



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Mid-Atlantic Region
D1416 B

Telephone (201) 331-2906

January 22, 1998

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

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

RELEASE

Richard Rowinski
Vice President
Worldwide Quality Control/Quality Assurance
Bristol-Myers Squibb Company
One Squibb Drive, P.O. Box 191
New Brunswick, NJ 08903-0191

REVIEWED BY RHA
C.O.

2/24/98
DATE

File No.: 98-NWJ-12

Dear Mr. Rowinski:

During a comprehensive inspection of your manufacturing facility located at One Squibb Drive, New Brunswick, NJ, conducted September 15 - November 6, 1997, Investigators from this office documented serious deviations from current Good Manufacturing Practices (cGMP's), Title 21, Code of Federal Regulations (CFR), Parts 210 & 211. These deviations were noted on the Form FDA483, List of Inspectional Observations, issued at the close of the inspection.

The above stated inspection revealed that drug products manufactured at your facility are considered adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug & Cosmetic Act (ACT), in that the methods, or the controls used in manufacturing are not in conformance with cGMP's, as follows:

1. Manufacturing process validation has not been completed for the following marketed injectable products: Delestrogen 40 mg/ml, Delestrogen 10 mg/ml, Delatestryl, Kenalog, Vetalog, Phosphotec, Prolixin, Pronestyl 500 mg/ml. Also, the vial filling process has not been validated for any of the above listed products, with the exception of Kenalog and Vetalog.
2. Process validation for several product lines was found to be inadequate. For example:
 - A. Two of the three process validation batches for Sincalide for Injection failed to meet pre-established acceptance criteria for Gall Bladder Contraction Assay. Validation and QC test data for these lots were grouped together to produce acceptable results.

was there evidence to support that the [REDACTED] could not be the cause of the low filled vials. This lot is being held for reworking.

3. Retest practices used to invalidate original out-of-specification (OOS) test results and subsequently release batches, were incomplete and unjustified by established written procedures. Individual product failures were reviewed by the QC Statistics group who formulated a resampling and testing plan on a case-by-case basis at the time of the failure. For example:
 - A. Original failing "content" (weight) results for Azactam batch #7E07503 were invalidated by resampling and testing 7 additional samples. This batch was released after obtaining a passing average of retest results that was within USP limits. However, 4 out of the 7 samples retested, as well as the average of the retests, failed to meet the firm's release limit. However, since the samples met USP specifications, the batch was released. There was no data to invalidate the original OOS result.
 - B. During release testing of Choletec batch #6K76360, 10 original and 20 additional vials failed to meet the USP RSD specification for weight variation. Subsequently, 60 additional vials were tested after the original failures, and the batch was released after passing results were obtained. The cause of the original failures was not determined.
 - C. Sincalide Injection batch #5J66972 failed the gall bladder assay at 12 month stability testing. Eight additional samples were taken from the batch, combined with the original seven samples (5 of which were failing), to produce an acceptable result. This batch was released, with no documented investigation into the original failing results.
 - D. Following an out-of-specification content uniformity result during release testing of Vetalog Suspension batch #6E06998, and a retest which confirmed this deviation with a result outside of USP limits, 43 additional vials were sampled, and passed USP limits. The failure was considered isolated and only one tote of vials was rejected, while the remainder of the batch was released.

4. There was inadequate documentation to support manufacturing processes or process deviations. For example:
 - A. Batch records for aborted media fill run #1996-009 on filling line 600, were discarded after 90% of the run was completed. Filled vials were not incubated or examined for contamination.
 - B. There was no documentation to support the conclusion that a misplaced "set-up" vial was the cause of the OOS content uniformity assay result for Kenalog Suspension batch #6J99561. Quality Assurance recommended the rejection of the first filling tote, and released the remaining totes of vials.
 - C. There was no documentation of any routine or non-routine maintenance performed on any of the sterile filling equipment.
5. Your firm has failed to conduct and document complete investigations following out-of-specification results, nor has it examined possible effects the discrepancy may have had on other batches manufactured. For example:
 - A. During aseptic processing of Fungizone batch #6L86849, 13 CFU's of gram negative rods were recovered from the filling head. The investigation considered this incident isolated, did not speciate the organisms, and did not evaluate the finished product quality. Microbial contamination could have been introduced into the vials prior to the sample being collected at the filling head where 13 CFU's were recovered. This is particularly important for aseptically filled products which do not undergo any further sterilization process.
 - B. 59 CFU's were recovered from a mechanic's glove who had performed the aseptic hose connection in the filling area during processing of Azactam Batch #6D96041. There was no further evaluation into the organism or finished product.
 - C. There was no documented investigation or preventative actions taken following the abortion of Vetalog batch #54385-008 due to the possibility of a glass chip in the compounding tank.
 - D. There was no investigation into glass fragments found in reconstituted Fungizone IV batch #'s 6C89479 and 6C89490, which have been released for marketing.

