DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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F. Dominic Cerrito, Esq.
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1155 Avenue of the Americas
New York, NY 10036

Docket No. 03P-0097/CP1

Dear Mr. Cerrito:

This letter responds to your petition dated March 12, 2003, on behalf of Jones Pharma Inc. (Jones Pharma) concerning the reference listed drug for levothyroxine sodium oral tablets. You ask the Food and Drug Administration (FDA) to:

- remove the designation in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) of any product other than Unithroid as a reference listed drug for levothyroxine sodium oral tablets;
- refuse to accept future abbreviated new drug applications (ANDAs) or supplemental ANDAs that designate any product other than Unithroid as the reference listed drug unless the applicant has submitted and FDA has granted the required petition; and
- refuse to approve any pending ANDAs or supplemental ANDAs that designate any product other than Unithroid as the reference listed drug unless the applicant submits and FDA grants the required petition.

This letter also responds to a March 28, 2003, comment on the petition submitted on behalf of Abbott Laboratories (Abbott) that supports your position. For the reasons that follow, the petition is moot in part and denied in part.

I. BACKGROUND

For several decades levothyroxine was marketed by multiple manufacturers without approved applications. On August 14, 1997, FDA published a Federal Register notice announcing its determination that levothyroxine sodium tablets were new drugs that required approved applications in order to be legally marketed. 62 Fed. Reg. 43535. The notice announced that manufacturers who wished to continue to market levothyroxine sodium tablets must obtain an approved application by August 14, 2000 or be subject to enforcement action. When it became apparent that FDA had underestimated the time it would take manufacturers to submit applications and obtain approval, the deadline for obtaining approval announced in the August 14, 1997 notice was extended until August 14, 2001. 65 Fed Reg. 24488 (April 26, 2000). In July 2001, FDA announced in a guidance entitled *Levothyroxine Sodium Products— Enforcement of August 14, 2001*

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Compliance Date and Submission of New Applications (July 2001 guidance) that it would exercise its enforcement discretion after August 14, 2001, with regard to levothyroxine sodium products that are marketed without approved applications by establishing a gradual phase-out of unapproved products. The guidance stated that all distribution of unapproved products should cease by August 14, 2003.

Unithroid is manufactured by Jerome Stevens Pharmaceuticals Inc. It was the first oral levothyroxine sodium product to obtain approval for its New Drug Application (NDA). It was approved on August 21, 2000. At the time of approval, FDA designated it as the reference listed drug to which generic applicants for levothyroxine sodium products should refer.

The July 2001 guidance stated:

> A manufacturer who wishes to submit an application for [a levothyroxine sodium product] after August 14, 2001, should submit an abbreviated new drug application (ANDA). FDA has designated Unithroid as the reference listed drug to which ANDAs should refer. However, the Agency would accept a petition to designate a second reference listed drug.

After Unithroid was approved the Agency approved other NDAs for levothyroxine. Levoxyl, manufactured by Jones Pharma, was approved on May 25, 2001. Levo-T, manufactured by Alara Pharmaceutical Corp.[1], was approved on March 1, 2002. Novothyrox, manufactured by Genpharm Inc., was approved on May 31, 2002. Synthroid, manufactured by Abbott Laboratories, was approved on July 24, 2002. Thyro-Tabs, manufactured by Lloyd, Inc., was approved on October 24, 2002. At the time of approval, each of these products was designated a reference listed drug in the Orange Book.[2]

Although FDA had already spontaneously designated Synthroid and Levoxyl as reference listed drugs, Mylan Pharmaceuticals (Mylan) submitted a citizen petition to FDA dated March 18, 2003, asking FDA to designate Abbott's Synthroid as an additional reference listed drug for levothyroxine sodium. Mylan submitted a second petition dated March 19, 2003, asking the Agency to designate Jones Pharma's Levoxyl as an additional reference listed drug for levothyroxine sodium. On May 6, 2003, FDA granted both Mylan petitions. *See* Docket Nos. 03P-0107 and 03P-0113.

