DEPARTMENT OF HEALTH & HUMAN SERVICES

20-823

Food and Drug Administration
Rockville MD 20857

AUG 16 1999

Dear [redacted]

Between January 5 and 13, 1999, Ms. Stephanie Hubbard, Mr. Allen Hall, and Dr. Robert Young, representing the Food and Drug Administration (FDA) conducted an inspection of monitoring by [redacted] Sandoz Pharmaceutical Corp.), and [redacted] This inspection is a part of 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 human subjects of those studies have been protected by appropriate monitoring of those clinical studies. At the conclusion of the inspection, Ms. Hubbard, Mr. Hall and Dr. Young issued to you a Form FDA 483 and discussed the inspectional findings with you, Jack Van Loon, Ann Humphreys, Linda Patterson, Cassandra Kennedy, Barbara Finn, and Roger Thies.

From our evaluation of the inspection report, the documents collected during the inspection, and your March 3, 1999, letter (with attachments) to Ms. Hubbard, Mr. Hall and Dr. Young, we conclude that you failed to ensure proper monitoring (21 CFR sections 312.50 and 312.52) in the following areas:

1. Failure to close monitoring visit reports in a timely manner. You repeatedly failed to either write, or review, and approve monitoring visit reports in a timely manner. In many instances monitoring visit reports were not either written soon after a monitoring visit, or written, but not reviewed and approved by a supervisor/manager at all, or for several months after the site visit monitoring report (itself) had been finalized by its author. Although FDA regulations do not specifically state that a monitoring visit report is complete and final only after two persons agree on its contents, the agency does subscribe to in (and practice in) more complex situations a two heads is better than one approach. The primary objective of the monitoring of an on going study is to promptly identify and correct problems and deficiencies which might imperil subjects and/or a study. Timely completion of site visit monitoring reports is an essential part in achieving this monitoring objective.

Your procedures, furthermore, required that review and approval be completed before monitoring visits reports became part of a protocol's study file. In these multicenter studies your failure to complete monitoring reports meant that an overall picture of how a study was progressing was

incomplete for months. Examples include, from Protocol B351 several examples of final site visit reports showing no review/approval; from Protocol B355 a site visit report completed on February 27, 1997, and reviewed/approved on May 27, 1997; and from Protocol 26 a report of a May 22, 1998, monitoring visit that was reviewed and approved on August 15, 1998.

2. Failure to follow your standard operating procedures [SOP(s)] on handling suspected scientific misconduct and/or possible fraud in clinical trials. A monitor for a Protocol B355 study site, through astute observation of study site procedures, personnel, and activities during his visits, related questionable activities at the site in his monitoring reports and separately to his supervisors. For example, he reported forged principle investigator signatures, questionable delegations of authority of study tasks to incompetent employees, possible overreaching in securing a study subject's continued participation in a study, etc.

The position that you took at the time was that the questionable activities reported by your monitor were not worth believing. Although we realize that it is not always easy to ferret out what exactly is going on during the conduct of a study, in spite of repeated demands by your monitor for follow up action, we found no documentation in support of your position. Additionally, we found no documentation of steps you took to further investigate the complained of situation be it to verify the credibility of your monitor, or activities at the site, replace the monitor, etc. In fact the record seems to suggest that this employee was actually hounded out of your organization for merely persisting in his line of questioning.

We understand that stricter procedures were instituted after and independent of the above events. We further understand that even tighter procedures were put into place as a result of the above events. Your March 3, 1999, letter is accepted as your assurance that corrective actions have been taken to prevent similar problems as are described above. Your letter has been added to your file. If information is requested from your file that relates to your letter, in accord with the Freedom of Information Act, our response includes related correspondence (except for appendices) in your file.

Although we encourage your efforts to date, we are troubled nonetheless by a perceived lack of commitment on your part to putting the research subject and research data first. Although we did not discuss the following matter with you as you had no direct control over it, we had received from [redacted], your parent, copies of drafts and a final report of a Quality Assurance (QA) visit to this same Protocol B355 site. In fact you personally initiated this quality assurance audit, received and reviewed the report, and forcefully recommended commensurate action. This team verified most of the suspected misconduct reported by the monitor. This team's report was as you may know subjected, however, to "legal" review, something we were told is not routinely d[redacted] There was an attempt to limit inclusion in the report of only those QA findings that met a kind of beyond a reasonable doubt test. Measured against this standard, few if any QA or monitoring findings would ever make it into reports. So long as the limitations that constrain reported findings are clear, it should be for the reader to credit the weight and import of findings.

We shall closely monitor your clinical trial monitoring practices in order to ensure that you have indeed implemented safeguards such as your revised procedures including employee training and to gauge the progress you have made to increase your sensitivity for uncovering misconduct and addressing allegations of misconduct at noncompliant sites.

We appreciate the assistance given during the inspection.

Sincerely,

/S/

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Office of Medical Policy
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Rockville, MD 20855

cc:

CFN:
Field Classification: ~~OAI~~
Headquarters Classification:
___1) NAI
___2) VAI-no response required
_X_3)VAI-response received, evaluated

If Headquarters classification is different classification, explain why:
Corrective action has been implemented and assurances accepted.

Deficiencies noted:
___1-Failure to establish adequacy of laboratory facilities
used by the clinical investigator
___2-Failure to maintain adequate records of drug accountability
___3-Absence of Standard Operating Policy
___4-Failure to review patient records
___5-Failure to assure IRB approval
___6-Failure to document monitoring visits
___7-Failure to visit study site before and during study
_X_8-Other: **Inadequate monitoring of clinical trials**

cc:
HFA-224
HFD-120:Division Director
HFD-120:Doc Room: NDA 20-823, NDA 21-025, IND 37-698
HFD-45 r/f
HFD-47 c/r/s GCP file#2172
HFD-47/Young
HFR-SE150/Kline
HFR-SE150/BiMo-Todd
HFR-SE150/Hubbard
HFR-PA2565/BiMo-Koller
HFR-PA250/Kozick
HFR-PA250/A. Hall

r/d:Young:
reviewd: AEH:
f/t:nlp:8/13/99