in an antineoplaston clinical study. Dr. Burzynski also stated that if a patient does not qualify or meet the criteria for a study protocol they may enter a clinical study through a special exemption from the FDA. He stated that a non-qualifier may also be referred to the (b) (4)

I then asked Dr. Burzynski to describe the informed consent process. He stated that an associate M.D. reads and explains the informed consent form to the patient and discusses the details of the clinical study. The patient is also asked to read the informed consent form. Dr. Burzynski stated that after the informed consent form is fully understood by the patient and the individual has no other questions, he will then explain the possible adverse events with the patient. After the adverse events are understood the patient and Dr. Burzynski sign the document. The patient is then started on the protocol. BRI's standard operating procedure for obtaining and documenting informed consent is attached as Exhibit 11.

I asked Dr. Burzynski to define an adverse event. He stated that an adverse event is any symptom/sign that occurs during the administration of the drug substance. He added that if a condition/adverse event is present prior to administration of the drug substance and then the condition presents itself after the administration of the drug substance during the study then that would not be considered to be an adverse event.

I asked Dr. Burzynski what other treatments are offered/done/given at this clinic. He stated that all other treatments are FDA approved treatments such as chemotherapy and radiation therapy.

I then asked Dr. Burzynski to describe the study procedures once the informed consent form is signed. Dr. Burzynski stated that a patient remains at BRI for (b) (4) days. He stated that during these (b) (4) days, treatment is administered under constant physician care. In addition the patient and/or relative are trained on

how to program the IV pump, load the IV pump with the proper amount of study medication, and self-administer the study medication upon their return to their residence. According to Dr. Burzynski the patient is seen by a senior M.D. during this (b) (4) day period.

When a patient returns home, a monitoring nurse calls the patient on a (b) (4) basis. Once a patient is released to return home, they are required to receive (b) (4) evaluations. Dr. Burzynski stated that either the patient will return to BRI for an evaluation by a physician knowledgeable about the study or the local co-investigator (patient's physician) will perform the (b) (4) evaluation. Dr. Burzynski stated that BRI's discharge summary is sent to the co-investigator. They are also required to sign an FDA 1572, Statement of Investigator.

I asked Dr. Burzynski how does he assure himself that all adverse events are being reported and/or captured. He stated that when a patient returns home his staff is in (b) (4) telephone contact with the patient. The patient is asked how they have been feeling and for any side effects. All side effects are evaluated for possible relationship with the study medication or if the side effect is attributed to the individual's disease condition. He added that the patient's co-investigator also monitors the patient's progress.

I asked Dr. Burzynski about the patient's dosage level. He stated that the amount of study drug to be received/administered to the patient is calculated on a (b) (4) basis. The patient is sent a (b) (4) supply. The study medication is sent at (b) (4). I asked how is the medication delivered to the patient. He stated that the study medication is sent via (b) (4).

I asked Dr. Burzynski for the duration of the patient's participation in the clinical study. He stated that they monitor and evaluate the patient's response as per the requirements of the study protocol. Dr. Burzynski explained that if a patient is found to be a complete responder then they advise the patient to continue intravenous treatment for an additional (b) (4). After (b) (4) the patient is discontinued from intravenous treatment. He then stated that if a patient is declared to be a partial responder, the individual is placed on maintenance therapy with A10 & AS2-1 (b) (4). Dr. Burzynski did not specify the time period the patient remains on maintenance therapy but did state that if a patient shows disease progression they are discontinued.

I then asked Dr. Burzynski about the protocol exceptions. He stated that these protocol exceptions are submitted to the FDA for approval. He mentioned protocol exceptions not requiring prior FDA approval include those individuals that have a (b) (4) the protocol requirement and (b) (4) different types of malignancies. He added that all protocol exceptions are submitted to the IRB daily for expedited review.

Dr. Burzynski then stated that with respect to foreign studies there are currently (b) (4) studies in (b) (4). Reportedly, these (b) (4) studies are under the supervision of the (b) (4) government. He also stated that in the past there have been single M.D.'s treating single patients in the (b) (4) but that currently there is no one. He stated that there are no clinical studies being conducted in the (b) (4).