[1] Mova Pharmaceutical Corporation held the NDA for Levo-T at the time of approval. That NDA was subsequently transferred to Alara Pharmaceuticals.

[2] Levolet, manufactured by Vintage Pharmaceuticals, was approved on June 6, 2003. It has not been designated a reference listed drug in the Orange Book.

II. ANALYSIS

A. Arguments of Jones Pharma and Abbott

You state that FDA should grant your petition because FDA's July 2001 guidance established procedures concerning designation of reference listed drugs for ANDAs for levothyroxine sodium. Although guidance is binding neither on the Agency nor on the public, you assert that FDA's decision to designate subsequent reference listed drugs without a citizen petition was a violation of these procedures and was arbitrary and capricious. You also state that FDA's action has left levothyroxine sodium manufacturers questioning the force of the July 2001 guidance. Petition at 6. Furthermore, you state that your position is consistent with FDA's policy as stated in the Orange Book:

> By designating a single reference listed drug as the standard to which all generic versions must be shown to be bioequivalent, FDA hopes to avoid possible significant variations among generic drugs and their brand name counterpart. Such variations could result if generic drugs were compared to different reference listed drugs. However, in some instances when multiple NDAs are approved for a single drug product, a product not designated as the reference listed drug and not shown to be bioequivalent to the reference listed drug may be shielded from generic competition. A firm wishing to market a generic version of an NDA listed drug that is not designated as the reference listed drug may petition the Agency through the Citizen Petition procedure . . . .

Orange Book, Preamble at x.

Abbott essentially repeats these arguments and emphasizes that FDA has not issued any policy statement about when it will automatically designate multiple reference listed drugs. Abbott also contends that using the citizen petition process to designate additional reference listed drugs provides an opportunity for the public to comment and for FDA to address any issues that may arise from having multiple reference listed drugs. Abbott also asserts that if FDA has filed a levothyroxine sodium application that references a product other than Unithroid, the Agency should stop reviewing the application on the theory that such an application would be incomplete without approval of a petition agreeing to designate the reference listed drug.

B. Discussion

Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)) allows the marketing of generic versions of previously approved drug products when the generic version is the subject of an approved ANDA. To gain approval, the ANDA must show, among other things, that the generic version has the same active ingredient in the same strength, that its labeling is the same (with certain limited exceptions), and that it is

bioequivalent to a listed drug, i.e., a previously approved drug product. Statutorily, every approved drug product is a listed drug to which an ANDA may refer, and thus FDA has the authority to approve a generic version of any approved drug product. See 21 U.S.C. 355(j)(2)(A), 355(j)(7) (defining all drugs approved for safety and effectiveness under 505(c) and all drugs approved under 505(j) as "listed drugs" eligible to be referenced in an ANDA).

Section 314.3 of the regulations (21 CFR 314.3) defines the terms *listed drug* and *reference listed drug* as follows:

> *Listed drug* means a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the act . . . . Listed drug status is evidenced by the drug product's identification as a drug with an effective approval in the current edition of FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the list) or any current supplement thereto, as a drug with an effective approval. A drug product is deemed to be a listed drug on the date of effective approval of the application or abbreviated application for that drug product.
>
> *Reference listed drug* means the listed drug **identified by FDA** as the drug product upon which an applicant relies in seeking approval of its abbreviated application. (Emphasis added.)

FDA's general policy on the designation of reference listed drugs is described in the preamble to the final rule establishing the requirements for ANDAs, published in the *Federal Register* of April 28, 1992 (57 FR 17950 at 17958):

> FDA will designate all reference listed drugs. Generally, the reference listed drug will be the NDA drug product for a single source drug product. For multiple source NDA drug products or multiple source drug products without an NDA, the reference listed drug generally will be the market leader as determined by FDA on the basis of commercial data. FDA recognizes that, for multiple source products, a product not designated as the listed drug and not shown bioequivalent to the listed drug may be shielded from direct generic competition. If an applicant believes that there are sound reasons for designating another drug as a reference listed drug, it should consult FDA.

