DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration
Detroit District
1560 East Jefferson Avenue
Detroit, MI 48207-3179
Telephone: 313-226-6260

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER
2000-DT-38

August 16, 2000

Michael Jandernoa
Chairman of the Board
Perrigo Co.
117 Water Street
Allegan, Michigan 49010

Dear Mr. Jandernoa:

During an April 26 - July 14, 2000 inspection of your manufacturing facility located in Allegan, Michigan, Investigators Cheryl Fuhs, David Perkins, and Anthony Petriella documented deviations from the Current Good Manufacturing Practice Regulations (CGMP - 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.

1. Failure to have a Quality Control Unit (QCU) adequate to perform its functions and responsibilities as demonstrated by the number and types of inspectional observations. [21 CFR 211.22] The FD 483, List of Observations is enclosed.

   For example:

   - There is no Standard Operating Procedure for trending Out of Specification results other than the Annual Report.
   - A raw material lot of honey, [redacted] failed to meet specifications but was entered into the computerized lot control system as "unrestricted", meaning it was available for use.
   - There is no procedure for entering or verifying microbiological test results of purified water in the computerized system.

2. Failure to have adequate procedures for investigating the failure of a batch or any of its components to meet specifications. [21CFR 211.192]

For example:

- The QCU failed to decide on the significance of in-process granulation dissolution test failures for Coated Acetaminophen raw material used in the manufacture of Acetaminophen Extended Release Tablets. Production of finished product continued in spite of all indications that the coating process was not consistent and reproducible.
- The Quality Assurance Auditor failed to adequately identify all product involved in a labeling mishap, which resulted in mislabeled product being distributed and eventually recalled (Acetaminophen Caplets lot 9JE0735). The QCU also failed to expand the investigation to evaluate all applicable Standard Operating Procedures (i.e. Finished Product Labeling examination).

3. Failure to document approval by the Quality Control Unit for corrective actions taken to preclude in-process granulation dissolution test failures for Coated Acetaminophen raw material. [21CFR211.100]
4. Failure to complete product evaluations annually and Standard Operating Procedure (SOP) does not require review of all CGMP data. [21 CFR 211.180(e)]

   For example - There is not a provision for selecting a representative number of batches/records involving manufacturing or packaging incident reports.
5. Failure to conduct a specific identity test on a representative sample for drug components.[21 CFR 211.84]

   For example - A representative sample for each shipment of a single lot means individual identity tests are done on each of the containers that are sampled based on your sampling plan. The identity test should not be done on a composite of those samples.
6. Failure to adequately examine packaged and labeled product during finishing operations to provide assurance that containers and packages in the lot have the correct label in that at least [redacted] bottles of Acetaminophen Caplets 500 mg., lot 9JE0735 were labeled and distributed as Ibuprofen 200 mg.[21 CFR 211.134]

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, pending NDA, ANDA, or export approval requests may not be approved until the above violations are corrected. We request that you take prompt action to correct these deficiencies and to ensure that your drug processing operations are in full compliance with the Act and regulations promulgated thereunder. Failure to make prompt corrections may result in regulatory action without further notice, such as seizure and/or injunction.

The Perrigo Company has multiple locations. This letter is an official notification that FDA expects all of your locations to be in compliance. We recommend that all of your locations be evaluated and that corrective action be taken corporate-wide if deficiencies are found.

We acknowledge receipt of Mr. Robert Flynn's July 27, 2000 response to the list of inspectional observations as well as the firm's commitments to take specific steps to correct the noted violations. We concur in your decision to seek the assistance of outside expertise to make the necessary corrections. We are concerned, however, that your firm not only react to FDA inspections, but that the QCU be proactive in assessing Perrigo's control systems to identify non-conformance with CGMPs and/or SOPs. Your letter states that Perrigo is implementing a global Corrective Action Plan, however, it fails to acknowledge the significant role of the Quality Control Unit in the cited deficiencies. The continuing pattern of the lack of complete investigations and resolution of failures and deviations by your Quality Control Unit must be addressed.

We look forward to meeting with your firm's representatives, Messrs. Flynn, Gibbons and Hendrickson on August 23, 2000. We understand that our agenda will include discussion regarding Perrigo's Global Corrective Action Plan as well as a review of the Acetaminophen Extended Release Tablet's status.

We assume the discussion will include not only future plans, but also address the disposition of the [redacted] quarantined in-process production lots of coated granulated Acetaminophen raw material, which have failed to meet specifications.

The corrections promised in your firm's letter have been made a part of the Perrigo Allegan, MI file and will be evaluated during the next inspection. Please notify this office in writing, within 15 working days of receipt of this letter, of any additional 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 additional corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which corrections will be completed.

Any additional correspondence should be directed to the Food and Drug Administration, attention Mrs. Judith A. Putz, Compliance Officer at the above address.

Sincerely,

Raymond V. Mleeko
District Director

Enclosure: FDA 483, July 14, 2000

cc: David T. Gibbons, President and CEO
Perrigo Co.
117 Water Street
Allegan, MI 49010