



DEPARTMENT OF HEALTH AND HUMAN SERVICES

4/29/98
Food and Drug Administration
Atlanta District Office

HEI-35 d1704b

60 8th Street, N.E.
Atlanta, Georgia 30309

March 30, 1998

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Charles M. Bentley
President/CEO
S.S.S./Pfeiffer Company
71 University Avenue
Atlanta, Georgia 30315

WARNING LETTER

Dear Mr. Bentley:

An inspection of your drug manufacturing facility was conducted between February 23 and March 18, 1998, by Investigator Leah M. Andrews and Chemist Don W. Thompson. Our inspection revealed several significant deviations from the Current Good Manufacturing Practice Regulations (GMPs) as set forth in Title 21 of the Code of Federal Regulations (21 CFR), Part 211. These deviations cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act).

You have failed to adequately validate the manufacturing processes for all of your drug products. You could not provide documented evidence which established a high degree of assurance that the manufacturing processes in use could consistently produce products meeting their predetermined specifications and quality attributes, both initially and throughout their labeled expiration date. This is particularly applicable to the products transferred from the Pfeiffer facility in Pennsylvania. You have attempted to concurrently validate these transferred products at your facility. This effort has been complicated due to the fact that the original processes had never been validated at Pfeiffer and no in-process data or specifications existed. In addition, the batch records for the transferred products were vague and failed to include critical manufacturing parameters.

You have failed to appropriately evaluate the Pfeiffer products and establish meaningful processes and parameters for the manufacture of these validation lots. This failure is evidenced by the number of initial batch failures, required reworks, and subsequent changes in the manufacturing processes. Most of the initial tablet batches were reworked and could not be used as validation batches due to the problems encountered.

You have failed to appropriately investigate and respond to out of specification (OOS) analytical results noted during in-process, finished product release, and stability testing. Numerous inconsistencies were noted in the handling of data and the decisions made in response to these OOS results. Many of these failures were attributed to the problem of improperly validated methods, although this could not be substantiated based on the available documentation. You have neglected to conduct failure investigations as appropriate. Any failure of a batch, or any of its components, to meet any of its specifications must be thoroughly investigated, whether or not the batch has been distributed.

This failure to react and properly investigate is exemplified by the litany of problems and failures associated with Rid-A-Pain lot 79101. This was the first lot of this product manufactured at this location. This lot failed in-process blend uniformity testing. These results were confirmed by retesting. Finished product release testing of Segment 3 failed content uniformity also. The analytical method was changed and a retest using ten additional samples gave acceptable results. Segments 1 and 2 were not retested using the new method. The lot was released and placed on accelerated stability. The 30 day accelerated testing failed aspirin assay and had initial dissolution failures. A retest contained additional dissolution failures. The method was changed twice and acceptable results were obtained.

The 60 day accelerated testing revealed acetaminophen assay and dissolution failures. The method utilized however was the initial method used at product release. A retest was conducted using the new method which also yielded dissolution failures. The product was retested a second time utilizing the new method and failing results were obtained. The recommendations from the OOS investigation were to further develop the sample preparation for assay and to change the formulation of the product. The 90 day accelerated testing again revealed failing assay and dissolution results. An OOS investigation was conducted and the same recommendations were made. No corrective action has been taken in regards to this product which remains in distribution. This decision is reportedly due to your firm's stated belief that this is a method validation problem. There was no documented rationale presented which would substantiate this conviction. You have failed to acknowledge that these OOS results could be indicative of true product quality problems. Our investigator was informed that no action would be taken unless the room temperature stability sample failed testing. Although this product was manufactured in October 1997, no room temperature stability samples have been tested.

Several instances were noted of your failure to conduct investigations into OOS results or the conducting of incomplete investigations. Krolephrin #1 syrup lot 62601 was reprocessed due to the failure of the [REDACTED] to dissolve. No investigation was conducted to determine the cause of the problem or prevent reoccurrence. Our review of the above lot of Rid-A-Pain revealed several deficiencies. The in-process blend uniformity failures were not investigated. The results of the OOS investigation conducted into the finished product release testing failures could not be supported with available data. The 30 day accelerated stability test failures were not investigated. Rid-A-Pain lot 10015 had failures at the 24 month test station conducted in November 1997. The retest performed in February 1998 again revealed dissolution failures. The investigation is considered to be ongoing by your firm. OOS investigations were noted to

be incomplete and the procedures for conducting these investigations were not followed for environmental monitoring failures noted during the production of lots 85 and 88 of 20/20 eye drops.

