



Department of Health and Human Services

Public Health Service
Food and Drug
Administration
Detroit District
300 River Place
Suite 5900
Detroit, MI 48207
Telephone: 313-393-8100
FAX: 313-393-8139

**WARNING LETTER
2010-DT-11**

April 29, 2010

VIA UPS

Joseph C. Papa
President and Chief Executive Officer
L. Perrigo Company
515 Eastern Avenue
Allegan, Michigan 49010

Dear Mr. Papa:

During our November 17, 2009 to January 14, 2010 inspection of your pharmaceutical manufacturing facility, L. Perrigo Company located at 515 Eastern Avenue, Allegan, Michigan, investigators from the Food and Drug Administration (FDA) identified significant violations of Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your drug product(s) to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 351(a)(2)(B)] in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We have reviewed your firm's response of February 1, 2010, and note that it lacks sufficient corrective actions.

Specific violations observed during the inspection include, but are not limited, to the following:

1. Your firm failed to reject drug products failing to meet established standards or specifications and any other relevant quality control criteria [21 C.F.R. § 211.165(f)].

For example, your firm failed to reject a lot of Ibuprofen Tablets 200 mg (lot 9BE1961) that was contaminated with metal shavings due to an equipment failure. Although your firm segregated a portion of the lot that was affected, you released and shipped a subportion of that segregated lot, resulting in a recall of the entire lot.

2. Your firm failed to thoroughly investigate the failure of a batch or any of its components to meet its specifications whether or not the batch has already been distributed and extend investigations to other batches of the same drug product and other drug products that may have been associated with the specific failure [21 C.F.R. § 211.192].

For example, your firm did not thoroughly investigate possible foreign tablet contamination in your filling equipment. After finding a brown, round Ibuprofen tablet (lot 8ME1624) in a lot of brown, oval Ibuprofen caplets (lot 8ME1731), you did not inspect the lot of orange, round Ibuprofen tablets (lot 8ME1728) that was packaged between lot 8ME1624 and lot 8ME1731. Without extending your investigation to lot 8ME1728, there is no assurance that this lot was not also contaminated.

Your response is inadequate in that it neither provides scientific rationale for excluding lot 8ME1728 from your investigation, nor does it address examination of any remaining product. Please comment.

3. Your quality control unit (QCD) failed to follow written procedures [21 C.F.R. § 211.22(d)]. For example:

- a. Your QCD failed to follow SOP **(b)(4)** with regard to editing and verifying label content for Cherry Flavored Milk of Magnesia. Failure to follow your written procedure resulted in release of mislabeled product, which you recalled. This recall, which was designated as Class II, was initiated on November 23, 2009.

- b. Your QCD failed to follow SOP **(b)(4)** with regard to verifying the accuracy of

label ingredient disclosure quantities of magnesium and calcium in Regular and Mint Flavored Milk of Magnesia and identifying incorrect values as changes from expected label specifications. Failure to follow your written procedure resulted in release of mislabeled product, which you recalled. This recall, which was designated as Class III, was initiated on December 7, 2009.

FDA investigators documented your firm's failure to follow Standard Operating Procedures (SOPs) during the last three FDA inspections, as well as in other inspections since 1998. Although your February 1, 2010 response acknowledges the procedural errors and recalls in both examples above, your response does not provide the corrective actions your firm plans to take to prevent reoccurrences in the future.

4. Your firm failed to adequately inspect the packaging and labeling facilities immediately before use to assure that all drug products have been removed from previous operations [21 C.F.R. § 211.130(e)]. For example:
 - a. Your firm failed to adequately inspect packaging equipment, as evidenced by foreign tablets observed by film packaging employees. Specifically, you did not remove all Ibuprofen tablets from a prior lot before packaging and labeling Ibuprofen caplets on December 10, 2008 (lot 8ME1731) and February 13, 2009 (lot 9BE1926).
 - b. Your firm failed to inspect packaging equipment, as evidenced by foreign tablets observed by firm packaging employees. Specifically, you did not remove all Ibuprofen orange caplets before beginning packaging and labeling of Ibuprofen brown caplets (lot 9DE1562) on April 10, 2009.

Your response states that you revised SOP **(b)(4)** in December 2009. You also commit to conduct deviation investigations, ensure appropriate corrective actions, initiate improvements to reduce or eliminate potential "hiding places" for drug product including equipment modifications, and provide updates on all such improvements to the Detroit District. Please provide all equipment modifications your firm plans to make to prevent reoccurrence of this issue; also thoroughly explain the rationale for your equipment modification decisions. In addition, please include a timeline for the completion of these modifications.

Your firm has had an ongoing program since 2005 to address mixups. However, your firm continues to receive complaints regarding this issue, and despite past assurances that previous enhancements would control this problem, deviations continue. Your firm failed to implement sustainable corrective actions to prevent mixups as well as other continuing problems. As a result, we have concerns regarding the failure of your firm, including the

QCU, to act proactively to ensure compliance with SOPs and the CGMP regulations. Please indicate how you intend to implement, support, and sustain a comprehensive quality system that is consistent with CGMP. Be advised that FDA expects that your corporate management will undertake a comprehensive evaluation of manufacturing operations to ensure compliance with CGMP.

The violations cited in this letter are not intended to be an all-inclusive statement of violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence and the occurrence of other violations. It is your responsibility to assure compliance with all requirements of federal law and FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts. Additionally, FDA may withhold approval of requests for export certificates, or approval of pending drug applications listing your facility, until the above violations are corrected. FDA may re-inspect to verify corrective actions have been completed.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step being taken to prevent the recurrence of violations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Additionally, your response should state if you no longer manufacture or distribute the drug product(s) manufactured at this facility, and provide the date(s) and reason(s) you ceased production.

Your reply should be sent to the following address: U.S. Food and Drug Administration, c/o Judith A. Putz, Compliance Officer, 300 River Place, Suite 5900, Detroit, Michigan 48207.

Sincerely,

/S/

Joann M. Givens
District Director
Detroit District Office