



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region *g1370d*

Telephone (973)526-6005

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

May 14, 2001

WARNING LETTER

CERTIFIED MAIL-
RETURN RECEIPT REQUESTED

Dr. Rafick Henein
President and CEO
IVAX Pharmaceuticals, Inc.
4400 Biscayne Boulevard
Miami, Florida 33137

File # 01-NWJ-24

Dear Dr. Henein,

During a February 26 through April 24, 2001 inspection of your drug manufacturing facility located at 140 Legrand Avenue, Northvale, New Jersey, an investigator from this office documented significant deviations from current Good Manufacturing Practice (cGMP) regulations as delineated in Title 21, Code of Federal Regulations, Parts 210 and 211.

The inspection revealed that the controls and procedures used during the manufacture, processing, packing, or holding of prescription drug products at this facility do not conform with cGMP's, and, therefore, are adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (Act). The following are examples of the significant deficiencies concerning your firm's Quality and Production systems that were cited by our investigator:

1. The Quality Unit failed to prevent the release of lots of Perphenazine tablets to the marketplace that were manufactured outside of the products established validated manufacturing ranges. For example, your firm validated the number of color coat applications required for Perphenazine 2mg tablets to be between [REDACTED] color coats. However, Perphenazine 2mg tablet lot #3667-107 was released to the market having only 26 color coat applications.

2. The Quality Unit failed to prevent the release of lots of Methocarbamol and Aspirin tablets to the marketplace that were manufactured using a non-validated manufacturing process. Specifically, your firm had no assurance that this product would meet assay requirements for each of the two active ingredients in this BI-layer tablet. Assay values and weights of individual layers were not evaluated during process validation and flow characteristics such as the rate of flow of each individual ingredient from hoppers to the tablet press were not assessed.
3. The Quality Unit failed to conduct an investigation into eight similar color complaints received for Perphenazine 2mg tablets. Despite having received the first complaint in November 2000, your Quality Unit failed to conduct and document an investigation into the cause of these complaints.
4. The Quality unit failed to implement corrective actions to prevent size and shape deviations seen in Perphenazine 2mg, 4mg, and 8mg tablets even though an investigation into complaints for these deviations revealed failing in process tablet size results. No explanation was provided for your Quality Unit's review and approval of this failed data without a need for further follow up or implementation of corrective actions. Additionally, your Director of Technical operations explained to our investigator during this inspection that consumers of this product would still receive the same dose of active ingredient even if the size of the tablets varied due to the manual applications of sugar coating on the product. However, it appears that patient non-compliance for visually different sized tablets of the same product was not taken into consideration during your investigation.
5. The Quality unit failed to review and approve a change in laboratory computer software from [REDACTED]
6. The Quality Unit failed to assure that stability chambers were properly qualified prior to use. Additionally, the Quality Unit failed to provide Standard Operating procedures for firm personnel to follow in order to address any out of specification temperature or humidity results.
7. Your firm had no product specific cleaning validation data, and failures were observed for both rinse and swab samples taken from manufacturing equipment. Furthermore, your validation summary report for manufacturing equipment mistakenly had results of rinse samples supporting the validation conclusion rather than the swab sample results that were actually used during the validation study.

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 government contracts. You should take prompt action to correct deficiencies at your facility. Failure to implement corrective measures may result in further regulatory action without notice. These actions may include seizure of your products or injunction.

We have not yet received a written response to the FDA-483 List of Inspectional Observations issued to the Director of Quality Assurance at this facility on April 24, 2001.

We acknowledge your intentions, as part of your corrective actions, to recall all lots of Perphenazine tablets within expiry from the marketplace. However, we have still not received distribution documentation, as promised, for the lots to be recalled.

You should notify this office in writing within 15 working days of receipt of this letter of your corrective action plan to address the deficiencies at your firm to prevent similar future events. If corrective actions can not be completed within 15 working days, please state the reason for the delay and the timeframe within which corrective actions will be completed. Your reply should be addressed to the New Jersey District Office, Food and Drug Administration, 10 Waterview Blvd., Parsippany, New Jersey 07054, Attn: Joseph F. McGinnis R.Ph, Compliance Officer.

Sincerely,



Douglas I. Ellsworth
District Director
New Jersey District