



Food and Drug Administration
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July 12, 2001

**CERTIFIED MAIL
RETURN RECEIPT REQUESTED**

**WARNING LETTER
CIN-WL-01-8476**

Werner Gerstenberg, President and COO
Boehringer Ingelheim Corporation
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

Dear Mr. Gerstenberg:

During the May 7-31, 2001 inspection of your manufacturing facility, Roxane Laboratories, Inc., located at 1809 Wilson Road and 330 Oak Street, Columbus, Ohio FDA Investigators documented significant deviations from the Good Manufacturing Practice Regulations (Title 21 Code of Federal Regulations, Parts 210 and 211). These deviations cause your sterile and non-sterile liquid drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act).

Our investigations revealed the following:

Failure to establish and maintain adequate laboratory controls that include the establishment of scientifically sound and appropriate specifications, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, and drug products conform to appropriate standards of identity, strength, quality, and purity.

Alert and action limits for environmental monitoring of critical and controlled environments for your firm's aseptic filling operations appear to be excessive and not based on adequate principles and concepts of statistical process control. For example, (Procedure UDVP 5125) for the "Out of Specification Procedure for [REDACTED] Particle Monitoring" of critical areas on aseptic filling lines, the alarm limit is triggered only when particle counts at [REDACTED] exceed [REDACTED] particles for [REDACTED] consecutive [REDACTED] readings. The action required when this level is reached is to verify that the [REDACTED] average particle count during the filling period is less than [REDACTED]. An additional monitoring period of [REDACTED] is then allowed to take place and if there are no excessive spikes in the data the filling operation is allowed to proceed. The procedure also states that if an assignable cause can be attributed to the particle counts exceeding the [REDACTED] average, the filling process can resume and no further action taken. There is no explanation of what constitutes an acceptable "assignable cause".

Also Departmental Procedure QC 890 Rev. No. 8 (Monitoring the Microbial Environment of the Respiratory Therapy Filling Room) states that for the microbial quality of air in non-critical areas of the aseptic filling operation in Fill Room, RT-3 there is an alert limit of [REDACTED] per [REDACTED] and an action limit of [REDACTED]. For the critical area in RT-3 [REDACTED] the action level is [REDACTED].

In addition, the surface sampling procedure QC 890 allows for an action limit of [REDACTED] per plate for [REDACTED] consecutive days in critical areas [REDACTED] including filling equipment.

Furthermore, written procedures for the testing and approval or rejection of components do not appear to be adequate. For example, your firm does not adequately characterize the microbial content of each component liable to contamination and to establish appropriate acceptance/rejection limits based on this bioburden. The procedure QC 890 allows for an alert limit of [REDACTED] and an alarm limit of [REDACTED] on [REDACTED] consecutive days on samples collected downstream of the first sterilizing filter. These limits are the same as the bioburden for product before the first filtration.

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.

During the filling of the second portion of Ipratropium Bromide, lot 057156, the particle counts increased until they were routinely above your firm's specification (alarm limit) of [REDACTED] for your [REDACTED] Critical Filling Area. The aseptic filling was not stopped and there was no record that an investigation was conducted as required by procedures QC 890 and UDVP 5125.

During the filling of Ipratropium Bromide lot 057155 there were many instances in which the particle (non-viable) counts in the [REDACTED] Critical Filling area were above your firm's specification (alarm limit) of [REDACTED]. At times the counts were as high as [REDACTED]. The average count at the end of the first portion of the fill was [REDACTED]. The filling operation was not stopped as required by procedure UDVP 5125. Although there was an investigation of the incident that concluded that the frequent spikes (observed by the particle counter ranging from [REDACTED] to [REDACTED] particles of [REDACTED] per cubic foot of air) distorted the average particle counts through out the filling operation, there were no comments on the UDV Filling History page concerning this problem. Furthermore, there was no indication that any corrective actions were taken due to the high particle counts.

There was a product spill during the start-up for aseptic filling of Cromolyn Sodium Inhalation Solution, lot 001839. The lot failed sterility testing due to contamination with gram negative bacteria and was rejected. Procedure UDVP 5042, "Inspection of Respiratory Therapy Blow-Fill-Seal Machines prior to and During Operation" requires that operators inspect the filling line for leaks each time they enter the room and during operation. There is no documentation that this spill was noticed during any of these inspections.

