DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDINGS AND OPPORTUNITY TO EXPLAIN (NIDPOE)

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

James Vestal, M.D.
Urology Associates of North Texas
1001 Waldrop Drive, #708
Arlington, Texas 76012

Dear Dr. Vestal:

Between January 9 and 21, 2004, Mr. Marc Dickens and Mr. Toby Hill, representing the Food and Drug Administration (FDA or agency), conducted an investigation to review your conduct of the following clinical study:

> **Protocol #[redacted] entitled:** "A 12 Month, Open-Label, Fixed-Dose Study to Evaluate the Safety, Tolerance, Pharmacokinetics, and Endocrine Efficacy of Two Doses of LA-2580 45 mg in Patients with Advanced Prostate Cancer". This study of the investigational drug LA 2580 45 mg (leuprolide acetate) was performed for Atrix Laboratories, Inc.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights and welfare of the human subjects of those studies have been protected.

At the conclusion of the inspection, Mr. Dickens presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We have reviewed the inspection report, the documents submitted with that report, and your written response to the Form FDA 483 dated January 27, 2004. We do not find your response to be acceptable in addressing the matters under complaint, which are described below.

Based on our evaluation of the information obtained by the agency, the Center for Drug Evaluation and Research (the Center) believes that you repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational products as published under Title 21, Code of Federal Regulations (CFR), Parts 312 and 50 (copies enclosed) and that you have submitted false information in required reports to FDA or the sponsor (21 CFR 312.70).

This letter provides you with written notice of the matters under complaint and initiates an administrative proceeding, described below, to determine whether you should be disqualified from receiving investigational products as set forth under 21 CFR 312.70. A listing of the violations follows. The applicable provisions of the CFR are cited for each violation.

1. **You submitted false information to the sponsor in a required report [21 CFR 312.70]**

   As part of the protocol for this study, you, as the principal investigator, were required to submit the case report forms (CRFs) and other study documents to the sponsor within 30 days following study completion. In correspondence with the[ ] Institutional Review Board[ ]IRB) dated October 1, 2003, and in discussions with the FDA investigator during the inspection, you acknowledged that you signed documents (i.e., the CRFs) indicating that you had performed certain required physical examinations that, in fact, you did not perform. For example, you signed a CRF on February 25, 2003, indicating that you conducted a physical examination at the day 84 visit for subject 3203. You admitted to the FDA investigator during the inspection that you did not conduct this examination. In addition, in your October 1, 2003, letter to Ms.[ ]of[ ]IRB, you acknowledged that, in some cases "[p]hysical exams were not performed by me, but I signed the documents verifying that the physical exams were performed." You also acknowledged that the majority of the required vital sign evaluations were apparently falsified. Your October 1, 2003, letter to[ ]IRB stated that "A majority of vital signs (weight, blood pressure, respiration, and pulse) and patient assessments were not performed and were fabricated by the study coordinator."

2. **You failed to ensure that the clinical trial was conducted according to the signed investigator statement, in that you failed to adequately supervise the above referenced clinical trial [21 CFR 312.60].**

   Your general responsibilities as a clinical investigator (21 CFR 312.60) include ensuring that the investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; protecting the rights, safety and welfare of subjects under your care; and ensuring control of drugs under investigation. When you signed the investigator statement (Form FDA 1572) for the above-referenced clinical investigation, you committed to taking on the responsibilities of a clinical investigator at your site. You specifically agreed to personally conduct or supervise the clinical study, and to ensure that all associates, colleagues, and employees assisting in the conduct of the study were informed about their obligations. While you may delegate certain study tasks to individuals qualified to perform them, as clinical investigator, you must adequately supervise those to whom you delegate authority. Our investigation indicates that your supervision of personnel to whom you delegated study tasks was not adequate to ensure that clinical trials were conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and in a manner that protected the rights, safety, and welfare of human subjects.

a. You delegated certain tasks to individuals not qualified to perform such tasks.

