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Dockets Management Branch (HFA-305)
Food and Drug Administration
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**PETITION FOR STAY OF ACTION
DOCKET NOS. 03P-0107 and 03P-0113**

The undersigned, on behalf of Abbott Laboratories ("Abbott"), submits this petition under 21 CFR 10.35 to request that the Commissioner of Food and Drugs (the "Commissioner") stay the effective date of his decision to grant petitions 03P-0107 and 03P-0113. This stay is for the limited purpose of allowing the agency the opportunity to consider the comments contained in the attached citizen petition.

A. DECISION INVOLVED

On March 20 and 21, 2003, Mylan Pharmaceuticals Inc. ("Mylan") submitted the above-referenced citizen petitions seeking to have Synthroid® (levothyroxine sodium tablets, USP) and Levoxyl designated as reference listed drugs in the Food and Drug Administration ("FDA") publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"). We understand that on or about May 7, 2003, the Commissioner granted these petitions.^{1/}

B. ACTION REQUESTED

The decision to grant petitions 03P-0107 and 03P-0113 was made without the benefit of comments from Abbott. Abbott has a strong interest in this

^{1/} On May 7, 2003, the agency's "Dockets Entered" page showed that FDA filed a "PAV" response to both petitions, indicating that they had been approved.

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matter; among other things, the Commissioner's decision means that the agency will now consider Abbott's product Synthroid® to be an appropriate reference standard against which applicants under section 505(j) of the Federal Food, Drug, and Cosmetic Act may seek approval. We previously informed the agency that Abbott intended to comment on these petitions. *See* Docket No. 03P-0097, Comments of Abbott Laboratories at 2 n.1 (Mar. 28, 2003).

By this petition, Abbott therefore seeks a stay of the Commissioner's decision granting petitions 03P-0107 and 03P-0113. This stay is for the limited purpose of allowing the agency to consider the comments contained in the attached citizen petition. As discussed in that petition, Abbott believes that the Commissioner's decision granting petitions 03P-0107 and 03P-0113 may lead to the inappropriate substitution of inequivalent levothyroxine products.

C. STATEMENT OF GROUNDS

Under 21 CFR 10.35, the Commissioner shall grant a stay in any proceeding where all of the following apply: The petitioner will otherwise suffer irreparable injury; the petitioner's case is not frivolous and is being pursued in good faith; the petitioner has demonstrated sound public policy grounds for the stay; and the delay requested is not outweighed by the public interest. In addition, the Commissioner may grant a stay if it is in the public interest and the interest of justice. 21 CFR 10.35(e). As demonstrated below, the present circumstances meet each of these criteria.

Without this stay, Abbott will suffer irreparable injury. As discussed in Abbott's citizen petition, confusion and inappropriate substitution may result from the decision to grant the Mylan petitions. These consequences threaten to put patients at risk and erode public confidence in Synthroid®. There is no mechanism by which Abbott will be able to recoup the resulting losses.

Abbott is in good faith seeking to ensure that the designation of multiple reference listed drugs will not result in the substitution of inequivalent levothyroxine products. Levothyroxine is a narrow therapeutic range drug for which precise and consistent dosing is essential to the safety and effectiveness of the product. *See generally* 62 FR 43535 (Aug. 14, 1997). As shown in the attached petition, the agency's approach to listing multiple reference products and multiple

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generics in the *Orange Book* may, in this instance, contribute to the inappropriate substitution of inequivalent products.

Finally, the purpose of using the citizen petition process to designate more than one reference standard within a given class is to provide FDA with the benefit of public comments before reaching a decision. See Docket No. 03P-0097, Comments of Abbott Laboratories (Mar. 28, 2003). Abbott informed FDA that it intended to comment on the Mylan petitions. *Id.* at 2 n.1. The agency, however, answered petitions 03P-0107 and 03P-0113 without the benefit of Abbott's comments and well before the time in which the agency is generally required to respond to a petition. See 21 CFR 10.30(e)(2).

