



DEPARTMENT OF HEALTH & HUMAN SERVICES

24633A

Food and Drug Administration  
Rockville MD 20857

MAR 29 2004

**WARNING LETTER**

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

Dr. Heinrich Scherfler  
Chief Executive Officer  
Sandoz GmbH  
Biochemiestrasse 10  
6250 Kundl, Austria

Dear Dr. Scherfler:

This letter is regarding the U.S. Food and Drug Administration (FDA) inspection of your Sandoz GmbH pharmaceutical manufacturing facility in Kundl, Austria conducted by Consumer Safety Officer Rebecca Rodriguez from November 3-10, 2003.

The veterinary drug manufacturing part of the inspection revealed significant deviations from cGMP under Title 21 of the Code of Federal Regulations (CFR) Parts 210 and 211. At the conclusion of the inspection, a three-item FDA-483, Inspectional Observations, was issued to you, Dr. Heinrich Scherfler, CEO. These GMP deviations cause your firm's approved veterinary pharmaceutical products to be **adulterated** within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act). Section 501(a)(2)(B) of the Act requires that the methods used in or the facilities or controls used for the manufacturing, processing, packing and holding of drugs be in conformity with cGMP. No distinction is made between human and veterinary drugs and the failure of either to comply with cGMP constitutes a failure to comply with the requirements of the Act.

We reviewed your firm's December 1, 2003, and January 23, 2004, responses to the FDA-483 observations signed by Dr. Elisabeth Schneider-Scherzer and Dr. Heinrich Scherfler. We found that the responses still lack sufficient detail, explanation, documentation or substantive corrective action plans to adequately address the deviations noted during the November 2003 inspection of your manufacturing facility in Kundl, Austria.

Page -2- Dr. Heinrich Scherfler

We acknowledge that your firm has made some changes and corrections in response to Agency findings and requests. However, we have found that while some individual cGMP deficiencies may have been corrected, your firm has failed to institute sufficient corrections to achieve cGMP compliance for an aseptic facility.

Our concerns include, but are not limited to, the following:

- A. There is a failure to develop control systems for your operation as are necessary to prevent contamination of the aseptic processing, which includes a system for monitoring environmental conditions. [21 CFR 211.42(c)(10)(iv)]
- B. A lack of appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile. [21 CFR 211.113 (b)]

In your responses to the FDA-483 item, you stated that your firm understands the concerns that the FDA investigator raised during the inspection. One of the FDA investigator's major concerns was that your firm has not adequately determined the root cause in the majority of the sterility failures. Some of your investigations found some equipment malfunctions and failures. These are possible introduction pathways for microorganism contamination. Why were the microorganisms not detected in the environmental testing? Your responses indicated that there were no sterility failures since June 2003 and no adverse trends in complaints. The absence of sterility failures and adverse reporting trends do not indicate to us that sterility assurance has been attained. Sterility assurance is achieved by showing the controls and procedures implemented to prevent microbial contamination.

You stated in the first response that your firm has organized an "Aseptic Task Force" to review and improve the aseptic operations. This group has recommended several procedures and improvements for the plant and is still investigating the plant operations. Within those recommendations was the need to review the media fill methodology, to review the environmental monitoring and to review the microbiology laboratory operations. Your firm has utilized the running of media fills as a primary tool to indicate sterility after each failure. However, one of the group's recommendations is to review the methodology for "enhancements". Also, during the inspection, [redacted] told the FDA investigator that your firm is evaluating the possibility that microorganisms may be occluded under an oily residue inside the lines and the media fill may not be effective in recovering the microorganisms. These reviews and investigations into the media fill methodology show an apparent lack of confidence in the methodology's ability to detect these microorganisms.

On February 25, 2004, your firm submitted an updated version of SOP 17.075, *Environmental Monitoring Procedure: Monitoring of the Microbial Counts on Surface and Air in the Clean room Areas of [redacted] Building [redacted]* Edition 12. The revised SOP includes additional sampling sites for detecting aerobic microorganisms and some frequency of testing changes

for detecting aerobic and anaerobic microorganisms. Since over fifty percent of the sterility failures were caused by an anaerobic organism, this revised SOP still lacks sufficient environmental testing improvements to address FDA's concern for adequate monitoring of the manufacturing facilities and prevention of microbial contamination.

