



DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

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January 7, 1997

**WARNING LETTER 97-NOL-24**

**CERTIFIED MAIL  
RETURN RECEIPT REQUESTED**

Mr. Peter J. Neff  
President and Chief Executive Officer  
Rhone-Poulenc, Inc.  
117 Campus Drive  
Princeton, New Jersey 08540

Dear Mr. Neff:

During an October 16-18, 21, and 25, 1996, inspection of your active pharmaceutical ingredient (API) manufacturing facility and your contract laboratory (██████████), both located in Luling, Louisiana, our investigator uncovered significant deviations from good manufacturing practices in the manufacture, control and testing of bulk Acetaminophen (APAP). These deviations cause this API to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act). Section 501(a)(2)(B) of the Act requires that all drugs be manufactured, processed, packed, and held according to current good manufacturing practices (CGMP's). No distinction is made between active pharmaceutical ingredients and finished pharmaceuticals, and failure of either to comply with CGMP's constitutes a failure to comply with the requirements of the Act.

Examples of failure to follow CGMP's in the production of APIs include, but are not limited to, the following:

1. Data is inadequate to show that the deionized (D.I.) water used in final isolation and purification steps is suitable for its intended use and does not adversely alter the quality of the API. In addition, the D.I. water system is not frequently sanitized and routine microbiological monitoring is inadequate to ensure water of appropriate chemical and microbiological quality at all points of use.

Our inspection disclosed that deionized water is used in the Acetaminophen U.S.P. manufacturing process to wash the centrifuge wet cakes before drying and to rinse

manufacturing equipment. DOC ID: LAP/SOP-PRD-023 states the D.I. water is produced from source water obtained from the Mississippi River that is sent to [REDACTED] water treatment facility where it is filtered, clarified and stored. This clarified water, reportedly containing silica, metallic ions, and coliform bacteria is then sent to the demineralized water treatment facility. This is again filtered, passed through a cation resin bed, an anion resin bed, a mixed D.I. bed, and an ultraviolet treatment unit on-line before being used at the APAP facility.

This D.I. water system has reportedly been in operation since 1978, but has not been validated to show that the deionized water used in final isolation and purification steps is suitable for its intended purpose and does not adversely affect the quality of Acetaminophen batches. In addition, the D.I. water system is not frequently sanitized (i.e., no sanitization SOP exists) and routine microbiological monitoring is inadequate to ensure water of appropriate chemical and microbiological quality for use in the APAP process. The D.I. water is continuously monitored by an on-line conductivity meter and is checked daily for turbidity. Microbiological monitoring, however, is limited to sampling two locations of the D.I. water distribution loop once per month and testing these for coliform bacteria.

DOC ID: LAP/SOP-PRD-002 states that the D.I. water used in the APAP process must meet the applicable EPA drinking water standards. The FDA has long maintained that potable water meeting EPA's National Primary Drinking Water Regulations (NPDWR) is acceptable for use in the early chemical synthesis stages of an API process, where high chemical quality is unnecessary. However, if water is used in later processing steps, such as the final wash of the filter cake or if the API is crystallized from an aqueous system, the water should be of a higher chemical and microbial quality, either meeting or exceeding the specifications for Purified Water, U.S.P.

Because of the well-recognized potential for microbial growth in deionizers used to produce purified water used in later isolation and purification steps, such systems must be properly validated and controlled. A typical validation program involves intensive daily sampling and testing of critical points of use for both chemical and microbial attributes for at least one month. In addition, the validation should account for seasonal variations in the quality of the source or feed water that may alter the functioning and efficiency of water pretreatment equipment and the deionization resin beds. Once validated, D.I. water systems require periodic regeneration, sanitization and microbiological monitoring to ensure water of appropriate microbiological quality at all points of use.

Please submit a written validation protocol for the deionized water system. This protocol should address the quality of the feed water, describe the pretreatment and D.I. equipment, and identify critical process parameters and operating ranges. It should also specify the sampling and test data to be collected to establish reproducibility and reliability of the system and to evaluate effects of seasonal changes. Furthermore, the validation should confirm the

appropriateness of alert/action levels and corrective actions taken when D.I. water samples exceed microbial limits or when objectionable organisms (e.g., *Salmonella*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*) are recovered from water samples.

2. The change control system in place is incomplete in that it does not clearly specify how to evaluate all anticipated and unanticipated changes in components, facilities, support systems, equipment, processing steps, and packaging materials that may affect the production and quality of the Acetaminophen active pharmaceutical ingredient.

Section III of Document ID: LAP/SOP-GMP-001, dated August 30, 1995, states that the first step in the validation of process change is to determine if a potential action, will, in fact, constitute a change to the process or the quality attribute of the finished product. The document also classifies GMP impacted changes into two types - those that are outside of accepted manufacturing limits, and those within accepted manufacturing limits but which have some potential for impacting the GMP. However, this document seems to address only changes in process parameters and it lacks action steps to be taken to insure that changes are properly managed. Furthermore, no documentation was provided during the inspection showing how all changes are approved, implemented, and most important, how changes are evaluated to determine the impact that these may have (i.e., carry-overs of impurities) on the Acetaminophen synthesis process or the quality of the final API.

