DEPARTMENT OF HEALTH AND HUMAN SERVICES

94998d

Public Health Service
Food and Drug Administration
Central Region

New Jersey District
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

Telephone (973) 526-6010

September 15, 2004

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Dr. Arvind Dhruv
President and CEO
Guardian Drug Company, Inc.
2 Charles Court
Dayton, New Jersey 08810-0915

04-NWJ-18

Dear Dr. Dhruv:

An inspection of your manufacturing facility located at 2 Charles Court, Dayton, NJ, was conducted from February 24 through April 23, 2004. During the inspection our investigator documented deviations from the Current Good Manufacturing Practice (CGMP) Regulations, Title 21 Code of Federal Regulations, Parts 210 & 211 (21 CFR 210/211) for drug products manufactured and tested at this site. 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 Act).

1. Failure to follow the procedures applicable to the quality control unit [21 CFR 211.22(d)] as demonstrated by:

   a. Failure to establish adequate written procedure for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess [21 CFR 211.100(a)]. For example, validation protocols for Infant Gas Relief Drops ([redacted] batch sizes) identified viscosity as a critical indicator of product uniformity: however, viscosity was not tested on any of the three [redacted] validation lots, and was only tested on bulk samples of the three [redacted] validation lots.

   b. Failure to assure that test procedures are scientifically sound [21 CFR 211.160(a) and (b)]. For example, the percent assay calculation of fructose/levulose (active ingredient) for the 3-month accelerated stability test point of Nausea Control Cherry Liquid was incorrectly calculated by including the addition of the area of the fructose peak with the area of an unknown peak to obtain passing results. Also, the acceptance of this deviation could impact on the validity of the two years expiration period.

   c. Failure to assure that investigations are performed and documented when unexplained discrepancies have occurred [21 CFR 211.192]. For example:

- There was no investigation of black particulates found in simethicone fluid raw material, nor were any of the other simethicone products reviewed to determine if other simethicone raw material obtained from the same vendor were similarly contaminated.
- Gastro Bismuth Liquid lot was returned by a customer due to product separation; however, no investigation was conducted to determine the cause of the product separation when this did not appear to be a normal occurrence.
- The [redacted]month stability test point failed the fructose assay and the phosphoric assay testing was not conducted during the stability testing of Nausea Control Cherry Liquid. No investigations or corrective actions were performed regarding these failures or omissions.

d. Failure to justify any manufacturing process deviation [21 CFR 211.100(b)]. Adjustments to the manufacture of Senna-Lax Tablets due to potency variation have been made without a written assessment or justification for the adjustment of microcrystalline cellulose versus agglomerated dextrose.

e. Failure to reject drug products failing to meet established standards or specifications and any other relevant quality control criteria [21 CFR 211.165(f)]. For example, during in-process and release testing of Senna-Lax Tablets, lot 159-6319, the quality control unit failed to observe that the tablets did not meet specification, in that the "GDC" imprint on the lower side of the tablets was missing. In fact, the analyst recorded that the product was properly imprinted. This lot was released and distributed.

2. Failure to establish scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160(b)(1)]. For example:

   a. From 2000 until the time of the inspection you allowed the use of industrial grade Adipic Acid in the manufacture of OTC drug products.

   b. No specifications for residues have been established for the Psyllium Husk raw material that has been ethylene oxide (ETO) sterilized and/or methyl bromide fumigated.

3. Failure to have and follow an adequate written stability program designed to assess the stability characteristics of the drug products [21 CFR 211.166(a)]. For example:

   a. There is no requirement that assay methods used during stability testing detect changes in product quality over time. Infant Gas Relief Drops, Gas Relief Softgels, and Dairy Relief Tablets (regular, extra-strength, and ultra-strength) do not have stability indicating methods. In addition, you have not conducted degradation studies on the active ingredients and/or

a literature search regarding the stability of inorganic ingredients of your products.

b. The Infant Gas Relief Drops release report includes a Defoaming test to assess drug product effectiveness. This test was observed to have been omitted without justification on nine occasions for three different stability lots since April 2002.

c. Written procedure 5.01, "Stability Program," is not followed in that the procedure requires that stability samples be tested within four weeks of the date they are pulled from the stability chamber. However, samples were observed being tested up to two months from the scheduled pull date.

4. Failure to assure that complete data derived from all tests are documented at the time of performance [21 CFR 211.160(a)]. For example:

   a. Stability samples of Nausea Control Liquid, lots [redacted], and [redacted] were allegedly tested on September 22, 2003, but the data was not recorded in the laboratory notebook until March 8, 2004. The Director of Quality Assurance and Regulatory Affairs included a note in the laboratory notebook regarding the delayed recording of the results and signed as the reviewer of the results, yet there was no evidence that the analysis actually occurred on September 22, 2003.

   b. During the March 12, 2004, acid neutralizing capacity test of Extra Strength Antacid Tablets, lot [redacted] the analyst believed that the sample was over-titrated; therefore, invalidated the test, and repeated the analysis. However, the analyst's action was not documented and reported to the laboratory supervisor. Only the data from the repeated analysis was recorded in the laboratory notebook.

5. Failure to clean equipment to prevent contamination that would alter the safety, identity, strength, quality, or purity of drug product beyond the official or other established requirements [21 CFR 211.67(a)]. For example, following the cleaning of the non-dedicated [redacted] mixer used in the manufacture of Infant Gas Relief Drops, lot [redacted] the mixer was observed to still contain drug product residue. There is no assurance that the manual cleaning procedure is validated since the firm does not document additional cleaning of equipment due to unsatisfactory visual inspection. In addition, there is no cleaning procedure and documentation that equipment cleaning is maintained for the [redacted] Separator used in the manufacture of Alkums [21 CFR 211.67(b) and (c)].

