



DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration
New England District

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WARNING LETTER

NWE-06-02W

December 7, 2001

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Norman Cardinale
President
Cardinal Enterprises, Inc.
184 John Clarke Road
Middletown, RI 02842

Dear Mr. Cardinale:

An inspection of your firm, located at 184 John Clarke Road in Middletown, RI, was conducted from October 16 through November 8, 2001 by FDA Investigator Daryl Dewoskin. This inspection revealed significant deviations from Current Good Manufacturing Practice (cGMP) Regulations (Title 21, Code of Federal Regulations (21 CFR), Parts 210 and 211). These deviations cause the drug products manufactured at this facility to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act).

Under Section 501(a)(2)(B), a drug shall be deemed to be adulterated, if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

Many of the violations documented during this inspection are similar to those that have previously been brought to your attention. This indicates a continuing pattern of non-compliance with regulations governing the minimum requirements for current good manufacturing practice for the preparation of drug products.

The deviations include, but are not limited to the following:

- 1) Batch production and control records do not include complete information relating to the production and control of each batch. Specific deficiencies in batch records include:
 - a) Failure to include dates of each significant step in the manufacture and processing of each batch of drug products [21 CFR 211.188(b)(1)—Form FDA 483, Observation 28]. The date of manufacture of the bulk blend was not recorded on batch records for, among others, the following products:
 - i) Sore Throat Spray Menthol (Lot K-106-JT)
 - ii) Tussin DM 065 (Lots K-111-JT and D-103-JK)
 - iii) Night Time Original (163) (Lot D-107-JK)
 - iv) Daytime (166) Cold Medicine (Lot H-102-JK)
 - v) Benadryl 037 (Sugar Free) (Lot H-104-JK)
 - b) Failure to include specific identification of each batch of component used to manufacture each batch of drug product [21 CFR 211.188(b)(3)—Form FDA 483 Observation 12]. Examples of batch records in which components were not identified include:
 - i) Night Time Original (164) (Lot J-125-JT): Doxylamine Succinate
 - ii) Tussin DM Sugar Free (Lot H-106-JK): Methylparaben and Propylparaben
 - iii) Night Time Original (163) (Lot D-107-JK): Propylene Glycol
 - c) Failure to include a statement of the actual yield at appropriate stages of manufacturing for each batch of drug product [21 CFR 211.188(b)(7)—Form FDA 483 Observation 9]. No actual yields can be calculated for any products manufactured using Tanks 11308 and 11321, since the load cells for these tanks are inoperative. Batch records for at least two products, Therapeutic Gel (Lot L-108-JT) and Antiseptic Cleansing Solution 818 (Lot B-106-JK), are deficient in this regard. This also represents a failure to comply with 21 CFR 211.103, which calls for the calculation by one person and independent verification by a second person of actual yields and percentages of theoretical yields at appropriate phases of the manufacturing process.
 - d) Failure to include a description of drug product containers and closures for each batch of drug product [21 CFR 211.188(b)(9)—Form FDA 483 Observation 23]. No descriptions of containers and closures were recorded on batch records for:
 - i) Daytime (166) Cold Medicine (Lot H-102-JK)
 - ii) Tussin DM 065 (Lot D-103-JK)
 - e) Failure to include the identification of the persons performing and checking each significant step in the operation for each batch of drug product [21 CFR 211.188(b)(11)—Form FDA 483 Observation 18]. Persons performing significant steps such as cleaning, mixing, heating, and filling are not always identified.

Examples include:

- i) Tussin DM 065 (Lot D-103-JK)
 - ii) Night Time Original (163) (Lot D-107-JK)
- f) Failure to include results of examinations made of packaged and labeled products for correct labeling [21 CFR 211.188(b)(13)—Form FDA 483 Observation 14]. Of 16 batch production records examined by our investigator, none contained specimens of labeling and none had any record of examinations for correct labeling, either prior to labeling (as required under 21 CFR 211.130(d)) or after labeling (as required under 21 CFR 211.134(c)). Our investigator found examples of reserve samples without any consumer labeling and at least one instance in which the lot number listed on the batch record for a distributed product was different from that on the labeling of product still remaining at your firm (Benadryl 037 Sugar Free, mislabeled with Lot Number H-102-JK, which is a lot number for the product Daytime (166) Cold Medicine).
- 2) As is exemplified by the foregoing incident, there is a lack of written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, and examination of labeling and packaging materials [21 CFR 211.122(a)—Form FDA 483 Observation 17]. Personnel who approve labeling reported not having been trained nor provided with a written procedure to follow. Strict control is not exercised over labeling issued for use in labeling operations [21 CFR 211.125(a)—Form FDA 483 Observation 15] and procedures for the issuance of labeling have not been written [21 CFR 211.125(f)—Form FDA 483 Observation 16].
- 3) Laboratory records are deficient in a number of areas. Written descriptions and validation data for finished product test methods were unavailable. No records demonstrating suitability for use could be provided for your firm's HPLC system. The authenticity of signatures (on finished product testing records) purporting to indicate review by a second person is in question. The person, who is represented as having performed this review, has stated to our Investigator that the signature appearing on a number of these records is not his. Examples include Tussin DM 065 (Lot D-103-JK), GingiPlus toothpaste (Lot H-103-JK) and at least six batches of Psoridx Active Exfoliator Gel [21 CFR 211.194—Form FDA 483 Observations 4, 5, 6, 7 and 8].
- 4) You have failed to maintain individual equipment logs reflecting cleaning and use of processing equipment, such as tanks (kettles) and mixers [21 CFR 211.182—Form FDA 483 Observation 11].
- 5) You have failed to establish adequate procedures designed to prevent objectionable microorganisms in drug products not required to be sterile. There are no written procedures for microbial testing. Your firm's deionized water system has never been qualified and is currently inoperative due to leaks in the system [21 CFR 211.113(a)—Form FDA Observation 13].

