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April 14, 2003

BY HAND DELIVERY

John Jenkins, M.D.
Director, HFD-020
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont Complex II
1451 Rockville Pike
Rockville, Maryland 20852

Re: FORMAL DISPUTE RESOLUTION REQUEST¹
Synthroid® (levothyroxine sodium tablets, USP)
IND 62,720

Dear Dr. Jenkins:

I am writing on behalf of Abbott Laboratories ("Abbott") to continue our appeal of the agency's decision to adopt a three pre-dose baseline correction method for sponsors seeking to show the bioequivalence ("BE") and therapeutic equivalence ("TE") of oral levothyroxine sodium drug products.

The agency informed Abbott of this decision in a January 14, 2003, letter issued by the Division of Metabolic and Endocrine Drug Products. Tab 1 (the "Division Letter"). We promptly appealed the decision. Tab 2 (the "February 12 FDR Submission"). On February 20, 2003, Abbott was informed that our appeal would be

¹ This document contains confidential commercial and/or trade secret information and is being designated as exempt from disclosure under 21 CFR 20.61(d).

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addressed by Robert Meyer, M.D., Director of the Office of Drug Evaluation II ("ODE II"). Tab 3. On March 7, 2003, Dr. Meyer denied our appeal and denied Abbott's request for a joint meeting of the Advisory Committee for Pharmaceutical Science ("ACPS") and the Endocrinologic and Metabolic Drugs Advisory Committee ("EMDAC"). Tab 4 (the "Office Letter").

Because the agency's pre-dose baseline correction method is not clinically supportable, and because it was adopted in violation of required procedures, we are compelled to continue our appeal. On Dr. Meyer's recommendation, we are appealing the January 14 and March 7 decisions to you, pursuant to 21 USC 360bbb-1 and 21 CFR 10.75, 312.48, and 314.103. We are continuing to follow the procedures outlined in the agency's Guidance for Industry: *Formal Dispute Resolution: Appeals Above the Division Level* (Feb. 2000) (the "FDR Guidance").

As discussed below, Abbott submitted a clinical study to the Center for Drug Evaluation and Research ("CDER") showing that the pre-dose correction method cannot distinguish levothyroxine products that differ in dosage by 12.5 percent. Tab 2 at 44.² This difference – for products intended to be interchangeable – is critical. Levothyroxine is dosed in increments as low as 12 mcg; many patients, including thyroid cancer patients, are sensitive to even finer differences. The Food and Drug Administration ("FDA") itself has argued that differences as small as 9 percent can lead to serious adverse events in levothyroxine patients. *See infra* at section IV.B.

We respectfully request that you withdraw use of the pre-dose correction method and refer the issue of BE criteria for levothyroxine products to an appropriate joint advisory committee. Thereafter, FDA is obligated to use its guidance process (or rulemaking) to develop a sound method of correcting for baseline hormone in BE studies of levothyroxine products. Until such a method is developed, the safety and efficacy of levothyroxine products approved on the basis of BE data cannot be assured.

I. ISSUES BEING APPEALED

By this letter, we are appealing three decisions:

² The pages of the attached documents are numbered sequentially, for ease of reference. For each reference, we will provide both a tab number and the sequential page number (*i.e.*, Tab __ at __).

- The *scientific* decision to adopt a pre-dose baseline correction method for evaluating the BE and TE of oral levothyroxine products;
- The *scientific and procedural* decision to deny Abbott's request to have the dispute over BE methodologies for levothyroxine products heard before a joint ACPS and EMDAC advisory committee; and
- The *procedural* decision to adopt the pre-dose correction method without following statutory and regulatory requirements, including the agency's "good guidance practice" regulations at 21 CFR 10.115.

See FDR Guidance at 5 (requesting that each issue on appeal be identified as "scientific, procedural, or both").