Dr. Burzynski said that the informed consent document will be translated for a (b) (4) patient but that they will sign the English version. He stated that he has individuals on staff that can translate informed consent forms into (b) (4) different languages. For example, (b) (4).

Dr. Burzynski stated that survival data is only determined/calculated for certain protocols. He said that for other protocols there is not enough data to calculate survival data.

He also mentioned that Karnofsky score data has not been required by the FDA to be reported but that he could present the data if required.

On 8-7-01, Dr. Steven Hirschfeld, M.D., Ph.D., Medical Officer, HFD-150 joined the FDA inspection team. He presented and issued an FDA 482, Notice of Inspection, to Dr. Burzynski.

On 8-8-01, the FDA inspection team was joined by the following:

- Larry E. Kun, M.D.
- James M. Provenzale, M.D.
- Sarah A. Taylor, M.D.

They presented credentials and an FDA 482, Notice of Inspection, was issued to Dr. Burzynski.

The following individuals accompanied us through the inspection and supplied relevant information and also identified individuals that could provide relevant information:

- Jaroslaw Paszkowiak, M.D., Supervisor, Department of Medical Documentation & Clinical Trials Supervision.
- Frank Coffey, Head of Department of Quality Assurance
- Barbara Burkhardt, Quality Assurance Monitor
- Dawn Bradley, Quality Assurance Regulatory Assistant

NOTE: Dr. Burzynski was available throughout the week to address any queries from the FDA inspection team.

Any FDA correspondence should be addressed to Dr. Burzynski.

(b) (4) this inspection (b) (7)(D) relative to BRI's compliance with regulations, actions taken by IRB members that could represent a conflict of interest, BRI's financial practices that represent billing for the study medication, and possible fabrication/adulteration of source documents. (b) (7)(D)

(b) (7)(D)

(b) (7)(D) Exhibit 13.

Refer to

(b) (7)(D) copies of IRB provisional approvals for compassionate exceptions for Protocol BT-12 patients. Refer to Exhibit 14. (b) (7)(D) these compassionate exceptions were approved and signed by Drs. Gabor Jurida and Barbara Szymkowski. These two individuals are listed as research associates under the Department of Pediatric Oncology and Department of Internal Medicine, respectively. (b) (7)(D) possible conflict of interest by an IRB member.

(b) (7)(D) a copy of a letter from an organization known as "Cancer Coalition-BVO" (Burzynski's Victims Organization). Refer to Exhibit 15. It appears that this letter was sent to Burzynski patients. (b) (7)(D)

(b) (7)(D) "Dear Patient" letter from Ms Barbara Tomaszewski, Manager in response to the Cancer Coalition letter. Refer to Exhibit 16.

(b) (7)(D) progress notes for patient (b) (7)(C) See Exhibit 17. (b) (7)(D)

(b) (7)(D)

(b) (7)(D) demonstrate that original progress notes are routinely changed, destroyed, and replaced in patient files with the revised progress notes. Progress notes of 11-2-00 (Exhibit 17 page 7) appear to have been significantly changed from:

"The patient is currently on treatment and receiving Antineoplastons A10 (b) (4) (b) (4) and AS2-1 (b) (4). The patient is tolerating it well and does not reports an side effect such as headache, dizziness, nausea, vomiting, diarrhea, constipation, pain, fever or chills an seizure activity."

To: "Patient is in the Hospital for evaluation of Hematuria and change in mental status. He is scheduled to have MRI of the brain today. He will remain off ATNP at this time."

(b) (7)(D) protocol (b) (4) entitled (b) (4)
 (b) (4)
 (b) (4) dated (b) (4). A statement of informed consent is also included with the protocol. Refer to Exhibit 18. He also provided a patient list for this (b) (4) protocol. Refer to Exhibit 19.

(b) (7)(D) patient records demonstrate that BRI is charging patients for the study medication. For example:

- A Treatment Billing Agreement (Exhibit 20) for patient (b) (7)(C)
- A Dr. Burzynski physician notice that states "*Medicare is likely to deny payment for Antineoplaston treatments and related IV supplies. *** Medicare does not pay for this because it is a treatment that has yet to be approved by the FDA, and because Medicare usually does not pay for related supplies.*"

The form also consists of the following statement: "*I have been notified by my physician that he believes that, in my case, Medicare is likely to deny payment for the services identified above, for the reason stated. If Medicare denies payment, I agree to be personally and fully responsible for payment.*" The form is signed by Patient (b) (7)(C). See Exhibit 21.

