



CBER 98 - 006

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

DEC 1 1998

WARNING LETTER

CERTIFIED - RETURN RECEIPT REQUESTED

Mr. Thomas Janssen
InfraServ GmbH & Co.
Emil-von-Behring-Str. 76
D-35001 Marburg Germany

Dear Mr. Janssen:

The Food and Drug Administration (FDA or the agency) conducted an inspection of InfraServ GmbH & Co., located at Emil-von-Behring-Str. 76, D-35001 Marburg, Germany, on August 31 through September 11, 1998. The inspection revealed deviations from subchapter C, Part 211 and Subchapter F, Parts 600-680, Title 21, Code of Federal Regulations, (CFR), as follows:

1. Failure to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile and to assure that such procedures include validation of any sterilization processes in that [21 CFR 211.113(b)].
 - a. The aseptic media fill procedure allows for the discard of weight check verification vials and the exclusion of growth promotion vials from proper incubation conditions. Also, these vials are not considered in evaluating results when calculating the percentage of the contamination level.
 - b. Load configuration patterns used for autoclave #. - were based on temperature profile evaluation of various load configurations and production materials used in a larger capacity autoclave —).
2. Failure to clean, maintain, and sanitize equipment at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product [21 CFR 211.67(a) and 600.11(b)]. For example:
 - a. There is no adequate data to support the identification of the — products used in

the cleaning validation of the lyophilizer # — as being the worst case for residual removal from the lyophilizer.

- b. There is no data available concerning the recoverability of the spiked material and the limit of detection of the swab testing method used during the cleaning validation of the lyophilizer # —
3. 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 [21 CFR 211.100(a)]. For example:
- a. The standard operating procedure (SOP) entitled “Operating Instructions for Autoclave No. —” does not describe the production load pattern used during routine steam sterilization.
 - b. The validation of lyophilizer # — used for the lyophilization of RabAvert® is incomplete in that there is no process validation run(s) to demonstrate the adequacy of the lyophilization process of RabAvert®.
 - c. Biological indicators were not included in the heat penetration studies during the validation of autoclave #. —
4. Failure of the personnel engaged in the manufacture, processing, packing, or holding of a drug product to wear protective apparel, such as head, face, hand, and arm coverings as necessary to protect drug products from contamination in that personnel in the aseptic filling areas do not wear eye covering [21 CFR 211.28(a)].
5. Failure to establish separate or defined areas or other control systems for manufacturing and processing operations to prevent contamination or mix-ups in that the — studies performed in the cleanroom cabinet — in building — do not demonstrate unidirectional air flow over the aseptic filling and they do not reflect the current configuration of the critical manufacturing areas at the time of the inspection [21 CFR 211.42(c)(10)].
6. Failure of the buildings used in the manufacturing, processing, packing, or holding of a drug product to be of suitable size, construction, and location to facilitate cleaning, maintenance, and proper operations in that there is no assurance that the floor tile and the tile’s sand, cement, and adhesive mixture in the aseptic filling area are sealed in a manner to prevent microbial contamination. [21 CFR 211.42(a)]
7. Failure of equipment used in the manufacture, processing, packing, or holding of drug products to be of appropriate design, adequate size, and suitability located to facilitate operations for intended use and for its cleaning and maintenance in that the cleaning nozzle and hose used to clean lyophilizer # — in the aseptic filling area is approximately - meters in length and there is no procedure describing the draining of the hose and nozzle to prevent standing water.[21 CFR 211.63].

We have reviewed your October 1998 written response which addresses the observations on the Form FDA 483 issued at the conclusion of the inspection. Corrective actions addressed in that letter may be referenced in your response to the Warning Letter, as appropriate. Although the majority of the responses appear to be adequate and will be verified upon reinspection, we have the following comment:

FDA-483 Item 7

Your response indicates that studies to compare product _____ will be performed to identify the most difficult to clean product residuals and that the _____ runs will be performed. Upon completion of the final validation report please submit the data for the agency's review as a supplement to your license.

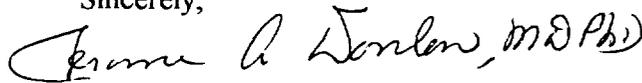
The above identified deviations are not intended to be an all inclusive list of deficiencies at your facility. It is your responsibility to exercise control of the establishment in all matters relating to compliance with all pertinent regulations.

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 license suspension and/or revocation, seizure and/or injunction. 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.

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 actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your written response should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200N, Rockville, Maryland 20852-1448.

Sincerely,



Jerome Donlon, MD, PhD
Acting Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research