Thus, the statute states that any approved drug is a listed drug, and the ANDA regulations and the preamble to the final rule adopting those regulations make clear that the Agency has broad discretion to designate reference listed drugs to ensure that no listed drug, particularly one with a significant market share, is unfairly shielded from generic competition. Accordingly, although FDA has identified the petition process as one route for an interested applicant to persuade FDA to designate a second reference listed drug,

any suggestion that FDA lacks the general authority to designate a second reference listed drug unless it has been requested to do so through a citizen petition is without merit.

As stated in the preamble to the proposed rule revising FDA's administrative practices and procedures, "citizen petitions were intended to serve as a mechanism by which individuals could request agency action on regulatory matters." 43 FR 51966 at 51967; November 7, 1978. Petitions are the primary way that FDA receives requests for action in areas that are of interest to more than an individual NDA or ANDA applicant. Accordingly, a manufacturer who wishes to submit an ANDA that refers to a listed drug that has not been designated a reference listed drug usually makes the request for designation of another reference listed drug in the form of a petition. However, although the petition process provides an orderly means for FDA to receive and act on requests for designation of multiple reference listed drugs under most circumstances, nothing precludes FDA from designating a drug as a reference listed drug in the absence of such petition.

Moreover, levothyroxine is not the usual case. Because levothyroxine sodium was widely marketed by multiple companies before approval, and Synthroid was the overwhelming market leader during the many years levothyroxine sodium products were marketed without applications,[3] it was clear from the outset that Synthroid should be designated a reference listed drug once an application for it was approved. As noted above, the preamble to the 1992 final rule establishes that the market leader will generally be designated as a reference listed drug for multiple source products. However, Synthroid was not the first levothyroxine sodium product to be approved. Therefore, FDA was faced with the problem of what to do regarding other applications approved after Unithroid, the first approved product. Because Synthroid's eventual approval was anticipated but not assured, as each new levothyroxine sodium product was approved, it was unclear who would be the eventual market leader among the approved products. Accordingly, after assessing the public health risk of designating multiple reference listed drugs and determining that risk to be acceptable, each product was designated by FDA as a reference listed drug spontaneously upon approval.

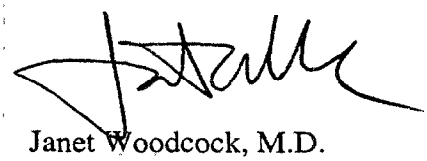
Because Synthroid and Levoxyl have now been designated reference listed drugs for levothyroxine sodium pursuant to citizen petitions submitted by Mylan and granted by FDA, with respect to these products, your request that FDA only designate reference listed drugs through the citizen petition process is moot. *See* Docket Nos. 03P-0107 and 03P-0113.[4] With respect to other levothyroxine products currently designated as

[3] "Synthroid is the number one prescribed treatment for hypothyroidism *and the second most-prescribed medication overall in the United States*." Abbott Press Release, July 24, 2002 (issued upon the approval of the NDA for Synthroid) (emphasis added).

[4] Abbott has filed petitions for stay of action in each of these dockets, requesting that approval of these petitions be stayed pending consideration of another citizen petition filed by Abbott (Docket No. 03P-0210/CP1) in which Abbott requests that FDA withdraw its decision designating Synthroid and Levoxyl as reference listed drugs. Abbott's petitions will be addressed in a separate petition response.

reference listed drugs, your petition to remove those designations is denied. For the reasons stated above, FDA does not deem it necessary at this time to remove those designations. Your petition is also denied to the extent it asks FDA to affirm that FDA may designate a second reference listed drug only if requested in a citizen petition.

Sincerely yours,



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