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BY HAND DELIVERY

Dockets Management Branch, HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 03P-0097/CP1
Comments of Abbott Laboratories

Dear Sir or Madam:

On behalf of Abbott Laboratories ("Abbott"), we submit the following comments under 21 CFR 10.30(d) in support of the citizen petition submitted by Jones Pharma Inc. on March 12, 2003 (the "Petition"). As shown in the Petition and as discussed below, the decision by the Food and Drug Administration ("FDA") to designate all oral levothyroxine sodium products with approved new drug applications ("NDAs") as generic reference standards was made in violation of law. In addition, FDA must refuse to receive, and must halt the review of, any abbreviated new drug applications ("ANDAs") that seek to reference a levothyroxine product that has not been properly designated as a "reference listed drug" ("RLD").

I. INTRODUCTION

Unithroid (levothyroxine sodium tablets, USP), manufactured by Jerome Stevens Pharmaceuticals Inc., was the first oral levothyroxine sodium product listed in FDA's publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "*Orange Book*"). FDA designated Unithroid as the reference standard against which proposed generic products should be compared. The only such product approved to date is a generic to Unithroid sponsored by Mylan Pharmaceuticals Inc.

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In guidance issued under the good guidance practice regulations (21 CFR 10.115), FDA stated that additional levothyroxine RLDs would be designated using the agency's citizen petition process (*see* below). The good guidance regulations require the agency to follow a specific process when deviating from published guidance (21 CFR 10.115(d)(3)). This requirement is grounded in the agency's governing statute, which itself requires that FDA ensure full public participation prior to implementing any form of guidance, and that FDA issue guidance only in conformity with duly issued regulations (21 USC 371(h)).

Despite the clear guidance given by the agency, and despite clear precedent for using the petition process to designate additional RLDs, FDA acted on its own to designate all NDA-approved oral levothyroxine sodium products as RLDs. The agency did so without requiring a citizen petition and without public process. The agency provided no explanation as to why, in numerous instances, it has required the submission of a citizen petition to designate an additional RLD but, in this instance, did not. The agency ignored its own guidance and precedent and, for reasons that remain unstated, chose to proceed without public participation.

Abbott therefore joins in requesting that FDA remove the RLD designations from all levothyroxine products other than Unithroid. Thereafter, additional RLDs should be considered only in the context of a properly submitted citizen petition.[1] Finally, and in addition to the relief requested in the Petition, the agency must halt the receipt and review of any application submitted for a levothyroxine drug that references a product *other than Unithroid.* Until a petition to add an additional RLD has been granted, applications that reference a product other than Unithroid are, as a matter of law, incomplete.

II. ANALYSIS

A. FDA Must Designate a Product as an RLD before the Product may be Referenced in an ANDA

Under the Food, Drug, and Cosmetic Act (the "FDCA"), the agency has the discretion to receive, review, and approve applications under section 505(j) that

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1 On March 18, 2003, Mylan submitted a citizen petition seeking to have Synthroid® designated as an RLD. Thus, at least one generic company appears to concede that such a petition is required. *See* Docket No. 03P-0107. Abbott intends to comment promptly on the Mylan petition. As discussed *infra*, review of any pending ANDAs that reference Synthroid® cannot proceed until a petition has been granted properly designating Synthroid® as an RLD.

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, for important medical and scientific reasons, the agency has developed a system in which it designates a preferred reference standard for each category of drug products. Additional reference standards may be added; the agency, however, directs sponsors to initiate a public process – through the filing of a citizen petition – to obtain the designation of additional reference standards.

According to the agency, this approach is designed "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. The scientific basis for the presumption in favor a single standard is further explained in a 1998 FDA petition response:

> [T]wo or more products are considered bioequivalent if there is no "significant difference" in the rate and extent to which the active ingredient becomes available at the site of drug action (21 CFR 320.1). Under this definition, then, bioequivalent products may have nominally different bioavailability profiles. These nominally different profiles could lead to significant variations, or "bio-drift," in the marketplace if multiple generic drug products were compared against innovators, each with nominally different bioavailability profiles. *Therefore, the Agency has devised a system that encourages generic applicants to reference the same innovator product as the standard for demonstrating bioequivalence.*

Docket No. 96P-0459, FDA Response (Nov. 2, 1998) at n. 8 (emphasis added).

