



DEPARTMENT OF HEALTH & HUMAN SERVICES m2526n

New York District

Food & Drug Administration
300 Pearl Street, Suite 100
Buffalo, NY 14202

April 9, 1999

WARNING LETTER NYK 1999-40

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Dr. V. Ravi Chandran, President & CEO
Signature Pharmaceuticals, Inc.
34 West Fulton Street
Gloversville, New York 12078

Dear Dr. Chandran:

An inspection was conducted at your manufacturing facility located in Gloversville, New York between December 11, 1998 and February 3, 1999. Our investigators documented deviations from the Current Good Manufacturing Practice Regulations (Title 21, Code of Federal Regulations, Parts 210 and 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. The most serious are listed as follows:

LABORATORY

1. Failure to establish and maintain written procedures for testing Polytine CS, Polytine D, and Co-Tussin Original. Based on records and comments provided by your analyst, the methods for testing these products appear to be variations of a test method for another product, Endotuss HD with a different composition including different combinations of active ingredients. [21 CFR 211.160].
2. Failure to adequately validate the test procedure for in-process testing of Endotuss HD. For example, the [REDACTED] test was performed on a different sample solution, preservatives were not included, and [REDACTED] of the method was not tested. [21 CFR 211.165 (e)].
3. Failure to calibrate the [REDACTED] used for testing in-process lots of all drug products for strength and identity of active ingredients. Performance qualifications should include [REDACTED] specifications [REDACTED]. A revalidation schedule is also required. Complete records pertaining to these requirements should be maintained. [21 CFR 211.160(b)(4) and 21 CFR 211.194(d)].

4. Failure to perform [REDACTED] The only written method on file [REDACTED] method for analysis of Endotuss HD. That method indicates [REDACTED] According to your analyst, the methods for each of your other three products are derivatives of the Endotuss HD method, and [REDACTED] testing is not performed when analyzing the other products either. [21 CFR 211.160(b)(4)].
5. Failure to perform calculations for [REDACTED] When [REDACTED] [21 CFR 211.160].
6. Failure of the analyst to fully document details of his work. Review of the analyst's notebooks revealed details such as weights and source of samples, raw materials, standards and reagents, and calculations are routinely missing. [21 CFR 211.194]
7. Failure to perform a thorough review of all analytical data by a competent and trained, second individual. The person charged with this responsibility is not a chemist and admittedly is incapable as a result of being untrained to perform all required duties. For example, he cannot [REDACTED] [21 CFR 211.194(a)(8)] .
8. Failure to develop adequate Standard Operating Procedures (SOP's) to address overall laboratory operations. For example, there is no SOP requiring calibration of the [REDACTED] Some SOP's are inadequate; the SOP for the analytical balance lacks a calibration schedule, and the SOP for the pH meter does not require standardizing where the expected pH value is bracketed. Finally, there is no SOP to interpret results when testing is [REDACTED] [21 CFR 211.160]
9. Failure to perform an appropriate check of each lot of finished drug product to determine satisfactory conformance with final specifications including the identity and strength of each active ingredient. Currently, the laboratory releases lots on the basis of analytical results of samples taken from in-process, bulk tanks as opposed to samples of finished, packaged products. [21 CFR 211.165 (a)].
10. Failure to adequately investigate either analytical failures or determine the cause of questionable, unexpected findings. For example, Endotuss HD, batch AA164, was tested [REDACTED] Phenylephrine hydrochloride [REDACTED] while the [REDACTED] result was both unreported and ignored without investigation. In another example, Polytine CS, lot AA154, the product was [REDACTED] findings for the ingredient Bromopheniramine maleate determined to be [REDACTED] The lot was released on the basis of the [REDACTED] value without investigation. [21 CFR 211.160]

11. Failure to develop a stability program capable of producing the scientific evidence necessary to support the two-year expiration dates assigned each of the four products manufactured and distributed. For example, there are three ongoing studies, none of which employ samples from commercial lots tested at room temperature. There is no ongoing study for one product, Polytine D. Analytical methods have not been adequately developed in a manner to measure degradents of active ingredients. The methods for Polytine CS and Co-Tussin are both written and unvalidated and designed to assay potency levels of active ingredients only. The SOP is inadequate in that it fails to address the aforementioned inadequacies. In addition, it sets the acceptance range for active ingredients at plus or minus 10% of the initial analytical value as opposed to 90% – 110% of the formulated level. As a result, a failing test result was deemed as passing. Co-Tussin, batch AA164, was tested at the one-month station, with a result of [REDACTED] for the active ingredient, hydrocodone bitartrate. [21 CFR 211.166]

MANUFACTURING

1. Failure to adequately validate the manufacturing processes for all products. This, according to batch records is evidenced by mishaps, which have occurred during routine production. For example, the batch record covering production of Polytine D, lot AA163, begun December 1, 1998, indicates the mixing tank drain was mistakenly left open allowing approximately [REDACTED] of the in-process batch, including active ingredients, to escape. A sample of the remainder of the lot was analyzed to determine the potencies of the active ingredients using an unwritten, unvalidated method. In fact, according to records, the potency for one ingredient could not even be determined due to interference with the preservative. Nevertheless, the lot was eventually released and distributed.

In another example, the batch record for Co-Tussin, lot AA161, the first commercial lot produced was begun on November 17, 1998. An excess of approximately [REDACTED] was added to the batch due to a control error. A corrective action was approved whereby a second portion was manufactured, less the amount of water added in excess in the first batch, then combined. The batch record fails to indicate the procedure used in mixing the two portions including time. The only analytical test results using a method both unwritten and unvalidated, appears to represent the bulk lot after combining the two portions. One of the two active ingredients, hydrocodone bitartrate was reported at only [REDACTED] of declared. The lot was released without additional sampling or further investigation. [21 CFR 211.110].

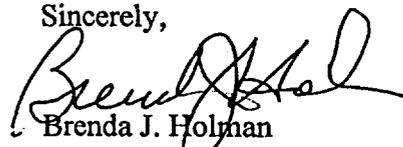
2. Failure to develop adequate Master production and control records for the four products manufactured. For example:

- The container-closure system is not addressed.
 - The records do not address all manufacturing steps. The record for Endotuss HD, fails to address the addition of [REDACTED] at the step in the process when [REDACTED] is added to the batch. Also, the record for Endotuss HD fails to address a final [REDACTED] which occurs at the very end of the process.
 - An in-process sampling procedure, which is performed on all products, on which quality control release is based, does not appear on any of the master records. [21 CFR 211.186]
3. Failure to maintain adequate batch production records. For example:
- The batch sizes routinely vary without justification. For example, the manufacturing process used is unique for each size or volume, and as a result should be individually validated.
 - Records are not maintained concurrently based on the fact that raw material lot numbers are first recorded on scrap paper, carried to another area, and then entered into the computer.
 - Finally, there are no verification procedures whereby two people witness such operations as weighing. [21 CFR 211.188]

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. 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. Additionally, neither New Drug Applications, Abbreviated New Drug Applications, nor export approval requests may be approved until the above violations are corrected.

We are in receipt of your letter dated March 5, 1999 providing individual responses to each of the observations listed on the FDA 483. Our assessment finds it to be inadequate and a meeting is indicated. The meeting should be scheduled as soon as possible, but within fifteen (15) working days from the date of this letter. Arrangements can be made to meet at our Brooklyn office or Buffalo office depending on the date. Please contact William J. Thompson, Compliance Officer, (716) 551-4461, extension 3124, for scheduling purposes.

Sincerely,



Brenda J. Holman
District Director