- Progress notes dated 4-21-97 for Patient (b) (7)(C) (Exhibit 22) document that the patient's father is angry "because he was asked to pay his bills, which he did not pay for a long time and he was told that he did not comply with the treatment protocol."
- A Non-face to face evaluation and management record dated 11-15-00 for Patient (b) (7)(C) (Exhibit 23) documents that the patient was off dosage for sometime as the patient could not afford it (antineoplaston treatment). The patient states "I said I was on the ANPA TX when I wasn't because I didn't want to be cancelled from the ANPA program."

(b) (7)(D)
 as Attachment 1.

Inspectional Observations

The following objectionable conditions/practices were observed during this inspection:

1. Protocol Violations:

Subjects were started on antineoplaston treatment prior to the protocol-specified interval following prior chemotherapy and/or radiation therapy.

Protocol Patient ID	Prior therapy	Last Date of Prior Therapy	Date Antineoplastons started	Interval
(b) (7)(C) BT-11 (b) (4)	Etopoxide	(b) (4)	4-24-98	(b) (4)
(b) (4)	Sterotactic radiation	(b) (4)	11-10-99	(b) (4)
(b) (7)(C) BT-22 (b) (4)	Etopoxide	(b) (4)	4-30-99	(b) (4)
(b) (7)(C) PA-02 (b) (4)	Combined Chemotherapy & Radiation	(b) (4)	8-5-99	(b) (4)

(b) (7)(C) BT-11 (b) (4) Refer to Exhibit 24.

(b) (7)(C) (b) (4) Refer to Exhibit 25.

(b) (7)(C) BT-22 (b) (4) Refer to Exhibit 26.

(b) (7)(C) PA-02 (b) (4) Refer to Exhibit 27.

2. Not all serious adverse events and adverse events are reported to FDA and IRB. Examples are shown in the following table.

Protocol Patient ID	Date	Serious Adverse Events or Adverse Events
(b) (7)(C) BT-07 (b) (4)	10-31-00	Subject became lethargic, with diarrhea and blood in the urine, and was hospitalized during which significant hematuria persisted
(b) (7)(C) BT-08 (b) (4)	12-4-00	Cystoscopy shoed severe hemorrhagic cystitis and necrotic bladder mucosa
(b) (7)(C) BT-11 (b) (4)	6-17-00	Left subclavian vein thrombosis
(b) (7)(C) BT-11 (b) (4)	8-14-00	Subject experienced shortness of breath, and his chest X-ray showed suspicious consolidations in right lung base
(b) (7)(C) BT-11 (b) (4)	8-20-00	Hospitalized, bronchoscopy and lavage revealed <i>Pneumocystis carinii</i>
(b) (7)(C) BT-11 (b) (4)	2-2-97	Pancreatitis; antineoplastons were discontinued for one week and restarted on 2-28-97.
(b) (7)(C) BT-11 (b) (4)	5-18-00	Patient developed pancreatitis again and required antineoplastons to be discontinued permanently on 5-10-97
(b) (7)(C) (b) (4)	5-20-00	Central line sepsis (blood culture positive for <i>Staphylococcus aureus</i>) requiring hospitalization
(b) (7)(C) (b) (4)	9-30-99	Broviac catheter had to be removed
(b) (7)(C) BT-21 (b) (4)	8-3-98	Hospitalized with fever for pneumonia and sepsis, deteriorated, requiring transfer to ICU. Subject expired on 10-17-99.
(b) (7)(C) BT-22 (b) (4)	8-3-98	Hospitalized for fever, hypotension, central line sepsis; subject also developed an aspiration pneumonia in hospital.
(b) (7)(C) BT-22 (b) (4)	6-26-99	Cushingoid features, steroid myopathy
(b) (7)(C) BT-22 (b) (4)	9-13-99	Renal acidosis requiring daily treatment with sodium bicarbonate
(b) (7)(C) BT-22 (b) (4)	10-4-99	Hypertension, requiring medication, e.g. Vasotec
(b) (7)(C) BT-22 (b) (4)	10-4-99	Venous thrombosis in left arm confirmed by venogram

