



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

**FILE COPY**

Mr. Robert A. Boutillier  
Mason, Taylor & Colicchio  
104 Carnegie Center  
Suite 201  
Princeton, New Jersey 08540

October 15, 1997

Dear Mr. Boutillier:

Your petition in response to the August 14, 1997 Federal Register notice regarding Levothyroxine sodium (62 FR 43535), was received by this office on 10/14/97. It was assigned docket number 97N-0314/CP1 and filed on 10/15/97. Please refer to this docket number in future correspondence on this subject with the Agency.

Please note that the acceptance of the petition for filing is a procedural matter in that it in no way reflects an agency decision on the substantive merits of the petition.

Sincerely,

A handwritten signature in cursive script, appearing to read "Lyle Jaffe".

Lyle Jaffe  
Dockets Management Branch

MASON, TAYLOR & COLICCHIO

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PLEASE REPLY TO PRINCETON

October 13, 1997

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VIA HAND DELIVERY

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
12420 Parklawn Drive  
Room 1-23  
Rockville, MD 20857

Re: **Docket No. 97N 0314**  
**(Prescription Drug Products;**  
**Levothyroxine Sodium**

Dear Sir or Madam:

Enclosed for filing is a citizen petition submitted by the undersigned, on behalf of a pharmaceutical manufacturer interested in marketing the captioned drug product, in response to the Notice published by FDA in the Federal Register on August 14, 1997.

Very truly yours,



Robert A. Boutillier

RAB/ac  
Enclosure(s)

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97N-0314

CP1

October 14, 1997

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
12420 Parklawn Drive, Room 1-23  
Rockville, MD 20857

**RE: Prescription Drug Products; Levothyroxine Sodium  
FDA Docket No. 97N-0314**

### **CITIZEN'S PETITION**

The undersigned, on behalf of a pharmaceutical manufacturer interested in marketing oral levothyroxine sodium drug products, hereby submits this petition requesting that the conclusions expressed in FDA's August 14, 1997 Federal Register notice regarding oral levothyroxine sodium products be rescinded and/or modified as specified below.

#### **A. Action Requested**

This Petition is submitted in response to the Federal Register notice published by FDA on August 14, 1997 entitled "Prescription Drug Products; Levothyroxine Sodium," 62 Fed. Reg. 43535. The portions of the decision challenged in this petition are 1) the decision that oral levothyroxine sodium products are "new drugs" for the reasons stated in the notice; 2) the decision that oral levothyroxine sodium products not yet marketed are "new drugs" and 3) the decision that, between August 14, 1997 and August 14, 2000, oral levothyroxine sodium products marketed on or before the date of the notice may continue to be marketed without any FDA approval whatsoever but that new oral levothyroxine sodium products may be marketed only after receiving FDA approval of a New Drug Application.

For the reasons stated below, Petitioner requests the following actions and declarations by the FDA:

1. Petitioner requests that FDA rescind the decision, published in the August 14, 1997 Federal Register, that oral levothyroxine sodium drug products are “new drugs.”

2. Petitioner requests that FDA rescind the decision, implicit in the August 14, 1997 Federal Register notice, that oral levothyroxine sodium drug products first marketed after August 14, 1997 are “new drugs.”

3. Petitioner requests that FDA rescind the decision, referred to in the August 14, 1997 Federal Register notice, to apply the “new drug” classification of oral levothyroxine sodium drug products immediately to new products entering the market after August 14, 1997 but to exempt from that classification until August 14, 2000, products marketed on or before August 14, 1997.

## **B. Statement of Grounds**

### **1. Introduction**

For many decades, well before the 1962 date referenced by FDA in its August 14, 1997 notice, oral levothyroxine sodium products have been manufactured and used safely and effectively as thyroid replacement therapy and for other purposes without any suggestion by FDA that those products are “new drugs” that require FDA approval under FDCA §505 prior to marketing. Indeed, even in the various Warning Letters and other regulatory actions taken by FDA in connection with the marketing of such products in the past, no mention has been made that FDA considered marketing of the products without NDA approval as a

violation of §505.<sup>1</sup> Instead, FDA appears simply to have concluded that it would prefer now to have all oral levothyroxine sodium drug products regulated as new drugs and has therefore declared it to be so.

