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CBER #99-012

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

MAR 3 1999

WARNING LETTER

Certified Mail
Return Receipt Requested

Robert W. Ashworth, Ph.D.
Knoll Pharmaceutical Company
3000 Continental Drive North
Mount Olive, NJ 07828-1234

Dear Dr. Ashworth:

During the period October 15-30, 1998, Ms. Mary Patricia Murphy, Mr. John Shea, and Ms. Shari Hromyak, investigators with the Food and Drug Administration (FDA), each met with personnel at one of the three clinical investigator sites selected for audit by FDA to review the conduct of the clinical study entitled _____

_____ The inspections are part of FDA's Bioresearch Monitoring Program which includes inspections designed to monitor the conduct of research involving investigational drugs.

Based upon review of the Form FDA 483s and the establishment inspection reports of three clinical sites (Site 4004-_____; Site 4038-_____; and Site 4062-_____) we identified significant deviations from applicable federal regulations as published in Title 21, Code of Federal Regulations, Part 312 [21 CFR 312]. Data submitted to FDA that are intended to demonstrate the test article's safety and efficacy also reveal serious deficiencies in the sponsor's obligations. These deviations include, but are not limited to, the following:

1. **Failure to perform adequate monitoring of on-going investigations.**
[21 CFR 312.56(a)]

Our inspections revealed there are no study records at the clinical sites to indicate that monitoring was performed. At the conclusion of a monitor's site visit, a report should be issued to the site following each visit to apprise the site of noted deviations and the general conduct of the study at the site in order to obtain consistent and reliable data and prevent future deviations.

2. Failure to provide the clinical investigators with the information they need to conduct an investigation properly. [21 CFR 312.50]

The sponsor failed to ensure that clinical investigators were aware of their responsibilities when participating in an IND study as evidenced by:

- A. The recommended dosing was not followed at each of the inspected sites.
- B. Recordkeeping deficiencies are significant at all of the inspected sites. For example:
 - i. There are no case report forms at the sites of _____
 - ii. _____ case report forms were completed by the sponsor.

According to documentation found during the inspection, the case report forms were completed by the sponsor in 4/93, nearly two years after the first subject and two months after the last two subjects completed the study. Items i. and ii. are serious departures from federal regulations regarding investigational new drugs. The lack of case report forms at sites and the completion of case report forms by sponsor personnel bring into question the reliability of the data. Please explain why there are no case report forms at two of the three inspected sites. Please explain why it was necessary for the sponsor to complete _____ case report forms.

- iii. Incomplete or inaccurate drug accountability records were found at each of the sites.
- iv. Start and stop times for administration of the test article were not always recorded, affecting the validity of the total amounts of test article received by some study subjects at the sites of _____
- v. Various required laboratory test values were not always fully reported. These tests include fibrinogen, hematocrit, and serum creatinine values critical to the evaluation of the test article's safety and effectiveness.
- vi. The following documents could not be found in _____ study files:
 - a. Drug accountability records.
 - b. Protocols.
 - c. Form FDA 1572(s).
 - d. Case histories including signed consent forms, progress notes, and case report forms.
 - e. IRB and sponsor files.

- C. _____ reported the administration of the test article on the case report forms as it was ordered, not as it was actually administered, affecting the validity of the calculated rates of infusion of the test article in the line listings.
- D. Three versions of consent forms at _____ site did not contain all of the basic required elements.
- E. There is no signed consent form for one subject at _____ site.

**3. Failure to provide the clinical investigators with an investigator brochure.
[21 CFR 312.55(a)]**

Protocol amendments collected at _____ site indicate that an investigator's brochure was not available to clinical investigators after July 1991. Was an investigator's brochure available prior to July 1991? If so, why was it discontinued?