	10-7-99 10-29-99 11-11-99	Central line sepsis, blood culture grew coagulase negative Staphylococcus that required treatment with Vancomycin Diarrhea with stool cultures positive for Clostridium difficile for which the subject was treated with Vancomycin
(b) (7)(C) LY-06 (b) (4)	9-19-99 9-22-99	Shortness of breath Lung biopsy revealed fibrosis of lung for which the subject was hospitalized and required Oxygen. The subject died on 10-1-99.
(b) (7)(C) (b) (4)	8-11-97	Occlusion of both subclavian veins
(b) (7)(C) UP-02 (b) (4)	7-3-98	Hospitalized for septic shock (fever, hypotension), was intubated and placed on ventilator the next morning and died at noon 7-4-98

(b) (7)(C) BT-07 (b) (4) Refer to Exhibit 28.

(b) (7)(C) BT-08 (b) (4) Refer to Exhibit 29.

(b) (7)(C) BT-1 (b) (4) Refer to Exhibit 30.

(b) (7)(C) BT-11 (b) (4) Refer to Exhibit 31.

(b) (7)(C) BT-15 (b) (4) Refer to Exhibit 32.

(b) (7)(C) BT-21 (b) (4) Refer to Exhibit 33. NOTE: The date of 3-8-98 was inadvertently cited on the FDA 483. The correct date is 8-3-98.

(b) (7)(C) BT-22 (b) (4) Refer to Exhibit 34. NOTE: The correct initials are (b) (7)(C). The FDA 483 cite has the initials of TGD.

(b) (7)(C) LY-06 (b) (4) Refer to Exhibit 35. NOTE: The date of 9-19-99 was inadvertently cited on the FDA 483. The correct date should be 9-15-99.

(b) (7)(C) (b) (4) Refer to Exhibit 36.

(b) (7)(C) UP-02 (b) (4) Refer to Exhibit 37.

BRI's standard operating procedures for the routine adverse experience reporting and reporting of serious adverse experiences are attached as Exhibit 38. It should be noted that an AE or SAE should be reported regardless of causality. During this inspection Dr. Burzynski prepared a memorandum (Exhibit 39) to address notification of serious adverse events.

3. Special exception treatment request (b) (4) dated 7-31-97 for (b) (7)(C) -PR-04 (b) (4) was approved based on the incorporation of certain statements into the consent form. Refer to Exhibit 40. The consent form signed by (b) (7)(C) (Exhibit 41) did not incorporate these statements. The statements included:

- (b) (4) patients with renal cell carcinoma who received antineoplastons had a response.

- (b) (4) patients with prostate cancer receiving antineoplaston infusions had a response.
4. Special exception treatment request (b) (4) dated 8-28-97 for (b) (7)(C)(b) (4) (b) (4) was approved based on the incorporation of certain statements into the consent form. Refer to Exhibit 42. The consent form (Exhibit 43) that Pt. (b) (7)(C) signed did not incorporate these statements that included:
- An awareness to the patient that (b) (4) is intended to measure response.
 - To date there have been (b) (4) from (b) (4) patients on this protocol.
 - (b) (4) in (b) (4) patients on Special Exception.
5. Failure to keep adequate drug accountability records. For example:

To evaluate BRI's drug accountability records and practices, I randomly selected lots of study medication from their Drug Release Record (Exhibit 44). This record was provided during the inspection. Dr. Paskowiak provided the referenced drug accountability records.

