DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

APR 2 6 2001

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Re: Docket No. 97N-0314/CP1

Dear Mr. Boutillier:

This letter responds to your petition dated October 13, 1997 (Petition), submitted on behalf of an unnamed pharmaceutical manufacturer. Your petition pertains to the publication by the Food and Drug Administration (FDA) of a *Federal Register* notice affecting oral levothyroxine sodium drug products (62 FR 43535; August 14, 1997). You request that FDA rescind the following decisions contained or implicit in that notice: (1) that oral levothyroxine sodium drug products are "new drugs"; (2) that oral levothyroxine sodium drug products first marketed after August 14, 1997, are "new drugs"; and (3) that the "new drug" classification of oral levothyroxine sodium drug products is to apply immediately to new products entering the market after August 14, 1997, but products marketed on or before August 14, 1997, are to be "exempted from that classification" until August 14, 2000 (Petition at 2).

I. Petition for Reconsideration

FDA regards your petition as a petition for reconsideration and has considered your requests in light of the standards in 21 CFR 10.33. FDA grants a petition for reconsideration only if (1) the petition demonstrates that relevant information or views contained in the administrative record were not previously or not adequately considered, (2) the petitioner's position is not frivolous and is being pursued in good faith, (3) the petitioner has demonstrated sound public policy grounds supporting reconsideration, *and* (4) reconsideration is not outweighed by public health or other public interests (21 CFR 10.33(d)). A petition for reconsideration may not be based on information and views not contained in the administrative record on which the decision was made (21 CFR 10.33(e)).

II. Discussion of Actions Requested

A. Rescind the decision that oral levothyroxine sodium drug products are "new drugs"

Your argument that the Agency should rescind this decision rests on the claim that FDA's findings of inconsistent potency and stability in oral levothyroxine sodium drug products are not valid grounds for a determination of new drug status. Despite FDA's presentation of

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documented evidence that these problems of potency and stability go back many years, you suggest that these problems may only be "transient" and

> can be corrected through proper product development and through application of [current good manufacturing practice (CGMP)] standards and procedures. . . . 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 [Federal Food, Drug, and Cosmetic Act (Act)] . . . .(Petition at 4)

This argument implies that because FDA could bring an action under the adulteration or misbranding provisions of the Act, and has in the past dealt with deficiencies in current good manufacturing practice for levothyroxine sodium products as a compliance matter, it is precluded from bringing an action under the Act's new drug provisions. To the contrary, FDA is not required to choose between finding current good manufacturing practice violations and finding that a drug is a "new drug" that requires an approved application to be legally marketed. As the court in *United States v. Baxter Healthcare Corp.*, 901 F.2d 1401 (1990) stated:

> Much of Baxter's argument appears to rest on the inaccurate view that the courts may not allow federal agencies to use more rigorous methods of enforcement of a statutory scheme when less rigorous methods would also be allowable under the statute. The fact that some of FDA's goals could be accomplished through the enforcement of "good manufacturing practices" standards does not mean that the FDA may not use its authority under Section 507(a) [now section 505] . . . . (901 F.2d at 1409)

See also *United States v. Premo Pharmaceutical Labs, Inc.*, 511 F. Supp. 958, 976 (D.N.J. 1981) (holding that postmarketing enforcement tools are not an adequate substitute for the drug application review process in protecting public health).

Moreover, there is nothing in the statutory definition of "new drug" at section 201(p) of the Act that limits FDA's legitimate areas of inquiry to only certain kinds of information about the safety or effectiveness of drug products. Your suggestion that FDA is so limited has no basis in law and is contrary to the broad remedial purposes of the Act. The definition of "new drug" must be liberally construed in order to effectuate the policy of the statute, which is the protection of public health and safety (*United States v. An Article of Drug . . . Bacto-Unidisk*, 394 U.S. 784, 798 (1969)).

Furthermore, "Congress' exclusion of 'generally recognized' drug products from the definition of a 'new drug' is a very narrow one . . . ." (*Premo Pharmaceutical Laboratories v. United States*, 629 F.2d 795, 802-803 (2d Cir. 1980)). See also "Positron Emission Tomography Drug Products; Safety and Effectiveness of Certain PET Drugs for Specific Indications" (65 FR 12999, 13002; March 10, 2000) (Congress recognized that PET drugs are new drugs because variations in manufacturing procedures can significantly affect identity, strength, quality, and purity).

