DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

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WARNING LETTER

January 14, 1999

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Jan Leschly, Chief Executive Officer
SmithKline Beecham
One Franklin Plaza
Philadelphia, PA 19101

Dear Mr. Leschly:

We have completed our review of the inspection of your parenteral manufacturing site located at 801 River Road in Conshohocken (Upper Merion), PA in Buildings 16 and 16A between October 13 and November 16, 1998 performed by the following Philadelphia District personnel: Monica S. King, Debra L. Pagano, Megan F. McLaughlin, Michael Gurbarg, Daniel Becker and Ann L. deMarco. This inspection revealed significant deviations from Current Good Manufacturing Practices (CGMPs) in the manufacture of sterile pharmaceutical products. A copy of the FDA 483 listing these observations is enclosed. These CGMP deviations cause aseptically processed products manufactured in these facilities, including both the cephalosporin products and Hycamtin®, to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (FD&C Act).

Our review also included your company's response letter dated December18, 1998 from Dr. Peter Manni. This letter indicates that many corrections have been initiated and additional ones will be implemented over time. However, we would like to point out that this is not the first corrective action plan your firm has implemented to assure compliance with CGMPs. A prior inspection at that site, performed 8/27-9/18/97, also revealed significant deviations from CGMPs. A copy of the FDA 483 issued at that time is also enclosed. The inspection was a preapproval audit of [redacted] for Injection formulated in Building 16A. At the conclusion of the inspection, FDA personnel requested that management evaluate operations in Building 16, in addition to those of Building 16A, since some of the problems appeared systemic. In response, SB management voluntarily proposed a very extensive corrective action plan.

In the thirteen months since we concluded the prior inspection, management at Upper Merion has initiated at least [redacted] internal audits they say were designed to identify problem areas and determine root causes. Yet despite these numerous audits, FDA personnel identified serious deficiencies during the current inspection - deficiencies that impact on the sterility assurance of the injectable products you manufacture at Upper Merion. Since the December 18 letter appears similar to the prior corrective action proposal in many ways, we are not fully convinced that this plan will eliminate root causes. Specific areas of concern include, but are not limited to:

1) Quality Control/Assurance has not consistently discharged their responsibilities for overseeing procedures impacting on quality and purity as follows:

   a) They failed to recognize and investigate significant environmental trends and out-of-specification microbial results in sterile areas. For example, environmental monitoring data identifies [redacted] instances of microbial contamination of critical equipment surfaces during the prior 9 months, [redacted] of which involved contamination of the filling needle area. On 8/28/98 microbial contamination was identified on five critical sites in fill room 3, including [redacted] CFU on one employee's gloves, [redacted] CFU on the [redacted], [redacted] CFU on the filling needle area, [redacted] CFU on the turntable, [redacted] CFU on the alcohol container.

   b) They failed to assure that SOPs are followed which prohibit employees who fail gown testing during media fills from working in the sterile core until they are retrained. For example, one employee failed gown testing on 7/22/98 and was not retrained until 10/9/98; another employee failed gown testing on 7/23/98 and was not retrained until 10/5/98. This employee also exceeded action limits for gloves during actual product filling on [redacted] other occasions in the 9 months before the date of retraining, including a microbial count of [redacted] on 9/14/98. This is the same employee mentioned in 1(a) above who had [redacted] CFU on gloves on 8/28. Both employees continued to work in the sterile core before retraining occurred.

The corrections described in your response center on improved procedures and data trending systems. However, the above deficiencies indicate that procedures are not being followed and that potentially serious events and trends are not always recognized despite data that are readily available. Similar deficiencies were addressed at the conclusion of the 1997 inspection of [redacted] for injection. That inspection revealed that Quality Control/Assurance had authorized use of untested, unqualified, industrial grade [redacted] in direct contact with the bulk parenteral solution without addressing its potential impact on product purity, and without following standard procedures that require qualification of ingredients and equipment before use.

