



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

D 1303 B

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

MAY 15 1997

WARNING LETTERCERTIFIED MAIL  
RETURN RECEIPT REQUESTED

Herwig Igel, Ph.D.  
Responsible Head  
Österreichisches Institut für Haemoderivate Ges.m.b.H.  
Industriestraße 67  
A-1220 Vienna, Austria

Dear Dr. Herwig:

During an inspection of your facility located at Industriestraße 67 A-1220 Vienna, Austria between February 17 and 28, 1997, our inspectors identified the following violations of Section 501 (a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and Title 21, Code of Federal Regulations (21 CFR), Parts 211 and 600-680:

1. Failure to establish scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity [21CFR 211.160(b)]. For example:
  - a. There has been no growth promotion testing of the microbial growth medium to demonstrate that the liquid medium is capable of promoting growth after the medium has been frozen to -20° C.
  - b. A smoke study to demonstrate that the HEPA filtered air in front of the lyophilizers maintains a sufficient degree of laminarity when the doors to the lyophilizers are opened has not been performed.
  - c. There is no enumeration of the biological indicators to assure that there is a quantifiable reduction of a biological challenge for the dry heat sterilizers used in Industriestraße [redacted]
  - d. The basis for quarterly disinfection of the lyophilizers used in Industriestraße [redacted] has not been established. (b)(4)
  - e. The parameters for revalidation for the humidification and heat inactivation process used in the [redacted] facility have not been established.

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- f. The recycled alcohol that is used in the Fractionation Operations is not tested to the same specifications as new alcohol.
    - g. The McFarland standard, used to provide a visual reference for microbial contamination, correlates to a high microbial concentration that is unlikely to be recovered in an aseptic manufacturing area.
  2. Failure to establish appropriate written procedures designed to prevent microbial contamination of drug products purporting to be sterile [21CFR 211.113(b)]. For example:
    - a. All containers used for sterile media fill do not go through the entire aseptic manufacturing process. One third of the total bottles (between [ ] are stoppered immediately after the filling operations and incubated, [ ] are stoppered after the transferring operations into and out of the lyophilizers, and [ ] are frozen at [ ] during the simulated freeze drying process prior to final incubation.
    - b. There are no simulated interventions performed during the media fill process to mimic routine stoppage of equipment, entry into the aseptic curtained area and/or substitution of personnel during the operations.
    - c. At the completion of media fill operation, production personnel perform their own monitoring, which include obtaining RODAC samples of their hands, elbows, chest, mouth, and hat.
  3. Failure to have or maintain 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 [21CFR 211.100]. For example:
    - a. The standard operating procedures for the Albumin water bath viral inactivation is inadequate in that it does not describe procedures to be taken when the viral inactivation cycle is interrupted.
    - b. There are no written procedures that describe the regeneration of the deionized beds or removal and replacement of the charcoal filter beds used in the older water system.
    - c. There are no written procedures describing the transportation of the water samples that are to be tested for the presence of bacterial endotoxin at the [ ] Laboratory.
  4. Failure to clean, maintain, and sanitize equipment at appropriate intervals to prevent malfunction or contamination that would alter safety, identity, strength, quality, or purity of the drug product, to establish or maintain written procedures for cleaning and maintenance of equipment, and to maintain records [21CFR 211.67]. For example:

(b)(4)

(b)(4)