For these reasons, the Agency concludes that your claim–that the Agency's findings of inconsistent potency and stability in oral levothyroxine sodium drug products are not valid grounds for a determination of new drug status–is unsupported by and indeed contrary to the law.

B. Rescind the implicit decision that oral levothyroxine sodium drug products first marketed after August 14, 1997, are "new drugs."

You state that FDA's grounds for declaring oral levothyroxine sodium drug products "new drugs" relate only to products marketed prior to publication of the August 14, 1997, *Federal Register* notice. You argue that it "does not flow from this conclusion" that a new product, i.e., one first marketed after publication of the August 14, 1997, *Federal Register* notice, is a "new drug" (Petition at 5).

The definition of "drug" under the Act (and thus the definition of "new drug") refers to specific drug products, not merely to the active ingredients. Differences in formulation can lead to differences in rate and extent of absorption and to different stability profiles, among other differences. Accordingly, one manufacturer's 100 microgram (mcg) tablet of levothyroxine sodium is not the same product (and, therefore, not the same drug) as another manufacturer's 100 mcg tablet of levothyroxine sodium. See *United States v. Generix Drug Corp.*, 460 U.S. 453, 461 (1983) ("[A drug product] is therefore a 'new drug' subject to the requirements of 505, until the product (and not merely its active ingredient) no longer falls within the terms of 201(p).").

Under section 201(p) of the Act, a drug product is regarded as a new drug if its composition is such that it is not generally recognized as safe and effective *or* if it has not been used to a material extent or for a material time. A drug such as yours that has never been marketed is, by definition, a new drug because it has not been used for a material extent or for a material time.

C. Rescind the decision that the "new drug" classification of oral levothyroxine sodium drug products is to apply immediately to new products entering the market after August 14, 1997, but products marketed on or before August 14, 1997, are to be "exempted from that classification" until August 14, 2000.

Your request implies inaccurately that FDA has "exempted" levothyroxine sodium products marketed on or before August 14, 1997, from classification as new drugs until August 14, 2000.[1] This is not the case. FDA classified all oral levothyroxine sodium drug products as new drugs, and this classification was effective for all such products upon publication of the August 14, 1997, *Federal Register* notice. The Agency has *deferred enforcement* of this classification for products marketed on or before August 14, 1997. Discretion of this kind is consistent with the decision in *Hoffmann-LaRoche, Inc. v. Weinberger*, 425 F. Supp. 890 (D.D.C. 1975) for the reasons discussed in the August 14, 1997, *Federal Register* notice. Moreover, FDA has taken precisely this kind of action in the past. For example, in the *Federal Register* of August 5, 1977 (42 FR 39721), FDA declared that certain forms of phenytoin are new drugs. With respect to phenytoin products already on the market at the time, on the basis of a finding of medical necessity, FDA deferred enforcement action for a specific period of time during which the Agency expected approval to be obtained. More broadly, the policy set forth in the August 14, 1997, *Federal Register* notice is consistent with FDA's general enforcement discretion. (*See Heckler v. Cheney*, 470 U.S. 821 (1985).)

There are two prongs to FDA's decision to defer taking enforcement action against marketed oral levothyroxine sodium products without approved new drug applications (NDAs) and to require premarket approval for new, unapproved oral levothyroxine sodium drug products. As discussed in the *Federal Register* notice, FDA has determined that (a) it is "medically necessary" that levothyroxine sodium drug products continue to be available during the time prior to application approval, and (b) there is a sufficient quantity of oral levothyroxine sodium drug products now on the market to fill this need without the introduction of additional unapproved new drugs. It is legally impossible (except in cases not relevant here) for a never-marketed oral levothyroxine sodium drug product, at the moment of its introduction, to be anything other than a new drug under the second prong of the "new drug" test.

[1] FDA extended this date to August 14, 2001, in a *Federal Register* notice published on April 26, 2000 (65 FR 24488).

III. Conclusion

For the reasons set forth above, you have failed to demonstrate that relevant information or views contained in the administrative record were not previously or not adequately considered and you have not demonstrated sound public policy grounds supporting reconsideration. Moreover, your petition is outweighed by the public health interests that were the basis of the August 14, 1997, *Federal Register* notice. Accordingly, because your petition does not satisfy all of the grounds for granting a petition for reconsideration, your petition is denied.

Sincerely yours,

Dennis E. Baker
Associate Commissioner
for Regulatory Affairs