John M Leonard, M D
Vice President, Global
Medical & Scientific Affairs

Abbott
100 Abbott Park Road, R432, AP9-1
Abbott Park, Illinois 60064-6120

t 847 938 4545
f 847 937 3918
john m leonard@abbott com

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BY HAND DELIVERY

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

Re: Comments to Docket No. 2005N-0137

Dear Sir or Madam:

Abbott Laboratories ("Abbott") submits the following comments on the issues raised during the May 23, 2005, Food and Drug Administration ("FDA") workshop on the therapeutic equivalence of levothyroxine sodium drug products.

The workshop, co-sponsored by the American Thyroid Association, the Endocrine Society, and the American Association of Clinical Endocrinologists (the "Societies"), was intended to assure the thyroid community that levothyroxine products deemed equivalent by FDA may be substituted "with great confidence and assurance of patient safety."[1] Unfortunately, significant questions about the methodology by which FDA determines the equivalence of such products – and about patient safety – remain unanswered.

Based on testimony heard at the workshop, there appears to be little confidence on the part of leading clinicians (represented by the Societies) regarding FDA's therapeutic equivalence determinations for levothyroxine products. In our view, the gulf between the clinical community and FDA will not be closed until the agency directly addresses the unanswered questions that the Societies and Abbott have repeatedly raised regarding levothyroxine substitution. The most significant of these unanswered questions are discussed below.

I. Adverse Events

The public presentations made at the workshop included several telling reports from clinicians whose patients have recently been switched to a "therapeutically equivalent" product. These clinicians provided first-hand reports of problems arising from the

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[1] FDA Transcript (published July 12, 2005) at 9.

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switch. As one clinical endocrinologist reported, "[i]n my own practice, . . . of the last 21 patients that were consecutively seen by me that were switched from a branded preparation, 18 required a dose change."[2]

Other clinicians who submitted written comments to the FDA workshop docket provided similar observations:

- "I have some recent examples in my practice that changing to generic [levothyroxine] has resulted in fluctuations in serum [thyroid stimulating hormone, or "TSH"] levels, causing concern, confusion, and leading to more tests. Recently, in a few patients with long-term thyroxine therapy and stable TSH levels, I have noted unexpected TSH elevations. With further inquiry, I have learned that at the pharmacy level brand thyroxine preparation was replaced with a generic form. My patients were surprised and dismayed, as I was."[3]

- "In the past year, since the flood of various generic [levothyroxine] preparations have reached pharmacies nationwide, I have had at least 20 patients who were switched from brand to generic [levothyroxine] preparations who required readjustment of their serum TSH concentrations to the desired level."[4]

Notwithstanding these first-hand reports, agency officials at the workshop held firm to the view that the equivalence of A-rated levothyroxine products is fully "confirmed" by bioequivalence data.[5] As one senior FDA official stated, such "anecdotes of changes in thyroid status after a switch *are not evidence of risk*."[6]

This is a remarkable statement, particularly when compared with the emphasis that FDA itself placed on such accounts in

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[2] FDA Transcript at 123-24.

[3] Comment of H. Gharib, M.D., F.A.C.E., of the Mayo Clinic College of Medicine, Docket No. 2005N-0137 (May 5, 2005).

[4] Comment of L. Braverman, M.D., of the Boston Medical Center and the Boston University School of Medicine, Docket No. 2005N-0137 (May 16, 2005).

[5] FDA Transcript at 202.

[6] FDA Transcript at 236.

1997 when the agency announced the need for greater regulatory control over levothyroxine products. At that time, FDA published several anecdotal reports from clinicians. For example:

- "[A] physician reported to FDA: 'I have noticed a recent significant problem with the use of [this levothyroxine product]. People who have been on it for years are suddenly becoming toxic on the same dose. Also, people starting on the medication become toxic on 0.1 mg [milligram] which is unheard of.'"

- "[A]nother physician reported that 15 to 20 percent of his patients using the product had become hyperthyroid although they had been completely controlled up until that time."

- "Another doctor reported in May 1984 that three patients, previously well-controlled on the product, had developed thyroid toxicity. One of these patients experienced atrial fibrillation."[7]

These latter accounts are markedly similar to the accounts being presented today. They were given ample weight in 1997 but, at the 2005 workshop, were readily dismissed. As one agency official stated at the workshop, "We have anecdotes that give you [the clinicians] concern, but your concern is based upon an *a priori* failure to accept the standard . . . ."[8] In other words, according to at least one FDA official, the clinicians' concerns and their first hand reports of clinical events stem from the clinicans' refusal to agree with FDA, rather than anything these doctors are experiencing in their own medical practices.