- A random selection of Lot 258C (A10 capsules) revealed that (b) (4) capsules were received at BRI (Exhibit 44 page 2) on 2-9-01. One accountability record accounts for (b) (4) capsules while a second accountability record accounts for (b) (4) capsules. Refer to Exhibit 45.
- Random selection of Lot 058B (AS2-1 capsules) revealed that (b) (4) capsules were received at BRI (Exhibit 44 page 2) on 1-10-01. Drug accountability records account for (b) (4) on one database and (b) (4) in a second accountability record. Refer to Exhibit 46.
- Random selection of Lot 823-1 (A10 500 ml bags) show that BRI received (b) (4) bags (Exhibit 44 page 6). Accountability records account for only (b) (4) NOTE: The FDA 483 inadvertently cited (b) (4) The correct number is (b) (4)

Mr. Noor Mangal, Shipping/Receiving employee determined that there were (b) (4) bags in current inventory. He counted the IV bags in my presence. Dr. Paszkowiak determined that the database accounted for (b) (4) bags. An additional (b) (4) bags had been sent to patients but had not been entered into the database. The BRI's in-house clinic drug accountability

record (Exhibit 47) accounted for (b) (4) bags. As a result (b) (4) IV bags are accounted for and the firm could not account for (b) (4) IV bags.

- BRI records for Lot 809 (A10 IV bags) show that (b) (4) bags were received. See Exhibit 44 page 4. Accountability records can account for (b) (4) bags Exhibit 48.
- Receipt records for Lot 199 (AS2-1) show that (b) (4) bags were received. See Exhibit 44 pages 4 and 5. Accountability records can only account for (b) (4) See Exhibit 49.

6. Failure to address and resolve patient overdoses documented in BRI query reports to determine the reason for the possible overdose and to take corrective actions to prevent recurrence. For example:

- (b) (7)(C) BT-07 (b) (4) query dated 11-8-00 (Exhibit 50).
- (b) (7)(C) BT-11 (b) (4) query dated 4-3-01 (Exhibit 51).
- (b) (7)(C) BT-11 (b) (4) query dated 8-7-01 (Exhibit 52).

7. Patient (b) (7)(C) BT-07 (b) (4) was observed to be receiving (b) (4) (b) (4) while on study.

Exhibit 53 page 1 shows the patient's dosage and treatment days for intravenous A10 and AS2-1. Treatment occurred from 12-2-97 to 3-16-98. Dr. Burzynski's progress notes, dated 3-11-98 (Exhibit 53 page 2), state "Without our office's knowledge, the patient (b) (4) (b) (4) which improved her condition temporarily." However it should be noted that a (b) (4) fax transmittal form dated 1-13-98 (Exhibit 53 page 3) from the patient's husband to the BRI informs the BRI that the patient's physician recommends (b) (4) (b) (4). Also a (b) (4) Consultation report dated 1-7-98 (Exhibit 53 pages 4 and 5) documents that the patient's husband is interested in (b) (4) (b) (4).

8. Inadequate/Inaccurate Record-keeping:

- a. There are discrepancies between the case report forms and the source documents for the following subjects:

Protocol Patient ID	Information of CRF	Information on Source Document
(b) (7)(C) BT-17 (b) (4)	Withdrawn on 11-27-96; Reason- Patient request	Patient was withdrawn with (b) (4) findings (6-18-96 vs 9-30-96) suggestive of recurrent tumor, <u>Exhibit 54</u> .
(b) (7)(C) BT-13 (b) (4)	Withdrawn 10-9-99	Patient continued on study until 11-9-99, <u>Exhibit 55</u> .

(b) (7)(C) BT-20 (b) (4)	Withdrawn on 7-30-96; Reason- Patient request	Patient was hospitalized on 7-30-96 with grand mal seizures and antineoplaston dose was reduced. Then, the patient decided to stop antineoplaston permanently. <u>Exhibit 56.</u>
(b) (7)(C) BT-22 (b) (4)	Withdrawn on 11-27-99; Reason-Worsening of clinical condition	Patient died the morning 11-27-99. <u>Exhibit 34.</u>
(b) (7)(C) LY-06 (b) (4)	Withdrawn on 12-29-99; Reason- Patient request	On 12-28-99, patient's abdominal CT of 11-23-99 was reported with splenomegaly and patient was recommended on 12-29-99 to undergo splenectomy and stop antineoplaston treatment. <u>Exhibit 57.</u>
(b) (7)(C) (b) (4) (b) (7)(C) UP-02 (b) (4)	Patient died on 11-27-97	Patient died on 21-27-97. <u>Exhibit 58.</u>
	Withdrawn on 7-4-98; Reason- Worsening of clinical condition	Patient was hospitalized in ICU on 7-2-98 for bacterial sepsis and died on 7-4-98. <u>Exhibit 59.</u>

b. Cross-outs and additions were made in source documents. For example,

In progress notes of Subject (b) (7)(C) BT-07 (b) (4) dated 11-3-00 is the statement "The patient will remain off antineoplastons at this time." This was crossed out and replaced with the sentence "The patient will discontinue antineoplastons permanently." This alteration was made despite many subsequent progress notes that contain the sentence, "The patient will continue to be off antineoplastons at this time." Refer to Exhibit 28.