Our investigation indicates that you delegated substantial responsibilities in the conduct of this study to your study coordinator, Ms. [ ] including the task of screening and enrolling subjects. Ms. [ ] lacked the necessary medical training to perform the functions which she was assigned by you to carry out. Prior to joining the Urology Associates of North Texas as a study coordinator, Ms. [ ] was employed as a phlebotomist, a laboratory technician, a medical instrumentation specialist, and a laboratory quality control officer. We believe that this background provided Ms. [ ] with insufficient medical training to properly obtain medical histories or evaluate subjects to determine whether they met inclusion or exclusion criteria.

b. You failed to adequately supervise study personnel to whom you delegated study tasks.

Our investigation indicates that, in addition to delegating substantial responsibilities in the conduct of this study to your study coordinator (including inappropriate delegation of study tasks—see item 2.a.), you failed to adequately supervise your study coordinator in the conduct of delegated tasks. For example, two of the three subjects enrolled by the study coordinator were ineligible for the study (see item 3.b. below). Had you provided any oversight of the screening and enrollment process, it would have been obvious from the subjects' medical records, as well as their enrollment forms, that two of the three subjects enrolled were ineligible.

3. **You failed to protect the rights, safety, and welfare of subjects under your care [21 CFR 312.60].**

a. You failed to perform patient monitoring intended to assure subject safety.

The protocol required that subjects have physical examinations at screening and at a minimum on days 84, 168, 252, and 336, and that vital signs be taken at 18 different study visits (including screening and baseline). During routine monitoring on September 8, 9 and 12, 2003, the sponsor's monitor discovered a number of irregularities. Because of the concerns identified during these monitoring visits, Dr. [ ] the Medical Director of Clinical Research at Urology Associates of North Texas, requested that each of your subjects (subjects 3201, 3202, and 3203) be brought in for an unscheduled visit to include a physical exam, vital signs, review of adverse events, review of concomitant medications, and visit specific patient questionnaire. These unscheduled visits took place during the week of September 14, 2003.

Each subject was first administered the study drug on a Tuesday and weekly study visits were scheduled for Tuesdays thereafter. As of Tuesday, September 16, 2003, subject 3201, who was administered the study drug on October 15, 2002, would have been in the study for 48 weeks (336 days) and should have had 4 or 5 physical exams and had vital signs taken 17 or 18 times (the subject was due to have a physical exam and vital signs taken at the day 336 study visit). Subject 3202, who received the study drug on October 29, 2002, would have been in the study for 46 weeks (322 days) and should have had 4 physical exams and had vital signs taken 17 times. Subject 3203, who received the study drug on November 12, 2002, would have been in the study for 44 weeks (308 days) and

should have had 4 physical exams and had vital signs taken 16 or 17 times (the subject was due to have vital signs taken at the day 308 study visit).

As you reported to [ ]IRB in your October 1, 2003, letter, during these unscheduled visits, each of the subjects stated that you performed physical examinations only on visits when the test article was administered (at the beginning of the study and at day 168). Each subject also indicated that vital signs were not taken on a regular basis. Specifically, one subject stated that vital signs were obtained "3 or 4 times" throughout the study; one subject stated that vital signs were obtained "pretty regularly early on, but not much in the last 6 months"; and one subject stated that vital signs were obtained "2 or 3 times". In addition, in correspondence with your IRB dated October 1, 2003, and in discussions with the FDA investigator, you acknowledged that you signed documents indicating that you performed physical examinations that, in fact, you did not perform. You also acknowledged that a majority of vital signs and patient assessments were not done and claimed that these vital signs had been fabricated by your study coordinator, Ms.[ ](see item 1).

The study enrolled subjects with significant disease (advanced prostate cancer). The study drug was administered in a single dose formulation intended to deliver the drug for six months without interruption. The protocol specifically identifies physical examinations and vital signs as important safety variables and components of the plan for evaluating the safety of the study drug. Notwithstanding the relatively sick patient population and safety concerns with the study drug, it is apparent that there were substantial deviations from scheduled safety monitoring. If the subjects' recollections are accurate, only half of the required physical exams were done and fewer than half of the required vital signs were done. Furthermore, you conceded in your October 1, 2003, letter to Ms.[ ]of[ ]IRB that physical exams were not performed by you, and that a majority of vital signs and patient assessments were not performed. Your failure to perform a substantial portion of required monitoring intended to assure subject safety exposed your subjects to unnecessary risks.

b. You enrolled subjects (3201 and 3202) who should have been excluded from the study for safety reasons.