**4. Failure to ensure that the study was conducted according to the protocol.
[21 CFR 312.50]**

There are significant protocol violations regarding an exclusion criterion, dosing of subjects at each site, use of additional anti-coagulating agents, fibrinogen and creatinine levels were not always monitored, and surgeries were conducted outside of recommended fibrinogen levels. For example:

- A. Subject _____ at _____ site met the exclusion criterion with clinically significant renal failure and entered the study.
- B. The protocol requires the initial infusion of the test article be administered at _____ of normal saline infused over a varying time period at the discretion of the clinical investigator. The maintenance dose of _____ is to be given as a continuous infusion over _____ hours, shortened or lengthened according to the fibrinogen level. The following examples from _____ site show the protocol prescribed dosing was not followed:

Doctor's Orders

Subject Number	Date	Dose
_____	12/27/91	54 u/250 mls _____ 6 hours
	12/28-29/91	27 u/250 mls _____ 3 hours
	12/30/91	40 u/250 mls _____ 24 hours
	12/31/91	40 u/250 mls _____ 10 mls per hour, then 5 mls hour
_____	2/3/92	77 u/12 hours, then 53.9 u/ per 24 hours
	2/5/92	0.7 u/kg/24 hours

Legend

u = units

*Subject's weight = 47.7 kilograms (kg)

**Subject's weight = 77 kilograms

- C. Subject _____ at _____ site initially received the test article 17 hours prior to surgery. The protocol states the test article is to be given at least 24-48 hours before coronary artery bypass graft (CABG) surgery.
- D. The protocol requires fibrinogen values to be maintained at 20-70 mg/dl prior to surgery, or the surgery is to be delayed until values fall within range. Also, the fibrinogen values are to be measured one hour prior to surgery. The following are deviations from the protocol at _____ site:
- i. Fibrinogen levels for subject _____ were not stable and varied from 5 to 258 mg%. The value obtained seven hours prior to surgery was 110 mg%.
 - ii. No fibrinogen level was measured one hour prior to surgery for subject _____
 - iii. The pre-surgical fibrinogen value for subject _____ was <5 mg% approximately one hour prior to surgery on 2/1/93. The surgery was not delayed.
- E. The protocol requires that subjects must not receive thrombolytic drugs, that anti-coagulant or anti-platelet therapy be discontinued prior to initiation of study drug therapy, and that all medications administered concomitantly with study medication be documented in the case report form. The following are deviations from the directives at _____ site:
- i. Subject _____ received study drug 12/27/91 - 1/3/92 and was treated with Urokinase, a thrombolytic drug, by the Cath Lab physician on 12/30/91.

- ii. Subject [redacted] received study drug on 2/3-6/92 and was treated with the anticoagulant heparin from 2/3-4/92.
- iii. Subject [redacted] received study drug on 2/3-6/92 and was treated with 10 mg of Vitamin K on 2/4-5/92, which was not reported on the case report form.

F. The protocol requires that serum creatinine levels be evaluated from samples drawn prior to initiation of the study drug treatment and at the end of treatment. The following are deviations from the protocol at [redacted] site:

- i. A pretreatment creatinine was not done on one subject.
- ii. A follow-up creatinine evaluation was not done on another subject until two days post treatment.

5. Failure to maintain control of the investigational drug. [21 CFR 312.61]

[redacted] released the test article to a physician, not listed on the Form FDA 1572, at another local hospital on 2/13/92 for use on an individual not enrolled in the study. This demonstrates lack of adequate training by the sponsor.

6. Failure of the sponsor to adequately review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator. [21 CFR 312.56(c)]

The sponsor failed to ensure that the PLA [redacted] Line Listings and Patient Narratives were consistent with source data. For example:

- A. The patient narrative for subject [redacted] site) submitted by the sponsor is not accurate as follows:
 - i. The subject received five doses of the test article. Total number of units administered is unknown but is at least 280 units, not 215 units as reported.
 - ii. The platelet count during test article therapy ranged from 18-45 thousand/mm, not the 25-45 thousand/mm reported.
 - iii. The initial fibrinogen value was 270 mg/dl not the reported 570 mg/dl.
 - iv. The subject's range of fibrinogen values is reported as 37-96 mg/dl during treatment with the test article. Numeric values for fibrinogen testing were not obtained for four tests. Real values for these tests could have been below 37. Laboratory records show "<50" was recorded on the laboratory records for the four tests. Three of these fibrinogen tests were correctly reported on the case report forms (CRF) as <50 mg%. One was not reported on the CRF or line listings. The sponsor's line listings incorrectly list the three values as 50 instead of <50.