- E. A Quality Unit investigation did not include increased sampling of the finished product or retraining of the operator following an OOS microbial result (8 cfu's/rodac), which was obtained from the operator's glove during loading of partially stoppered vials containing Kinevac (Sincalide) Injection batch #6E76685.
 - F. There was inadequate follow-up into high vial accountability following packaging of Isovue 200 batch #7E07107. At the conclusion of packaging, there were 22 extra vials.
 - G. There was no investigation into a low assay value obtained during release testing of Sincalide for Injection batch #6B76239. Following this failure, the expiration date was reduced from 18 months to 12 months without justification, and the batch was released.
6. There was inadequate evaluation of impurities in Choletec. During manufacturing of bulk active ingredient, Mebrofenin batch #55113-002, an unidentified, insoluble impurity caused clogging of the sterilizing filter. Investigation into this impurity was inadequate in that it did not determine the source of the impurity; there was no validated analytical method to evaluate levels of the impurity; the solubility of the impurity has not been determined; there was no evaluation of levels of this impurity in finished product lots on the market; and specifications have not been established for this impurity. There are currently two finished product lots released for distribution using this active ingredient: 7A98053 and 7D86139.
7. There were no established impurity limits for the following finished product injectables: Fungizone, Kenalog, Vetalog, Equipoise, Prolixin, Delatestryl, Tubocuraine Chloride, Vesprin. For 3 batches of Fungizone which were evaluated for impurity levels, the range was [REDACTED] for "Other Impurities".
8. Firm practices and procedures regarding microbiological and environmental testing were inadequate. For example:
- A. Bioburden sampling for several bulk pre-sterilized solutions is only performed on one batch per year per product. Additionally, there was no routine Bacterial Endotoxin Testing performed on the following active ingredients that were used in the formulation of finished product injectables: Cyanocobalamin, Estradiol Valerate, Fluphenazine Decanoate,

Fluphenazine Enanthate, Fluphenazine HCl, Mebrofenin, Methylene Diphosphonic Acid, Procainamide HCl, Sodium Pyrophosphate, Testosterone Enanthate, Triflupromazine HCl, and Tubocurarine Chloride.

Also, the firm has written microbial limits for only one of the 24 active ingredients used in finished product injectables. Only 5 of 53 inactive ingredients were monitored for microbial quality.

The lack of filter validation, combined with the current bioburden and endotoxin sampling programs does not assure product quality throughout all processing steps.

- B. Environmental monitoring in Class 100 filling areas is inadequate. An eight hour filling period only requires 2 eleven minute viable air samples, and sampling from only one person associated with the aseptic filling process. This does not provide representative conditions for an aseptic filling process which can take up to 12 hours to complete, and up to five people present.
 - C. WFI sampling procedures do not mimic actual usage procedures. As per Procedure No. 720, production flush times are 1 minute. Documented flush times for resamplings during investigations range from 5 minutes to 20 minutes.
 - D. There was no data to support that sterile media fill incubation temperatures of 32 +/-2°C for the first seven days and 25 +/-2°C for an additional seven days would allow the growth of normal flora found in products.
9. Investigations into exceeded action limits do not routinely include the identification of recovered microorganisms to the genus and species level, as per SOP #5-3. For example: On two separate occasions, action limits were exceeded when samples were taken from employees' gloves. In both instances, organism identification was not documented in the investigation report, as required by SOP #5-3. Batch release decisions were made without regard to the species of organisms found.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the current Good Manufacturing Practice Regulations. Federal agencies are advised of the issuance of all warning letters about drugs so

Bristol-Myers Squibb Co.
New Brunswick, NJ 08903
Warning Letter 98-NWJ-12

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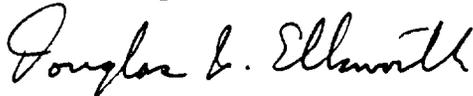
that they may take this information into account when considering the award of contracts. You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Possible actions include seizure and/or injunction.

We are in receipt of your written response, dated November 18, 1997 to the FDA483 List of Inspectional Observations. We have reviewed your response which indicates disagreement with many of the observations listed. We would like to meet with you to discuss these issues and necessary corrective actions.

You should notify this office in writing, within 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 15 working days, state the reason for the delay and the time within which corrections will be completed.

Your reply should be sent to the New Jersey District Office, FDA, 10 Waterview Blvd., 3rd Floor, Parsippany, NJ 07054, Attention: Joy R. Kozlowski, Acting Compliance Officer.

Sincerely,



DOUGLAS I. ELLSWORTH
District Director
New Jersey District

JRK:np