Thus, all drugs approved under sections 505(c) or 505(j) of the FDCA are eligible to be referenced in an abbreviated new drug application (ANDA) under section 505(j). However, the agency has chosen to implement the statute by requiring that only those drugs that have been specifically designated by the agency be referenced. *See* 57 FR 19750, 17958 (Apr. 28, 1992) (final rule) (replacing proposed language allowing sponsors to select RLDs with language stating that the agency must designate each RLD product). The agency initially will designate a single reference drug but allows sponsors to petition to designate additional RLDs. *See* Docket No. 96P-0459 at 7-8.

B. FDA Violated the Law When it Designated Additional Levothyroxine RLDs without Requiring a Citizen Petition

As shown, FDA has reserved the discretion to designate more than one RLD in appropriate circumstances. 57 FR at 17958. The agency, however, has – through policy and precedent – committed to using the citizen petition process as the basis for deciding whether to designate multiple RLDs (*see* 21 CFR 10.30). In the case of levothyroxine products, the agency specifically stated that the petition process would be used to designate additional RLDs. Nevertheless, the agency reversed field and designated all approved levothyroxine products as RLDs, without any public process and without any explanation or notice.

FDA relies upon the preface to the *Orange Book* to set forth policy on matters such as the assignment of equivalence ratings and the designation of RLDs. With respect to the process for designating multiple RLDs, the *Orange Book* states:

> [I]n 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 . . . . When the Citizen Petition is approved, the second NDA will be designated as an additional reference listed drug and the petitioner may submit an Abbreviated New Drug Application citing the designated reference listed drug.

Orange Book at x-xi. This approach – of using a citizen petition to initiate the designation of additional RLDs – allows interested persons to comment and allows the agency to address any issues that may arise from having multiple RLDs for a particular category of products. *See, e.g.,* Docket No. 94P-0208, FDA Response (Nov. 7, 1995) at 2 (addressing concerns regarding possible confusion among generic diltiazem products).

While FDA may have wide discretion in this area, it must act within boundaries – both statutory and self-imposed. Here, the agency has set forth a scientific basis in support of the single RLD system. It also has set forth a process by which sponsors may seek a product-specific exception to the designation of a single RLD. And, in fact, that is the process which sponsors and FDA have been

following. *See* Docket No. 01P-0356 (May 31, 2002) (petition to designate RLDs for hydrocortisone); Docket No. 01P-0353 (May 23, 2002) (same for albuterol); Docket No. 00P-0219 (May 17, 2000) (same for verapamil); Docket No. 98P-0429 (Jul. 31, 1998) (same for a diltiazem product); and Docket No. 94P-0208 (Nov. 7, 1995) (same for another diltiazem product).

In contrast, the agency has not issued any standards or any explanation of the circumstances under which it will deviate from the single RLD policy and automatically designate multiple RLDs. Again, while the agency may have wide discretion, it must exercise that discretion in a well-reasoned, consistent, and even-handed manner.

Finally, with respect to levothyroxine, the case in favor of using the petition process is overwhelming. As the agency stated in the last of a series of guidance documents on levothyroxine products,

> 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.