1. The protocol excluded patients who had experienced a myocardial infarction within six months before baseline. Subject 3201 was enrolled in the study and subsequently administered leuprolide on October 15, 2002, despite having experienced a myocardial infarction (MI) on August 20, 2002, (less than 2 months before being administered the study drug). We note that by a facsimile dated October 10, 2002, you appear to have requested the sponsor's approval to enroll this subject after screening. However, this document (entitled "Atrix Laboratories, Inc. Potential Patient Fax Sheet[ ] as faxed back to your site by the sponsor states that the "patient meets all criteria and can be enrolled in the study." The fax also comments that "the approval is valid only after the patient signs the prostate cancer history page before dosing." No documentation was available indicating that the subject's prior MI, an exclusion criterion, was considered by you or the sponsor before enrollment, nor is the available documentation sufficient to constitute a waiver of the exclusion criterion for this subject.

2. The protocol excluded patients with a cancer diagnosis without a history of stability/remission for greater than five years, with the exception of non-metastatic basal and/or squamous cell carcinomas of the skin. Subject 3202 was enrolled in the study and subsequently administered leuprolide on October 29, 2002, despite a cancer diagnosis with active disease within the last 5 years. The subject had a cancerous left kidney removed on February 12, 2002. There is no indication that the sponsor or the IRB granted a waiver of this exclusion criterion prior to the subject's enrollment. We note that Ms.[ ] appears to have notified[ ]IRB of the enrollment of this patient despite the exclusionary medical history in a letter sent by Ms.[ ]to[ ]IRB on January 13 or 14, 2003. In a "Protocol Deviations" form signed by Ms.[ ]and dated January 20, 2003, there is a notation that the "patient was granted a protocol deviation." There is no documentation that any protocol deviation, or waiver, was granted by the sponsor or the IRB prior to enrollment of the subject or, indeed, prior to the date of this form.

By administering leuprolide to these subjects, you exposed them to unnecessary risk of exacerbation or other complications of their disease or condition.

4. You failed to conduct the study according to the investigational plan [21 CFR 312. 60].

a. Two of the three subjects you enrolled (3201 and 3202) were enrolled in the study despite meeting exclusion criteria (see item 3.b. above).

b. The protocol required that physical examinations be performed at study visits on days 84, 168, 252, and 336. As discussed in item 3.a., physical examinations were not performed on days 84 and 252 for subjects 3201, 3202, and 3203.

c. The protocol required that vital signs be taken at 18 visits over the course of the study. As discussed in item 3.a., many of these vital signs were not taken.

d. The protocol stated that the central laboratory[ ]would provide each investigator with a manual regarding the appropriate procedures for sample collection, preparation and shipping. The laboratory manual required that ambient specimens collected during the study be shipped on the day of collection. Specimens received by[ ]beyond 48 hours post-collection could result in test cancellation. During the inspection, Ms.[ ] study coordinator from September 2003 to study completion, stated that when she arrived at the site to take over Ms.[ ] position as study coordinator she found several specimens in the refrigerator that were up to two weeks old and had not been shipped to[ ] Shortly after Ms.[ ] observation, Ms.[ ]shipped the referenced samples to[ ]for analysis.

5. **You failed to obtain adequate informed consent [21 CFR 50.20].**

Informed consent is required for all subjects who participate in a study, including those who ultimately are not enrolled, but who undergo clinical interventions as part of the screening process. There is no documentation that informed consent was obtained for Subject[ ] Although the subject was ultimately not enrolled in the study, the subject participated in the study by undergoing study-specific screening procedures, including blood draws for hematology and chemistry, and therefore informed consent should have been obtained from him prior to his participation.

6. **You failed to prepare and maintain adequate and accurate case histories [21 CFR 312.62(b)].**

a. For subject 3201, there are two laboratory sample report forms: one indicates that the blood sample for the day 280 visit was collected on July 30, 2003, while the other form states that the sample for the day 280 visit was collected on July 22, 2003.

b. For subject 3203, the following discrepancies were noted:

1. Subject 3203 received the test article on November 12, 2002, at 1025. The day 0, 4 hour collection time point should have been 1425; however, the sample requisition form for this sample documents the collection time as 1228. This time was changed on the sample requisition form to 1428 and the change, initialed by[ ]was marked as having been made on November 12, 2002. Subsequent laboratory reports record the time of sample collection as 1228.

