



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region 91993d

Telephone (973) 526-6009

Food and Drug Administration  
Waterview Corporate Center  
10 Waterview Blvd., 3rd Floor  
Parsippany, NJ 07054

November 8, 2001

**WARNING LETTER**

**CERTIFIED MAIL –**  
**RETURN RECEIPT REQUESTED**

Henri Temier  
Chief Executive Officer  
Genzyme Corporation  
One Kendall Square  
Cambridge, Massachusetts 02139

**File No.: 02-NWJ-10**

Dear Mr. Temier:

During an inspection of your firm, Genzyme Biosurgery, located at 1125 Pleasant View Terrace, Ridgefield, New Jersey, from September 13 - October 2, 2001, investigators from the Food and Drug Administration (FDA) determined you manufacture Synvisc® Hylan G-F 20, an injectable elastoviscous fluid, in pre-filled syringes. Synvisc® is a medical device within the meaning of section 201(h) of the Federal Food, Drug and Cosmetic Act (the Act).

The above referenced inspection determined your firm is not in compliance with applicable regulations concerning medical devices, which renders them adulterated within the meaning of section 501(h) of the Act, in that the methods used in, or the facilities or controls used for manufacturing, packing, storage or installation are not in conformance with the Quality System/Good Manufacturing Practice (QS/GMP) for medical devices as required by 21 Code of Federal Regulations (CFR) Part 820, as follows:

**Corrective and Preventive Actions (CAPA)**

1. A review of nine Medical Device Reports (MDR) for Synvisc® Hylan G-F 20, lacked documentation to support that these events were adequately reviewed and investigated by Quality Assurance (QA) to determine if the device failed to meet product specifications. Furthermore, many reports lacked justification to support the rationale for not conducting a further investigation, prior to close-out. For example:

- MDR No. 2246315-2001-00004
- MDR No. 2246315-2001-00002
- MDR No. 2246315-2000-00003

2. A review of twenty three product complaints for Synvisc® Hylan G-F 20 evaluated as non-MDR events, lacked documentation to support that these complaints were adequately investigated by Quality Assurance to determine if the device failed to meet product specifications prior to close-out. For example:
  - SYN037-MOI GER, dated 3/26/01
  - SYN034-MOI GRC, dated 3/20/01
  - SYN241-MOI FRA, dated 4/23/01
  - SYN141-MOI USA, dated 4/03/01
  
3. Not all data from quality data sources are analyzed to identify existing and potential causes of nonconforming product and other quality problems. For example, a review of the batch production filling records for Synvisc® Hylan G-F 20, revealed numerous rejected units, that were not considered as process loss. Furthermore, acceptance criteria have not been established for reject types. For example:
  - Batch VQ0119 - [REDACTED] units rejected ([REDACTED] units related to empty syringes; [REDACTED] units for fill checks; 50 units for "other syringe rejects")
  - Batch VQ0108 - [REDACTED] units rejected ([REDACTED] units related to empty syringes; [REDACTED] units for "no stopper"; [REDACTED] units broken; [REDACTED] units for fill checks; [REDACTED] units for "other syringe rejects")
  - Batch VP0113 - [REDACTED] units rejected ([REDACTED] units for fill checks; [REDACTED] units related for "other syringe rejects")

#### **Production and Process Controls**

4. Not all parameters and data points were evaluated to support the validation of the triple batch filling process for Synvisc® Hylan G-F 20. For example:
  - The fill yield range of [REDACTED] applied for the triple batch fill was established for the single fill process and not demonstrated to be equivalent.
  - There was no documentation to demonstrate that rheology analysis was performed in accordance with the validation protocol.

#### **Management Controls**

5. Management reviews of medical incidents are held separately from other quality system reviews and not attended by all responsible managers representing manufacturing, Quality Assurance and Quality Control, to consider potential process-related issues.

#### **Design Controls**

6. There is no documentation to support that a risk assessment was considered for the design change from the existing Synvisc® blister tray to the new tray.

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 Act and regulations. The specific violations noted in this letter and on the Form FDA483 issued at the conclusion of the inspection may be symptomatic of serious underlying problems within your establishment's quality system. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be system problems, you must promptly initiate permanent corrective and preventive actions.

Federal agencies are advised of the issuance of all Warning letters about devices so that they may take this information into account when considering the award of contracts. Additionally, no premarket submissions for Class III devices to which the QS/GMP deficiencies are reasonably related will be cleared or approved until the violations have been corrected. Also, no requests for Certificates to Foreign Governments will be approved until the violations related to the subject devices have been corrected.

We have received a written response from your firm, dated October 16, 2001. We acknowledge your firm's commitment to the Quality System Regulations, however in order to complete our review, we will need more documentation of your corrective actions. Regarding the overall response to FDA483 Observations 3, 4 and 5, your firm commits to forwarding all complaints from the Pharmacovigilance Department to the Quality Assurance Department for review and investigation. Complaints received without lot numbers, will be trended and monitored and further investigated when a significant trend is identified. Your procedures should identify how you will determine what constitutes a significant trend and assign the Quality Assurance Department the responsibility for documenting the justification when no further investigation is warranted. Regarding FDA483 Observation 9, your response indicates that rheology samples were taken as indicated in the validation protocol, but not forwarded and documented due to human error. Your response does not mention whether a review of other data sources used to support process validation activities, which may have been affected by this oversight, were also reviewed.

We note that the triple batch size for filling Synvisc® syringes was reported as a single comment to the agency in your Annual Report, dated August 3, 2000, and did not include information on process changes, such as adjusting the bulk vessel pressure range, which were made to accommodate the larger batch size.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action being initiated by the FDA without further notice. These actions include, but are not limited to, seizure, injunction and/or civil penalties.

Genzyme Biosurgery  
Ridgefield, NJ 07657

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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 being taken to identify and make corrections to any underlying systems problems necessary to assure that similar violations will not recur. Your response should be directed to the New Jersey District, FDA, 10 Waterview Blvd., 3<sup>rd</sup> Floor, Parsippany, New Jersey 07054, Attn: Mercedes Mota, Compliance Officer.

Sincerely,

*Edward H. Wilkins, for*  
Douglas I. Ellsworth  
District Director  
New Jersey District

cc:

