



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

JAN 30 1997

WARNING LETTER

Certified-Return Receipt Requested

Ms. Carol M. Moore
Responsible Head
Bayer Corporation
800 Dwight Way
P.O. Box 1986
Berkeley, CA 94701

Dear Ms. Moore :

During an inspection of Bayer Corporation (Bayer), 3525 North Regal Street, Spokane, Washington, conducted on August 5-16, 1996, FDA inspector/investigators documented significant deviations from Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act and Title 21, Code of Federal Regulations (21 CFR), Parts 211 and 600 with respect to the manufacture of your products. The inspectional findings concerning the pre-approval inspection

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With respect to the findings of the August 1996 inspection, it is FDA's view that the conditions at Bayer demonstrate noncompliance with the following areas of the current good manufacturing practice (CGMP) regulations: training of personnel, buildings and facilities, equipment, production and process controls, records and reports, and laboratory controls as follows:

Organization and Personnel

1. Failure of the personnel engaged in the manufacture, processing, packaging, or holding of a drug product to be adequately trained in the particular operations that the employee performs and in CGMP including regulations and written procedures required by these regulations as they relate to the employee's functions [21 CFR 211.25(a)]. CGMP training is not conducted on a continuing basis with sufficient frequency to assure that employees remain familiar with applicable CGMP requirements. Moreover, during an aseptic gowning demonstration the aseptic operator was observed pre-assembling the sterile

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aseptic operator does not wear sterile gloves until fully gowned. This lack of adequate training is also evidenced by many of the deviations listed below.

Building and Facilities

2. Failure to have separate or defined areas or other control systems as necessary to prevent contamination [21 CFR 211.42(c)] in that:
 - a. There is no primary barrier such as laminar flow coverage during the transportation to and loading of partially stoppered vials into the lyophilizer.
 - b. Smoke studies to support the manual filling, manual stoppering, intermediary storage, transport, and loading of partially stoppered vials to the lyophilizer has not been performed in Room X

3. Failure to establish an adequate system for cleaning and disinfecting the room and equipment to produce aseptic conditions [21 CFR 211.42(c)(10)(v)] in that the effectiveness of the cleaning and sanitizing of the X pass-through has not been established.

4. Failure to maintain buildings used in the manufacture, processing, packing, or holding of a drug product in a clean and sanitary condition [21 CFR 211.56(a)] in that:
 - a. Live insect, dust, and debris were observed near the raw material sampling area.
 - b. Sunflower seeds were observed near the X holding tank.
 - c. Residual tape, foam, a loose washer, and a plastic tie were observed inside the Class X production area during the aseptic filling of X X X

5. Failure to maintain buildings used in the manufacture, processing, packing, or holding of a drug product in a good state of repair [21 CFR 211.58] in that:
 - a. A dislodged diffuser panel under the Class X production area was observed during the set-up of X X
 - b. Chipped paint and a rolled metal tag were observed on the X housing located above an uncovered mixing container in room X

Equipment

6. Failure to assure that the equipment used in the manufacture, processing, packing, or holding of a drug product is of appropriate design and of adequate size for its intended use [21 CFR 211.63] in that there are no incoming receiving specifications for the HEPA filters (pre-filters and terminal filter) used in the Class X and Class X production areas.

7. Failure to clean, maintain, and sanitize equipment and utensils to prevent malfunction or contamination that would alter the safety, identity, strength, quality, or purity of the drug

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product [21 CFR 211.67(a)] in that:

- a. The cleaning process for the ~~the~~ syringes used during the sterile filling of allergenics has not been validated.
 - b. The effectiveness of the cleaning and sanitizing process to remove sanitizer residues from critical equipment, i.e., filling lines and the ~~the~~ tunnel has not been established.
 - c. Residue limits for sanitizer agents used in critical production areas have not been established.
 - d. Two leaks were observed on the feed line between the ~~the~~ ultrafiltration unit and the ~~the~~ still.
 - e. Out of service particulate monitoring sample ports in filling room ~~the~~ were covered with wipes.
8. Failure to adequately validate the ~~the~~ ~~the~~ system software used for inventory tracking of quarantined, rejected, and released materials for finished products and for release and materials transfer functions [21 CFR 211.68].

Control of Components and Drug Product Containers and Closures

9. Failure to open, sample, and reseal containers in a manner designed to prevent contamination of their contents and contamination of other components, drug product containers, or closures [21 CFR 211.84(c)(2)] in that ~~the~~ material was stored partially uncovered (with the tail out of the bag).

Production and Process Control

10. Failure to establish and/or follow written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess and to assure that such procedures, including any changes, are drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit [21 CFR 211.100] in that:
- a. There is no written procedure outlining the steps for performing production line start-up.
 - b. There is no written procedure addressing periodic evaluation of new environmental microbial isolates with the firm's sanitizer efficacy/effectiveness studies.
 - c. The written procedure entitled "Raw Materials/Extraction" was not followed in that the exhaust fan/hood was not continuously operating during the weighing of ~~the~~ ~~the~~ source material.
 - d. It was observed that employee practices for aseptic processing technique, equipment sanitization, and component mixing is inadequate.
11. Failure to establish control procedures to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing

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17. Failure to maintain adequate and complete batch production and control records for each batch of drug produced [21 CFR 211.188(b)(7)] in that the batch records for processed on July 8, 1996, and Cat Pelt Extract lot 34582 did not include the actual yield and the percentage of theoretical yield statements.
18. Failure to maintain adequate records of the history of the manufacture or propagation of each lot of source material intended for the manufacture of final allergenic products [21 CFR 680.2(f)] in that the source material supplier did not specify the origin of the house dust source material.
19. Failure to determine that licensed biological products are safe, effective, and not misbranded under prescribed, recommended, or suggested conditions of use [21 CFR 601.26] in that grain mill extract, which contains unknown components (components which may be Category III product(s)) is available for distribution as a Category IIIA product.

The above identified deviations are not intended to be an all inclusive list of deficiencies at your facility. Federal agencies are advised of the issuance of all warning letters about drugs so that they may take this information into account when considering the awards of contracts. It is your responsibility to exercise control of the establishment in all matters relating to compliance with all pertinent regulations.

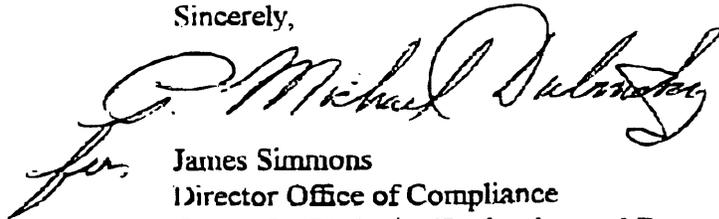
We acknowledge your September 3, October 4, November 18, and December 9, 1996, responses to the Form FDA 483 issued at the close of the inspection. Your response(s) to items 1-4, 6, 7, 9, 10, 12, 19-21, 23-25, 29, 35, 38, and 45 of the Form FDA 483 are inadequate or incomplete in that they failed to address risk assessment (impact on product); equipment and personnel monitoring; clean room personnel qualification; control and critical production area airflow patterns; complete investigations (assessment); scientifically sound internal specification acceptance limits; complete validation studies; summary history of the manufacture of allergenic source material; and sanitizer residual limits. The remainder of your responses appear to be adequate and will be verified upon reinspection.

Please notify this office, in writing, within 15 working days of receipt of this letter of any additional steps you have taken to correct the noted violations and to prevent their recurrence. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Failure to promptly correct these deviations may result in regulatory action without further notice. These actions include license suspension and/or revocation, seizure, and/or injunction.

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Your reply should be sent to my attention in the Office of Compliance, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200N, HFM-600, Rockville, Maryland, 20852.

Sincerely,



James Simmons
Director Office of Compliance
Center for Biologics Evaluation and Research

cc: Carol M. Moore
Vice President, Worldwide Regulatory Affairs
Responsible Head

James G. Crocicchia
Vice President
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