



August 07, 2003

**WARNING LETTER**  
**CIN-03-16736**

**SENT VIA FEDERAL EXPRESS**

Howard Solomon,  
Chief Executive Officer  
Forest Laboratories, Inc.  
909 Third Avenue  
New York, NY 10022

Dear Mr. Solomon:

This letter is in reference to the inspection of your finished pharmaceutical manufacturing plant, Forest Pharmaceuticals, Inc., located at 5000 Brotherton Road, Cincinnati, OH 45209, conducted on January 28 - February 20, 2003, and to your firm's continued marketing of Levothroid® (levothyroxine sodium tablets, USP) without an approved application.

Levothyroxine sodium tablets are drugs within the meaning of Section 201(g) and are new drugs within the meaning of Section 201(p) of the Federal Food, Drug, and Cosmetic Act (the Act). New drugs may not be introduced in interstate commerce unless there is an approved application under the provisions of Section 505 on file with the Food and Drug Administration (the agency).

On August 14, 1997, the agency announced in the Federal Register (62 FR 43535) that orally administered levothyroxine sodium drug products are new drugs. The notice stated that by August 14, 2000, manufacturers who wished to continue to market these products must obtain approved applications as required by section 505 of the Act and Title 21 Code of Federal Regulations part 314 (21 CFR 314). The notice stated that levothyroxine sodium drug products are used to treat hypothyroidism, and that no alternative drug is relied on by the medical community as an adequate substitute. Because of this, the agency announced it would exercise enforcement discretion, permitting unapproved orally administered levothyroxine sodium drug products to remain on the market until August 14, 2000. This timeline was designed to give manufacturers time to conduct the required studies, prepare applications, and gain approval.

On April 26, 2000, when it became apparent that few, if any, levothyroxine sodium products would obtain approval by August 14, 2000, the agency issued a second Federal Register notice

(65 FR 24488) announcing a continued exercise of enforcement discretion and extending the deadline for obtaining approved applications until August 14, 2001. On July 13, 2001, FDA issued another Federal Register Notice (66 FR 36794) indicating that because levothyroxine was a medically necessary product and because the process of switching patients from unapproved to approved products would take place over several months, FDA would continue to exercise enforcement discretion and allow companies with submitted applications until August 14, 2003 before it would take enforcement action against them. The July 13, 2001 Notice stated, however, that this continued exercise of enforcement discretion would be contingent on a manufacturer's voluntary compliance with a gradual phase out of production to take place over two years.

This gradual phase out was permitted in order to maintain adequate levothyroxine sodium supplies to supply the market while manufacturers of approved products scaled up their production. It was further designed to allow patients taking unapproved products a reasonable time to transition to approved products. All distribution of unapproved levothyroxine sodium drug products was to cease by August 14, 2003.

Our investigators determined that you have failed to obtain an approved application and have made a deliberate decision not to follow the agency's gradual phase-out plan that allows for the continued distribution of unapproved orally administered levothyroxine sodium drug products under limited circumstances. According to the phase down schedule proposed, by February 1, 2003, average monthly distribution in the preceding 3 months should have been reduced to 30% of the average distribution over the 6 months proceeding August 1, 2001. Instead, as of the quarter ending January 2003, you have increased distribution to 128% of the August 1, 2001 baseline sales. Moreover, you have failed to obtain an approval for a levothyroxine sodium product in the six years that have elapsed since the 1997 Federal Register notice has published. Because of this, you are no longer entitled to the enforcement discretion granted by the agency, and are hereby on notice that the distribution of your unapproved product, Levothroid®, remains in violation of Section 505 of the Act.

During this same inspection, our investigators also documented deviations from current Good Manufacturing Practice for drug products set forth in Title 21, Code of Federal Regulations, (21 CFR) Parts 210 and 211. These deviations affect the manufacture of Levothroid® (levothyroxine sodium tablets, USP); Armour Thyroid® (thyroid tablets, USP); and Thyrolar® (liotrix tablets, USP) drug products. These deviations cause your drugs to be adulterated within the meaning of section 501(a)(2)(B) of the Act. Examples include:

1. Laboratory controls do not include the establishment of scientifically sound and appropriate specifications designed to assure that components, in-process materials, and drug products conform to appropriate standards of identity, strength, quality and purity. 21 CFR 211.160(b)