- 6) Master production and control records are not prepared, dated, and signed by one person with a full handwritten signature and independently checked, dated and signed by a second person. Master production records are generated from a computer as electronic records without any apparent controls to assure authenticity and integrity [21 CFR 211.186(a)—Form FDA Observation 21].
- 7) You have failed to ensure that all people engaged in the manufacture, processing, packing or holding of drug products have the education, training and/or experience required to perform their assigned functions. Various production personnel reported to our investigator that they had not read procedures relating to their assigned duties and had not been trained in current good manufacturing practice [21 CFR 211.25(a)—Form FDA 483 Observation 25].
- 8) Reports of analysis from component suppliers are accepted in lieu of testing each component for conformity with all appropriate written specifications without establishing the reliability of a supplier's analyses through appropriate validation of those test results at appropriate intervals. Personnel reported to our investigator that no certificates of analyses for incoming components have ever been verified through auditing or verification through independent testing [21 CFR 211.84(d)(2)—Form FDA 483—Observation 24].
- 9) Separate or defined areas to prevent contamination or mix-ups are deficient regarding operations relating to the quarantine storage of drug products prior to release. Jars of product, identified to our investigator by your personnel as Psoridx Gel being held for destruction, were observed stored on a pallet with no labeling on either the jars or the pallet as to the identity, lot number or status of the product. Six (6) other instances of inappropriate storage or segregation of products were noted. [21 CFR 211.42(c)(7)].
- 10) Written production and process control procedures are not followed in the execution of various production and process control functions [21 CFR 211.100(b)]. Examples of procedures that are not being routinely followed include:
 - a) Procedure #17 *Incoming Raw Material Receiving and Control Program and Warehouse Distribution Format* (Form FDA 483 Observations 19, 24)
 - b) Procedure #26 *Mixing Kettles/Tanks and Agitators/Mixers Cleaning Procedure* (Form FDA 483 Observation 11)
 - c) Procedure #33 *Batch Production and Control Record* (Form FDA 483 Observation 1)
 - d) Procedure #70 *Cleaning Sanitization, and Validation of All Manufacturing, Filling and Package Equipment* (Form FDA 483 Observation 4)
 - e) Procedure #94 *Master Production and Control Record* (Form FDA 483 Observation 22)
- 11) You have failed to implement a written program of stability testing that could be used to determine appropriate storage and expiration dates. Stability data was not available for a number of products, including Tussin DM 065, Night-Time Original

163, Daytime 166, and Benadryl 037 Sugar Free [21 CFR 211.166—Form FDA 483 Observation 29]. You should also be aware that, under 21 CFR 211.137 (h), OTC drug products with labeled dosage limitations must bear a specific expiration date.

- 12) Written procedures for production and process controls designed to assure drug product quality have not been implemented, insofar as no data could be supplied demonstrating successful process validation for a number of your products [21 CFR 211.100(a)—Form FDA 483 Observation 4]. Examples include Tussin DM 065, Tussin 080, Sore Throat Spray (Cherry and Menthol), Night Time Original (163), GingiPlus toothpaste, Daytime 166, and Benadryl 037 Sugar Free.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. As a manufacturer of human drugs, you are responsible for ensuring that your overall operations and the products you manufacture and distribute conform to each requirement of the Act and the regulations.

Other 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. They may elect to defer or discontinue payment for any health care product in violation of federal law.

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

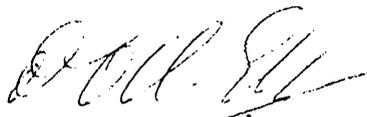
Please notify this office in writing within fifteen (15) working days of the receipt of this letter of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to identify and make corrections to any underlying system problems necessary to assure that similar violations will not recur. 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. You should also provide copies of any available documentation demonstrating that corrections have been made.

In your written response, please provide any plan of action you intend to take, as a result of this letter, with regard to products that are already in commercial distribution as well as those finished products in your control that were produced under these violative conditions.

Furthermore, we request that you update this office in writing as full corrective actions are completed and ultimately when you believe that your facility is in compliance with cGMP regulations, so that a verification inspection can be scheduled. Only when corrections have been verified will this office withdraw our advisory to Federal agencies concerning the award of government contracts. Any delays in implementing a full corrective action plan may result in an inspection by FDA and contemplation of further regulatory action.

If you have any questions concerning this matter, please contact Mark Lookabaugh, Compliance Officer at **781.596.7751**.

Sincerely,

A handwritten signature in black ink, appearing to read "Gail Costello". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

Gail Costello *JK*
Director
New England District