DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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Docket Nos. 03P-0210/CP1, 03P-0107/PSA1 and 03P-0113/PSA1

Dear Mr. Fox:

This letter responds to your citizen petition (Petition) and two petitions for stay of action (PSAs), all dated May 13, 2003. All three submissions concern levothyroxine sodium and were submitted on behalf of Abbott Laboratories (Abbott). In the Petition, you ask the Food and Drug Administration (FDA) to reopen Docket Nos. 03P-0107 and 03P-0113 to allow for the submission of Abbott's comments. You also ask FDA to defer or deny Mylan Pharmaceuticals' (Mylan's) request that FDA designate additional reference listed drugs for levothyroxine sodium tablets in the Agency's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) on the ground that designation of multiple reference listed drugs for levothyroxine sodium would pose a safety hazard. The PSAs ask FDA to stay the effective date of our decisions in Docket Nos. 03P-0107 and 03P-0113 so that we might consider the comments contained in the Petition. We have considered the comments that you have submitted and for the reasons that follow, your Petition and your PSAs are denied.

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 FR 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 FR 24488 (April 26, 2000). In July 2001, FDA announced in a guidance entitled *Levothyroxine Sodium Products— Enforcement of August 14, 2001 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.

03P-0113

PDN 1

From well before the time the 1997 Federal Register notice was published up until the present, Synthroid, currently manufactured by Abbott, has been the overwhelming market leader for levothyroxine sodium tablets. Levoxyl, manufactured by Jones Pharma ("Jones"), has the second largest market share. After FDA published the August 14, 1997, notice, Jerome Stevens was the first sponsor to receive approval of an NDA to market levothyroxine sodium tablets. Its new drug application (NDA) for Unithroid was approved on August 21, 2000, and, at the time of approval, FDA designated Unithroid as the reference listed drug to which abbreviated new drug applications (ANDAs) 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.

The Agency has now approved six other NDAs for levothyroxine sodium tablets. Levoxyl 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 was approved on July 24, 2002. Thyro-Tabs, manufactured by Lloyd, Inc. was approved on October 24, 2002. Levolet, manufactured by Vintage Pharmaceuticals, was approved June 6, 2003. FDA designated Levoxyl, Levo-T, Novothyrox, Synthroid, and Thyro-Tabs as reference listed drugs after approval.

On March 12, 2003, Jones submitted a petition (Jones petition) objecting to the designation of each approved levothyroxine drug as a listed drug in the absence of approval of a citizen petition as described in the July 2001 draft guidance. *See* Docket No. 03P-0097. You submitted a comment in support of the Jones petition on March 28, 2003. On March 18, 2003, while the Jones petition was pending, Mylan submitted a citizen petition of the type described in the July 2001 guidance, asking FDA to designate Synthroid as a reference listed drug. On March 19, 2003, Mylan submitted a second petition asking FDA to designate Jones' Levoxyl as a reference listed drug (collectively, "the Mylan Petitions"). On May 6, 2003, FDA granted the 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.

In effect, your Petition asks FDA to reconsider its decision to grant the Mylan petitions in light of the new argument you have now provided.

II. Petition (Docket No. 03P-0210/CP1)

a. Procedural objections to decision granting Mylan petitions

Your first objection to FDA's decision to grant the Mylan petitions is that the decision "was made without benefit of comments from Abbott, despite the fact that we informed the agency of our intent to comment." Petition at 1. There is no regulatory requirement that the Agency hold open a citizen petition docket to await comments.[2] Moreover, Abbott did in fact comment on the issue of multiple reference listed drugs for levothyroxine sodium tablets in its comment to the Jones petition. That comment challenged FDA's decision to designate multiple reference listed drugs for levothyroxine sodium without first receiving citizen petitions seeking such designation, and objected that FDA has not issued any policy statement announcing when it will automatically designate multiple reference listed drugs in the absence of such a petition.[3] The Agency responded to the Jones petition (including Abbott's comment to the petition) on October 1, 2003 (copy enclosed).

b. Substantive objections to decision granting Mylan petitions

The more substantive basis for your request that FDA defer response to or deny the Mylan petitions relates to the way FDA lists multiple reference listed drugs and generic drugs in the Orange Book. You suggest that FDA's system of listing multiple reference

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[2] FDA's regulation concerning comments on citizen petitions states that "[a]n interested person may submit written comments to the Dockets Management Branch on a filed petition, which comments become part of the docket file. The comments are to specify the docket number of the petition and may support or oppose the petition in whole or in part. A request for alternative or different administrative action must be submitted as a separate petition." 21 CFR § 10.30(d).

