



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region

Telephone (973) 526-6010

Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

September 19, 2000

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Hans Vemer, President
Organon, Inc.
375 Mt. Pleasant Avenue
West Orange, New Jersey 07052

FILE NO.: 00-NWJ-54

Dear Mr. Vemer:

The U.S. Food and Drug Administration, New Jersey District, conducted an inspection of your manufacturing facility located at 375 Mt. Pleasant Avenue, West Orange, NJ, between July 17 and August 23, 2000. The inspection revealed significant deviations from Current Good Manufacturing Practice regulations (Title 21 Code of Federal Regulations (CFR), Parts 210 & 211) for both sterile and non-sterile products. These deviations cause articles of drugs to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act). A discussion of the significant deviations follows:

Sterile products are not manufactured in an environment that adequately controls microbiological contamination. This lack of control is due to poor personnel practices, failure to follow procedures, and lack of adequate supervision. For example:

- 1) Filling pumps and stoppering equipment were not sterilized prior to filling Follistom lot #3499306B. Failure to run the autoclave cycle was not noticed until 4 hours into the filling operation resulting in the rejection of the lot.
- 2) Non-sterile materials were taken into sterile manufacturing room #373 during a validation study.
- 3) Personnel conducting a validation study in room #373 were not trained in proper gowning techniques and were not monitored by QC Microbiology personnel.
- 4) Operators failed to sanitize sterile manufacturing room #373 prior to filling Follistim lot #2199306B. Environmental monitoring conducted at the time resulted in high counts for mold on a door panel and an operator's glove. The lot was released.
- 5) Following the normal 3X sanitization of the sterile manufacturing area and equipment after a shutdown, 14 sites were found to have high microbial counts. An additional 3X sanitization was required to reduce the counts, resulting in a

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lack of assurance that the cleaning procedures are adequate or that the procedures are being followed appropriately.

- 6) Personnel responsible for conducting environmental monitoring of sterile manufacturing areas and personnel failed to label Rodac sampling plates during media fill #MD0999363, resulting in the same sampling plate being used to monitor two individuals.
- 7) Manufacturing personnel were operating without supervision and conducted an unauthorized spray cleaning of the [REDACTED] lyophilizer while Follistim lot #999306B was being filled and partially stoppered for loading into the [REDACTED] lyophilizer. The lyophilizers are in the same sterile processing room.
- 8) Personnel were routinely cited as the source of the microbiological growth when high counts were observed during routine environmental monitoring and during media fills. Personnel are not routinely recertified or retrained in gowning procedures, nor is there a system to track which personnel have participated in media fills to assure that all sterile manufacturing personnel participate on a regular basis. In one instance, an individual had not been recertified in five years. Poor practices included passing non-sterilized equipment through the airlocks into the sterile core, an individual failing to notify anyone of his participation in a media fill resulting in no monitoring by QC Microbiology personnel, high counts during personnel monitoring were not followed by retraining and recertification of the operators.

The environmental integrity of the sterile manufacturing area and sterility test suite is questionable because:

- 1) Zemuron, batch #500450, subplot A-1, exhibited growth during sterility testing. The organism, identified as Bacillus circulans, was found during environmental monitoring of the sterility test suite. In addition, six other Bacillus species and Staphylococcus epidermidis were found during environmental monitoring of the sterile manufacturing area on the date of manufacture of the Zemuron batch. A passing retest was used to invalidate the failing test and also to release the batch.
- 2) Environmental monitoring of sterile processing room #373 during filling of Follistim lot #2199306B produced two high counts for mold growth (door panel and operator's gloves). The room exhibited growth of the same mold species on subsequent days during filling of Norcuron lot #3099441A, Raplon lot #499490B, and Norcuron lots #3299441 A & B. The investigation found that a housing covering the door switch panel was missing screws, missing caulk, contained moisture, and appeared to be discolored.

The ability of both sterile products and non-sterile (oral) products to meet all specifications throughout the labeled expiry period has not been demonstrated. For example:

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- 1) Wigraine Tablets are labeled with an expiry period of 24 months and the assay specification for Ergotamine tartrate is [REDACTED]. At 18 months, two lots were at the minimum of 90% and two additional lots were at 92% and 93%. No investigation was conducted. At the 24-month time period, the assay results inexplicably rose by 7-8% without explanation or investigation.
- 2) Norcuron 10mg/vial stability lots were reconstituted and assayed. The specification for reconstituted product is [REDACTED]. At the initial and 6-month time points, two lots produced low results of 94% and 93% respectively, however the expiration period is 24 months. The test method for the reconstituted assay has not been validated, yet it is being used for stability testing.
- 3) Three additional lots of Norcuron 10mg/vial failed the pH specification at the 18-month time point; the expiry period is 24 months. The specification is [REDACTED] yet all three lots had results of 4.3. No investigation was conducted even though pH is a finished product specification.