In short, the public interest favors considering the views of interested persons such as Abbott before reaching a final decision on this type of petition. Moreover, given the medical issues associated with the need for precise and consistent dosing of levothyroxine, the public interest favors entry of a stay to consider comments on the potential for confusion among reference products and possible generics.

D. CONCLUSION

For these reasons, we respectfully request that the Commissioner stay the decision on petitions 03P-0107 and 03P-0113 to allow the agency to consider Abbott's comments. These comments are contained in the citizen petition submitted herewith.

Respectfully submitted,



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CITIZEN PETITION

On behalf of Abbott Laboratories ("Abbott"), the undersigned submits this petition pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 CFR 10.25(a), and 21 CFR 10.30 to request that the Commissioner of Food and Drugs (the "Commissioner") withdraw his decision granting petitions 03P-0107 and 03P-0113.

On March 20 and 21, 2003, Mylan Pharmaceuticals Inc. ("Mylan") submitted petitions 03P-0107 and 03P-0113 seeking to have Synthroid® (levothyroxine sodium tablets, USP) and Levoxyl designated as reference listed drugs ("RLDs") in the Food and Drug Administration ("FDA") publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"). On or about May 7, 2003, the Commissioner granted both petitions.^{1/}

The decision to grant the petitions was made without the benefit of comments from Abbott, despite the fact that we informed the agency of our intent to comment. See Docket No. 03P-0097, Comments of Abbott Laboratories (Mar. 28, 2003) at 2 n. 1. As shown below, the agency's approach to listing three or more inequivalent reference products, with multiple generics to each, is likely in this instance to cause confusion among patients, pharmacists, and prescribers, and may lead to medication errors. For this reason, Abbott is submitting this petition (and

^{1/} On May 7, 2003, the agency's "Dockets Entered" page showed that FDA filed a "PAV" response to both petitions, indicating that they had been approved.

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the accompanying petition for stay of action) to ensure that Abbott's views are considered.

A. ACTION REQUESTED

By this petition, Abbott requests that the Commissioner re-open docket Nos. 03P-0107 and 03P-0113 to allow for the submission of Abbott's comments as set forth below. Further, based on the information and views set forth below, Abbott requests that the agency defer or deny the request to designate additional levothyroxine reference standards. The agency at this time lacks an adequate approach for designating multiple levothyroxine reference standards and for distinguishing among generic products that may reference each standard. Given the likelihood of confusion, and the medical implications in this instance of inappropriate substitution, the petitions (03P-0107 and 03P-0113) must be deferred or denied.

B. STATEMENT OF GROUNDS

1) Introduction

Unithroid was the first oral levothyroxine product approved under a new drug application ("NDA") and listed in the *Orange Book*. FDA designated Unithroid as the reference standard against which proposed generic products should be compared. One generic application, sponsored by Mylan, has been approved and others may be pending.

As each of five levothyroxine NDAs (subsequent to Unithroid) have been approved, the agency has designated each as an additional RLD. *See, e.g., Orange Book* at 1-39 (July 2002 Supp.) (designating Synthroid®). These designations were challenged on procedural grounds by Jones Pharma Inc. ("Jones") in a March 12, 2003, citizen petition. Docket No. 03P-0097. Abbott submitted comments in support of that petition on March 28, 2003. Subsequent to Jones's filing, Mylan submitted the above-referenced petitions seeking to have Synthroid® and Levoxyl designated as RLDs. FDA has not yet responded to the Jones petition.

Abbott is submitting these comments because the current method by which FDA lists multiple RLDs and generic drugs within the same class in the *Orange Book*, when applied to levothyroxine products, is likely to lead to confusion and inappropriate substitution. This confusion has special implications for

levothyroxine, given the known medical consequences of improper or imprecise levothyroxine dosing.

In short, the *Orange Book* currently (albeit improperly) lists six different brand-name levothyroxine products as RLDs. Only one other *Orange Book* product has more than two brand name reference standards (diltiazem extended release capsules) with multiple generics and, as shown below, the listing for that product has been specifically identified by the agency as problematic. The agency's current approach clearly would be inappropriate for a product such as levothyroxine, where precise and consistent dosing is critical to patient care.