[3] A footnote on page 2 of Abbott's March 28 comment to the Jones petition stated, "Abbott intends to comment promptly on the Mylan petition." The Mylan petitions were not answered until May 6, 2003, more than one month after Abbott's March 28 footnote. This period gave Abbott sufficient opportunity to comment on those petitions had it sought to do so. Because Abbott and Jones were arguing that no ANDA could be received for filing until a citizen petition, such as the Mylan petitions, designating a drug as a reference listed drug was approved, Abbott had an incentive to delay commenting on, and thus to delay FDA approval of, the Mylan petitions. Under the view Abbott has advocated, any delay in the response to the Mylan petitions would delay the possible availability of generic competition for Synthroid. Given Abbott's obvious disincentive to comment expeditiously, Abbott could not have reasonably expected FDA to delay acting on those petitions indefinitely while awaiting its promised comments. However, now that it has received Abbott's substantive objections to the Mylan petitions, FDA has considered and addressed them in this response to your Petition and PSAs.

listed drugs in the Orange Book is likely to lead to confusion and inappropriate substitution of levothyroxine sodium products, which has the potential to adversely affect patients. You request that FDA deny or defer action on the Mylan petitions until it develops a new system that eliminates this anticipated confusion. For the reasons that follow, FDA declines to do so.

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 and dosage form, that it has the same labeling (with certain limited exceptions), and that it is bioequivalent to a listed drug, i.e., a previously approved drug product. 21 U.S.C. 355(j)(2)(A); 355(j)(4). Statutorily, every approved drug product is a listed drug to which an ANDA may refer. Thus, FDA has the authority to approve a generic version of any approved drug product when applicable market protections for that drug product have expired. 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). This system implements both the words of the statute and the policy underlying the Drug Price Competition and Patent Term Restoration Act ("Hatch-Waxman amendments") – to allow innovators certain protections from generic competition for a limited time period and, when that time has expired, to subject those drugs to the potential for generic competition.

Although all drugs approved under § 505 are statutorily eligible for generic competition, in order to minimize unnecessary confusion, FDA's policy is to designate a single reference listed drug for a multiple source product unless to do so would unfairly shield a competitor product from such competition. 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.
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> *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 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) as follows:

> 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.

FDA's policy is further described in the Orange Book preface:

> 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, Preface at x.

When choosing which product to designate as reference listed drug, FDA usually will choose the market leader because this is the drug that ANDA applicants are most likely to seek to reference. FDA ordinarily learns that a potential ANDA applicant seeks to reference a product other than the reference listed drug that FDA has designated when that potential applicant files a citizen petition requesting FDA to designate an additional reference listed drug. Given the broad statutory and regulatory definitions of listed drug, FDA has never refused a citizen petition to designate an additional reference listed drug. The agency has designated multiple reference listed drugs for diltiazem (indicated for cardiac conditions) and albuterol (indicated for asthma), among others. See also Docket Nos. 99P-0189, 99P-2146, 00P-0219, 01P-0353, 01P-0356 (designating multiple reference listed drugs).

In the case of levothyroxine sodium products, Synthroid, the undisputed market leader, was one of the last levothyroxine sodium products to obtain approval, and Unithroid, the first to obtain approval, held a relatively small market share. Given this unusual situation, FDA designated Unithroid a reference listed drug upon approval and assumed that ANDA applicants would seek to reference drugs in addition to Unithroid when those drugs obtained approval. Therefore, FDA proactively designated subsequently approved levothyroxine products as reference listed drugs after they obtained approval. See FDA response to Jones petition (copy enclosed).

Mylan confirmed FDA's assumption that ANDA applicants would seek to reference drugs other than Unithroid when it filed the Mylan petitions seeking designation of Synthroid and Levoxyl as reference listed drugs. Consistent with the policy expressed in the preamble to the 1992 regulations and in the preface to the Orange Book, FDA granted the Mylan petitions on May 6, 2003. FDA concluded that Synthroid and Levoxyl have significant market shares, and the policies behind the Hatch-Waxman amendments require that these products not be shielded from generic competition merely by virtue of the fact that another NDA applicant sought and obtained approval more diligently or quickly.