9. The subject case report forms do not always contain complete and concurrent patient information such as:

a) (b) (4) tumor measurements for patients (b) (7)(C) BT-11 (b) (4) or (b) (7)(C) BT-11 (b) (4) do not contain the tumor measurements that were done by the consultants.

- (b) (7)(C) BT-11 (b) (4): The case report form Tumor measurements are attached as Exhibit 60. Dr. Schellinger's case review is attached as Exhibit 61.
- (b) (7)(C) BT-11 (b) (4) The case report form Tumor measurements and progress notes are attached as Exhibit 62. The consultant's assessments are attached as Exhibit 63.

Dr. Burzynski stated that he has been contracting consultant radiologists since approximately 1996. I asked Dr. Burzynski if he reports the consultant radiologists' evaluations, i.e. tumor measurements. He said no. I explained to Dr. Burzynski that all tumor assessments should be reported in the case report forms. He stated that he was unaware of a requirement to report the consultant's tumor measurements. I explained that to include the consultant's assessments would enable complete reporting of all assessments in the case report form. He stated that he understood.

- b) The case report forms for patients (b) (7)(C) BT-23 (b) (4) (Exhibit 64), (b) (7)(C) BT-23 (b) (4) (Exhibit 65), and (b) (7)(C) BT-09 (b) (4) (Exhibit 66) do not contain inclusion/exclusion criteria entries.

Discussion with Management

At the conclusion of the inspection an FDA 483, Inspectional Observations, was issued to and discussed with Dr. Burzynski. Also present were Dr. Paszkowiak, Mr. Coffey, Ms. Burkhardt, Ms. Bradley, and Barbara Tomaszewski, Business Manager.

I first explained that the list of inspectional observations should not be meant to be all inclusive as we had not reviewed all patient files. Dr. Burzynski stated that he understood. Because the inspectional observations cited specific patient examples, I explained that they should look beyond the inspectional observation when attempting to implement corrective measures and not limit the applicability of corrective actions to the examples cited in each response.

I then read each FDA 483 observation. In response to FDA 483 #1, Dr. Burzynski stated that the FDA allows the acceptance of entry into protocols of individuals other than what is in the protocol. In other words, FDA allowed the entry of individuals into study protocols even though they did not meet the protocol criteria. Dr. Burzynski also mentioned that FDA allowed a special exemption for those patients listed as part of the inspectional observation to enter a study protocol. Dr. Burzynski stated he was sure they had documentation on file to cover these patients' enrollment, i.e. patients listed on the inspectional observation.

In response to FDA 483 #2, Dr. Burzynski stated that an SAE is reported only if the event is related to antineoplastic treatment/administration, i.e. possibly or probably related to the study medication. He stated that if an SAE or AE is related to other causes then that SAE/AE is not reported. He added that SAE's/AE's are usually related to the individual's disease condition and/or previous treatments. Dr. Burzynski then committed to reporting all AE's/SAE's in the future. It should be noted that BRI's standard operating procedures CS-002 and CS-003 (Exhibit 38) require to report AE's and SAE's regardless of causality.

In response to FDA 483 #3 and #4, Dr. Burzynski stated that they always incorporate what is asked of them by the FDA and that he would have to review the informed consent documents.

In response to FDA 483 #5, Dr. Burzynski explained that the individual primarily responsible for the inventory of the study medication was out of the country and that he was the individual that could provide an accurate accountability. I asked Dr. Burzynski in his absence who is responsible for the drug accountability. I

explained that shipments (of study medication) continue in his absence, therefore, other individuals should be trained and have full knowledge about the maintenance of study medication accountability. I explained to Dr. Burzynski that while this individual is gone and because this individual will not be present 100% of the time he should have a back up person responsible for the accountability. He stated that he understood.

