



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

3/11/97  
D1241B

PHILADELPHIA DISTRICT

**WARNING LETTER**

900 U.S. Customhouse  
2nd and Chestnut Streets  
Philadelphia, PA 19106  
Telephone: 215-597-4390

97-PHI-17

March 6, 1997

**CERTIFIED MAIL**  
**RETURN RECEIPT REQUESTED**

Michel de Rosen, Chairman and CEO  
Rhône-Poulenc Rorer Pharmaceuticals, Inc.  
500 Arcola Drive  
Coliegeville, PA 19426-0107

GEN.	SPEC.
RELEASE	
F# _____	DATE <u>3-11-97</u>
Reviewed by: <u>Michel de Rosen, CEO</u>	

Dear Mr. de Rosen:

Between September 30 and October 24, 1996 Philadelphia District Investigator Denise M. DiGiulio and Philadelphia District Chemist Michael Gurbarg, conducted an inspection of your contractor [REDACTED] located at [REDACTED] which manufactures theophylline extended release pellets for you. During the inspection, deviations from Current Good Manufacturing Practices (CGMP) regulations codified as Title 21 Code of Federal Regulations (21 CFR) Parts 210 and 211 were documented. These deviations cause theophylline pellets to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (FD&C Act). These adulterated beads are subsequently shipped to a [REDACTED] plant in [REDACTED] where they are encapsulated as Slo-bid™ extended release capsules for commercial distribution. The key deviations which result in adulteration are summarized as follows:

1. Production and process control procedures for theophylline pellets are not designed to assure that each batch of pellets will have the quality and purity it purports to have [211.100(a)].
  - a) It is your practice to selectively blend aliquots of four different batches containing non-conforming pellets in order to produce a final product that meets dissolution specifications. The batch to batch variability in dissolution profiles for theophylline pellets raises concerns about the adequacy of your process to produce uniformly coated extended release pellets.
  - b) Either of two different grades of theophylline active drug substance can be used, at the discretion of the operator, depending on whether "fast" or "slow" pellets are intended for subsequent blends. Also, there are no discriminating specifications for physical characteristics of the two grades of theophylline raw material which account for these functional differences.
  - c) Theophylline time release pellets are prepared by hand coating theophylline powder separate times, and pharmaceutical glaze solution times, to

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beads as they rotate in a coating pan. This manual process results in formation of agglomerates and in an accumulation of ingredients on the sides of the coating pan. Operators sporadically scrape this undistributed material off of equipment surfaces and manually break up agglomerates by randomly sieving or by hand crushing them during processing.

2. Sample size for testing cannot assure that quality across a batch is validly assessed [211.160(b)]. We believe that the variability inherent in your manual manufacturing process cannot be assessed with a singlet determination. Furthermore, quality is literally tested into the product since it is resampled and retested to meet final product specifications for dissolution.
3. Failure to evaluate the quality standards of theophylline pellets to determine the need for changes in manufacturing or control procedures [211.180(e)].

We have reviewed Dr. Ramona Lloyd's November 11, 1996 response to the FDA 483 issued to Lane Sattler, Manager of Quality on October 24, 1996. Dr. Lloyd's letter fails to recognize our concerns relating to theophylline pellets. In this regard, we would like to point out that the FD&C Act states in section 501(a)(2)(B) that a drug is deemed adulterated if the methods, controls or facilities used for manufacture do not conform with "current" good manufacturing practice. The preamble to the final drug regulations published 9/29/78 explains that Congress intended the phrase "current" to have a unique meaning, so that good manufacturing practice regulations will represent "sound, current methods, facilities and controls for the production of drugs". Dr. Lloyd's comment that your current manufacturing process was approved in ANDAs you submitted many years ago does not address our concern that you have failed to manufacture with processes and controls that, by present standards, would be considered sound and current and which will assure reproducibility of quality characteristics for every batch of pellets.

The above is not intended to be an all-inclusive list of violations. As top management, it is your responsibility to ensure that all requirements of the FD&C Act and its associated regulations are being met.

You should take prompt action to correct the deviations cited for the referenced product and for any other products where these deficiencies in controls apply. 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.

Please advise this office in writing within fifteen (15) days of receipt of this letter of the

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specific steps you have taken to correct cited 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 directed to the attention of Ann L. deMarco, Compliance Officer, at the address noted on the letterhead.

Sincerely yours,

  
Charles B. Thorne  
Acting District Director  
Philadelphia District

cc: Robert E. Bastian, Director  
Division of Primary Care and Home Health Services  
Pennsylvania Department of Health  
P.O. box 90  
Harrisburg, PA 17120