



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

HFI-35

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WARNING LETTER

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

JUL 22 1998

Henri A. Termeer
President
Chief Executive Officer
Genzyme Corporation
One Kendall Square
Cambridge, Massachusetts 02139

Dear Mr. Termeer:

During the period of May 13-14, 1998, your firm was visited by Mr. Richard Wright, an investigator from the Food and Drug Administration's (FDA) New England District Office; Mr. Paul Stein, an investigator from FDA's Buffalo District Office; and Ms. V. Michelle Chenault, Ph.D., Scientific Reviewer, Office of Device Evaluation, Center for Devices and Radiological Health. The purpose of that visit was to conduct an inspection to determine whether your firm's activities relating to the _____ complied with applicable FDA regulations. This product is a device as that term is defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval Applications (PMA), and Premarket Notification [510(k)] submissions are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

Title 21, Code of Federal Regulations (21 CFR) Part 812 - Investigational Device Exemptions and section 520(g) of the Act were used as guidance to audit your study. The deviations that were noted during the inspection were listed on Form FDA-483, "Inspectional Observations," which was presented to and discussed with Mr. David H. Schubert, Director of Regulatory Affairs, at the conclusion of the inspection. A copy of the FDA-483, "Inspectional Observations," was mailed to you at the above address on May 20, 1998. Among the deficiencies noted were:

1. Failure to ensure proper monitoring of the clinical investigation.

- Genzyme Corporation has not monitored the _____ or reviewed the source data obtained from the off-site facilities involved in the study. (FDA-483 item #5)
- Ms. Alodia Ruiz, Director of Regulatory Affairs, stated that the firm did not establish monitoring procedures for the referenced study. Ms. Ruiz further stated that Genzyme did not monitor/review any of the source data obtained from the off-site facilities involved in the study.

- The _____ currently in place, _____ was not used for the _____ This procedure does not contain provisions to assure that all future clinical studies sponsored by Genzyme follow the referenced _____ (FDA-483 item #6)

Although Genzyme had developed written procedures for monitoring clinical investigations, the _____ was not monitored according to the referenced procedure established for the Clinical Affairs Department. The current procedures, as written, do not contain provisions for assuring that the Clinical Affairs Department is included in the decision making process for all future clinical studies conducted by the firm. Genzyme was previously advised of monitoring deficiencies in a letter dated September 12, 1996, which cited inadequate written procedures as the cause of deviations found during a June 1996 inspection of Genzyme's _____. In its response, Genzyme stated that it would enhance its procedures for monitoring clinical studies. We note, however, that Genzyme failed to implement its own monitoring plan as it pertains to the _____

2. Failure to provide accurate, complete, and current information.

- There was no review of source data performed to verify the accuracy of disease determination and code used to establish the African American normal population reference data for the _____ (FDA-483 item #1)

The data submitted by Genzyme to the FDA was generated by _____

_____ Unconfirmed and unverified data from these sites was used to establish the normal base for the African American population. An inspection at the _____ site revealed source data discrepancies in the categorization of subject's disease state. For example, subject _____ was reported in the Har-Bass Pre-Beta (source) Data Table as having two different disease states (code=0, normal and code=1, diseased) for two separate tests. Data submitted to FDA on April 1, 1998, listed the subject as normal (code=0) with inclusion in the normal base population. However, the subject should have been excluded from the study since the disease state was unresolved. Similarly, subject _____ was coded as normal in data reported in the Har-Bass Pre-Beta Data Table but was categorized as diseased in the _____ and was excluded from the "African American Subjects with Disease=0/No Table." A sponsor is responsible for assuring that the data submitted to FDA in support of premarket notifications are accurate and complete and for ensuring proper monitoring of the investigation.

- There was no documentation available to establish that verification and validation, where appropriate, of the pre-beta data used to define

performance characteristics has been done. (FDA-483 item #2)

A review of the pre-beta source data and corresponding laboratory result charts at _____ showed multiple sample analyses for some subjects _____ with no explanation documented. Subjects _____ were identified as the same subject from a review of patient files. However, the Master Har-Bass Pre-Beta Source Data shows different results for laboratory test results. There were no procedures in place to verify and validate patient data. Subject _____ was included as part of the normal (Reference) population when, in fact, subject _____ should have been excluded, according to the exclusion/inclusion criteria.

- **The _____ database identifies _____ African American subjects; however, the performance characteristics sample size is referenced as _____ subjects and no documentation is provided to justify the discrepancy. (FDA-483 item #3)**

A subset of _____ subjects from the _____ database comprised of _____ African American subjects was used in the performance characteristics determination. Of the six subjects eliminated, only five subjects were verified as eliminated due to missing relevant data points. There was no documentation available to justify the discrepancy.

3. Failure to establish an investigational plan.

- **No protocols were established for the _____ For example, no procedures were defined for the assessment of the sinking pre-beta values by _____ for Genzyme nor for the assessment of _____ values by _____ for Genzyme. (FDA-483 item #4)**

When asked if protocols were established for the referenced study, Ms. Ruiz stated that a protocol established between the _____ was used by Genzyme. However, the _____ study protocol was not designed for the _____. Sponsors are required to have an IRB-approved protocol in place before initiation of a clinical study.

We acknowledge your response dated June 12, 1998, to the New England District Office which addresses the items listed on the Form FDA-483. We note that Genzyme has acknowledged the observations and plans to take appropriate corrective actions to address the deficiencies noted during the inspection. Genzyme's proposed corrective measures include the revision of standard operating procedures relating to the conduct and monitoring of clinical trials. We also note that Genzyme intends to perform an audit of data that was submitted in support of the _____. During a teleconference call with the Office of Device Evaluation's Integrity Officer, Carl DeMarco, on June 23, 1998, Genzyme was advised that the proposed audit must be conducted by an independent third party and that the entire database should be audited. Genzyme

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stated that a proposed audit plan will be submitted to FDA addressing the scope of the audit.

The above deviations are not intended to be an all-inclusive list of deficiencies which may exist in your clinical study. It is your responsibility to assure adherence to each requirement of the Act and regulations.

Please assure that Genzyme's proposed audit plan concerning the _____
_____ be submitted as follows: send four copies of the proposed audit plan to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2098 Gaither Road, Rockville, Maryland 20850, ATTN: Mr. Robert K. Fish, Consumer Safety Officer.

Please direct all questions concerning this matter to Mr. Robert K. Fish at (301) 594-4723, ext. 138.

Sincerely yours,

Charma Konnor, RPh

for

Lillian J. Gill
Director
Office of Compliance
Center for Devices and
Radiological Health