Fibrinogen Values from Laboratory Reports

Date/Time	Values	Comments
7/18/92 0330	<50	Listed as 50 in line listings
7/18/92 1600	<50	Listed as 50 in line listings
7/18/92 2135	<50	Not included on CRF or line listings
7/18/92 0400	<50	Listed as 50 in line listings

B. Because documentation at _____ site indicates a sponsor representative completed the case report forms for his subjects, the deficiencies noted below are attributable to the sponsor.

i. Subject _____

- a. There are seven unreported fibrinogen values. Four were below normal limits. The values were obtained in the two day period following treatment with the test article and post surgery.
- b. There are no source documents to verify a fibrinogen value reported by the sponsor of 106 mg% at 12:30 on 6/26/91.
- c. There are 13 unreported serum creatinine values for the subject. Results for twelve of the 13 tests were above normal limits. Specimens were collected post treatment with the test article and post-coronary artery bypass graft surgery.
- d. The sponsor reports the subject received 92 units of _____. The dispensing record indicates only 70 units were dispensed. The case report form does not include the documentation of the dispensation of the test article for this subject.

ii. Subject _____

- a. Five maintenance and one post-treatment serum creatinine values for the subject are not reported by the sponsor in line listings. The results are within normal limits.
- b. One pre-treatment and one post-treatment hematocrit values are not reported by the sponsor in line listings for the subject. Both values are within normal limits.

iii. Subject _____ first exposure to the test article:

- a. Medical records for the subject indicate the test article dose administered was 50 units over 12 hours (= 4.16 units/hour). The sponsor reports 34 units were given over 12 hours and the rate was 2.8 units/hour.

- b. Eight fibrinogen results from post-treatment/post-surgery are not reported. All results are within normal limits.
 - c. Seven post-treatment/post-surgery hematocrit values are not reported. These results are all below normal limits.
 - d. One pre-treatment and thirteen post-treatment serum creatinine values are not reported. These values are within normal limits.
- C. The deficiencies noted below from _____ site are attributable to the sponsor.
- i. The sponsor incorrectly reports the test article start date for subject _____ as 8/3/93 in the Demographic Information table of the line listings. The correct date is 8/4/93, according to drug dispensing records.
 - ii. The sponsor incorrectly reports the test article start date for subject _____ as 10/27/93 in the Demographic Information table of the line listings. The correct date is 10/28/93, according to drug dispensing records.
 - iii. The sponsor lists the weight of subject _____ as 73.6 kg in the Demographic Information table of the line listings. A more accurate weight is 77 kg noted on the Infusion Record at the site on 2/3/92.
 - iv. The data manager at _____ site indicated the sponsor's study monitor advised her not to report itching as an adverse event to the sponsor for subject _____. The subject experienced itching attributed to an allergic reaction to heparin prior to receiving the test article. However, the following reactions appear to be possibly related to the test article. The test article was initially administered to the subject on 10/28/93. The subject experienced itching and reddening of the knees on 10/29/93 following administration of the test article. The subject was treated with Benadryl™ and Decadron™. On 11/1/93, the subject experienced itching and a small amount of epistaxis following the test article administration. We wish to emphasize that all adverse reactions are to be reported to the sponsor.

We note the case report forms do not capture the use of blood products, an important concern that prospectively could impact the safety and efficacy of the test article. Our inspections revealed that on 5/7/93 the sponsor sent a questionnaire to _____ for subjects _____ and _____ regarding the use of a large number of blood products used post CABG at his site. _____ indicates for both subjects that the "blood products were used to reverse low fibrinogen." _____ also indicates that approximately 100% of CABG patients received blood products at his site.

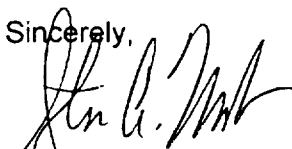
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This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Federal Food, Drug, and Cosmetic Act, as well as the Public Health Service Act, and relevant regulations. Please notify this office in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step you plan to take to prevent a recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which corrections will be completed. Your response should include any documentation necessary to show that correction has been achieved.

Failure to promptly correct these deviations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, termination of Investigational New Drug Applications (INDs) and/or injunction.

Your response should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, Division of Inspections and Surveillance, 1401 Rockville Pike, Rockville, Maryland 20852-1448, Attention: Debra Bower, HFM-650.

Sincerely,

A handwritten signature in black ink, appearing to read "Steven A. Masiello". The signature is fluid and cursive, with a large initial "S" and "M".

Steven A. Masiello
Acting Director
Office of Compliance and Biologics Quality
Center for Biologics and Evaluation
and Research