

FDRR



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 62,720

3/7/03

Abbott Laboratories
Attention: Douglas L. Sporn
Divisional Vice President
Global Pharmaceutical Research and Development and Life Cycle Management
100 Abbott Park Road
Abbott Park, IL 60064-6091

Dear Mr. Sporn:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Synthroid (levothyroxine sodium tablets, USP).

Your February 12, 2003, request for formal dispute resolution (FDRR), received on February 13, 2003, concerned the January 14, 2003, denial of your October 10, 2002, request for a meeting to discuss the suitability of current bioequivalence testing requirements for levothyroxine sodium tablet drug products.

In the FDRR, you request that the Food and Drug Administration (FDA) hold a full Advisory Committee meeting of the Advisory Committee on Pharmaceutical Science and the [Endocrine and] Metabolic Drugs Advisory Committee on the issue of assessing bioequivalence (BE) of levothyroxine sodium products. You also request a full explanation of the contents of a letter from Dr. David Orloff, Director of the Division of Metabolic and Endocrine Drug Products, sent to Abbott Laboratories on January 14, 2003. Please note that although your FDRR was sent to Dr. Janet Woodcock, the Director of CDER, the Office of Drug Evaluation II is answering it in accord with CDER policy on FDRRs. [This jurisdictional decision was conveyed to you in the February 20, 2003, acknowledgment letter sent by Kim Colangelo.]

I have fully reviewed your appeal and would like to address both elements of relief requested in the FDRR, starting with offering an explanation of Dr. Orloff's letter of January 14, 2003.

As you are aware, the FDA issued a formal Guidance to Industry on the topic of assessing bioavailability and pharmacokinetics of levothyroxine (LT4) in December of 2000. Indeed, the data supporting the approval of NDA 21-402 for Synthroid were based on the recommendations of this guidance (including the critical dosage-form comparability study). This guidance does not and is not intended to directly address the data necessary for the establishment of BE for the purposes of generic approval. On October 10, 2002, you submitted an amendment to IND 62,720 that contained a report of study M02-417, which Abbott conducted to explore the impact of various methods of correction for endogenous baseline levothyroxine (LT4) in healthy volunteers for the purposes of bioequivalence testing. This study was a single-dose, three-period

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crossover study in which volunteers received either 600 mcg, 450 mcg, or 400 mcg, with blood samples taken beginning 24 hours before dosing and up to 96 hours following dosing. There was a 40-day washout period between doses. FDA reviewed these data, which proved to be quite interesting and illuminating. The study results showed that using values uncorrected for baseline led to insensitivity to dose differences, such that 600 mcg was not distinguishable from either 450 mcg or 400 mcg by typical BE standards. Abbott then compared the data using three different methods of correcting for baseline LT4 levels or baseline correction methods. While each of these provided enhanced sensitivity to dose, it is the belief of FDA that the first method (subtraction of baseline values from each dosing period from the post-dose concentrations for that same dosing period) was the most appropriate of these corrections. Indeed, the data from the first method showed an ability to clearly distinguish 600 mcg from 400 mcg as well as 450 mcg on AUC_{0-24} and C_{max} . Based on these data and FDA's prior experience, FDA believes that this method of baseline correction would be the most appropriate to establish BE for levothyroxine products, utilizing a single-dose crossover study in healthy volunteers (similar to that described in the BA guidance).

In your FDRR letter of February 12, 2003, you state that Abbott believes this method (as well as the others utilized in your study) of correction is flawed, because it fails to distinguish between two dosing regimens that differ by 12.5 % (400 mcg vs. 450 mcg). However, FDA does not find this objection persuasive. This is mostly due to the dose comparison - 400 mcg vs. 450 mcg - being well below the 600 mcg dose which the Agency has recommended in its BA guidance and which would be the recommended comparison in any BE study done in healthy volunteers. The lower the dose utilized in this healthy volunteer study, the more endogenous LT4 will contribute to the resultant serum determinations, thus decreasing the 'signal-to-noise' for the test. Therefore, we would not expect this study and test-method to distinguish differences of exposure when doses significantly below 600 mcg are compared. While Abbott suggests that utilizing athyroid individuals would be a preferred study design, you provided no data to support this assertion and we are unaware of any data that would support that studies done with this population would enhance sensitivity of the test nor add to its validity. Therefore, as indicated in Dr. Orloff's letter of January 14, FDA plans on recommending the three pre-dose baseline subtraction method to sponsors wishing to do BE testing.

In order to assure that this recommendation is the most reasonable and scientifically valid approach given the data available, FDA will present the approach to the Advisory Committee for Pharmaceutical Sciences (ACPS) on March 13, 2003, as part of an awareness session on bioequivalence and bioavailability testing of endogenous substances. It is my understanding that Abbott is presenting at this meeting and the Agency's rationale will likewise be presented. In your FDRR, you request a full meeting of both the ACPS and the [Endocrine and] Metabolic Drugs Advisory Committee (EMDAC) to discuss this matter. I do not find this request compelling at this time for the following reasons. The purpose of having EMDAC participation in a discussion of levothyroxine BA/BE testing would seem most appropriately aimed at providing clinical context, since this committee is not chosen for having specific expertise in biopharmaceutics. I believe the clinical importance of levothyroxine and having the correct dosage is very clear to the Agency's own medical experts as evidenced by the BA guidance (as quoted by your FDRR letter) on levothyroxine. Indeed, the background for this guidance includes a clear discussion of the clinical importance of proper dosing and the clinical issues

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involved in the ascertainment of exogenous exposure, given that such exposure is not readily distinguishable from endogenous LT4. Based on the current circumstances - including Abbou's arguments as stated in your letter - I do not see that a full session with the EMDAC would provide additional, useful clinical insight into this Agency's recommendations for BE approaches for levothyroxine. Indeed, I see the issue at this point as being driven by concerns related to clinical pharmacology and biopharmaceutics, and therefore I believe the review of LT4 BE issues is occurring before an appropriate panel of experts. Given the scope of the Agency's current questions related to BA/BE testing for levothyroxine, the session planned at the March 13, 2003, meeting with the ACPS is sufficient and a joint EMDAC and ACPS meeting exclusively on this topic is not warranted at this time.

In summary, after a full and thorough review of your submitted letter and data and the Agency's information on this disputed action, I am providing the Agency's rationale for its current thinking on the BE/BA testing of levothyroxine as requested. I am confident this rationale will be further articulated in the March 13, 2003, ACPS meeting. As for your second request for relief, I do not find the request for a full Advisory Committee meeting on this topic with combined panels from the EMDAC and ACPS compelling or warranted at this time.

If you wish to appeal this decision to the next level, your appeal should be directed to Dr. John K. Jenkins, Director, Office of New Drugs, Center for Drug Evaluation and Research. The appeal should be sent again through the Center's Dispute Resolution Project Manager, Kim Colangelo. Any questions concerning your appeal should be addressed via Kim Colangelo at (301) 594-5479.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Robert Meyer
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