2) Analysis

a. *Single Reference Standards Are Preferred; When FDA Adopts Multiple Reference Standards, the Agency Has Acknowledged That it Must Take Steps to Prevent Product Confusion*

Under the FDCA, the agency has the discretion to receive, review, and approve applications under section 505(j) that reference new drugs previously approved under sections 505(c) or 505(j). 21 USC 355(j); see 21 CFR 314.3(b). FDA, however, does not allow sponsors to reference any approved drug product of their choosing. Instead, the agency has developed a system in which it designates a preferred reference standard for each category of products. According to the agency, "[b]y 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." *Orange Book* at x (2002).

The scientific basis for the presumption in favor of a single standard is further explained in a 1998 petition response, in which FDA states that because bioequivalence is defined as the lack of a "significant difference" in two products' bioavailability ("BA"), equivalent products may nonetheless have nominally different BA profiles. Docket No. 96P-0459, FDA Petition Response (Nov. 2, 1998) at 7 n. 8. These differences could lead, over time, to significant variations, or "bio-drift," if multiple generics were compared to multiple innovators. "Therefore," FDA "has devised a system that encourages generic applicants to reference the same innovator product as the standard for demonstrating bioequivalence." *Id.*

FDA has, nevertheless, recognized that additional reference standards may be added to the *Orange Book* through the citizen petition process. See Docket No. 03P-0097, Comments of Abbott Laboratories (Mar. 28, 2003). In the few instances in which FDA has sought to designate multiple reference standards within a class, the agency has acknowledged that it must take steps to minimize the potential for confusion. See, e.g., Docket No. 94P-0208, FDA Petition Response (Nov. 7, 1995) at 2 (addressing concerns regarding confusion among generic diltiazem products).

In this instance, the need for adequate steps to prevent confusion among levothyroxine products is especially critical. Orally administered levothyroxine sodium products have a narrow therapeutic range and must be precisely and consistently dosed to be safe and effective. Maintenance of a euthyroid state is critical to the health and well being of the patient. The need for precise levothyroxine dosing means that inappropriate substitution of products that are not therapeutically equivalent will have adverse consequences for patients, as they become alternatively hypo- or hyperthyrotic. See, e.g., 62 FR 43535, 43536 (Aug. 14, 1997).

b. *The Current Method Used to Designate Multiple RLDs is Insufficient to Prevent Confusion Among Levothyroxine Products*

To date, FDA has sought to minimize confusion among multiple RLDs in the same class by assigning a numerical indicator to the TE code of each inequivalent product (e.g., "AB1," "AB2"). The products that bear the same three-digit TE code are considered to be therapeutically equivalent. *Orange Book* at xvi. Based on a review of the *Orange Book*, we know of only one instance in which FDA has had to assign more than two numerical indicators (i.e., an "AB3" code) within a single class. *Id.* at 3-123-3-124 (diltiazem extended release capsules).

The effectiveness of FDA's numerical indicator policy in minimizing confusion and preventing improper product substitution has never been validated. The potential for confusion is greatest in situations involving more than two inequivalent reference standards, with multiple firms marketing generics to each. Indeed, FDA acknowledged this problem when, several years after beginning use of these numerical indicators, it issued a guidance document on the placement of TE codes on prescription drug labels. Draft Guidance for Industry: *Placing the Therapeutic Equivalence Code on Prescription Drug Labels and Labeling* (Dec. 1998)

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(the "TE Guidance"). With regard to multiple reference standards, the agency stated:

When multiple reference listed products exist with the same established names and strengths, chances increase that a generic product will be dispensed to a patient that is not therapeutically equivalent to the one intended or previously prescribed. For example, four inequivalent reference listed products exist for Diltiazem extended-release capsules, each of which has overlapping strengths with the same established name.

