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Food and Drug Administration  
555 Winderley Pl., Ste. 200  
Maitland, Fl 32751

CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

WARNING LETTER

FLA-99-52

April 16, 1999

Dr. Allen Chao  
President and Chief Executive Officer  
Watson Laboratories, Inc.  
311 Bonnie Circle  
Corona, California 91720

Dear Dr. Chao:

During an inspection of your facility located in Miami, Florida on January 7 through 15, 1999, FDA Investigators Victor Spanioli, Angela Rhodes, and FDA Chemist Dennis Cantellops, found conditions that are in violation of the Current Good Manufacturing Practice (GMP) Regulations (Title 21, Code of Federal Regulations, Parts 210 and 211). These conditions cause products manufactured by your firm to be adulterated within the meaning of section 501(a)(2)(B) of the Act as follows:

- Failure to adequately investigate out of specification (OOS) blend uniformity test results to support decision to invalidate original results based on re-testing.
- Failure to evaluate or determine appropriate corrective action when OOS test results are attributed to "analyst" or "analytical" error.
- The Standard Operating Procedure (SOP) relating to final blend sampling lacks the necessary specificity relating to sampling equipment and handling.
- Failure to document that personnel responsible for sample collection have been adequately trained in the SOP covering that specific sample collection.

- Failure to have stability data to support the 48 month expiration date place on Lorazepam 2 mg. Tablets.

We have received your responses dated February 4 and February 15, 1999, including the decision to recall Lorazepam 2 mg. Tablets, lot #PC-1163, because of the lack of stability data, and will evaluate the corrections listed during our next inspection. We are concerned, however, that observations pertaining to inadequate investigation of OOS results, use of "analyst error" in lieu of indepth investigations, and inadequate training keep appearing in investigators' Lists of Observations (FDA 483) dated back to 1996. For example: In June, 1997, lack of adherence to the firm's SOP covering GMP training; in October, 1996, attributed blend test failures to chemist error, then related it to the sampling thief, changing the sample size (very much like the present observation); and, in May, 1996, insufficient investigation as to the cause of the test failures, failures attributed to chemist error, and repeat testing and discarding of OOS results. We realize that a number of these occurred prior to Watson's purchase of Royce Laboratories, but the ongoing nature of these is a cause for concern on the part of FDA that needs to be brought to your attention for necessary corrective action.

Additional information is needed regarding the February 4<sup>th</sup> response concerning the size of the blend samples and the different sampling thieves used. The response states that going from a thief that provided large blend samples to one providing unit-dose blend samples corrected the problem of OOS blend sample results. Experience has shown that samples that are too large or too small can run into separation of blend granules, caused by electrostatic charges, for example. That is why qualification of sampling methodology (including the thief used) is necessary prior to its on-line use. Was the sampling methodology qualified prior to its use in this case? Which thief was used when the method was qualified? Has the sampling method been requalified since the sampling thief was changed?

This letter is not intended to be an all-inclusive list of deficiencies at your facility, nor does it cover any issues other than those involving GMP's. It remains your responsibility to ensure adherence to all requirements of the Act and regulations. For your information, we are attaching the List of Observations for the current inspection as well as the previous ones mentioned.

You should take prompt action to correct these violations. Failure to promptly correct these violations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil penalties.

Please notify this office in writing within fifteen (15) working days of receipt of this letter, of the specific steps you have taken to correct these violations and to prevent the recurrence of similar violations. If the corrective action cannot be completed within fifteen (15) working days, state the reason for the delay and the time within which corrections will be completed.

Your response should be sent to the Food and Drug Administration, Florida District Office, 555 Winderely Place, Ste. 200, Maitland, Florida 32751, Attention: Martin E. Katz, Compliance Officer.

Sincerely,

  
Douglas D. Tolen  
Director, Florida District

Attachment

cc: Loren R. Gelber  
Vice President, Regulatory Compliance  
16600 N.W. 54<sup>th</sup> Street  
Miami, Florida 33014