Because during the review of accountability records I observed one patient ^{(b) (7)(C)} (b) (4) to be listed under the "IND#" column as (b) (4) (Exhibit 49), I asked Dr. Burzynski about this (b) (4) study protocol. I explained that I had seen in one of the accountability records that a patient was listed under the IND column as being enrolled under an (b) (4) protocol. I asked Dr. Burzynski if (b) (4) was a research study. He said these patients are not in clinical trials. He said they are treated with standard chemotherapy regimens. I asked Dr. Burzynski what did (b) (4) stand for. He said the (b) (4) meant Group (b) (4). The (b) (4) stood for patient and (b) (4) stood for various treatments. I asked what treatments did he mean. He said any chemotherapy and specifically mentioned (b) (4) (b) (4). He said (b) (4) of these patients receive chemotherapy. I asked Dr. Burzynski if there was a study protocol. He said there were many protocols according to the patient's treatment. I asked Dr. Burzynski if he is collecting data (to support of a future submission). He said he is collecting data because he wants to know how many survive and how they die. He said he wanted to conduct standard treatment(s) in a "more scientific manner" in order to document patient response to "traditional" medical practice.

I asked Dr. Burzynski if he obtained informed consent from these individuals and if so if he had a blank copy of the informed consent form. He said patients do sign a consent form but declined to provide a copy as he felt that this (b) (4) protocol was not within the scope of this data audit inspection. He said this is a general practice procedure and not clinical research, therefore, fell under private practice. I asked Dr. Burzynski how many individuals had been enrolled in this (b) (4) protocol. He said he could not give an exact figure but would approximate about (b) (4) individuals.

Finally, I asked Dr. Burzynski if the (b) (4) dosage involve capsules, tablets, intravenous administrations. He said it involves (b) (4) and (b) (4) administrations.

It should be noted that Patient ^{(b) (7)(C)} was also on antineoplaston treatment. A "Medicine Inventory Form" (Exhibit 68) documents shipments of A10 and AS2-1 to the patient. In addition, progress notes, dated 11-2-00, document that this patient under the (b) (4) protocol was taking (b) (4) (b) (4). Refer to Exhibit 68. A database listing (Exhibit 69) provided by Dr. Paszkowiak shows other patients on the (b) (4) protocol. Also note that this database listing (Exhibit 69 pages 7 and 9) documents patients on two other protocols, i.e. (b) (4) and IND# (b) (4).


In response to FDA 483 #6, Dr. Burzynski stated that he would have to find out why he was not alerted and that these queries should have been corrected immediately. He said that he addresses a query on the same day it is received. That currently he had none pending on his desk referring to the one query dated 8-7-01. I explained that perhaps the one dated 8-7-01 was too soon to have been addressed but could not understand why he was not aware of it. I also explained that the two other queries were old enough that they should have been investigated to determine what exactly had happened with the overdose incident to prevent a recurrence.

In response to FDA 483 #7, Dr. Burzynski stated that he does not specifically remember this case. He added that the FDA does allow for individuals to receive (b) (4) while on study. He mentioned that they must have correspondence for this patient to have been able to receive (b) (4) while on study. He said that he was aware of a few cases like this one.

In response to FDA 483 #8, Dr. Burzynski explained that the last day of the study is defined as the day a patient receives his/her last dose. He said errors do occur and that errors will be corrected as soon as they are found. During the inspection (b) (7)(D) (b) (7)(D) (b) (7)(D) Refer to Exhibit 70.

In response to FDA 483 #9, Dr. Burzynski agreed with the observation and stated that he would begin to report the consultant's evaluations in the case report forms.

To conclude Dr. Burzynski stated that he appreciated the remarks and that he would implement corrections. He also stated that a written response would be submitted.