You have failed to establish validated analytical methods to assure that they have the required accuracy, sensitivity, specificity, and reproducibility. Many of the methods validated since our previous inspection have been brought into question by S.S.S. management due in part to the short period time in which they were developed. You freely acknowledge that problems with the methods are becoming evident as products are manufactured and subsequently tested. No additional work has been undertaken to investigate these questionable methods unless it is in direct response to a failed analytical result. Previously validated methods have been changed when in-process, finished product, and stability testing failures occurred. No additional analytical data or documented rationale was available to justify these changes in methodology.

Our inspection noted inconsistencies in the method validation protocols for similar products containing similar ingredients. There was no formal analytical methods transfer between the Pfeiffer facility and S.S.S. Problems with the initial validation attempts have already been acknowledged. You should make a concerted effort to assure that your next efforts are scientifically valid and standardized. These inconsistencies were noted in the requirements for accuracy, method precision, ruggedness, and linearity.

The initial validation for Kolephrin/DM caplets failed the accuracy acceptance criteria for acetaminophen. Although the validation failed, the method was allowed to be used for product release. The assay was later revalidated using a new protocol. The new protocol expanded the accuracy acceptance criteria and the acetaminophen passed testing. Concern was also raised as to the wide range of variability allowed with some of the accuracy and precision RSD's and linearity values currently employed with your method validation protocols.

The available stability data from your accelerated stability program was inadequate to support the tentative expiration date for many of your products. Products are assigned a tentative expiration date of up to three years based on [REDACTED] days of accelerated stability testing. The parameters in use were reviewed by the Center for Drug Evaluation and Research and found to be unacceptable for the assigning of a three year expiration date. Although you have room temperature data for some of these products, which were transferred from Pfeiffer, the manufacturing processes are not the same as currently employed at S.S.S. The manufacturing process for tablets has been significantly altered as they are now [REDACTED] and [REDACTED]. Some of these products were never manufactured at Pfeiffer.

You have failed to assure that each person engaged in the manufacture, processing, and packaging of your drug products have the education, training, and experience to enable that person to perform their assigned functions. There is no formal training program for the employees in the chemistry and microbiology laboratories to evaluate their analytical skills. One employee involved in the collection of environmental monitoring samples had never participated in a media fill and had no documented training other than viewing a video on aseptic filling.

This employee was identified as the potential cause of high environmental monitoring counts noted during the filling of a lot of eye drops.

Several instances were noted where the written procedures on file were not being followed by your employees. These procedures included testing of raw materials, retesting of active raw materials, allowable temperature parameters for room temperature stability studies, growth promotion testing on air sampling media, and the cleaning schedule for the clean room.

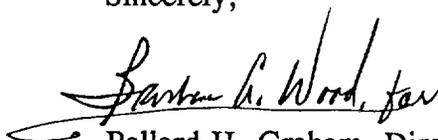
You have failed to appropriately validate the cleaning procedures currently in use. Validation had been completed, which included a documented review of the data and a final report, on only one piece of equipment. No evaluation has been conducted to determine the adequacy of the cleaning process in removing the sanitizing solution used on multiple pieces of equipment or its effectiveness in removing the surfactant cleaner used. No evaluation had been conducted to determine if pediculicide residues are removed from the non-dedicated filler in use.

Many of the above deviations were included on the FDA 483 (Inspectional Observations) which was issued to, and discussed with, you at the conclusion of the inspection. The violations noted in this letter and in the FDA 483 could be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. The deviations discussed above and included on the FDA 483 should not be construed as an all inclusive list of violations which may be in existence at your firm. It is your responsibility to ensure adherence to each requirement of the Act.

You are responsible for investigating and determining the causes of the violations identified by FDA. You should take immediate actions to correct these violations. Failure to promptly correct these deviations may result in legal sanctions provided by the law such as product seizure and/or injunction, without further notice to you. Federal agencies are advised of the issuance of all warning letters involving drugs so that they may take this information into account when considering the award of contracts.

You should notify this office in writing, within fifteen (15) working days of receipt of this letter, of any additional 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 response should include your rationale for continued distribution of the Rid-A-Pain product discussed above. In light of some of the comments made to our investigator at the closeout discussion, you may want to arrange a meeting to discuss these observations in greater detail at our office. Your response should be addressed to Philip S. Campbell, Compliance Officer, at the address noted in the letterhead.

Sincerely,

A handwritten signature in cursive script, appearing to read "Ballard H. Graham, Director".

Ballard H. Graham, Director
Atlanta District