The reasons given in the Federal Register for the agency's new conclusion may be accurately stated but, as explained below, they are not valid grounds for reaching such a conclusion. In addition, and of even greater concern to Petitioner, the manner in which the agency has announced it will implement its new conclusion involves an unfair and completely arbitrary exception applicable only to oral levothyroxine sodium drug products marketed on or before August 14, 1997. This exception is not only arbitrary; it is wrong to allow continued unapproved marketing of older products, whose problems with stability and consistency form the very basis for the FDA action, while forbidding the market introduction of newer products similarly unapproved but developed, tested and validated under stringent GMP and quality standards currently applicable to all drug products.

## **2. The Grounds Cited By FDA Are An Invalid Basis For Declaring Oral Levothyroxine Sodium Drug Products To Be New Drugs**

Although stated and restated in numerous ways, FDA's grounds for declaring oral levothyroxine sodium drug products to be "new drugs" boil down to one, single objection: currently marketed formulations of the drug are not consistent. This point is made by reference to 1) anecdotal reports of patients who exhibit signs of having received more or less thyroid supplementation than had been expected; 2) changes in product formulations that are alleged to have significantly affected the potency of the products and 3) failures of some lots of existing products to maintain potency through their labeled shelf life. At the same

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<sup>1</sup> The two Warning Letters specifically referenced in the August 14, 1997 Federal Register notice, for instance, address GMP concerns regarding the quality and stability of levothyroxine sodium products but make no mention whatsoever of a possible FDA view that the products violated the "new drug" provisions of §505 of the FDCA. (See the June 3, 1992 Warning Letter to Northview Labs and the March 1, 1993 Warning Letter to Pharmaceutical Basics, Inc., attached as Exhibit 1.)

time, the agency concludes that:

. . . the active ingredient levothyroxine sodium is effective in treating hypothyroidism and is safe when carefully and consistently manufactured and stored, and prescribed in the correct amount to replace the deficiency of thyroid hormone in a particular patient.

62 Fed. Reg. at 43538. Thus, it is apparent that the sole ground for the agency's declaration that levothyroxine sodium products are "new drugs" is the allegation that existing products have often been manufactured in violation of good manufacturing practice requirements designed to assure that products have the identity, strength, quality and purity that they are purported or represented to have (FFDCA §501(a)(2)(B)) or that they otherwise have failed to meet compendial standards (FFDCA §501(b) — all of which requirements are applicable to "new drugs" and "old" drugs alike.

Petitioner does not purport to speak for current manufacturers of levothyroxine sodium drug products. We point out, however, that problems with product consistency may be transient and, once identified, can be corrected through proper product development and through application of GMP standards and procedures. We also point out that significant changes in product formulation affecting potency or bioavailability are already required (by the misbranding provisions of the FFDCA §§502(a), (f) and (j)) to be accompanied by appropriate disclosures to alert prescribers to possible changes in therapeutic effects. None of these requirements are contingent on "new drug" status. If these standards are not met, the products are subject to regulatory action to remove them temporarily or permanently from the market under the general adulteration and/or misbranding provisions of the FFDCA regardless of whether the products are "new drugs" or not.

For these reasons, the August 14, 1997 Federal Register notice does not present adequate grounds for declaring oral levothyroxine sodium drug products to be "new drugs" generally, or for making such a declaration specifically with respect to any particular levothyroxine sodium product. This is particularly so in light of 1) the agency's above-quoted conclusion that levothyroxine sodium is safe and effective and 2) the agency's additional conclusion that "[l]evothyroxine

sodium products are medically necessary because they are used to treat hypothyroidism and no alternative drug is relied upon by the medical community as an adequate substitute.” (Id.) Moreover, the agency has cited no expert opinions, qualified or otherwise, contradicting these conclusions with respect to any particular levothyroxine sodium drug product or oral levothyroxine sodium drug products generally. For these reasons, Petitioner respectfully submits that the agency’s declaration that levothyroxine sodium drug products are “new drugs” is arbitrary and capricious and in excess of the legal authority conferred by the FDCA.

