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PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
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WARNING LETTER

FEDERAL EXPRESS

WL No. 320-99-04

JUN 23 1999

Mr. H.J.M. Hanstede
Site Manager
Solvay Pharmaceuticals B.V.
Veerweg 12
8121 AA Olst, The Netherlands

Dear Mr. Hanstede:

The U.S. Food and Drug Administration has completed its review of the recent inspection of your sterile pharmaceutical manufacturing facility in Olst, The Netherlands conducted by Investigator Thomas J. Arista and Analyst Robert D. Tollefsen during the period of February 19-25, 1999. The inspection revealed significant deviations from current good manufacturing practices (CGMP) in the manufacture of [ ]
The deviations were presented on an FDA-483, List of Observations, at the close of the inspection. These CGMP deviations cause your sterile pharmaceuticals to be adulterated and unacceptable for use in the United States, since, under United States law, those CGMP deviations make your products adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

Our review included your firm's response to the FDA 483 dated April 12, 1999. We have found your response deficient in that it lacks sufficient details, explanations and documentation to address some of the observations found during the February inspection.

The following are the most significant CGMP deviations noted during the inspection:

1. The [ ] computer system, used to monitor and maintain such critical systems as the [ ] and [ ] systems, has not been validated.

Our inspection revealed that the [ ] computer system is used to monitor temperature, conductivity, water pressure and time (in hours) for replacement of [ ] for the [ ] System. Additionally, this system monitors the differential pressure between the aseptic core and surrounding areas. The [ ] System, which has been in place since January 1998, has not been validated.

Your 4/12/99 written response to the FDA 483 indicates that the [ ] System will be validated according to the Validation Master Plan for 1999. However, this response is deficient in that it does not detail your plans for monitoring the parameters of the [ ] system and [ ] system while the [ ] computer system is being validated. You

must assure that these parameters are monitored by reliable methods. Please provide us with a copy of the validation protocol.

2. The unit, used to compare the computer line's air pressure measurement readings with equipment air pressure measurements, has not been calibrated. Additionally, there has been no periodic maintenance to assure that the unit is operating appropriately.

This issue becomes even more critical due to the fact that the[ ]computer system is not validated. It is essential that this unit, used to compare the readings of the computer with the air pressure monitoring equipment, be accurate and reliable.

3. The differential air pressure for the aseptic filling areas and surrounding support areas is monitored at rest (static) rather than under dynamic conditions.

4. Failure of the Quality Control Unit to establish a system for reviewing microbiological laboratory data to assure completeness and accuracy.

As revealed during our inspection, reviews of multiple entries in microbiology laboratory notebooks were not performed in a timely manner. For example, data in notebook included raw data from tests performed between July and September 1998. Documentation in the notebooks revealed that the review date for all of the data within that time frame was January 6, 1999.

Additionally, data (from this testing) was entered into the Laboratory Information Management System (LIMS) prior to the documented review of the data. This is a concern to us especially because our investigators observed the Responsible Pharmacist releasing product based only on the computer data. Therefore, it is conceivable that product is released to the market prior to a second review of raw data.

According to your firm, the review signature in the laboratory notebooks does not imply that data was reviewed for completeness and accuracy. As stated by your firm, this signature simply indicates that someone "looked at" the notebook. This review signature is the only documentation that raw data in the laboratory notebooks was reviewed.

Your response indicates that management's review of laboratory data will be documented. Please provide a copy of the written procedures describing the review of raw data.

5. Validation of the autoclave, used to sterilize equipment, stoppers and filled syringes, is inadequate in that:

   a. The worst case load configuration has not been established.
   b. There were no written procedures to describe load configurations.
   c. A minimum sterilization time of minutes was required for each autoclave cycle, however, the autoclave timer was not calibrated in order to assure accuracy.

Although heat penetration studies were performed using an assortment of rubber stoppers, there is no data to support that these materials represent the worst case load configuration.

Additionally, the data generated does not demonstrate the efficacy of sterilization cycles for different load configurations and locations.

Based on the above-mentioned deficiencies, we conclude that there is no assurance that the sterilization cycle is effective for all materials. You must have data to justify that the load pattern selected as the worst case is representative of all materials sterilized in the autoclave. Additionally, you must show that the validated load configurations are used in order to assure that all materials are sterilized in each autoclave cycle. As such, load configurations should be defined in written procedures for consistency between operators.

Your written response indicates that a validation protocol related to the load configurations in the [ ] Autoclave will be written. Please provide a copy of this protocol. Additionally, provide a copy of the SOP detailing the load configurations.