None of the environmental sampling/testing for viable particles during the aseptic filling operation of the Cromolyn Sodium Inhalation Solution, lot 001839 showed a problem even though your firm's investigation of the non conformance, concluded that gross microbiological contamination existed the throughout aseptic filling operation system. However, reliance on environmental testing/sampling has been used by your firm in determining to take no corrective actions when non-viable particle counts were above your firm's alarm limit specifications for critical areas i.e., [REDACTED] during the aseptic filling of drug products, e.g., Ipratropium Bromide, lot 057155.

There is no procedure to initiate an investigation when environmental sampling (e.g. gowning rodac plate counts) are above specifications. There were instances where the aseptic room logbook was marked to indicate that rodac plate samples had been taken but there were no analytical results for the rodac plate samples. The database for gowning rodac plate results indicated "pass" in some instances where the results were above specifications. Also, in some instances for which there were no rodac plate result sheets, the database showed "pass".

There is no procedure in place to investigate the impact on product quality when HEPA filters are found to have leaked during the aseptic filling operation. For example, the testing of HEPA filters on 6/1/00 in filling room RT-12 revealed that one HEPA filter leaked. The filter was replaced but there was no investigation performed to determine if any product filled during the time the HEPA filter was leaking was compromised. In addition, when HEPA filters are changed the reason for the change is not always documented e.g., the shroud HEPA filter in room RT-8 on 5/1/00 (work order 265457).

The sterilizing filters, product lines, and filling equipment are steam sterilized in place. Thermocouples used to monitor the temperature during steam sterilization of the equipment used in the aseptic filling operation in room RT-3 are not in the same locations as they were during validation of the sterilization process.

Failure to establish an adequate system for monitoring environmental conditions in production and filling areas.

Particle counts taken in the filling rooms outside of the shrouded [REDACTED] area are taken while the rooms are not operational. This area outside of the shroud is classified as [REDACTED] by your firm. However, the FDA Investigators were told that due to numerous particles caused during the filling operation (e.g., the formation of the molded vials), the [REDACTED] conditions can only be obtained under static conditions.

Particle counts were not obtained in the room or around the filling head in aseptic filling room RT-3. Filling room RT-3 does not have a shrouded area [REDACTED] around the filling head. There are no particle counts taken either in the room or near the filling head (a critical area). Your NDA product, Alupent[®] is processed in RT-3.

Airflow rates in the critical areas [REDACTED] of filling rooms are not recorded before any adjustments or repairs are made. Only results after adjustments are made are recorded and there is no record of conditions that existed during filling operations prior to these adjustments.

Failure to maintain buildings used in the manufacture, processing, packing, or holding of a drug product in a good state of repair.

For aseptic filling room RT-3 where your NDA product, Alupent® is aseptically filled, the filling head and needles are not in a [REDACTED] critical filling area. The filling head is not enclosed or protected from the room environment.

In filling room RT-3 there is a bypass tube around each of the [REDACTED] sterilizing filters in the filling machine. These bypasses are used during in place steam sterilization of the filling lines and the filters. These bypasses have manual valves at both ends which are manually opened and closed during the steam sterilization cycles. There is no procedure in place to assure that these valves are completely closed during all portions of the filling operation and that no product bypasses the sterilizing filters.

The gowning room (anteroom) for RT-3 opens directly into the filling room and not into an aseptic corridor. Individuals not yet wearing their aseptic attire, gowns, gloves, etc. stand in that gowning room.

In filling room RT-3 areas of the ceiling were not a smooth surface. In various parts of the ceiling above the filling equipment the caulking had not been smoothed out and contained many peaks. In addition, many areas of the floor were chipped exposing portions of the floor that is not sealed. Walls in the filling room are not flat and smooth. The walls consist of cement blocks that are coated and painted. There were indentations in the cement blocks.

The filling equipment in filling room RT-3 has metal support pads where the legs meet the floor. There are rust spots on these pads. There was a movable metal ladder in the room and there were rust spots on the lower portions of the legs of the ladder.