The practicing clinicians' first-hand reports should be taken seriously, and should not be rejected without a full inquiry.[9] In

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[7] 62 FR 43535, 43536 (Aug. 14, 1997).

[8] FDA Transcript at 206 (emphasis added).

[9] In addition to the reports presented at the workshop and in other written comments, Abbott is submitting with these comments several reports it has received of adverse drug experiences that occurred after patients were switched from Abbott's Synthroid® to one of the A-rated levothyroxine products. On their face, these adverse events are attributable to the substituted products. Most likely, there exist many similar reports not known to Abbott (because the event would typically be associated with the product to which the patient was switched). As noted in the text, the agency

light of the agency's focus on patient safety, as underscored at the opening of the workshop, FDA officials should be soliciting more such reports, to learn as much as possible about a palpable clinical concern. Instead, the agency spent much of the workshop deflecting these reports as inconsistent with "the standard" and contrary to FDA's decades-old bioequivalence methods. In point of fact, the reports presented at the workshop are as valid and powerful as the reports relied upon by FDA in the 1997 levothyroxine proceeding.

II. Sources of Variability

Abbott presented data during the workshop demonstrating that each source of dose-to-dose variability represents another hurdle that physicians and thyroid patients must overcome to establish the desired euthyroid state.[10] Given the clinical importance of precise levothyroxine dosing, all avoidable sources of variability from product substitution should be minimized.

The agency failed to address this issue at the workshop. Rather, the agency focused on its historical effort to upgrade the regulation of levothyroxine products, to ensure that all contain as close to 100% of the labeled dose as possible.[11] This accomplishment only underscores, however, the questions that remain regarding the approval as "equivalent" of levothyroxine products that release 9% and 12.5% more drug than their reference drugs. If there is an explanation as to why FDA has not simply traded one source of variability in dosing for another, it was not offered at the workshop. This issue – of FDA's past effort to eliminate significant potency differences *versus* its current approvals as equivalent of products that release significantly different amounts of drug – surfaced repeatedly throughout the workshop, but was never addressed by FDA.

For example, FDA discussed at the workshop the pre-1997 problem of "overlapping dosage strengths," in which a 100 mcg levothyroxine tablet with an overage contains more drug than a 112 mcg tablet at the end of its shelf life: "And so, the prescribing physician doesn't know exactly what dosage strength, when they titrate to dose,

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should be seeking ways to elicit more such reports, rather than ways to dismiss or marginalize such reports.

[10] FDA Transcript at 75-90 (Slide Deck available at www.fda.gov/cder/meeting/levothyroxine/ Abbott.ppt).

[11] FDA Transcript at 32-43, 43-52, 226-30.

they don't know exactly what strength to continue to provide."[12] FDA officials spoke at length about their success in correcting this problem; they ignored, however, today's equivalent problem of overlapping dosage strengths caused by the substitution of levothyroxine products that release 9% or 12.5% more drug than their counterpart.[13]

III. Methodology

In its 2004 decision on levothyroxine bioequivalence methods, FDA predicted that its "standards for levothyroxine sodium products *will not allow products that differ by 9 percent or more in potency or bioavailability to be rated therapeutically equivalent.*"[14] Nevertheless, two of the three levothyroxine products A-rated to Synthroid® have been shown to release an average of 9% and 12.5% more drug in the body than Synthroid®. The gap between FDA's prediction and the results of *in vivo* bioequivalence studies was raised at the meeting but thoroughly avoided by the FDA speakers.[15]

At the workshop, FDA also emphasized that none of the approved levothyroxine products contains excipients that are likely to affect absorption, and that all are rapidly dissolving formulations that perform like solutions. Thus, according to FDA, it is safe to assume "*a priori*" that they will all perform alike in the body.[16] The agency officials at the workshop repeatedly characterized the *in vivo* data as "confirmatory" of this premise,[17] but those data, in fact, show otherwise. Two products that were formulated to be equivalent to Synthroid®, when tested *in vivo*, released an average of 9% and 12.5% more drug than Synthroid® – or the equivalent of approximately one full dosing increment. Another product, marketed by Mylan, was formulated with 5% more drug than Unithroid® but was shown *in vivo* to be 8% *less* bioavailable.[18]

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12 FDA Transcript at 36.

