TO: → HFI-35 5/28/98
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

NEW YORK DISTRICT
850 THIRD AVENUE
BROOKLYN, NY 11232
TEL. (718) 340-7000

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Joseph A. Errigo
President
Time-Cap Labs, Inc.
7 Michael Avenue
Farmingdale, New York 11735

May 12, 1998

REF: 28-NYK-98

Dear Mr. Errigo:

During an inspection of your drug manufacturing facility located in Farmingdale, New York, conducted between the dates of March 26, 1998 and May 5, 1998, our investigators documented deviations from the Current Good Manufacturing Practice Regulations (Title 21, Code of Federal Regulations, Parts 210 and 211). Such 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 as follows:

1. Failure to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process materials and drug products:

a) The full range of the amount of timing solution actually used in the production of active stock pellet batches for Nitroglycerin Extended Release Capsules has not been validated.

b) The process of gravity feed delivering of nitroglycerin pellet blends to encapsulation from bulk ,"mule", containers has not been validated.

c) Reworking processes have not been validated, as follows: the use of [redacted] to remove timing solution on lot M087H, Phenylephrine HCL Pellets; the reblending processes associated with Cold Capsules, lots A009J and A052J; the removal of sugar coating with water and recoating of Bisacodyl 5 mg Enteric Coated Tablets, lots J022H and J060H; the recovery and reapplication of material from active pellets to lot C043J, Papaverine 150 mg Capsules.

d) Formulation changes have not been validated. For example, the use of [redacted] in processing batches of Nitroglycerin 2.5 mg. ER Capsules, lots F056H and J062H, the use of in-house prepared [redacted] solution in the manufacture of Bisacodyl 5 mg. Enteric Coated Tablets, lots J022H and J060H, the manufacturing of Bisacodyl 5 mg. Tablets using a [redacted] excess of active ingredient and increasing the amount of enteric coating.

2. Master production and control records fail to include complete manufacturing and control instructions:

a) Manufacturing instructions for modified release products, for example, Nitroglycerin ER Capsules, fail to include a limit or range for the quantity of timing solution used in the manufacture of pellet batches.

b) The procedure for application and the amounts of [redacted] and [redacted] are not specified for the sealing of Nitroglycerin Pellets prior to application of the active ingredient, and for the coating of neutral pellets.

c) There are no specific instructions for application of active ingredient on to pellets, including Nitroglycerin Pellets, Phenylephrine Pellets, Phenylpropanolamine Pellets, Chlorpheniramine Maleate Pellets, Phenyltoloxamine Citrate Pellets.

d) No description or parameters for coating spraying equipment used in the manufacture of timed stock pellets including Nitroglycerin Pellets, Phenylephrine Pellets, and Phenyltoloxamine Citrate Pellets.

e) Failure to specify the mixing equipment to be used in the manufacture of batches of Phenylephrine Pellets and Pheniramine Maleate Pellets.

f) Failure to provide specific instructions relating to the timing process for Phenylpropanolamine Pellets, Chlorpheniramine Maleate Pellets and Phenyltoloxamine Citrate Pellets.

3. Batch production records fail to include complete and accurate information relating to the production and control of batches:

a) The recovery, milling, and reapplication of material left over from active pellet timing operations, such as, for Papaverine HCL Pellets, lot CO43J, are not documented in the batch record.

b) The quantities of [redacted] and [redacted] actually applied during coating of neutral pellets for Nitroglycerin ER Capsules are not recorded on the batch records.

c) The batch record for Phenylephrine HCL Pellets, lot M087H, fails to document the equipment used and the quantities and lot numbers of the materials used for the removal of timing solution reworking process.

d) There are no records documenting the visual inspections after final coating of tablet batches.

e) A batch production record for Enteric Coated Aspirin 7.5 gr. Tablets, M032H, could not be found.

f) The batch records for Bisacodyl 5 mg. Enteric Coated Tablets, lots J022H and J060H, fail to document the removal of the sugar coatings associated with the reworking of these lots.