2. The day 189 visit was documented as having occurred on May 20, 2003. This date was changed to May 23, 2003, on July 10, 2003. The blood sample collection date on the sample requisition form was May 20, 2003, but was changed to May 23, 2003. The laboratory report documents the date of collection as May 20, 2003.

3. The day 308 visit is marked as having occurred on September 25, 2003, according to the summary source document for that visit. Four laboratory reports for this visit indicate that the laboratory sample was collected on September 25, 2003, while two other laboratory reports for the same visit indicate that the sample was collected on September 18, 2003. The narrative for this patient does not mention blood being drawn on September 25, 2003, although it does state that labs were drawn on September 18, 2003, which is identified there as being Day 308.

4. The day 336 visit occurred on October 23, 2003. The sample collection date on the sample requisition form was originally dated October 16, 2003, but changed on November 23, 2003, to October 22, 2003. Additionally, the requisition form for the Day 336 visit states that blood was collected on September 23, 2006.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational drugs. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations. We acknowledge your January 27, 2004, response to the FDA Form 483, in which you outlined the actions that your firm is implementing to address the observations listed on the FDA Form 483, and to bring your site into compliance for future studies. Despite these assurances, FDA believes, based on the serious nature of the above listed violations, that you should not remain eligible to continue to receive investigational products.

On the basis of the above listed violations, FDA asserts that you have submitted false information to FDA or the sponsor in a required report and that you have repeatedly or deliberately failed to comply with the cited regulations. Accordingly, FDA proposes that you be disqualified as a clinical investigator. You may reply to the above stated issues, including an explanation of why you should remain eligible to receive investigational products and not be disqualified as a clinical investigator, in a written response or at an informal conference in my office. This procedure is provided for by regulation at 21 CFR 312.70.

Within fifteen (15) days of receipt of this letter, write or call me at (240) 276-8819 to arrange a conference time or to indicate your intent to respond in writing. Your written response should be forwarded within thirty (30) days of receipt of this letter. Your reply should be sent to:

Gary Della'Zanna, D.O., M.Sc.
Director
Division of Scientific Investigations (HFD-45)
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
7520 Standish Place, Room 103
Rockville, Maryland 20855

Should you request an informal conference, we ask that you provide us with a full and complete explanation of the above listed violations. You should bring with you all pertinent documents, and a representative of your choosing may accompany you. Although the conference is informal, a transcript of the conference will be prepared. If you choose to proceed in this manner, we plan to hold such a conference within 30 days of your request.

At any time during this administrative process, you may enter into a consent agreement with FDA regarding your future use of investigational products. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement between you and FDA.

FDA's Center for Drug Evaluation and Research (the Center) will carefully consider any oral or written response you make to this proceeding. If your explanation is accepted by the Center, the disqualification process will be terminated. If your written or oral responses to our allegations are unsatisfactory, or we cannot come to terms on a consent agreement, or you do not respond to this notice, you will be offered a regulatory hearing before FDA, pursuant to 21 CFR Part 16 (enclosed) and 21 CFR 312.70 (enclosed). Before such a hearing, FDA will provide you notice of the matters to be considered, including a comprehensive statement of the basis for the decision or action taken or proposed, and a general summary of the information that will be presented by FDA in support of the decision or action. A presiding officer free from bias or prejudice and

who has not participated in this matter will conduct the hearing. Such a hearing will determine whether or not you will remain entitled to receive investigational products. You should be aware that neither entry into a consent agreement nor pursuit of a hearing precludes the possibility of a corollary judicial proceeding or administrative remedy concerning these violations.

Sincerely yours,

{See appended electronic signature page}

Gary Della'Zanna, D.O., M.Sc.
Director
Division of Scientific Investigations (HFD-45)
Office of Compliance
Center for Drug Evaluation and Research

Enclosures:

#1 - 21 CFR 312
#2 - 21 CFR 50
#3 - 21 CFR 16
#4 – Consent Agreement

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

/s/

Gary DellaZanna
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