### **3. The Grounds Cited By FDA Provide No Basis For Declaring Levothyroxine Sodium Drug Products Not Yet Marketed To Be New Drugs**

As pointed out above, the grounds cited by FDA for declaring oral levothyroxine sodium drug products to be “new drugs” relate only to the specific quality and consistency attributes (or problems) associated with levothyroxine sodium drug products that had been marketed prior to the publication of the notice. The agency conclusion is stated very narrowly, in light of its prior conclusion that levothyroxine sodium is safe and effective:

However, no currently marketed orally administered levothyroxine sodium product has been shown to demonstrate consistent potency and stability and, thus, no currently marketed orally administered levothyroxine sodium product is generally recognized as safe and effective.

(Id.) It does not flow from this conclusion that any new orally administered levothyroxine sodium drug product is a “new drug.” Indeed, the conclusion itself appears to acknowledge that, given the agency’s finding regarding the safety and effectiveness of levothyroxine sodium, a product with demonstrated consistent potency and stability would not be a “new drug.” This acknowledgment by the agency is also reflected in the agency’s provision for the submission of Citizen Petitions showing that particular levothyroxine sodium drug products are not “new drugs.” (Id.) If it is possible for individual previously-marketed drug products to be exempt from “new drug” status, then it is certainly possible for newly marketed

drug products to be so exempt based on a demonstration of consistent potency and stability in accordance with current good manufacturing practice requirements.

For these reasons, the agency's extrapolation of the cited observations regarding the quality and consistency of previously-marketed levothyroxine drug products to a conclusion that ". . . any orally administered drug product containing levothyroxine sodium is a new drug . . ." (*id.*) is unwarranted, arbitrary and capricious and should be rescinded.<sup>2</sup>

#### **4. The Agency Must Extend The Temporary Exemption Providing For The Continued Unapproved Marketing Of Levothyroxine Sodium Products To All Unapproved Levothyroxine Sodium Products**

Despite declaring their status as "new drugs," FDA has declared a moratorium, until August 14, 2000, on enforcement actions against levothyroxine sodium drug products marketed without approved new drug applications. Thus, FDA has effectively "stayed" its "new drug" declaration so that affected products can continue to be marketed and the acknowledged medical need for the products can be filled. This is responsible and appropriate, even assuming that the "new drug" declaration is justified in fact and in law. But, in doing so, FDA has purported to extend the "stay" only to an arbitrarily privileged group of firms who happened to have introduced their products into the market on or before the publication of the notice. There is no justification for creating such a privileged class of manufacturers in this situation and the August 14, 1997 notice does not even attempt to offer one.

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<sup>2</sup> Petitioner hereby incorporates by reference the data, information and views expressed by other persons who may submit Citizen Petitions in response to the August 14, 1997. Recognition by FDA, as requested in any such Petitions, that any existing levothyroxine sodium drug product is not a "new drug," will provide further support to the position stated above that newly marketed levothyroxine sodium drug products that are in full compliance with GMP requirements are also not "new drugs." As also argued above, however, given the grounds cited by the agency for declaring current levothyroxine sodium drug products to be new drugs, Petitioner submits that that conclusion cannot be extended to newly-marketed drug products even if the conclusion properly applies to all currently marketed products.

The inappropriateness of this distinction is obvious from the fact that the only grounds cited for the agency's "new drug" determination for levothyroxine sodium drug products are the product-specific quality and consistency problems identified with respect to previously marketed products. The agency's decision to let those products remain on the market without approval, while forbidding new products to enter the market on that same basis, is completely illogical. Even if the findings on which the new drug determination were based could be said to apply to the active ingredient and not solely to product-specific quality and consistency problems, the provision of a temporary stay of that finding with respect to existing products would necessarily have to apply to new products as well. Fundamental principles of fairness, as well as the Administrative Procedures Act (5 U.S.C. §706(2)(A)) and Constitutional (U.S. Const., Amendments 5 and 14) proscriptions of arbitrary and capricious distinctions between similarly situated persons requires such equal treatment.