Airflow below the HEPA filters in critical areas of your firm's aseptic filling rooms is not maintained as vertical laminar flow air having a velocity sufficient to sweep particulate matters away from the filling/closing area. For example, filling rooms RT-6, RT-9, RT-11, and RT-12 can have average air flow velocities of only [REDACTED]. Management at your firm told the FDA Investigators that your firm does not require laminar flow of the HEPA filtered air past the vial molds and filling areas.

Failure of the personnel engaged in the manufacture, processing, packaging, or holding of a drug product to assure that they wear clean clothing appropriate for the duties they perform and protective apparel as necessary to protect products from contamination.

The gowning procedure UDV 5002 (Gowning Procedure-Respiratory Therapy) for your firm's aseptic filling processes allows for gloves to be sprayed with alcohol after the operator touches the floor or face area rather than requiring that the glove be changed.

Individuals who have not received training in your firm's gowning procedures are allowed to enter the aseptic filling suite e.g., the filling suite entry logs indicated that an individual who works in production technology and an engineer were in filling room RT-

9 on 1/26/01 and a technician for production was in filling room RT-9 on 1/9-11 & 13-15/01. There is no documentation that these individuals had been qualified to gown and enter the aseptic filling rooms.

There is no sink for hand washing at or near the gowning rooms. Goggles and rubber boots that are used in the aseptic filling rooms are stored in lockers that are not located in the aseptic gowning area. In addition, the goggles worn in the aseptic filling rooms are not sterilized. One individual's goggles were observed being stored on the outside of a boot.

The door from the gowning room to the aseptic corridor for filling rooms RT-5 through RT-9 and the door to filling room RT-3, and the doors to the aseptic corridors from filling rooms RT-5 through RT-9, RT-11, and RT-12 have handles that must be turned and pulled. One filling room operator was observed making several exits and re-entries into a filling room without changing gloves.

One operator in the filling room did not remove a wedding band, a walkie-talkie and a key chain before gowning-up, even though your firm's gowning procedure instructs filling room operators to do so. [REDACTED] a shift, each person in the aseptic filling rooms was to take rodac samples of his/her own gown and gloves before leaving the aseptic area. One person was observed to spray his gloves and gown with alcohol just before this rodac sampling procedure.

Failure to adequately validate your firm's aseptic filling process.

During media fills procedures were not consistent as to the areas to be monitored. For example, most of the media fill reports showed that [REDACTED] samples were taken upstream of the first sterilizing filter and [REDACTED] samples downstream of the first filter (between the first filter and final filter). No samples were taken after the second filter (final filter). All of the media fills for the various filling rooms had these four samples taken except for RT-6 and RT-7. For RT-6 only the upstream samples were taken and for RT-7 only the downstream samples were taken. Also, microbial air samples were taken near the filling nozzles during some but not all the media fills.

During the sterile fill validation for the bulk product, Alupent Inhalation Solution 0.4%, Lot 780503 (period covered 6/30/00-7/1/00) the viable microorganisms (cfu) on surface contact plates on the floor (front of machine) and on the floor (left of machine) were > [REDACTED]. This far exceeds your firm's specifications of [REDACTED] for counts for floors, walls, ceiling and machine surfaces for environmental surface testing for fill lines.

During the in-place sterilization of filling equipment (e.g. sterilizing filters, product lines, and filling needles) used during aseptic filling operations, a steam cup which encases the filling needles. With the exception of room RT-3, no biological indicators were used to monitor the outer surface of the filling needle assembly and the inner surface of the steam cup during the validation of this process. This is significant because there is no path for steam to flow between the outer surface of the outer needle and the steam cup. In addition, the ability of the steam sterilization cycle to sterilize the top surface of the steam cup was not challenged during the validation runs.

Validation of the in-place sterilization process did not include starting the cycle with product still in the system. This is significant because aseptic filling of most products takes several days and sometimes during this process the sterile fill system may be sterilized without changing the filters. When the filters are not changed product is drained out of the filters but can not be drained from the line between the filters and the filling nozzles.

During process validation for compounding products your firm only performed limited testing to assure proper mixing and homogeneity. Only [REDACTED] samples from the bulk tank and [REDACTED] samples from the beginning, middle, and end of filling were tested to assure proper mixing and product homogeneity. There is no indication that there was extensive sampling throughout the batch to show proper mixing and homogeneity e.g., Sodium Polystyrene Sulfonate Suspension.