4. Failure to justify deviations from written production and process control procedures, and there is no written procedure relating to changes in production and control records. For example, the use [redacted] in pellet batches for Nitroglycerin 2.5 mg. ER Capsules, lots F056H and J062H, and the manufacture of lots

J022H and J060H of Bisacodyl Enteric Coated Tablets using an in house prepared [redacted] sealant.

5. Failure to establish adequate quality control procedures to assure that any unexplained discrepancy or failure of a drug product to meet any of its specifications is fully and thoroughly investigated.

a) No documented investigation into the failure to meet in-process testing specifications for acid stage dissolution requirements for batches of Enteric Coated Aspirin Tablets, including, lots K069H, K024H, J090H, and B011J.

b) No documented investigation into the failure of lot B039G, reworked Enteric Coated Aspirin Tablets, 5 gr., to meet drug release specifications.

c) No documented investigation into the failure of lots J022H, and J060H, Enteric Coated Bisacodyl Tablets, 5 mg. to meet drug release testing specifications.

d) No documented investigation into the failure to meet stability testing specifications for the drug release test result at the room temperature 3 month test interval for Bisacodyl 5 mg. Enteric Coated Tablets, lot # A014H, and for accelerated stability out-of-specification potency and/or drug release test data for Bisacodyl Enteric Coated Tablets, such as, lots K045H, F015H, and L043H.

e) The investigation into foreign pellets associated with the encapsulation of Cold Capsules, lot K028H, failed to document any investigation into other drug products which may have been associated with the discrepancy, such as, an examination of the products processed immediately before and after lot K028H.

f) No documented investigation into the failure to meet assay specifications for phenylpropanolamine after reblending processes associated with the manufacture of Cold Capsules, lot A009J.

6. Laboratory records fail to include complete or includes discrepant data derived from tests necessary to assure compliance with specifications.

a) Analytical data could not be found in the lab notebooks to support the out-of-specification stability test result (drug release testing) for the 3 month test interval for Bisacodyl 5 mg. Enteric Coated Tablets, lot A014H, reported on the stability summary record. The stability summary record for lot A014H fails to report 6 and 9 month test interval data as reported in the laboratory notebook.

b) Discrepant, failing versus passing, laboratory stability test results (first hour release rate) for lot L035E, Comhist LA Capsules, are reported on the hand written version versus the typed version of the stability data summary record for the 18 month room temperature test interval.

7. Failure to conduct stability testing on batches of Comhist LA Capsules, M069H, and Com-time ER Capsules, lot A025J, which were manufactured using reworked Phenylephrine HCL Pellets.

8. Failure to establish time limitations for the holding of intermediate and active pellets for encapsulation, including Nitroglycerin Pellets and Chlorpheniramine Maleate Pellets.

9. Failure to conduct an annual evaluation of the quality standards for each drug to determine the need for changes in drug product specifications or manufacturing or control procedures.

10. Failure to have equipment cleaning and usage records for bulk containers, "mules", used for storage and delivery of pellets and drug blends to encapsulation and compression equipment.

11. Failure to record an individual inventory and usage record for pellet "anti-static" powder, lot #C009HI.

12. Failure to store drug product labels in a restricted access area. During the inspection, drug labels were observed in the general quarantine warehouse.

The above identification of violations and the observations on the FDA 483 issued at the end of the inspection are not intended to be an all-inclusive list of violations. As a manufacturer of drugs, you are responsible for assuring that your overall operation and the products you manufacture and distribute are in compliance with the law. Federal agencies are advised of the issuance of all warning letters about drugs 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 promptly correct these deviations may result in regulatory action without further notice. These include seizure and/or injunction.

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

Your reply should be sent to Compliance Branch, Food and Drug Administration, New York District, 850 Third Avenue, Brooklyn, NY 11232, Attention: Laurence D. Daurio, Compliance Officer.

Sincerely,

Brenda J. Holman

Brenda J. Holman
District Director