II. BACKGROUND

A. The Approval of Oral Levothyroxine Sodium Products

In August 1997, FDA determined that all oral levothyroxine products would, going forward, be regulated as "new drugs" and would require premarket approval under section 505 of the Food, Drug, and Cosmetic Act (the "FDCA"). 62 FR 43535 (Aug. 14, 1997). Prior to this time, levothyroxine products had been marketed without approved new drug applications ("NDAs"). FDA took action in 1997 to require premarket approval based on the concern that levothyroxine products lacked consistent potency and bioavailability ("BA"). According to the agency, patients could not be assured of receiving a consistent therapeutic dose with the marketed products. As the agency stated, "[l]evothyroxine sodium products are marketed in multiple dosage strengths, that may vary by only 12 micrograms ["mcg"], thus permitting careful titration of dose. Because of levothyroxine sodium's narrow therapeutic index, it is particularly important that the amount of available active drug be consistent for a given tablet strength." *Id.* at 43538.

To assist sponsors in preparing NDAs, and to provide information to health care providers, FDA published a series of guidance documents following the August 1997 decision. See Guidance for Industry: *Levothyroxine Sodium Products Enforcement of August 14, 2001 – Compliance Date and Submission of New Applications* (July 2001); Guidance for Industry: *Levothyroxine Sodium Questions and Answers* (Feb. 2001); Guidance for Industry: *Levothyroxine Sodium Tablets – In Vivo*

Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing (Feb. 2001) (the "BA Guidance" or the "guidance"). Tab 5.

On August 21, 2000, FDA approved the first NDA for an oral levothyroxine product, Unithroid (levothyroxine sodium tablets, USP). Abbott's product, Synthroid® (levothyroxine sodium tablets, USP), gained approval on July 24, 2002.³ Currently, there are six brand-name oral levothyroxine products listed in the agency's *Approved Drug Products with Therapeutic Equivalence Evaluations*. One additional product, a generic to Unithroid sponsored by Mylan Pharmaceuticals Inc., has also been approved.

B. Endogenous T4 and FDA's Bioavailability Guidance

FDA's February 2001 BA Guidance recognizes that the primary confounding factor in conducting BA studies of levothyroxine products is the presence in the body of baseline levels of endogenous or "naturally-occurring" thyroid hormone ("T4" or "LT4"). As the agency stated in the guidance, "[i]t is a challenge to determine the bioavailability of levothyroxine sodium products because levothyroxine is naturally present in minute quantities in the blood, with the total levels reaching 5.0-12.0 [mcg]/dl and free (or unbound) levels reaching 0.8-2.7 ng/dl in a healthy adult." Tab 5 at 63.

The agency, however, also recognized the inherent variability of endogenous levothyroxine concentrations in study subjects. Thus, at the time the guidance was issued, the agency recommended against the "adjustment of baseline levels since endogenous levothyroxine concentrations are unpredictable during the course of the study." *Id.* at 65. Rather, the guidance recommends the use of "several times the normal dose" of levothyroxine. The large dose is intended to raise the level of the drug sufficiently above "baseline" to allow for valid measurement. *Id.* at 63. That is, the exogenous levothyroxine dose (or "signal") has to be sufficiently greater than the endogenous baseline (or "noise") to ensure that the signal is not lost in the

³ Abbott's predecessor, Knoll Pharmaceuticals, challenged the agency's August 1997 determination that Synthroid® is a "new drug" requiring premarket approval. In a citizen petition dated December 15, 1997, Knoll argued that Synthroid® meets the "general recognition" standard under section 201(p) of the FDCA and, therefore, does not require approval under an NDA. FDA Docket No. 97N-0314. On April 26, 2001, the agency denied the petition. *Id.* Rather than challenge that denial, Abbott agreed to submit an NDA in support of Synthroid®.

noise. The guidance recommends, but does not require, a 600 mcg test dose, *i.e.*, “a multiple of the highest tablet strength” *Id.* at 64.

C. The Abbott Clinical Study Program

In November 2001, Abbott initiated a simulation study to evaluate the impact that baseline T4 levels may have on the assessment of bioequivalence. Abbott based the study on data generated in support of the Synthroid® NDA, on the study designs outlined in the BA Guidance, and on general criteria for evaluating the bioequivalence of oral drug products. The simulation study suggested that products that differ by 33 percent or more may be declared equivalent, unless steps are taken to correct for baseline. Tab 2 at 30.

Based on these results, Abbott initiated a clinical study, M02-417 (IND 62,720, Serial No. 014), to determine whether the conclusions suggested by the simulation study could be confirmed. Study M02-417 was a three-period crossover study in normal subjects based on three levothyroxine dosing regimens (600, 450, and 400 mcg). The intent was to determine in a controlled clinical study whether three significantly different doses could be found to be “equivalent” using standard BE criteria. The study also sought to determine whether, with the use of a baseline correction method, the three different doses (*i.e.*, 600, 450, and 400 mcg) could be appropriately distinguished.

