



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region *main*

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

Telephone (973) 526-6001

September 28, 1998

WARNING LETTER

RELEASE

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. James R. Schleck
President
Jame Fine Chemicals, Inc.
100 West Main Street
Bound Brook, NJ 08805

REVIEWED BY *JPR* *10/1/98*
C.O. DATE

FILE NO.: 98-NWJ-40

Dear Mr. Schleck:

During an inspection of your firm located at the above address between April 22 and May 6, 1998, our investigator documented violations from current Good Manufacturing Practice (cGMP) regulations in the manufacture of Active Pharmaceutical Ingredients (APIs).

The aforementioned inspection revealed that API products manufactured and released at this facility are considered adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the "Act").

No distinction is made between API and finished pharmaceuticals. Failure to comply with cGMPs constitutes a failure to comply with the requirements of the Act.

Examples of deviations from cGMPs were outlined on the FDA-483, List of Inspectional Observations, issued to you on May 6, 1998. Deficiencies regarding APIs include, but are not limited to the following:

1. Your firm failed to establish formal impurity limits for the bulk drug substances your firm manufactures.

In your written response, dated May 15, 1998, it was stated that your impurity specification is [REDACTED] However, it was determined during the inspection, that your firm did not revise individual product sheets to include this specification. It was also noted during the inspection that your firm did not establish known vs. unknown impurity limits.

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2. Your firm lacks impurity studies to determine possible degradation products of Pseudoephedrine Tannate, Ephedrine Tannate, and Carbetapentane Tannate.

Your response indicated that your firm is working on determining possible impurities in the future. Your response did not provide a timeframe for completion. Your response also claims you have not seen significant degradation for the Tannate products below the [REDACTED] level. We do not understand how Jame Fine Chemicals can make this assumption, without having impurity data for these products nor forced degradation studies.

3. Your process validation for Dichloralphenazone is inadequate. This is evidenced by the following:

- A. In 1997, three lots out of [REDACTED] failed to meet minimum assay specifications upon release testing. These lots, numbers 6283, 6284, and 6287, were subsequently destroyed.

- B. Your firm's investigation and corrective action regarding the above was also inadequate. Your firm determined that the chloral hydrate was degrading, due to the heating of the solution. On June 24, 1997, your firm eliminated the heating steps for chloral hydrate solution and antipyrine solution. Subsequent to this, an out of specification assay result occurred when lot numbers 6300 and 6298 were blended to form lot number 6305. Your response does not address the disposition for the lot numbers in question, 6298, 6300, and 6305.

- C. There was no data to show how specific changes to manufacturing processes and procedures were determined. For example: In February 1998, Jame Fine reinstated the warming of the solution but to a lower temperature range than the previous temperature. Your firm did not have data to show how the new temperature range was developed nor data to show the new warming step was validated.

Your response states that your firm recognizes the Dichloralphenazone process validation has problems and you have committed to solving the validation problem and revalidating. According to your July 6, 1998, written response, the revalidation of the Dichloralphenazone process is to be completed by the end of September 1998. While we recognize that the Dichloralphenazone process was your first priority, a timeframe for completion of process validation studies for your Tannate products was not provided.

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4. Your firm lacks an adequate system for conducting validation of the revised Tannate processes. For example,
 - A. The system does not require that process related impurities and possible degradation products be reevaluated when manufacturing process changes occur.
 - B. The system did not require that all validation lots of products manufactured via revised processes be placed on full stability and monitored for impurities.
 - C. Specific operating parameters, i.e. mixing times and temperatures, were not established prior to initiation of validation.

Your written response stated you will send new and/or revised procedures regarding the above. Please forward these procedures to our office upon completion.

5. Your quality assurance system for evaluating validation reports and revising batch records did not assure that conclusions/recommendations, which were made in validation reports, were implemented in the master batch records. For example,
 - A. Pyrilamine Tannate validation report, dated March 4, 1998, stated that a mixing time of [REDACTED] minutes would be incorporated into the batch record. The master batch record, dated March 10, 1998, listed a mixing time of [REDACTED] minutes, with instructions not to exceed [REDACTED] minutes. There was no data to demonstrate that a mixing time of [REDACTED] minutes was adequate for the completion of the reaction.
6. Your firm lacks complete validation data for the "HPLC Method for Tannate" on the [REDACTED] HPLC System. For example,
 - A. System suitability calculations, such as relative standard deviation, tailing factor, and resolution were not recorded.
 - B. Desired resolution between the Tannic Acid peak and the solvent front peak was not stated nor calculated.
 - C. Sample dilution were not reached.

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The revalidation of your HPLC method will be reviewed during our next inspection of your firm.

7. Your firm failed to validate your revised cleaning procedures for Phenylephrine Tannate, Pyrilamine Tannate, Chlorpheniramine Tannate, Carbetapentane Tannate, Pseudoephedrine Tannate, Ephedrine Tannate, Dichloralphenazone, and Isometheptane Mucate.

Your written response indicates that the analytical lab had to complete the recovery studies before validation efforts could begin and that the recovery studies were on-going. Please inform our office when you begin to validate your revised cleaning procedures.

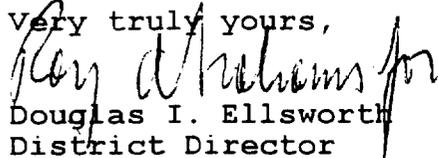
We are in receipt of your written responses, dated May 15, 1998, and July 6, 1998. We have reviewed your written responses and have included our comments after each Warning Letter item, above. Verification of corrective action will be determined during our next scheduled inspection of your firm.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the Good Manufacturing Practice regulations. 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 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 being taken to prevent the recurrence of similar 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 the Food and Drug Administration, New Jersey District Office, 10 Waterview Boulevard, 3rd Floor, Parsippany, New Jersey 07054, Attention: Vincent P. Radice, Compliance Officer.

Very truly yours,



Douglas I. Ellsworth
District Director
New Jersey District Office