



Food and Drug Administration
1141 Central Parkway
Cincinnati, OH 45202

April 9, 1998

**WARNING LETTER
CIN-WL-98-244**

**CERTIFIED MAIL
RETURN RECEIPT REQUESTED**

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

Dear Mr. Solomon:

During a February 2 through March 13, 1998 inspection of your finished dosage drug manufacturing facility, Forest Pharmaceuticals, Inc., located at 5000 Brotherton Road, Cincinnati, Ohio, our investigator documented significant deviations from the Current Good Manufacturing Practice (CGMP) regulations for drugs (Title 21, Code of Federal Regulations, Parts 210 & 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 (the Act). These deviations include the following:

1. Failure to establish appropriate in-process sampling of Levothroid® (levothyroxine sodium tablets USP) during compression, in that the QC sampling procedures used do not assure uniformity of individual tablet weights (Observation 4).
2. Failure investigation of uniformity/dissolution problems associated with recall of Levothroid®, 75 mcg, lot 99618 was inadequate in that 6 tablets from the original sample were removed from stage II of the dissolution test (Observation 2A), yet removal of the tablets, including at least one low weight tablet, was not documented in the investigation report (Obs. 2B).
3. Out-of-specification test results are not appropriately investigated and original test results are discarded without sufficient justification. For example, when in-process blend samples for two lots of Levothroid® 125 mcg and 88 mcg tablets failed assay, they were retested and failed two more times, then were accepted based on one or two new blend samples yielding passing results (Observation 2C).

Re-sampling without evidence of laboratory error or documented evidence of inappropriate sampling is not sufficient reason for invalidating the initial results. I suggest you re-evaluate your out-of-specification testing SOP.

4. Failure to maintain and control a purified water system that will consistently produce production water of suitable microbiological quality, in that:
 - (a) between February and March 1997, production samples of water used for manufacture of Armour® Thyroid tablets failed to meet appropriate microbiological limits for heterotrophic plate count and *Pseudomonas* sp. on at least five days, other failures were also observed during routine water sampling (Observation 1B).
 - (b) written sanitizing procedures (SOP 211) do not address the action to be taken when purified water fails to meet specifications for *Pseudomonas* or coliform (Observation 1E);
 - (c) the purified water system was observed to be leaking at several different points in the system on at least two days of the inspection (Observation 1F).

5. Failure to perform appropriate and timely failure investigations when production water is found to be microbiologically contaminated with *Pseudomonas* sp. For example:
 - (a) no intermediate or finished product testing was performed for the presence of *Pseudomonas* for two lots of Armour® Thyroid when production water failed testing for *Pseudomonas* (Observation 1A)
 - (b) no failure investigation report exists for purified water lot PW97505 which failed testing for *Pseudomonas* (Observation 1C)
 - (c) your firm's failure investigations and finished product tests are not expanded to other lots of product that may be affected by microbial contamination (Observation 1D).

In addition, three samples of Levothroid® (levothyroxine sodium tablets USP) were collected during the inspection, as follow-up to the GMP deficiencies observed and discussed under items 1-3 above. FDA's analysis of one of these samples, Levothroid®, 150 mcg tablets, lot 109736, found this product to be adulterated under Section 501(b) of the Act, in that it fails to meet the USP23 specifications for uniformity of dosage. The other two lots sampled passed our analyses.

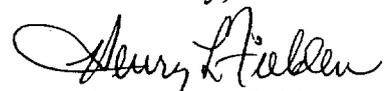
The above identified deficiencies should not be construed as an all inclusive list of violations at your facility. It is your responsibility to ensure that all requirements of the Federal Food, Drug, and Cosmetic Act and regulations promulgated thereunder are being met. Federal agencies are advised of the issuance of all warning letters about drugs and devices, so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these violations. Failure to promptly correct these violations may result in enforcement action being initiated by FDA without further notice. Possible actions include seizure and/or injunction.

You should notify this office in writing within fifteen (15) working days after receipt of this letter of the specific actions you have taken to correct these violations. Your response should include: (1) each step that has or will be taken to completely correct the current violations; (2) the time within which corrections will be completed; (3) any reason why the corrective action is not completed within the response time; and (4) any documentation necessary to indicate correction has been achieved. You should also advise this office immediately of your intended actions regarding the uniformity of dosage failure of Levothroid®, 150 mcg tablets, lot 109736.

Your reply should be sent to the Food and Drug Administration, 1141 Central Parkway, Cincinnati, Ohio 45202 to the attention of Charles S. Price, Compliance Officer.

Sincerely,



Henry L. Fielden
Acting District Director
Cincinnati District

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cc: Terrill J. Howell,
Plant Manager
Forest Pharmaceuticals, Inc.
5000 Brotherton Road
Cincinnati, OH 45209

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