The Quality Control (QC) Unit has failed to carry out investigations and perform QC functions to assure that products are manufactured in a state of control and meet all finished product specifications. For example:

- 1) Black spots were found during compression of Wigraine Tablets Validation lot #398542. A single drum of tablets was visually examined. The Quality Unit released the lot, and did not conduct an investigation into the source or identity of the black spots. The black spots were not mentioned in the validation report.
- 2) Wigraine Tablets, lot #299542, was manufactured and placed on accelerated stability to qualify a new supplier of caffeine. At the 3-month accelerated time point, the tablets failed the appearance specification because they had a brownish appearance. The Quality Unit did not evaluate the lot for an increase in impurities, and the new caffeine supplier was approved.
- 3) Wigraine Tablets, lot #100542, was manufactured to qualify a new supplier of caffeine. Although the lot failed several in-process tests, including caffeine assay and disintegration, manufacturing continued and final release testing was conducted. In spite of these failures, QC personnel approved a Certificate of Analysis stating "Released for Use" for lot #100542. The lot was still in quarantine at the start of the inspection. During the inspection, a final decision to destroy the lot was made, however, the new caffeine supplier was approved.
- 4) Raplon batch #199490 failed the appearance specification for color. Quality Control personnel do not use a color standard for comparison, nor did they perform an investigation into the failure and rejection of Batch #199490.
- 5) The Quality Unit routinely fails to review and approve documents that are integral to the evaluation of the manufacturing processes and equipment performance. Items such as Validation Reports, Qualification Reports, Media Fill records, and Product Variance Reports were not reviewed and approved for periods ranging

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from 4 months to 24 months, and some reports had not been reviewed and approved as of the close of the inspection.

- 6) Quality Control analysts and supervisors failed to initiate an investigation when Raplon 10ml vials, lot #499490B, exhibited an out-of-specification result for Unknown Impurities upon initial release testing in August 1999. Although a July 2000 retrospective investigation, conducted during the inspection, determined that the result was erroneously reported, the lot was released for use by the QC Unit at the time of the initial release testing.

Equipment is not maintained in a manner sufficient to assure that products can be manufactured according to the validated processes. For instance:

- 1) On numerous occasions, the [REDACTED] Oven could not maintain the specified drying temperature. The problem of temperature drops occurred during the drying of at least three lots of Wigraine Tablets and one lot of Cotazym S Tablets. No maintenance work was conducted on the oven.
- 2) Shelf temperatures and vacuum levels could not be maintained by the lyophilizers during the processing of at least eight batches of Follistim and Norcuron. These equipment problems caused delays during lyophilization and also caused lyophilization steps to be repeated. As a result, the validated lyophilization process was not followed.

The above list of violations is not considered to be an all-inclusive list of the violations at your facility. It is your responsibility to ensure that all requirements of the Federal Food, Drug and Cosmetic Act and all applicable federal regulations are met. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deficiencies. Failure to correct the deviations may result in regulatory action without further notice. This includes seizure and/or injunction.

Please notify this office within 15 working days of receipt of this letter regarding the specific steps you have taken to correct the noted violations. This should also include an explanation of each step taken to prevent the recurrence of similar violations. If the corrective actions cannot be completed within 15 working days, state the reason for the delay and the time needed to complete the corrections.

We have received your correspondence dated September 7, 2000, written in response to the FDA-483 issued to your firm on August 23, 2000. We are in the process of reviewing it.

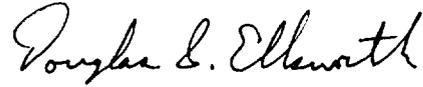
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Please submit any additional response to: U.S. Food and Drug Administration, 10
Waterview Boulevard, 3rd Floor, Parsippany, New Jersey 07054, Attn: Sarah A. Della Fave,
Compliance Officer.

Sincerely,



Douglas I. Ellsworth
District Director
New Jersey District

cc: Michael G. Ferrante
Director, Quality Assurance