Id. at 1-2. FDA emphasized that, in cases like the one above, "safety issues" could prompt the agency to request a code's placement. *Id.* at 6.

Mylan itself submitted comments on the TE Guidance. As Mylan argued, "[s]ince the label of a generic product currently provides only the established name, strength and in some instances the daily dose of the product, *it is difficult for the pharmacist to determine [to] which reference listed drug product the generic product has established bioequivalence.*" Docket No. 98D-1266, Comments of Mylan Pharmaceuticals (Mar. 16, 1999) at 1 (emphasis added); *see also* Tab A (presenting the labels of two non-substitutable Mylan nitroglycerin products, each available under the same established name and strength and otherwise appearing to be interchangeable).

Diltiazem, the product cited in the TE Guidance, provides a ready example of how confused the listing of multiple RLD products can become. The current *Orange Book* listing for diltiazem extended release capsules lists four inequivalent reference standards and *fifty* separate brand name and generic products. The listing appears in the *Orange Book* as follows:

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DILTIAZEM HYDROCHLORIDE, Capsule, Extended Release; Oral

AB3	<u>CARDIZEM CD</u> + AVENTIS PHARM	120MG	N20062 001 AUG 10, 1992	AB3		180MG	N75116 002 DEC 23, 1999
AB3	+	180MG	N20062 002 DEC 27, 1991	AB3		240MG	N20939 003 JAN 28, 2000
AB3	+	240MG	N20062 003 DEC 27, 1991	AB3		240MG	N75116 003 DEC 23, 1999
AB3	+	300MG	N20062 004 DEC 27, 1991	AB3		300MG	N20939 004 JAN 28, 2000
				AB3		300MG	N75116 004 DEC 23, 1999
AB1	<u>CARDIZEM SR</u> + AVENTIS PHARM	60MG	N19471 001 JAN 23, 1989	AB1	MYLAN	60MG	N74910 001 MAY 02, 1997
AB1	+	90MG	N19471 002 JAN 23, 1989	AB1		90MG	N74910 002 MAY 02, 1997
AB1	+	120MG	N19471 003 JAN 23, 1989	AB1		120MG	N74910 003 MAY 02, 1997
				AB2		120MG	N75124 002 MAR 18, 1998
AB3	<u>CARTIA XT</u> ANDRX PHARM	120MG	N74752 002 JUL 09, 1998	AB2		180MG	N75124 003 MAR 18, 1998
AB3		180MG	N74752 001 JUL 09, 1998	AB2		240MG	N75124 001 MAR 18, 1998
AB3		240MG	N74752 003 JUL 09, 1998	AB3	PUREPAC PHARM	120MG	N74984 001 DEC 20, 1999
AB3		300MG	N74752 004 JUL 09, 1998	AB3		180MG	N74984 002 DEC 20, 1999
				AB3		240MG	N74984 003 DEC 20, 1999
				AB3		300MG	N74984 004 DEC 20, 1999
AB2	<u>DILACOR XR</u> + WATSON LABS	120MG	N20092 001 MAY 29, 1992	AB1	TEVA	60MG	N74079 001 NOV 30, 1993
AB2	+	180MG	N20092 002 MAY 29, 1992	AB1		90MG	N74079 002 NOV 30, 1993
AB2	+	240MG	N20092 003 MAY 29, 1992	AB1		120MG	N74079 003 NOV 30, 1993
				AB2	TORPHARM	120MG	N74943 003 DEC 19, 2000
AB2	<u>DILTIAZEM HCL</u> ANDRX	120MG	N74852 001 OCT 10, 1997	AB2		180MG	N74943 002 DEC 19, 2000
AB2		180MG	N74852 002 OCT 10, 1997	AB2		240MG	N74943 001 AUG 06, 1998
AB2		240MG	N74852 003 OCT 10, 1997				
AB1	BIOVAIL	60MG	N74845 001 SEP 15, 1999	BC	TIAZAC +BIOVAIL	120MG	N20401 001 SEP 11, 1995
AB1		90MG	N74845 002 SEP 15, 1999	BC	+	180MG	N20401 002 SEP 11, 1995
AB3		120MG	N20939 001 JAN 28, 2000	BC	+	240MG	N20401 003 SEP 11, 1995
AB1	BIOVAIL	120MG	N74845 003 SEP 15, 1999	BC	+	300MG	N20401 004 SEP 11, 1995
AB3		120MG	N75116 001 DEC 23, 1999				
AB3		180MG	N20939 002 JAN 28, 2000			360MG	N20401 005 SEP 11, 1995
						420MG	N20401 006 OCT 16, 1998