- Drug product release specifications are not appropriate to assure drug products will meet specifications throughout their shelf life. Levothroid® (levothyroxine sodium tablets, USP) can be released with assays as low as [REDACTED] even though your stability data show potency drops of 11-16% in some samples before the expiration period. If these lots were released at [REDACTED] potency, they would fall below the 90% USP lower limit for levothyroxine sodium tablets, USP during their shelf life.
  - In-process blend uniformity assays do not account for variability between individual sample results.
  - Although not cited on the FDA-483, it was observed that your firm failed to establish appropriate specifications, standards and controls to assure incoming components are appropriate for use in a USP product in that non-USP, "Industrial Grade" ethanol was used to manufacture levothyroxine tablets, USP.
2. Your firm lacks adequate written procedures 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)
- Your firm lacks written procedures for temperature and moisture controls for in-process materials that are sensitive to heat and moisture.
  - Process validation of the Thyrolar® (liotrix tablets, USP) was considered successful even though the lot failed to meet individual blend uniformity specifications and was eventually recalled due to super potent stability assay results. The validity of this process also comes into question because several other lots of this product were either rejected due to super potency or found super potent upon original analyses but accepted based upon retest results. These original results were voided and the retest results accepted without justification.
3. Results of stability testing are not used in determining appropriate storage conditions and expiration dates. 21 CFR 211.166(a)
- Although not cited on the FDA-483, it was determined that stability samples for Levothroid® are not stored under appropriate conditions. Your records indicate these samples were moved from ambient relative humidity conditions at  $25^{\circ}\pm 2^{\circ}\text{C}$  to  $60\%\pm 5\%$  relative humidity at the same temperature for a period of approximately 8 months. Stability testing showed at least one unit dose packaging system was failing potency before its expiration date. You then returned the product to what you described as

ambient humidity conditions. However, our investigators observed that the room that was designated as having ambient humidity was not being maintained at ambient humidity. On 1/28/03 our investigators observed a dehumidifier in the room and the humidity chart showed levels below 15%. Stability results based on such artificially reduced humidity conditions are not appropriate to assure valid estimates of stability.

4. Acceptance criteria for the sampling and testing conducted by the quality control unit are not adequate to assure that batches of drug products meet each appropriate specification as a condition for their approval and release. 21 CFR 211.165(d)
  - When a unit dose sample fails a leak test, only part of the batch produced since the last acceptable leak test is quarantined and sampled as part of the failure investigation. Eight separate instances were observed where the unit dose samples failed the leak testing and those portions were destroyed, yet no further portions of the sampled lots or prior lots were examined.
5. Packaging facilities are not inspected immediately before use to assure all drug products have been removed from previous operations. 21 CFR 211.130(e)
  - Since January 1, 2001 there have been 14 instances where foreign tablets were found during packaging on line 2.

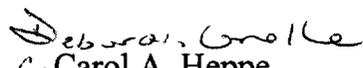
We received a letter from Karl Fricke, Ph.D., Director of QC/QA, and Gregory Yurchak, Plant Manager, dated March 19, 2003, which was in response to the observations listed on the Form FDA-483 issued at the close of the inspection. The corrective actions offered in Mr. Fricke's response were taken into account in preparing this letter.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. A copy of the Form FDA-483 is enclosed for your information. It is your responsibility to assure that all products distributed by your firm meet the requirements of the Act and its implementing regulations.

We request that you notify this office in writing within 15 working days of receipt of this letter stating the action you will take to discontinue the marketing of your Levothroid® (levothyroxine sodium tablets, USP) drug products and to bring your other drug products into compliance. Your reply should include an estimate of the amount of Levothroid® that is in inventory under your control. Failure to achieve prompt correction may result in regulatory action without further notice. The Act provides for seizure of illegal products and/or injunction against the manufacturer and/or distributor of illegal products.

Your reply should be sent to the attention of Charles S. Price, Compliance Officer, U.S. Food and Drug Administration, 6751 Steger Drive, Cincinnati, Ohio 45237. Any questions regarding this letter may be directed to Mr. Price at telephone (513) 679-2700 extension 165.

Sincerely,

  
for Carol A. Heppe  
District Director  
Cincinnati District

Enclosed - Form FDA 483

Cc: Gregory Yurchak,  
Plant Manager  
Forest Pharmaceuticals, Inc.  
5000 Brotherton Road  
Cincinnati, OH 45209