In addition, there was no statistical analysis of assay results of the samples to show uniformity. The only requirement for the assay results of the [REDACTED] samples was that they be within specifications for bulk liquid and finished product. There was no requirement that the assay results even be close to each other.

Failure to adequately assure that each batch of liquid drug product is of uniform character and quality.

Mixing of liquid drug products is achieved using subjective mixing intensities as determined by visual criteria such as gentle, standard, and intense. As a result production records for most liquid products do not specify an agitator speed e.g., for Alupent lot 690552Z no specific agitator speeds or RPMs are listed.

During the production of Sodium Polystyrene Sulfonate, lot 156906 on 5/9/01 the FDA Investigators observed a vortex in the liquid being mixed in tank number 65 which involves mixing steps 7-10. During these steps a standard mix is utilized which is not suppose to have a vortex per your firm's training video.

Step 16 for the mixing of Sodium Polystyrene Sulfonate, lot 156906 called for an "intense" mix which is suppose to be at the maximum practical attainable speed. At this step the batch was thicker and there was a greater volume than in step 5. Step 5 was also an "intense" mix. However, in step 5 the mixer was set at a higher setting than for step 16.

When the procedure involves dissolving an ingredient during the production of liquid drug products the production records only indicate that the ingredient was to be dissolved and does not give a minimum mixing time e.g., Master Manufacturing Formula for Sodium Polystyrene Sulfonate Suspension USP and Alupent Inhalation Solution 0.6%.

Failure to have adequate procedures in place that would assure the stability for the intended period of use for some of your drug products.

There is no written procedure to adjust the release assay specifications for drug products based on stability data. For example, for Midazolam Hydrochloride Oral Solution 2 mg/ml (ANDA 75-873) the release specifications and stability requirements are the same,

██████████ of label claim for Midazolam. A review of the stability data indicated a drop in potency from the initial assay result at accelerated storage condition of over 7% after ████████ months and a drop of about 4% after ██████ months at room temperature storage. Based on the stability data, if a batch of the drug product were released at 94% of label claim for Midazolam, the batch could be sub-potent before ██████ months.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and in the FDA 483 issued at the closeout of the FDA inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems.

You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems you must promptly initiate permanent corrective actions. 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. Also, NDA, ANDA or export approval requests may not be approved until the above violations are corrected.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action being initiated by the Food and Drug Administration without further notice. Possible actions include, but are not limited to, seizure and/or injunction.

We received the June 4, 2001 letter from Peter Dickinson responding to the Form FDA 483 issued to management at the close of the FDA inspection. This letter of response did not adequately address all of the deficiencies observed during the inspection.

We are aware that your firm has voluntarily agreed to officially close down filling room RT-3 and not make any more sterile products using the older UDV equipment in that filling room. However, the letter did not indicate what you plan to do about product in commercial distribution that was aseptically processed in room RT-3.

The letter also indicated that improvements will be made to the gowning rooms for other aseptic filling rooms and to aseptic procedures but construction and procedural changes will not be completed until the end of this year. In the mean time does your firm plan to continue using these gowning rooms as part of your aseptic processing operation? What do you plan to do about product in commercial distribution that was aseptically processed in these filling rooms?

In addition, some of your firm's commitment to making changes in your manufacturing processes only pertained to new products e.g., the commitment to test more samples during validation; the commitment to use actual mixer speeds instead of subjective mixing intensities such as gentle, standard, and intense; and mixing times for dissolving ingredients in your liquid drug products. There was no commitment to address the problems with existing products.

Please notify this office in writing within fifteen (15) working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each

step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within fifteen (15) working days, state the reason for the delay and the time within which the corrections will be completed.

Your response to this Warning Letter should be sent to Evelyn D. Forney, Compliance Officer, Food and Drug Administration, 6751 Steger Road, Cincinnati, Ohio 45237.

Sincerely,



Henry L. Fielden
District Director
Cincinnati District

Cc: Peter J. Dickerson, Vice President of Operations
Roxane Laboratories, Inc.
1809 Wilson Road
Columbus, Ohio 43228