Guidance for Industry: *Levothyroxine Sodium Products Enforcement as of August 14, 2001* (July 2001) at 4 (the "Enforcement Guidance"); *see also* Guidance for Industry: *Levothyroxine Sodium Questions and Answers* (Feb. 2001) at 5 ("Unithroid is the reference listed drug to which ANDAs should refer."). There is no indication in this language that the agency would designate additional levothyroxine RLDs on its own and without a petition. In fact, the agency made this statement in the context of a larger discussion of the need for caution when switching patients from one levothyroxine product to another. *See* Enforcement Guidance at 2. The designation of a single reference standard (Unithroid), along with the use of the petition process, is consistent with the agency's oft-stated concerns about precise dosing and about switching from one manufacturer's levothyroxine product to another. *See id.*

In sum, when FDA made the decision to designate multiple levothyroxine RLDs, it did so in violation of law. The agency's decision to act on its own, rather than by petition, was arbitrary and capricious. 5 USC 706(2)(A). It was contrary to precedent and contrary to the only well-stated and well-grounded procedural standard the agency has in place for designating RLDs. It was contrary to the medical concerns raised in the Enforcement Guidance. And, it was contrary to binding law, which requires that FDA follow its own guidance. Despite issuing numerous guidance documents and pronouncements on levothyroxine, the agency

has provided no evidence of an "appropriate justification" and "supervisory concurrence" to support the departure from the Enforcement Guidance. *See* 21 CFR 10.115(d)(3).

C. FDA Must Refuse to Receive and Must Halt the Review of ANDAs that Reference Products other than Unithroid Until a Petition has been Granted

An ANDA must be "sufficiently complete" before it may be filed by FDA for substantive review. *Id.* at 314.101(a)(1). Among other things, the application must contain all of the information required under 21 CFR 314.94 (outlining the basic format and content requirements of an ANDA). No ANDA requirement is more basic or fundamental than the need to refer to an appropriate listed drug. *Id.* at 314.94(a)(3). As stated in the rule, an ANDA "must refer to a listed drug" and the listed drug "[o]rdinarily . . . will be the drug product selected by the agency as the reference standard for conducting bioequivalence testing." *Id.* Until an approved drug is properly designated as a reference standard, it cannot be relied upon as a listed drug in an ANDA. *See* 57 FR at 17958.[2]

Moreover, where the submission of an ANDA is contingent on the approval of a petition under 21 CFR 10.30 – as is the case here – the ANDA must include a reference to the FDA docket number and "a copy of FDA's correspondence approving the petition." 21 CFR 314.94(a)(3)(iii); *see also Orange Book* at xi ("When the Citizen Petition is approved, the second NDA will be designated as an additional reference listed drug and the petitioner may submit an Abbreviated New Drug Application citing the designated reference listed drug.").

The end result is that the review of any levothyroxine applications that have already been filed, and that reference a drug other than Unithroid, must be halted. Such applications are facially and fundamentally incomplete. *See* 21 CFR 314.101(d). Any new applications that seek to reference a product other than Unithroid must likewise be refused filing until the agency completes the RLD petition process. *See* 21 CFR 314.101(a)(1) and (d); 21 CFR 314.94(a)(3). Unless and until a petition to designate one or more additional levothyroxine products is granted, such applications can neither be filed nor reviewed. *See, e.g.,* Letter from

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[2] While the term "ordinarily" suggests some latitude, the agency in fact has read the regulation as prescriptive. In both the preamble to the final rule and the *Orange Book*, the agency has emphasized that until a product is designated as an RLD, it is effectively prevented from being referenced in a generic drug application. 57 FR at 17958; *Orange Book* at x.

FDA's Office of Generic Drugs to J. Dubeck dated Sept. 9, 1998 (refusing to file ANDA until the granting of an RLD petition).

III. CONCLUSION

The agency has provided no basis for departing from the policy and precedent of requiring sponsors to submit petitions to designate additional RLDs. With respect to levothyroxine products, the outcome is clear: procedurally, the agency committed to using the petition process for levothyroxine products; substantively, the medical concerns associated with levothyroxine therapy clearly support the need for a public process on the designation of additional reference standards.

The law therefore compels FDA to grant the Petition and refuse receipt of all ANDAs (other than those referencing Unithroid) until the RLD citizen petition process is completed. The review of any pending ANDAs that reference products other than Unithroid must likewise be halted.

As always, we thank you for your careful attention to this matter.

Sincerely,

DM Fox

David M. Fox