DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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

OCT 23 2002

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Walter N. Gaman, M.D.
North Texas Clinical Research
4301 N. MacArthur Blvd., Suite 200
Irving, Texas 75038

Dear Dr. Gaman:

Between May 12 and July 21, 1998, Mr. Phillip D. Waldron and Ms. Kelly J. Pegg of the Food and Drug Administration (FDA) conducted an inspection of your clinical study: "A Study to Evaluate the Effects of Lansoprazole Compared with Ranitidine on NSAID-Induced Gastric Ulcers in Patients Continuing to take NSAIDS" (protocol[ ] of the investigational drug lansoprazole, performed for TAP Holdings, Inc. This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the subjects have been protected.

We have evaluated the inspection report, the documents submitted with that report, pertinent documentation obtained from[ ] and correspondence to the Division of Scientific Investigations (DSI) from Tap Holdings, Inc. dated December 18, 1997. We conclude that you submitted false information to the sponsor in required reports, and repeatedly or deliberately failed to comply with the regulations governing the proper conduct of clinical studies involving investigational products as published under Title 21, Code of Federal Regulations (CFR), Part 312 (copy enclosed).

We have also reviewed the July 30, 1998, response from your attorney, Mr.[ ] to the Form FDA 483, Inspectional Observations. In this response, Mr. [ ] acknowledges that extensive fabrication and falsification of data occurred. However, Mr.[ ] contends that your study coordinator,[ ] was responsible for the falsification of study data, including your signature and the signatures of Drs. [ ] and[ ] He further asserts that you had no knowledge of the falsifications until December 1997.

We remind you that it is your responsibility, as the investigator of record or Principal Investigator, to ensure that the investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations. According to the signed investigator statement, you are responsible for personally conducting or supervising the clinical investigation. While in a supervisory role, you may delegate authority to perform certain research procedures to other qualified personnel. However, such delegation requires careful supervision of those to whom you delegate authority. As the investigator of record, you remain responsible for overseeing and reviewing their work, particularly the clinical aspects, and must make certain that they are following the investigational study plan. Regardless of what responsibilities you may delegate, you remain ultimately responsible for the proper conduct of clinical studies in which you are the investigator of record.

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. FAILURE TO SUPERVISE THE CLINICAL INVESTIGATION [21 CFR 312.60]

You failed to conduct and adequately supervise the clinical study. The Statement of Investigator (Form FDA 1572) you signed requires you to personally conduct or supervise the clinical investigation. As described in violations 2-6, study records were falsified and submitted to the sponsor, the study protocol was not adhered to, there was a failure to prepare and maintain adequate and accurate study records, there was a failure to maintain adequate records of drug disposition, and there was a failure to obtain valid informed consent.

2. SUBMISSION OF FALSE INFORMATION TO THE SPONSOR [21 CFR 312.70]

a. You reported in your February 11, 1998, letter to[ ]president of TAP Pharmaceuticals that your study coordinator "created three patient charts on this study". We note that at the beginning of the inspection you admitted, and FDA subsequently confirmed, that: 1) all study related records were falsified for subjects 1014[ ]1015 [ ]and 1154[ ](see table below); and 2) the pathology reports documenting lack of malignancy were falsified for subjects 1013[ ] 1155[ ] and 1156[ ]

b. Our inspection revealed that an additional study subject was fabricated. Specifically, all study related records including informed consent, laboratory results, Case Report Forms (CRFs), and EGD reports were falsified for subject 1158[ ]

(1) The informed consent document bears a subject signature that appears to be falsified.

(2) The informed consent document bears a signature of your name, which you claim is not authentic.

(3) The laboratory results and CRFs bear a signature of your name, and a signature of Dr. [ ]name; you claim neither signature is authentic.

(4) Three EGD reports in the subject's file dated 9/23/97, 11/6/97, and 11/26/97 appear to be signed by Dr.[ ] However, there were no records on file at the[ ] of EGDs performed on these days. Dr.[ ]has stated that his signature was forged on these three reports. The only EGD report on file at [ ]for this subject was dated 8/21/97 and was unrelated to this study. This one report documents that this subject had a healed gastric ulcer and, according to Dr. [ ]bears his true signature.

c. Dr.[ ]the subinvestigator responsible for conducting the EGD's, also stated that his signature was forged on the falsified EGD reports discovered for the other fabricated subjects (1014[ ]1015[ ]and 1154[ ]in the study[ ] Please see Table 1.