Our current inspection is similar in that Quality Control/Assurance failed to respond when data repeatedly indicated a problem with sterility of critical surfaces such as the filling needle assembly. In fact, Quality Control/Assurance has established identical microbial limits for very diverse surfaces which raises concern about their ability to assess environmental data. For example, the Alert and Action limits for microbial contamination of the filling needle assembly are identical to the limits for contamination of the trash can and the telephone. This type of one-spec-fits-all approach can cause personnel to lose perspective in assessing the impact on sterility assurance. Certainly, microbial contamination of the filling needle assembly must be assessed more critically. In fact, any contamination of the filling needle assembly is unacceptable.

The failure to recognize serious environmental trends and make informed judgments is very clearly demonstrated when employees were permitted to work in the sterile core despite known problems with maintaining sterile technique. One of these employees repeatedly exceeded microbial action

limits but was permitted to routinely operate in the sterile core without consideration of the potential impact on finished product.

In addition, Quality Control/Assurance routinely tests additional samples of finished product in connection with investigations of manufacturing anomalies and environmental contamination. FDA places great emphasis on process simulation studies (media fills) and environmental monitoring programs precisely because laboratory testing alone cannot assure sterility across a batch. Therefore, while additional sterility testing can be informative in some circumstances, it cannot be used as justification for poor employee practices. Please clarify what significance additional sterility testing, and environmental data overall, plays in product release decisions.

2) Responsible management failed to assure timely corrective action as illustrated by the following examples: Environmental data for the sterile side of the autoclave trough showed microbial contamination [redacted] from 2/98 because of a leaking steam pipe. The leak was not repaired until 10/31/98. In addition, the 11/4/98 report of delinquent work orders indicates that requests for leak testing of [redacted] lyophilizer compressors, identified as "critical" priority, were open from [redacted] to [redacted] days.

Despite the prior corrective action plan and observations by FDA investigators during other inspections, management has repeatedly failed to assure that requests for equipment maintenance and repair are handled in a timely fashion. The inability to remedy this very fundamental issue is of great concern since product sterility and quality are so intimately dependent on equipment performance. It is unclear how the additional review of maintenance work orders described in the response as corrective action is sufficient to eliminate these delays. Please explain how this is so and why such measures had not been implemented previously.

This latest response letter from Dr. Manni reports that you have recently hired more personnel and are recruiting additional "management resources." Please note that Dr. Manni initiated a major reorganization of personnel and hired additional employees prior to the August 1997 inspection. Yet these personnel changes failed to eliminate CGMP deficiencies. The CGMPs require that you maintain an adequate number of qualified employees for all activities involved in the manufacture of your drug products. Please clarify how long it will take for these new employees to be fully trained and how you will assure you can achieve full compliance with CGMPs in the interim.

The CGMP deviations identified above and on the FDA483s issued to your firm are not an all-inclusive list of the deficiencies at your firm. FDA inspections are audits which are not intended to determine all deviations from CGMPs that exist at a firm. Furthermore, it is not the role of the FDA to inspect a firm into compliance. As top management, the responsibility to ensure that all requirements of the FD&C Act and its associated regulations are being met belongs to you.

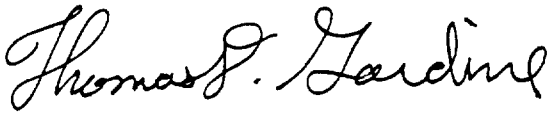
You should take prompt action to correct all CGMP deficiencies. In addition, please advise us what you intend to do about products on the market that were manufactured under questionable environmental conditions.

Failure to promptly take corrective action may result in regulatory action without further notice. Possible actions include seizure and/or injunction. 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. Also, the Philadelphia District Office will recommend disapproval of any new applications listing your firm as the manufacturer of sterile drug products.

Please respond to this letter within fifteen (15) days of receipt. Since a 13 month period for voluntary compliance with CGMPs has already elapsed, please outline your commitment to ensure full compliance with CGMPs without any further delay.

Your reply should be directed to the attention of Ann L. deMarco, Compliance Officer, at the address noted on the letterhead.

Sincerely yours,



Thomas D. Gardine
District Director
Philadelphia District

cc: Robert E. Bastian, Director
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