Neither is there a precedent for such an arbitrary distinction. For instance, the instant situation is legally and factually distinct from earlier actions where FDA stopped issuing new approvals (or "conditional" approvals) of products while it pursued the withdrawal of existing approvals. (See, for instance, the agency action on Pentaerythritol Tetranitrate Drug Products at 49 Fed. Reg. 40213, October 15, 1984.) The present situation is also distinct from actions where FDA stopped issuing new "conditional" approvals based on a final conclusion that particular products had been shown to be effective under the Drug Efficacy Study Implementation review but, consistent with that finding, imposed new data requirements on any further approvals. (See, for instance, agency notices on Nitroglycerin Transdermal Systems, 58 Fed. Reg. 58129, July 15, 1993, and Nitroglycerin Ointment Drug Products, 51 Fed. Reg. 31371, September 3, 1986.) In those instances, the agency made a decision and acted consistently with that decision as against all affected parties in accordance with their respective legal status. In the current situation, however, no one has an approval to market oral levothyroxine sodium products. Thus, consistent with the agency's position that such products are all "new drugs," it can take only two actions — it can proceed to remove all of the products from the market by seizing them (or seeking to enjoin their marketing), or it can defer regulatory action against all such products until some appropriate later date (e.g., to allow NDAs for some or all of the products to be approved without a disruption in medically necessary supplies). The agency

cannot consistently say that some manufacturers can sell the drug without an approval while others cannot. There is no basis in the law for such a distinction. Neither is there a basis in fact. As pointed out above, given that it is the existing products that have exhibited the quality and consistency problems the agency cites as the basis for its "new drug" determination, to say that only the existing products may be sold without approval is simply perverse.

On the other hand, the levothyroxine situation is analogous to the agency's DESI program, in which drugs that were the subject of less-than-effective "probably effective" or "possibly effective" evaluations could be the subject of "conditional approvals" while FDA decided whether to proceed to withdraw previously issued approvals. (See e.g., 58 Fed. Reg. 58129, July 15, 1993, and 37 Fed. Reg. 26623, December 14, 1972, as amended.) In that manner, FDA ensured fair and equal treatment of similarly situated firms up until the time when it issued a notice of opportunity for hearing stating the agency's conclusion that the products failed to comply with the effectiveness requirements of the 1962 Drug Amendments Act. Everyone was treated at all times in a manner consistent with FDA's conclusions.<sup>3</sup> The same must be done here where FDA has reached a conclusion but has stayed its effectiveness for three years.

The arbitrary and unfair nature of the agency's distinction between existing and new unapproved levothyroxine products for purposes of the three-year marketing exemption is underscored by two factors. First, in light of the long-

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<sup>3</sup> This is true, as stated above, even though, once withdrawal proceedings were initiated, FDA refused to issue additional "conditional approvals." FDA rationally took the position that as long as it was claiming in withdrawal proceedings that the approved drugs were not effective, it would not be consistent for it to approve additional products.

The recent example of the January 3, 1997 approval of Baker Norton's ANDA for a generic terfenadine provides another example of the requirement that the agency act consistently with its conclusions. In that case, the Baker Norton product was approved while the agency was actively preparing to issue a notice of opportunity for hearing proposing to withdraw the approval of the listed drug on which the ANDA was based. That NOOH was in fact issued on January 14, 1997, less than two weeks after the ANDA approval. (62 Fed. Reg. 1889) Until FDA acted against the listed drug, however, the agency properly concluded that it was required to permit additional firms to enter the market for the drug.

unchallenged “old” drug status of levothyroxine sodium products, manufacturers interested in selling new versions of those products could have spent (and at least one firm in fact spent) considerable resources developing such products prior to August 14, 1997, with the completely reasonable expectation of launching those products as soon as their development work was complete.<sup>4</sup> Had there been advance notice that FDA anticipated imposing prior approval requirements before such a product could be marketed, those development plans may not have been pursued. If pursued at all, such plans would have been based on significantly different assumptions, particularly with respect to the uncertainty of FDA approval requirements and review times. The surprise announcement by FDA of its new position on August 14, 1997 should not deny the reasonable expectations of such responsible manufacturers who prepared to meet the requirements in effect prior to that announcement — particularly if the new requirements are being stayed with respect to products marketed prior to that notice which may never have undergone the testing currently required to bring even an “old” drug to market.