Orange Book at 3-123-3-124. Beyond the original innovator, Aventis Pharmaceuticals, this listing shows seven other manufacturers, each with generics to the various RLDs. One firm, Biovail, holds three approved applications for

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products of the same strength (120 mg), equivalent to two reference standards, and markets a fourth product (Tiazac) as an additional RLD.

The agency would be hard-pressed to deny the complexity of the diltiazem listing in the *Orange Book*. Nor is it difficult to envision pharmacists being confused by this listing and, even worse, failing to maintain an adequate supply of generics for each RLD product. FDA has recently placed an emphasis on reducing preventable medication errors. *See, e.g.*, Commissioner McClellan's Remarks to the Food and Drug Law Institute (Apr. 1, 2003) (declaring the prevention of avoidable medication errors one of the five key elements in FDA's strategic plan).^{2/} In this light, it is imperative that the agency rethink the approach to designating multiple RLDs, especially for a product such as levothyroxine.

As the agency has acknowledged, the health consequences of imprecise dosing of levothyroxine products are serious. The need to minimize confusion among brand name and generic products is that much more important in this situation. Moreover, the agency is currently (albeit improperly) listing no less than six levothyroxine RLDs. Each reference product uses the same established name and is available in numerous overlapping strengths.^{3/} As Mylan itself anticipated in its comments to the TE Guidance, the labels and labeling for generic versions of each such product will be nearly identical and indistinguishable. Thus, the situation for levothyroxine fully tracks the safety issues previously described by the agency.

Finally, the shortcomings of the present system were highlighted when FDA launched a new on-line search engine to bring together information regarding brand name and generic drugs – Drugs@FDA. To illustrate, we have included under Tab B, attached, search results for Cardizem SR, the first extended release diltiazem product. The search results show just how confusing the situation has become. For example, the initial search shows 29 different generic “matches” for Cardizem SR. In fact, many of the listed generics are not appropriate substitutes for Cardizem SR. A second level search of “generics” for Cardizem SR shows numerous “AB2” and “AB3” rated products, suggesting that each is considered by

^{2/} Available at www.fda.gov/oc/speeches/2003/fdli0401.html.

^{3/} Current marketed strengths of levothyroxine sodium include 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg.

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FDA to be a generic substitute for Cardizem SR. This is incorrect; looking just at the 120 mg strength product, for example, only three of the nine generics listed are therapeutically equivalent to Cardizem SR. A consumer or pharmacist looking at these pages would likely be unable to understand which generic products are appropriate substitutes for which brand name products. Again, when such a system is applied to levothyroxine, the potential for confusion, and for improper substitution, is unavoidable.

3) Conclusion

The addition of a numerical indicator to the TE codes of RLDs is insufficient to address the potential health consequences of inappropriate substitution of levothyroxine products. Given the recognized risks of confusion, and the recognized risks associated with inappropriate levothyroxine dosing, the agency must rethink its response to petitions 03P-0107 and 03P-0113. Until the agency develops a valid means of distinguishing among different levothyroxine products, petitions 03P-0107 and 03P-0113 should be deferred or denied.

C. ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to a categorical exclusion under 21 CFR 25.31.

D. ECONOMIC IMPACT

Information on the economic impact of this proposal will be submitted upon request of the Commissioner.

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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 that are unfavorable to the petition.

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cc: Docket No. 03P-0107
Docket No. 03P-0113