6. Validations of the [ ] were inadequate because the biological indicators (BIs), used to verify the effectiveness of the sterilization cycles, were not enumerated prior to performing these studies. Additionally, there were no records documenting that the BIs were stored in the required [ ]

Your written response indicates that SOP [ ] describes the analysis of BIs to assure the required spore concentration. Please provide the English translation for this procedure.

7. Media fill procedures were inadequate for the following reasons:

    a. They did not adequately simulate the aseptic processing operations.

It was explained that the initial aseptic connections made prior to beginning filling operations include [ ]

Your response states that SOPs [ ] and [ ] provide instructions for making aseptic connections during media fills. Please provide the English translations of the pertinent sections of these SOPs regarding your corrective actions.

    b. There was no documentation to indicate the reasons for discarded media filled syringes.
    c. Media fills that exceeded the established limits of [ ] contaminated syringes were accepted.

Review of media fill documentation revealed that [ ] media fills in 1998 exceeded the established contamination limit. There is no documentation to indicate the reasons for discarding the syringes during these media fills. For example, [ ] syringes were discarded during media fill [ ] dated 11/4/98.

The CGMP deviations identified above are not to be considered an all-inclusive list of the deficiencies at your facility. FDA inspections are audits which are not intended to

determine all deviations from CGMPs that exist at a firm.

We recommend that you evaluate your facility on an overall basis for CGMP compliance. If you wish to continue to ship your products to the United States, it is the responsibility of your firm to assure compliance with U.S. standards for current good manufacturing practices for pharmaceutical manufacturers. Failure to promptly correct the aforementioned deficiencies may result in your products being denied entry into the United States. These articles may be refused admission as stated in Section 801(a)(3) of the Federal Food, Drug & Cosmetic Act, in that the methods and controls used in their manufacture do not appear to conform to current good manufacturing practice within the meaning of Section 501(a)(2)(B) of the Act.

Until FDA has confirmed that your firm is in CGMP compliance, we will not recommend approval of any applications listing your firm as a supplier of sterile drug products.

Please respond to this letter within 30 days of receipt. We request that all documents submitted to the U.S. Food and Drug Administration include English translations of pertinent sections. This will assist us in reviewing your responses in a timely manner.

Additionally, we request further details regarding the steps being taken by your firm to correct the other CGMP deficiencies cited in the FDA 483.

Your responses to Observation #10c and 10e on the FDA 483 indicates that the cleaning procedure was revised. Please describe the revisions made to the procedure. Additionally, cleaning parameters were added to the procedure. Please explain the reasons and justifications for the new wash times, rinse times etc..

Your written response to Observation #13a regarding the shipping conditions of biological indictaors (BIs) differs from the verbal response to the Investigator during the inspection. Your firm indicated verbally that BIs received by your firm would be visually inspected as defined in an SOP. Please indicate if you still plan to perform and document this visual check.

Your response to Observation #15 includes a copy of raw data related to differential air pressure alarms that was added to the Operation Qualification (OQ) report. This information differs from the raw data provided to Investigator Arista at the conclusion of the inspection. Please provide an explanation for this discrepancy.

Your response to Observation #20 includes a copy of the data reports from the [ ]System related to the retrospective validations of the [ ]systems. It is unclear as to the time frame covered by these reports. Please explain these documents and state whether these data reports represent a summary of all data, and indicate if these parameters are continuously monitored.

Your response to #20a indicates that there was a [ ]n use during the [ ] system Operational Qualification. However, the Investigator reported that he was told there was no [ ]n place at the time of the OQ. Please clarify this discrepancy. If you have documentation to support the fact that a [ ]was in fact in place during the OQ, then please provide it with your response.

Your response to Observation #26 indicates that laboratory worksheets will be controlled. Please describe how you intend to control these worksheets.

Please contact Compliance Officer Alicia M. Mozzachio or John Dietrick, Team Leader, [telephone: (301) 594-0095; fax: (301) 594-2202] of this division at the above address if you have any questions. Within your written response to this letter, detail corrective actions you plan to take or have taken to bring your operations into compliance. Please include a timetable of when each of the corrections will be completed and attach English translations of supporting documents. Please reference **CFN# 9610742** within your written response.

To schedule a reinspection of your facility, after corrections have been completed and your firm is in compliance with CGMP requirements, send your request to: Director, Division of Emergency and Investigational Operations Branch, HFC-134, 5600 Fisher's Lane, Rockville, MD 20857. You can also contact that office by telephone at (301) 827-5653 or by fax at (301) 443-6919.

Sincerely,

Joseph C. Famulare

Joseph C. Famulare
Director
Division of Manufacturing and Product Quality