



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region *g1116d*

Telephone (973) 526-6009

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

April 9, 2001

WARNING LETTER

**CERTIFIED MAIL -**  
**RETURN MAIL RECEIPT**

Frank Condella  
Chief Executive Officer  
Purepac Pharmaceutical Company  
650 From Road, 5<sup>th</sup> Floor South  
Paramus, New Jersey 07652

File No.: 01-NWJ-23

Dear Mr. Condella:

On January 23 through March 12, 2001, FDA conducted an inspection at your drug manufacturing facility located at 200 Elmora Avenue, Elizabeth, New Jersey. During the inspection, investigators documented significant deviations from the regulations covering Current Good Manufacturing Practices for Finished Pharmaceuticals, found in Title 21, Code of Federal Regulations, Parts 210 and 211 (cGMPs).

The inspection revealed that drug products manufactured at your facility are adulterated within the meaning of Section 501(a)(2)(B) of the Act, in that the methods used in, or the facilities or controls used for their manufacture, processing, packing, or holding do not conform with cGMPs, to assure that such drug products meets the requirements of the Act. At the conclusion of the inspection, the investigators cited the following significant deficiencies concerning your firm's Quality System:

1. The Quality Unit failed to monitor and report unknown impurities in Diclofenac Sodium 50 mg and 75 mg Delayed Release Tablets, USP. These unknown impurities were not observed in the chromatographs initially used to support the application. A retrospective review of batches manufactured since 1995 revealed that three lots manufactured in 1997, lots 237JF, 238J7 and 297K7 resulted in individual unknown impurity values of 2.5%, 2.1% and 2.5%, respectively. The Analytical Development Group, with concurrence of Quality and Manufacturing Units, decided not to monitor or report these impurities, even though they had not yet been identified.

Annual product reviews submitted to the agency from January 1995 to March 2000, did not contain any information concerning this impurity issue or the retrospective review of impurity trends in this product.

As a result of the recent inspection, your firm recently identified six additional lots, within expiry, with unknown impurity peaks in excess of 1%.

2. The Quality Unit failed to conduct a thorough investigation concerning the unknown impurity peaks in Diclofenac Sodium 50 mg and 75 mg Delayed Release Tablets, USP. The cause of unknown impurities was thought to be a reaction of the coateric coating material with the active core. However, there was no contact with the manufacturer of the coateric material to determine if changes were made in the coating formulation that may have affected your product, since these impurities were not seen in product development.
3. The Quality Unit released batches of Morphine Sulfate 100 mg Extended Release Capsules, which did not meet release specifications. For example,
  - Lot 497F9, Expiry 5/2001, failed Level 3 dissolution testing at the four-hour point, and was released prior to completion of the laboratory investigation. It was later determined that the lot was released by the QA Supervisor based on bulk reassay results rather than finished product results. This lot was also placed on stability, since it was later discovered that a coating component was used past the manufacturer's warranty date.
  - Lot 496F9, Expiry 5/2001, and Lot 498F9, Expiry 5/2001, were initially tested at the four-hour point with passing results. However, since bulk capsules were held in excess of the 90 day allowable hold time, both lots were re-assayed twice. Each lot tested exhibited one in-specification and one out-of-specification result and were subsequently released using stability specifications, rather than release specifications.

In addition, your procedure, QC-041-D, *Reassay of Finished Pharmaceuticals Stored in Bulk*, allows for products to be tested and released using stability specifications.

4. The Quality Unit released batches of Phentermine Hydrochloride 37.5 mg Tablets, which failed in-process specifications for blend uniformity. Out-of-specification results for Lots 559G9, 560G9 and 562G9, were invalidated due to sampling error, without adequate justification.
5. The Quality Unit allowed batches of various products to be manufactured with potential metal contamination, relying solely on a metal detection system to reject affected finished products. For example,
  - Trazadone Hydrochloride 50 mg Tablets, USP, batch 308M9, the fourth batch in a campaign of eight, was found to be contaminated with metal particles. The source of metal contamination was determined to be from the excipient material, Lactose, D.T. Lot 9950601. The Quality Unit failed to reject this lot of excipient material and allowed further

manufacturing to occur. All finished batches were passed through a metal detector and the remainder of the Lactose material was then rejected and returned to the supplier.

- Hydrochlorothiazide 25 mg Tablets, batch 547L8, the fifth batch in a campaign of six, was found to be contaminated with metal. The source of metal contamination was determined to be from the active pharmaceutical ingredient, which was used in all six batches and two additional batches of Hydrochlorothiazide 50 mg Tablets. All batches were passed through a [REDACTED] metal detector, which was not qualified for this use.

The above list is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure that the drug products you manufacture are in compliance with the Act and the regulations promulgated under it. Federal agencies are routinely advised of Warning Letters issued so that they may take this information into account when considering the award of contracts. You should take prompt action to correct deficiencies in your Quality Unit. Failure to implement corrective measures may result in regulatory action, including seizure and/or injunction, without further notice.

We have received your written responses, dated March 23 and April 6, 2001. We recognize the extensive investigative work initiated after our inspection, with regard to identifying the unknown impurities in Diclofenac Sodium Delayed Release Tablets, USP, thought to be a testing artifact. However, it should be noted that this information was unknown at the time when an assessment was made by your Quality Unit not to monitor or report this phenomenon. With regard to inspectional observations concerning the activities of your Quality Unit, we note that corrective actions implemented after the inspection, include procedural revisions and re-training, where indicated. These corrective actions will be verified during the next inspection.

You should notify this office in writing, within 15 working days of receipt of this letter, of any additional corrective actions, including an explanation of each step being taken to prevent the recurrence of similar conditions. Your further response should include plans to improve and monitor the Quality Unit. If corrective action cannot be completed within 15 working days, state the reason for the delay and the timeframe within which corrections will be completed. Your reply should be addressed to the New Jersey District Office, Food & Drug Administration, 10 Waterview Blvd., 3<sup>rd</sup> Floor, Parsippany, New Jersey 07054, Attn: Mercedes Mota, Compliance Officer.

Sincerely,



Douglas I. Ellsworth  
District Director  
New Jersey District, FDA

**Purepac Pharmaceutical Co.**  
**Elizabeth, NJ 07207**

**Warning Letter 01-NWJ-23**  
**April 9, 2001**

cc: John M. Johnson, Jr.  
Vice President Quality Assurance/Quality Control  
Purepac Pharmaceutical Company  
200 Elmora Avenue  
Elizabeth, New Jersey 07207