You now imply that levothyroxine sodium should not have multiple reference listed drugs regardless of the process for designating them. You suggest that levothyroxine sodium presents a special case because it treats a serious condition and improper substitution can have serious consequences for patients. In spite of the fact that Synthroid itself was approved under a 505(b)(2) application at a time when the potential for confusion was already relatively high (because four other applications for levothyroxine sodium tablets had been previously approved without showing bioequivalence to each other), you assert that any incremental confusion posed by multiple generics referencing these multiple reference listed drugs would be unacceptable. You further assert that the AB1/AB2 system[4] in the Orange Book is inadequate to prevent improper substitution of levothyroxine sodium products and resultant harmful medication errors. To avoid this asserted incremental confusion, you

[4] The Orange Book explains the system as follows: "In certain instances, a number is added to the end of the AB code to make a three character code (i.e., AB1, AB2, AB3, etc.). Three-character codes are assigned only in situations when more than one reference listed drug of the same strength has been designated under the same heading. Two or more reference listed drugs are generally selected only when there are at least two potential reference drug products which are not bioequivalent to each other. If a study is submitted that demonstrates bioequivalence to a specific listed drug product, the generic product will be given the same three-character code as the reference listed drug it was compared against. . . . Drugs coded as AB under a heading are considered therapeutically equivalent only to other drugs coded AB under that heading. Drugs coded with a three-character code under a heading are considered therapeutically equivalent only to other drugs coded with the same three-character code under that heading." Preface at xv-xvi.

suggest that FDA must delay acting on the Mylan petitions until it revisits and redesigns its longstanding system for designating multiple reference listed drugs in the Orange Book.

The fact that levothyroxine sodium treats a serious condition (hypothyroidism) and requires careful dosing does not distinguish levothyroxine sodium from other drugs or conditions for which the Agency has approved petitions to allow more than one reference listed drug. As noted above, the Agency has designated additional reference listed drugs for diltiazem (cardiac conditions) and albuterol (asthma), among others. Moreover, you do not provide any evidence to support the assertion that the AB1/AB2 system is inadequate to prevent improper substitution. Instead, you cite an withdrawn draft guidance for industry on *Placing the Therapeutic Equivalence Code on Prescription Drug Labels and Labeling* (December 1998) as ostensible evidence of the inadequacy of the existing system.[5]

The draft guidance you cite has been withdrawn. Moreover, the fact it was drafted in the first place demonstrates only that the Agency has considered options to further reduce the possibility of potentially harmful medication errors; it does not demonstrate that medication errors have occurred or will occur because of any confusion allegedly generated by the AB1/AB2 system. Your petition has identified no such errors that have occurred as the result of any alleged confusion created by this system.

In sum, you have failed to show that the AB1/AB2 system has led to patient harm in general, let alone that this will be the case with respect to levothyroxine sodium in particular. In contrast, it is clear that a reversal or stay of the decision to approve the Mylan petitions while a new Orange Book system is being developed could unfairly disadvantage Jerome Stevens for being the first applicant to diligently pursue and obtain approval for levothyroxine sodium tablets. It would also unfairly disadvantage generic manufacturers seeking to reference a listed drug other than Unithroid, and consumers seeking generic alternatives to levothyroxine sodium products other than Unithroid.

You suggest that FDA should not designate any reference listed drugs for levothyroxine sodium except for Jerome Stevens' Unithroid until FDA has created (and presumably tested) an entirely new system for designating multiple reference listed drugs. Such a policy would deny generic applicants the opportunity to compete with, and consumers the opportunity to obtain, generic alternatives to Synthroid and Levoxyl, two of the drugs with the largest share of the levothyroxine sodium market. This result would be contrary not only to the language of the Hatch-Waxman amendments (which permits any drug

[5] The withdrawn draft guidance stated at pages 1-2 that, "[w]hen multiple reference listed products exist with the same established names and strengths, chances increase that a generic product will be dispensed to the patient that is not therapeutically equivalent to the one intended or previously prescribed."

approved under 505 to serve as listed drug referenced in an ANDA) but also to the intent of those provisions. Moreover, it would penalize Unithroid for obtaining a rapid approval, and reward Levoxyl and Synthroid for taking longer to do so.

Because your request is not warranted by the statute or regulations and is not supported by evidence that distinguishes levothyroxine sodium from other approved drug products with multiple reference listed drugs, FDA affirms its decision to grant the Mylan petitions. Your Petition (which essentially seeks reconsideration of the May 6 decision to grant the Mylan petitions) is denied.

III. PSAs (Docket Nos. 03P-0107/PSA1 and 03P-0113/PSA1)

Your PSAs state that you have requested the stays "for the limited purpose of allowing the agency to consider the comments contained in the [Petition]." The Agency has considered your comments and has responded to them herein. However, because FDA has already acted on the Mylan petitions and has not stayed or reversed its decision to grant those petitions, your PSAs are denied.

Sincerely yours,

William K. Hubbard
Associate Commissioner
for Policy and Planning

Enclosure