DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

D1201B

WARNING LETTER

19900 MacArthur Blvd., Ste 300
Irvine, California 92715-2445
Telephone (714) 798-7600

February 18, 1997
WL-10-7

Mr. Hampar L. Karageozian, President and CEO
Prima Pharm, Inc.
3443 Tripp Court, Suite A
San Diego, CA 92121

Dear Mr. Karageozian:

During an inspection of your drug manufacturing facility located at 3443 Tripp Court, San Diego, California, conducted between October 28, 1996 and November 15, 1996, our investigators documented serious deviations from the Current Good Manufacturing Practice Regulations (Title 21, Code of Federal Regulations, Parts 210 & 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. For example:

1. Failure to provide and/or follow complete and adequate written procedures for production and process control designed to assure that drug products have the identity, strength, quality and purity they purport or are represented to possess in that validation of your processes is incomplete [21 C.F.R. 211.100(a) and (b)]. Specifically, there has been no validation of your purified water system in that no Installation Qualification, Operational Qualification, or Performance Qualification was performed and no testing for chemical and microbiological contamination was done to assure consistent water quality.

2. Failure to ensure that equipment used in the manufacture, processing, packing or holding of drug products is of appropriate design for its intended use in that there was no Installation Qualification on the [redacted] crimping machine, the [redacted] gallon mixing tank and the [redacted] gallon mixing tank [21 C.F.R. 211.63].

3. Failure to routinely calibrate, inspect, or check equipment according to a written program designed to assure proper performance in that periodic testing of the water from the purified water system for chemical and microbiological purity is not routinely performed. You failed to follow your own SOP #QA-32, which specifically states that "water is tested once a month" for pH, conductivity, and microbiological monitoring. Routine or periodic testing of water in this manner can only be performed after the system has been thoroughly validated. Water from this system was used in the manufacture of at least one commercially distributed drug product, Astringyn 25.9% Aqueous Solution. [21 C.F.R. 211.68(a)].

4. Failure to always conduct adequate investigations into the failure of batches of drug product to meet specifications. Specifically, two lots of Orascan 1% Toluidine Blue O Bulk Solution failed to meet in-process assay specifications of 0.90 - 1.10% of Toluidine Blue O, the active ingredient. Lot #PHG-05-04, manufactured 5/16/96, was assayed at 0.87% and Lot #PHG-05-06, manufactured 5/16/96, was assayed at 1.12%. Both lots were adjusted to meet specifications and an investigation was conducted by your firm. However, the investigation failed to make any specific conclusions as to why the two lots had to be reworked and there was no followup specified which would prevent future incidents of similar nature [21 C.F.R. 211.192].

In addition, we have the following concerns regarding the structure and responsibilities of your firm's Quality Control (QC) unit.

(A) The responsibilities and authorities of the Quality Control unit are defined in the Current Good Manufacturing Practice Regulations which can be found in 21 C.F.R., Parts 210 and 211. Part 211.25(c) states,"There shall be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing or holding of each drug product." Therefore, we are concerned that the QA Technical Director and QC Manager positions as given in your firm's SOP identified as QA-1, "Duties and Responsibilities of Quality Assurance", have never been filled.

(B) Our review of some of your firm's batch records reveals that the final review of these records has, at different times, been done by the Director of Manufacturing and a QC chemist, and approval and release sign off has been done, at different times, by the Vice President of Quality and a QC chemist. This is not in accordance with your own SOP and does not meet the requirements of the regulation 211.22(d). This regulation requires that the responsibilities and procedures of the Quality Control unit to be in writing and that they be followed. Your SOP identified as QA-1, which is not being followed, indicates batch approval, and failure investigations should be done by the QA group, consisting of a Technical Director and a QC Manager.

(C) The regulation, 21 C.F.R. 211.192, clearly specifies that the QC unit is responsible for conducting thorough investigations of any batch which fails to meet any of its specifications and that such investigations will include conclusions and followup. The two investigations noted in item #4, above, are not adequate in that they do not address why the product failed to meet specifications and there is no followup recommendation.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. A list of observations (FDA 483) was issued and

discussed with you at the conclusion of the inspection. It is your responsibility to assure adherence with each requirement of the Good Manufacturing Practice regulation and other applicable regulations. 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.

You should take prompt action to correct these deviations. Failure to do so may result in regulatory action without further notice, including seizure and/or injunction.

We have recieved your FDA-483 response addressed to Elaine C. Messa, District Director of FDA's Los Angeles District office dated January 31, 1997. The corrective actions you describe will be verified upon re-inspection.

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

Dennis M. Farley, Compliance Officer/Drug Group
U.S. Food and Drug Administration
19900 MacArthur Blvd., Ste. 300
Irvine, CA 92715

Sincerely,

Elaine C. Messa

Elaine C. Messa
District Director