Second, we point out that, by the terms of its August 14, 1997 notice, FDA allowed manufacturers who were lucky enough to receive early or simultaneous notice of its publication to commence marketing of levothyroxine products on that day and therefore fall within the exemption for “currently” marketed products. (According to FDA custom, the August 14, 1997 notice was placed on public display on August 13, 1997. (See FOI Services, Inc., RegiFax<sup>TM</sup>, August 13, 1997.) Manufacturers who responsibly chose not to rush their products into the market in order to beat the FDA exemption deadline should not be punished. Neither should manufacturers who simply did not have notice that there was a one or two day opportunity to bring their products to market and thereby to qualify for an exemption that would permit them to market for three additional years without approval.

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<sup>4</sup> The manufacturer on whose behalf this Petition is being submitted, for example, had spent over \$750,000 on its levothyroxine development project before August 14, 1997.

Finally, we point out that although it may be consistent with the case of *Hoffman-La Roche v. Weinberger*, cited in the August 14, 1997 notice, for FDA to declare a class of products to be new drugs and to allow marketing of such products to continue based on their medical necessity, neither that case nor any other permits FDA arbitrarily to create a favored class of products that may be marketed without approval and a disfavored class that is threatened with immediate enforcement for attempting to compete with the favored class.

For these reasons, FDA should immediately amend its August 14, 1997 notice to remove the limitation on the three-year marketing exemption so that it applies equally to all oral levothyroxine sodium products regardless of when they were first marketed, subject to the same requirements that they obtain marketing approval by August 14, 2000 or be removed from the market by that date.

### **C. Environmental Impact**

Petitioner claims a categorical exclusion from the requirement of an environmental impact assessment under 21 C.F.R. §25.24(a)(1), §25.24(c)(6) and, by analogy, §25.24(c)(1).

### **D. Economic Impact**

Information on economic impact will be submitted upon request.

Dockets Management Branch  
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### **E. Certification**

.The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

*Robert A. Boutillier/pdj*

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**WARN 06/03/92 NORTHVIEW LABS, INC.**

**WARN 06/03/92 NORTHVIEW LABS, INC.**

June 3, 1992

WARNING LETTER  
CHI-703-92

CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

Martin J. Spalding, President  
Northview Laboratories, Inc.  
1880 Holste Road  
Northbrook, Illinois 60062

Dear Mr. Spalding:

During an inspection of your contract laboratory facility, Northview Laboratories, Inc., 1880 Holste Road, Northbrook, Illinois, from March 5 through 24, 1992, Investigators Anne E. Kelly and Stephen D. Eich documented deviations from Title 21, Code of Federal Regulations, (21 CFR 210 & 211), as follows:

1. Failure to validate the bacteriostatic/fungistatic assay method used to perform sterility audits.
2. Inappropriate or inadequate investigation into the invalidated sterility test on 1/28/92, for ampicillin trihydrate.
3. Failure to conduct a complete validation of the The system is used to identify isolates based on analysis of metabolic gases, but validation did not consider such variables as atmosphere, amount of inoculum, type of medium, and length of incubation.
4. The USP HPLC assay for Levothyroxine tablets shows a degradate peak for one product which was not completely resolved from the Levothyroxine peak.

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. Until these violations are corrected, federal agencies will be informed that FDA recommends against the award of contracts for affected products. We are also recommending withholding of any product approvals associated with your testing laboratory.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice.

Please notify this office in writing, within fifteen (15) working days of receipt of this letter, of the specific 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 corrective action cannot be accomplished within 15 working days, please state the reason for the delay, and the time within which the corrections will be completed. We acknowledge your letter of April 29, 1992, which responded to the investigators' findings and which described the corrective actions which you have planned or already implemented. Your notification to this office may refer to that response wherever

appropriate, however any corrective actions initiated are subject to verification during the next inspection.

Your written response should be directed to the Food and Drug Administration, 300 South Riverside Plaza, Suite 550 South, Chicago, Illinois 60607, Attention: Jerome Bressler, Director, Compliance Branch.

Sincerely,

Raymond V. Mlecko  
District Director