Your responses promised numerous corrective action plans and procedural revisions with various goal dates. These revisions and corrective action plans should be documented to FDA with copies of any protocols, reports, procedures, records, and documentation referenced as well as copies of any raw data generated. In addition, our review has identified specific areas that will require additional information for a complete evaluation of your corrections. We require the following additional documentation:

- While SOP 17.015, Edition 12 provided types of samplers, sample locations, sample frequency, etc., we require the data and the analysis of the data generated from this monitoring including any trending data. Also, include information as to when the surfacing monitoring occurs and the methods of sampling, e.g., by swabs, contact plates, etc. At a minimum, we recommend the surface monitoring be conducted at the end of each shift.
- The equipment cleaning and sanitization procedures should be revalidated. The revalidation should be accomplished after the completion of design improvements in clean-in-place system and the data submitted.
- Submit the data from the proposed filtration of the cleaning oil through a [REDACTED] filter showing what if any effects the filtration has on the bioburden.
- Submit the revalidation data from the media fill procedure or the "enhanced" media fill procedures and specifically document the extraction and detection of *Propionibacterium acnes* from the formulation vessels.
- Submit the identification of the independent reference typing laboratory associated with confirming the strain of contaminants and submit any protocols used by this laboratory for the analysis of your products.
- Submit any documentation on the proposed enhancements to the lyophilization tray transport procedure, including any updates to the facility personnel flow diagrams, equipment, and relevant SOPs. The proposed syringe bowl disinfection procedure and sterilization of the stainless steel covers should be validated and the data submitted.
- Submit by general correspondence or annual reports any future media fill results and any sterility failures with investigational findings.

The cGMP deviations identified above or on the FDA-483 issued to your firm at the close of the recent inspection are not to be considered an all inclusive list of the deficiencies at your facility. FDA inspections are audits and are not intended to determine or disclose all problems or deviations that exist at a firm. We recommend that you continually evaluate your facility on an overall basis to determine cGMP compliance.

Page -4- Dr. Heinrich Scherfler

You should take prompt action to correct these violations. Failure to promptly correct these violations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil penalties. Further, if corrections are not made, we will recommend that your firm's products be placed on import alert and be denied entry into the United States. Articles can be refused admission pursuant to Section 801(a)(3) of the Act if the articles are adulterated 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.

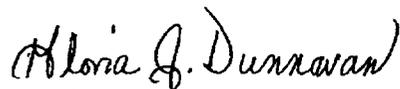
Please notify this office in writing within 15 days of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to identify and make correction to any underlying systems problems necessary to assure that similar violations will not recur. Please include any and all documentation to show that adequate correction has been achieved. In case of future corrections, an estimated date of completion, and documentation showing plans for correction should be included with your response to this letter. Please address your response and any questions to the Food and Drug Administration, Center for Veterinary Medicine, William Bargo, Compliance Officer, 7500 Standish Place, Rockville, Maryland 20855.

Until such time as FDA can confirm compliance with 21 CFR Part 210 and 211, Current Good Manufacturing Practice, and that correction of the deficiencies noted above has been achieved, we will recommend a "pending correction" status of any NADA/INAD applications for your firm.

We wish to point out that it is not the responsibility of the U.S. Food and Drug Administration or the Center for Veterinary Medicine to translate documents. Therefore, it will be necessary that you submit not only the original documents but an adequate and accurate translation of each document into the English language. Failure to submit such translations will prevent us from reviewing whatever response or submission you make.

Remember to include your Firm Establishment Indicator number (3002806523) in all your correspondence.

Sincerely,



Gloria J. Dunnavan

Director

Division of Compliance (HFV-230)

Office of Surveillance and Compliance

Center for Veterinary Medicine