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- a. The effectiveness of the dry heat sterilizers, autoclaves, depyrogenation tunnels, and lyophilizers in Industriestraße [~] has not been established in that the number of consecutive and successful runs performed upon initial testing or any subsequent testing does not yield a high degree of assurance that the equipment will perform as necessary. (b)(4)
- b. The testing for the effectiveness of the dry heat tunnels in Industriestraße which are used for production line [—] is inadequate in that a bacterial endotoxin challenge to demonstrate a 3-log reduction of a known endotoxin concentration was not included.
- c. The testing for the effectiveness of the dry heat sterilizers used in Industriestraße [→] is inadequate in that:
  - i. heat distribution studies for the dry heat sterilizers did not include testing with a full load in order to demonstrate that the temperatures are effective in reducing a known level of bacterial endotoxin when the chamber contains equipment.
  - ii. the written standard operating procedures (SOPs) for the load pattern of the sterilizer do not include the specific steps to be followed.
  - iii. the load pattern used in 1989 is not the configuration that is currently used. (b)(4)
  - iv. written procedures do not describe where the biological indicators are to be placed for the 6 month biological indicator sterilization challenge.
- d. The relative humidity in the storage unit in Industriestraße [→] which is used to store bioindicators, is not monitored to determine whether the manufacturer's specifications are maintained.
- e. There are no written procedures:
  - i. for calibration of the timer and the ohm meter system check for the lyophilizer in Industriestraße [~]
  - ii. to describe when to perform the [—] Protein Assay Instrument standards which is used in the Ethanol Fractionation area in Industriestraße [~] and no written procedures to indicate whether the standards are rerun after the Protein Assay Instrument is shut down and restarted.
  - iii. to describe the calibration of the [—] temperature probes for the Water For Injection storage tank and the Water For Injection water loop in Industriestraße [→] (b)(4)
  - iv. that describes performing a periodic evaluation of the older water system in Industriestraße [~] or other older equipment.

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- f. There is no cleaning record for:
- i. the small utensils at the [ ] location that are used for the manual transfer operations.
  - ii. the stainless steel cylinders that are used for the heat inactivation process and the stainless steel funnels at the [ ] location.
  - iii. the purification transfer hose, filter hoses, and [ ] buffer solution tanks used in Industriestraße [ ]
- g. There is no record of calibration for:
- i. the timer in the [ ] location that is used during the initial validation of the heat inactivation process.
  - ii. the [ ] filter manometers, which are used in the older water system, to assure that the air pressure does not exceed the manufacturer's recommendations.
  - iii. the water system's conductivity meters.
  - iv. the internal thermometer or external electronic thermometer used in the Plasma storage freezer in Industriestraße
- h. There is no record to document:
- i. that the 6 millibars of pressure for the required 5 hour hold time is achieved for the integrity test of the humidifying unit. This pressure hold time is a critical step in assuring that the humidifying unit in the Benatzkygaße location is operating appropriately.
  - ii. the periodic removal and replacement of the in-line filter manometers in the older water system.
  - iii. the removal and replacement of the 99.99 HEPA pre-filter that has been installed on the [ ] Dilution system.

(b)(4)

(b)(4)

5. Failure to assure an adequate system for monitoring environmental conditions [21CFR 211.42 (c)(10)(iv)]. For example:

- a. The [ ] area in front of the lyophilizers in Industriestraße [ ] has only one probe for monitoring non-viable particles in an area of approximately 10.4 m x 1.75 m. The location is inadequate in that the probe cannot monitor the air in front of two of the three lyophilizers.
- b. The RODAC sampling locations that are selected when performing environmental monitoring in the [ ] areas are not adequately defined.
- c. The stainless steel slide in the aseptic filling area that is used to guide the rubber stoppers is not routinely monitored for microbial contamination.

(b)(4)

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6. Failure to assure an adequate system for cleaning and disinfecting aseptic processing areas and equipment [21CFR 211.42 (c)(10)(v)]. For example:
  - a. There is no assurance that use of a single disinfectant rather than the rotational use of multiple disinfectants has the necessary degree of microbial effectiveness.
  - b. There is no assurance that the concentrations of the disinfectant used is not detrimental to the nutritive properties of the microbial growth media.
  - c. There is no assurance that the disinfectant does not damage the panels that are used in the lyophilization area.
7. Failure for each person engaged in the manufacture, processing, packing, or holding of a drug product to have education, training, or experience to enable that person to perform the assigned functions [21CFR 211.25 (a)] in that there are no training records to document that the individuals who perform non-viable monitoring of the classified areas have been trained for the following procedures: "Leak Test of the Final Filters and Filter Housing with DEHS Aerosol", "Measurement of Particles in the Air", "Gowning Procedure for Pharmaceutical Production ( )", and "Air Velocity Measurement of the HEPA filters."
8. Failure to subject to microbiological tests before use each lot of component, drug product container, or closure that is liable to microbiological contamination that is objectional in view of its intended use [21 CFR 211.84 (d)(6)] in that points of use for the Water For Injection in Industriestraße #131 are not sampled on a periodic basis.
9. Failure to routinely calibrate, inspect, or check equipment according to a written program designed to assure proper performance [21CFR 211.160(b)(4)]. For example:
  - a. The ( ) thermometers probes that are used to monitor the media fill incubation room have not been calibrated.
  - b. The timer for the controlling device used in Industriestraße ( ) for the water bath has not been calibrated.
10. Failure to withhold from use each lot of components, drug product containers, and closures until the lot has been sampled, tested or examined, as appropriate and released for use by the quality control unit [21CFR 211.84 (a)] in that water used for the final rinse of vials prior to use in the aseptic filling area did not meet USP Water For Injection specifications for conductivity.
11. Failure to handle and store components and drug product containers in a manner to prevent contamination [21CFR 211.80 (b)]. For example:

(b)(4)

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(b)(4)

- a. The raw material in freezer storage room [ ] is not labeled. In addition, the status of the material is not identified, i.e., approved, non-approved, or quarantined.
  - b. Two plastic totes used to store units of inspected plasma in the 4° C anti-room in the Plasma receiving area were not secured. The plastic ties were broken and had not been resealed.
12. Failure to report to the Director, Center for Biologics Evaluation and Research (CBER), important proposed changes in equipment, for any product for which a license is in effect [21 CFR 601.12(a)] in that CBER has not been notified of a new water system in Industriestraße which has been in operation since November 1996.

We acknowledge receipt of your written responses dated March 14, 1997, March 27, 1997 and April 25, 1997, which addresses the inspectional observations on the FDA Form-483 issued at the close of the inspection. Corrective actions addressed in your letter may be referenced in your response to this letter, as appropriate. Although we have not completed a full review of your responses, we have several comments addressing the adequacy of some of your corrective actions. Please note that any remaining comments will be addressed under separate cover. Our comments and requests for further information regarding corrective action and clarification are detailed below. The items correspond to the items listed on the Form FDA-483:

#### Media Fill Operations

3. Please submit the [ ] entitled "Microbial Control for the Production of Sterile Bulk Solutions" when completed.
5. Please submit the calibration data for the [ ] temperature probes that are used to monitor the media fill incubation room when completed.

(b)(4)

#### Validation and Production

- 5c. In order to ensure that the manufacture's storage requirements are met, please indicate how you will monitor the relative humidity of the refrigerator in which the biological indicators are stored.
- 18a. In order to assure better control over the freezer that contains plasma units, we recommend that a large sign be posted on the exterior part of the freezer to remind staff that only approved material is to be stored inside. In addition, the Quality Assurance department should be involved in maintaining appropriate control of approved and quarantine products in this area.

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22. Please provide the rationale for not testing recycled alcohol to the same specifications as new alcohol. Recycled alcohol should be treated as new raw material and identity testing should be performed.
23. Although you indicate that the thermometers were within the required ranges at the time that they were checked, regulations require that thermometers be calibrated at suitable intervals and that a record of the calibration be maintained.
25. Your response indicates that the commercial breeder guarantees the SPF-status of the mice. Please clarify the meaning of "SPF-status."

#### Environmental Monitoring

5. Your response regarding points-of-use testing addresses only the Purified water system. Please indicate for the Water For Injection the monitoring system for the points-of-use.

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deviations. It is your responsibility as Responsible Head, to assure that deviations corrected in one product system or area are also corrected in other product systems or areas of this facility as well as all facilities under your control to assure overall compliance with current Good Manufacturing Practices.

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 award of contracts.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such action includes seizure, license suspension and/or revocation.

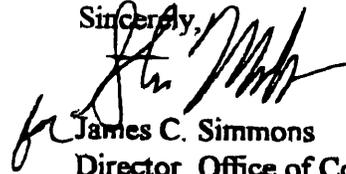
You should notify this office in writing, within 15 working days of receipt of this letter, of specific steps you have taken or will take to correct or prevent these deviations. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

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Your reply should be sent to the following address: U.S. Food and Drug Administration; Center for Biologics Evaluation and Research; HFM-600; 1401 Rockville Pike, Suite 200N; Rockville, MD 20852-1448.

Sincerely,



**James C. Simmons  
Director, Office of Compliance  
Center for Biologics Research  
and Review**