Table 1. Evidence of data falsification for fictitious subjects

Subject #	EGD			Pathology Report						Consent Form
				Gastritis			*H. pylori*		Malignancy	
	Wk 0	Wk 4	Wk 8	Wk 0	Wk 4	Wk 8	Wk 0	Wk 8		
1014†f	F(S)	F(S)	F(S)	F	NAv	F	F	F	F	Forged
1015†f	F(S)	F(S)	F(S)	F	NAv	NAv	F	NAv	F	Forged
1154†f	F(S)	F(S)	F(S)	F	NAv	NAv	F	NAv	F	Forged
1158†f	F	F	F	F	NAv	F	F	F	F	Forged

†f Fictitious subject; F = falsified report; (S) = Dr[ ]claimed his signature was forged on the falsified EGC reports; Forged - the fictitious subject's signature was forged on the consent form; NAv = not available; sample not received.

d. In addition, we found that for subjects 1159[ ]and 1337[ ]the pathology results indicating that no malignancy existed were falsified.

We note that of the ten study subjects enrolled, subject 1157[ ]is the only study subject with no apparent falsified records.

3. FAILURE TO ADHERE TO THE APPROVED PROTOCOL [21 CFR 312.60]

a. Although subject 1155[ ]had a duodenal ulcer and did not meet inclusion criteria, he was enrolled in the study. The screening EGD report and the corresponding EGD photograph for subject 1155[ ]dated 5/22/97, document a duodenal ulcer rather than gastric ulcer. According to the protocol, only patients with gastric ulcers meet the inclusion criteria for the study. While the subject's file contains two EGD reports indicating the presence of a gastric ulcer, review of the records at the[ ]document only one true EGD report, dated 5/22/97, indicating that subject 1155[ ]had a duodenal ulcer. The endoscopist, Dr.[ ]confirmed to the FDA investigator that the photo showed a duodenal, not a gastric ulcer. Therefore, this subject did not have a gastric ulcer, and should not have been enrolled in the study.

b. The protocol required that gastric ulcer biopsies be performed at screening to rule out malignancy. Gastric ulcer malignancy screening was not performed on any of the six real study subjects (#1013, #1155, #1156, #1157, #1159 and #1337). As a result, the rights, safety and welfare of these subjects were not protected.

4. FAILURE TO PREPARE AND MAINTAIN ADEQUATE AND ACCURATE CASE HISTORIES [21 CFR 312.62(b)]

a. It is obvious that inaccurate case histories exist for the fabricated subjects 1014[ ] 1015[ ]1154[ ]and 1158[ ]

b. In addition, there were no valid pathology reports for gastric ulcer biopsies required to be performed on all subjects at screening to rule out malignancy. For example, each of the screening CRFs for subjects 1337[ ]and 1159[ ]has a notation signed by Ms. [ ]that the gastric ulcer biopsy did not show malignancy "per pathologist." There is no record at[ ]that such examinations were performed.

c. Biopsy reports for gastritis were not available for 3 of the required biopsies. Specifically, there were no screening and week 4 reports for subject 1157[ ]and no screening report for subject 1337[ ]

d. No protocol specified *H. pylori* evaluation reports from the[ ] pathology department were available in the records at your site. While 6 "FAX Memos" sent by [ ]to your study coordinator were available in the records at your site, these "FAX Memos" merely indicated whether the samples were negative or positive for *H. pylori* colonization, and do not constitute the required evaluation reports as specified in the protocol.

5. FAILURE TO MAINTAIN ADEQUATE AND ACCURATE DRUG ACCOUNTABILITY RECORDS [21 CFR 312.62(a)]

a. There were no source documents regarding drug disposition for subject 1156[ ]

b. In addition, it is obvious that any drug accountability records for the four subjects who were fabricated are false.

6. FAILURE TO OBTAIN VALID INFORMED CONSENT [21 CFR 312.60]

a. The signed consent forms for subjects 1157[ ]1159[ ] and 1337[ ]were not the latest version approved by the IRB.

b. It is obvious that valid informed consent to participate could not have been obtained from subjects 1014[ ]1015[ ]1154[ ]and 1158[ ]whose signatures were forged on informed consent documents.

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

On the basis of the above listed violations, FDA asserts that you have submitted false information and repeatedly or deliberately failed to comply with cited regulations and 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 21 CFR 312.70.

Within fifteen (15) business days of receipt of this letter, write or call me at (301) 594-0020 to arrange a conference time or to indicate your intent to respond in writing. If you intend to respond in writing, your written response must be forwarded within thirty (30) calendar days of receipt of this letter. Your reply should be addressed to:

Joanne L. Rhoads, M.D., MPH
Director
Division of Scientific Investigations, HFD-45
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 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 calendar 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 (Center) will carefully consider any oral or written response. 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,

Joanne L Rhoads M.D.

Joanne L. Rhoads, M.D., MPH
Director
Division of Scientific Investigations, HFD-45
Office of Medical Policy
Center for Drug Evaluation and Research

Enclosures:
21 CFR Part 16
21 CFR § 312.70
Consent Agreement