6. Failure to have and follow a written procedure that describes the preparation of master production and control records that include complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed [21 CFR 211.186].

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure that drug products your firm manufactures are in compliance with the Act and the regulations promulgated under it. Federal Agencies are advised of the issuance of all warning letters about drug products so that they may take this information into account when considering the award of contracts.

We have received your response dated May 27, 2004, concerning the Form FDA 483, List of Inspectional Observations, issued at the conclusion of the inspection. Your response did not provide sufficient evidence that the deviations have been or will be satisfactorily corrected so that you can attain substantial compliance on a long-term basis. In your response, you have not addressed the total failure to follow the procedures outlined for the quality control unit. We have the following comments:

Regarding Observation 1 (Warning Letter items 2a and 2b), your response indicates that you kept the Adipic Acid raw material on hold as soon as the investigators made you aware that industrial grade material was being used for manufacturing. However, you continued to ship finished product that had been made with industrial grade material. In addition, your response makes it appear that the change in manufacturer of Adipic Acid is a recent event, but the same industrial grade material has been received since 2000 with the warning "Not for use as a Food or Drug Additive" printed on the raw material container.

Regarding the repeated ethylene oxide (ETO) sterilization and methyl bromide fumigation cycles for the Psyllium Husk, you indicated that the ETO process will not alter the characteristics of the product in any way. You also indicated that by following the recommended methyl bromide fumigation procedure, the manufacturer ensures that there will be no methyl bromide residues in the product. However, there is no assurance that there is no ETO and methyl bromide residue on the product, since you have never established specifications for residuals of both nor tested for them.

Regarding Observation 3 (Warning Letter items 1b and 1c), your response states that the Nausea Control Cherry Liquid is a dietary supplement. In fact, this product is subject to the drug regulations since it is not labeled as a dietary supplement and it bears disease claims on its label.

You also indicated that an investigation was made to explain why the area of the unknown peak was included in the calculation with the fructose peak and that the product was sent to a contract laboratory for analysis of total sugars. However, this laboratory has not been qualified and the test methods have not been validated for Guardian's product; therefore, any results generated by the contract laboratory are suspect. You also stated that the phosphoric acid test was not conducted for a period of time because the test method for the stability samples was found to be inappropriate. However, during the inspection there was no documented evidence or investigation of any potential problems with the phosphoric acid test method to deem it inappropriate.

Regarding Observation 5 (Warning Letter item 1c), your response states that the simethicone raw material was placed on hold pending investigation and that samples were sent to the raw material manufacturer for evaluation. You also indicated that the same raw material was used in the manufacture of tablets at Guardian, but black particles were not observed in your products and in the Simethicone fluid raw material at your plant. However,

after [redacted] (the softgel capsule contract manufacturer) notified you of the black particles in simethicone raw material lots [redacted] and [redacted] on March 12, 2004, there is no documentation that product (softgel capsules and compressed tablets) was placed in quarantine. Furthermore, an investigation was not conducted until after the close of the inspection on April 23, 2004.

Regarding Observation 6 (Warning Letter item 1e), to clarify, the investigators reviewed a process deviation investigation report not an internal audit report as stated in your response. The response did not address the quality control unit personnel and procedures that failed to notice the missing imprint on the tablets that had been subjected to numerous in-process checks and quality control testing.

Regarding Observation 7 (Warning Letter items 3a, 3b, and 3c), to clarify, the observation relates to the lack of appropriate stability protocols. We disagree with your response that all methods used are stability indicating, since you provided a list of stability methods, including several titration methods. In addition, you indicated that one lot of each product will be placed on stability every other year rather than one per year. We feel that placing one lot on stability every other year is not adequate given the amount of products that your firm produces each year. Further, we feel that by placing one lot of drug product on stability every other year, you will not have sufficient information to adequately assess the long-term stability characteristics of your drug products.

Regarding the defoaming activity test for Infant Gas Relief Drops, your response indicates that this test was not required at the time the samples were placed on stability (around December 2001). However, the United States Pharmacopeia/Official Monographs has required the defoaming activity test for Simethicone Emulsion, Oral Suspension, and Tablets since 2000.

Regarding Observation 8 (Warning Letter item 4b), your response indicates that the analyst added an extra drop or two of solution during titration, overshooting the pH. You also indicated that although the analyst thought it was an error, in reality it was not. However, the original test results that the analyst invalidated should have been documented and reported to the laboratory supervisor. Only the data from the repeated analysis was recorded in the laboratory notebook.

Regarding Observation 10 (Warning Letter item 5), your response indicates that the cleaning of the equipment is assured by production and quality departments and details are documented in the equipment use and cleaning log. However, your response did not address the need to retrain operators on equipment cleaning nor the documentation of additional equipment cleaning due to unsatisfactory equipment visual inspection.

Regarding Observation 15, your response indicates that the computer software was initially validated in April 2001 and that it was going to be revalidated in May 2004. You also included the validation report of the software used for maintenance of the complaint. However, the adequacy of the challenges to the computer systems cannot be fully assessed since the validation protocols were not provided.

Guardian Drug Company
Dayton, New Jersey 08810
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You should take prompt action to correct deficiencies at your facility. Failure to do so may result in further regulatory action without notice. These actions may include seizure of your products or injunction.

You should notify this office within 15 working days of receipt of this letter of the corrective actions you plan to implement to address the deficiencies at your firm. If corrective actions cannot be completed within 15 working days, please state the reason for the delay and the time frame within which corrective actions will be completed.

Your response should be addressed to: U.S. Food & Drug Administration, 10 Waterview Boulevard, 3rd Floor, Parsippany, New Jersey 07054, Attn: Sarah A. Della Fave, Compliance Officer.

Sincerely,

Douglas I. Ellsworth
District Director
New Jersey District