13 For example, data presented at the workshop showed that a 100 mcg tablet of Sandoz's levothyroxine product has approximately the same average bioavailability as a 112 mcg tablet of Synthroid®.

14 FDA Petition Response, Docket No. 2003P-0387 (June 23, 2004) at 27 (emphasis added).

15 FDA Transcript at 78-79.

16 FDA Transcript at 231.

17 FDA Transcript at 8, 193, 197, 202, 203, 232, 254.

18 Petition for Reconsideration, Docket No. 2003P-0387 (July 23, 2004) at 24.

Finally, the agency refused to entertain any proposals to narrow the bioequivalence acceptance limits for levothyroxine products. The traditional limits of 80 – 125% are designed to prevent differences of 20% or more between products.[19] Many urged that these "goalposts" be narrowed, to reflect the maximum difference that can be tolerated for levothyroxine products.[20] The senior FDA official at the workshop quashed this proposal several times, stating that narrowing the goalposts would only cause applicants to conduct larger bioequivalence studies.[21] This reflects a significant misunderstanding.

Narrowing the goalposts – based on the accepted dosing intervals associated with levothyroxine therapy – would serve a valid purpose; it would ensure that two products that differ in bioavailability by more than one full dosing increment are not deemed "therapeutically equivalent." Were applicants to conduct larger studies, the confidence intervals around their measurements may be narrowed, but the revised goalposts would still prevent levothyroxine products from differing by more what had been determined to be a clinically significant amount.[22] Clearly, this is an issue that requires more careful consideration, in light of the concerns and evidence presented at the workshop.

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The guiding principle of levothyroxine therapy is to maintain patients within a normal TSH range by providing precise and consistent dosing. Variability in dose or bioavailability, whatever the source, is contrary to good patient care. In 1997, the agency successfully addressed one source of variability when it took steps to require that levothyroxine products target 100% of their labeled amount of active ingredient at release. As described above, first-hand physician reports played a key role in FDA's 1997 case for regulatory action.

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19 Approved Drug Products with Therapeutic Equivalence Evaluations (25th ed. 2005) at Preface 1.3.

20 FDA Transcript at 166, 198, 205, 253.

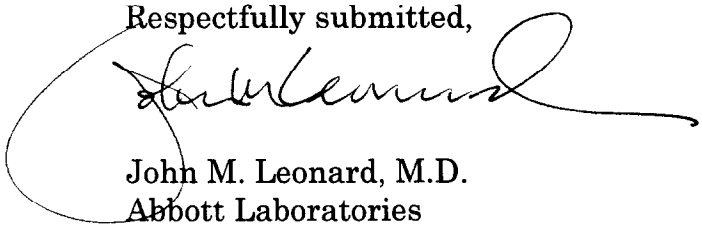
21 FDA Transcript at 205-06, 253-54.

22 As FDA recognized when it finalized the generic drug regulations in 1992, the root question for all equivalence testing is: How much of a difference is too much for the drug being tested? 57 FR 17950, 17973 (Apr. 28, 1992) ("The determination of a significant difference requires first a judgment as to what difference in a bioequivalence parameter of interest is medically important . . . ."). FDA has repeatedly declined to address this question.

The compelling issue remaining from the agency's workshop is the appearance that FDA has now simply traded one source of variability for another. It is undeniable, for example, that *in vivo* data indicate that two "equivalent" levothyroxine products release an average of 9% and 12.5% more active ingredient than their reference drug. And yet this issue, which has been raised repeatedly by Abbott and others, has been ignored by the agency. In so doing, FDA also has ignored the same sort of physician reports on which it relied in 1997.

Put simply, FDA must address this issue before it can meet its goal of assuring the thyroid community that patient safety will not be compromised by the substitution of A-rated levothyroxine products.[23]

Respectfully submitted,



John M. Leonard, M.D.
Abbott Laboratories

Attachments

cc: Janet Woodcock, M.D.
Steven K. Galson, M.D., M.P.H.
David G. Orloff, M.D.
Jane A. Axelrad, J.D.
Kevin M. Fain, J.D.
FDA Docket No. 03P-0387
FDA Docket No. 03P-0126

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[23] For example, the agency may decide to remove these products' therapeutic equivalence ratings. Such ratings are, in FDA's view, merely advisory and can be changed without further process. The agency also maintains a more appropriate "B*-rating" that may be assigned to any approved drug for which further investigation is needed.