Joel Martinez
Investigator
Dal-DO/San Antonio Resident Post

Attachment 1- (b) (7)(D)
(b) (7)(D)

Exhibits:

- 1- May 1984 Final Judgment of Permanent Injunction
- 2- CDER correspondence dated 8-14-97

- 3- BRI organizational charts
- 4- List of people that assisted during the inspection
- 5- Dr. Burzynski CV
- 6- List of Complete and Partial Responders
- 7- Dr. Lewy CV
- 8- Dr. Bestak CV
- 9- Dr. Weaver CV
- 10- Associate M.D.'s CV's and resumes
- 11- SOP CS-001, Obtaining and Documenting Informed Consent
- 12- BRI correspondence dated 2-19-01
- 13- (b) (4) Notes for Patient Chart Review
- 14- IRB provisional approvals for compassionate exceptions
- 15- Cancer Coalitoin correspondence
- 16- Ms. Tomaszewski correspondence
- 17- Patient (b) (7)(C) progress notes
- 18- Protocol (b) (4)
- 19- List of patients under protocol (b) (4)
- 20- Treatmetn billin Agreement
- 21- Patient (b) (7)(C) HN-02- (b) (4) beneficiary agreement
- 22- BT-12-01 progress notes
- 23- Dr. Burzynski Non-face to face evaluation and management form
- 24- Patient (b) (7)(C) BT-11- (b) (4) History and Physical
- 25- Patient (b) (7)(C) BT-22- (b) (4) history and Physical
- 26- Patient (b) (7)(C) BT-22- (b) (4) History and Physical
- 27- Patient (b) (7)(C) PA-02- (b) (4) History and Physical
- 28- Patient (b) (7)(C) BT-07- (b) (4) progress notes
- 29- Patient (b) (7)(C) BT-08- (b) (4) records
- 30- Patient (b) (7)(C) BT-11- (b) (4) progress notes
- 31- Patient (b) (7)(C) BT-11- (b) (4) progress notes
- 32- Patient (b) (7)(C) BT-15- (b) (4) progress notes
- 33- Patient (b) (7)(C) BT-21- (b) (4) progress notes
- 34- Patient (b) (7)(C) BT-22- (b) (4) progress notes
- 35- Patient (b) (7)(C) LY-06- (b) (4) progress notes
- 36- Patient (b) (7)(C) (b) (4) records
- 37- Patient (b) (7)(C) UP-02- (b) (4) records
- 38- SOP CS-002, routine Adverse Experience reporting
- 39- Dr. Burzynski memo dated 8-7-01
- 40- HFD-150 fax dated 8-1-97
- 41- Patient (b) (7)(C) PR-04- (b) (4) informed consent form
- 42- HFD-150 fax dated 8-30-97
- 43- Patient (b) (7)(C) (b) (4) informed consent form
- 44- Drug Release Record
- 45- Batch 258C drug accountability record
- 46- Batch 058B- (b) (4) drug accountability record
- 47- Batch 823- (b) (4) drug accountability record
- 48- Batch 809- (b) (4) drug accountability record

- 49- Batch 199[REDACTED] drug accountability record
- 50- BRI discrepancy report dated 11-8-00
- 51- BRI Query Report dated 4-3-01
- 52- BRI Query report dated 8-7-01
- 53- Patient [REDACTED] BT-07 [REDACTED] records
- 54- Patient [REDACTED] BT-17 [REDACTED] records
- 55- Patient [REDACTED] BT-13 [REDACTED] records
- 56- Patient [REDACTED] BT-20 [REDACTED] records
- 57- Patient [REDACTED] LY-06 [REDACTED] records
- 58- Patient [REDACTED] [REDACTED] records
- 59- Patient [REDACTED] UP-02 [REDACTED] records
- 60- Patient [REDACTED] BT-11 [REDACTED] tumor measurements
- 61- Patient [REDACTED] BT-11 [REDACTED] records
- 62- Patient [REDACTED] BT-11 [REDACTED] tumor measurements
- 63- Patient [REDACTED] BT-11 [REDACTED] records
- 64- Patient [REDACTED] BT-23 [REDACTED] records
- 65- Patient [REDACTED] BT-23 [REDACTED] records
- 66- Patient [REDACTED] BT-09 [REDACTED] records
- 67- Patient [REDACTED] medicine inventory form
- 68- Patient [REDACTED] History and Physical
- 69- Drug accountability record
- 70- Dr. Burzynski memo dated 1-23-01