To ensure a continued state of process control, the FDA expects API manufacturers to establish and set up a formal change control system to evaluate all changes that may affect the production and control of the active pharmaceutical ingredient. These written procedures should provide for the identification, documentation, appropriate Q.C. review and approval of both anticipated and unanticipated changes in components, facilities, support systems, equipment, processing steps, and packaging materials. The evaluation should determine if and to what extent revalidation is needed and specify additional testing (i.e., API stability, impurity profiles, polymorphism, or other physical attributes) that will be conducted to evaluate the potential impact of any changes on the critical attributes of the API.

3. Process validation studies do not include data to show that reprocessing or reworking operations for Acetaminophen U.S.P. have been validated and resulted in batches that comply with all established standards, specifications, and characteristics.

Document ID: LAP/SOP-GMP-003, dated August 30, 1995, allows for the reprocessing or reworking of Acetaminophen batches that have failed to pass product quality specifications or which have been returned by customers. For example, Page 4 of the Acetaminophen U.S.P. Validation Report, approved on September 26, 1995, shows that Acetaminophen Lots ~~XXXXXX~~ failed to conform to release specifications for ~~XXXXXX~~ Stability and

Limit of Color due to improper pre-treatment of the carbon tower and exhaustion of the carbon, respectively. In addition, some lots (i.e., [REDACTED]) have been returned due to the presence of microscopic metal fragments or black specks.

Several of these non-conforming or returned lots (i.e., [REDACTED], and possibly lots [REDACTED] and [REDACTED]) were reprocessed, but the information provided does not show how these were reprocessed (i.e., repeating a chemical reaction or reprocessed by physical manipulations). Most important, no data was provided to demonstrate that the reprocessing steps have been subjected to appropriate validation to show that these steps consistently perform the intended functions and result in Acetaminophen batches that comply with all established standards, specifications, and characteristics.

Please provide us with a copy of your reprocessing protocol, specific batch production records covering the reprocessing and subsequent handling of these batches, and the results of all tests conducted on the reprocessed materials to ensure that the reprocessing did not adversely affect the identity, strength, quality, or purity of the active pharmaceutical ingredient.

4. Validation of the APAP computerized process control system is incomplete in that specific critical functions have not been tested or validated. In addition, your computer validation protocol is deficient in that it does not address change control and/or software maintenance, nor does it provide for a back up system or schedule.

Our inspection revealed that approximately two thirds of the Acetaminophen facility controls have been switched from a pneumatic panel control system to a computer driven system currently using [REDACTED] as the operator interface software. This current revision and previous revisions of the [REDACTED] have been installed without prior testing or scanning for viruses. In addition, validation of the APAP computerized process control system is incomplete in that specific critical functions have not been tested or validated. These include the reactor cooling water flow and temperature, acetic anhydride flow to reactor, and the demineralized water system's in line [REDACTED] system and water conductivity meter.

Furthermore, the computer validation protocol fails to address process changes and software maintenance and does not provide for a back up system or schedule nor specify who has authority to access specific programs or make software changes.

5. Your SOP addressing follow-up to failed analytical test results allows averaging a single out of specification result with one retest result and use of this average to determine if the API batch is in compliance with U.S.P. monograph specifications.

The FDA expects firms to investigate laboratory out of specification (OOS) test results to determine if the OOS result may be attributed to laboratory error. If attributed to the laboratory, the OOS test result should be invalidated and a retest value substituted for the original. In addition, all test results must be retained.

The deficiencies cited on the Form FD-483 (Inspectional Observations) presented at the conclusion of the October 1995 inspection and those enumerated in this letter are not intended to be an all-inclusive list of deficiencies that may exist at your Luling, Louisiana facility. FDA inspections are not intended to uncover all CGMP deviations that exist at a firm. We recommend that you conduct a complete evaluation of your facility for CGMP compliance.

You should take prompt action to correct the above deviations. Failure to do so may result in regulatory actions without further notice. These include seizure and/or injunction. Until the violations have been corrected and verified, this office will recommend disapproval of all drug applications listing your firm as a supplier of bulk Acetaminophen.

You should notify this office in writing, within 15 working days of receipt of this letter, of the steps you have taken to correct the noted deficiencies, including an explanation of each step being taken to prevent the recurrence of similar deficiencies. If corrective action cannot be completed within 15 working days, state the reason for this delay and the time within which the corrections will be completed.

Your response should be directed to Carolyn S. Olsen, Compliance Officer, U.S. Food and Drug Administration, 4298 Elysian Fields Avenue, New Orleans, Louisiana, 70122-3848, telephone number (504) 589-7166. Should you have any questions concerning the contents of this letter, or if you desire a meeting with the agency staff, do not hesitate to contact Mrs. Olsen.

Sincerely,



*acting*  
James E. Gamet  
District Director  
New Orleans District

Enclosure: FDA-483

cc: Mr. Richard C. Wesley  
APAP Plant Manager  
Rhone-Poulenc, Inc.  
P.O. Box 174  
Luling, Louisiana 70070

CP [REDACTED]