The final report for Study M02-417 included three key findings:

- Without baseline correction, all three comparator pairs (600 *versus* 450 mcg, 600 *versus* 400 mcg, and 450 *versus* 400 mcg) were found to be bioequivalent;
- With baseline correction, the 450 and 400 mcg doses could be distinguished from 600 mcg; *however*, the 450 and 400 mcg doses still could not be distinguished from each other; and
- Baseline correction appears to be confounded by the diurnal fluctuation of endogenous T4 production and by the suppressive effect of the specific dose.⁴

⁴ See Tab 2 at 47-51 for the pharmacokinetic measures for each arm of the study, with adjustment using each of three correction methods. The clinical study report referenced here is lengthy, and was

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In short, Study M02-417 showed that without correction for baseline, products that differ by 25 to 33 percent or more may be declared bioequivalent. Even with correction, products that differ by 12.5 percent (*i.e.*, 450 *versus* 400 mcg) could not be distinguished. *Id.* at 52.⁵ When applied to the range of doses used in clinical practice, a 12.5 percent difference is critical.⁶

D. The Denial of Abbott's Meeting Requests and the Agency's Decision to Adopt a Correction Method

On May 8, 2002, Abbott submitted its simulation study to clinical and biopharmaceutics officials in CDER, along with a request for a meeting. Tab 2 at 26. The purpose of the meeting was to discuss the study with the relevant experts in CDER. The meeting also would have provided an opportunity to discuss Abbott's protocol for its clinical study, M02-417.

On May 20, 2002, CDER denied Abbott's meeting request. *Id.* at 36. In a letter from the Division of Metabolic and Endocrine Drug Products (the "Division"), the agency stated that the request would be reconsidered after Abbott submitted the final study report. Abbott continued to keep the agency apprised of the study (*id.* at 38), and on October 10, 2002, the company formally submitted the results of Study M02-417. *Id.* at 40. With the submission, Abbott renewed its request for a meeting.

Three months later, the agency again denied the meeting request. In a letter dated January 14, 2003 (and received on January 24, 2003), the Division informed Abbott that the agency had decided the matter and that the meeting was

submitted to IND 62,270 (Serial No. 020) on October 10, 2002. We have not attached a copy of the report because of its size; however, it is available from the review division, and is wholly incorporated herein. The clinical study report synopsis is attached. *Id.* at 44.

⁵ Study M02-417 demonstrated that doses that differ by 12.5 percent (*i.e.*, 450 mcg *versus* 400 mcg) cannot be distinguished by the three pre-dose baseline correction method. Given the margins by which the 450 and 400 mcg doses were declared BE, however, it is likely that FDA's baseline correction method would not distinguish doses that differ by more than 12.5 percent. For example, there is good reason to believe that, had they been tested, 475 and 400 mcg doses (*i.e.*, an 18.75 percent difference) would have been declared BE. See Tab 2 at 50.

⁶ Current marketed strengths of levothyroxine sodium include 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg.

now “unnecessary.” Tab 1 at 1. The Division Letter stated that FDA had adopted “a three pre-dose baseline subtraction method to evaluate total thyroxine” when considering levothyroxine products for AB therapeutic equivalence ratings. *Id.* The letter also stated that FDA would recommend the method to levothyroxine sponsors. The letter provided no explanation in support of the decision and no indication as to who had been consulted, what factors were considered, or how this guidance was being communicated. Nor did the letter address the data from Study M02-417 showing that such a correction method cannot distinguish doses that, in fact, differ by 12.5 percent.

Per the recommendation in the Division Letter, on February 12, 2003, Abbott initiated dispute resolution under the FDR Guidance. Tab 2.⁷ Abbott presented the key findings of Study M02-417: (1) Without baseline correction, levothyroxine doses that differ by 33 percent or more cannot be distinguished; and (2) with baseline correction, doses that differ by 12.5 percent cannot be distinguished. Abbott also explained why, as a clinical matter, failure to distinguish between doses that differ by 33 percent, 12.5 percent, or less, can have serious adverse health consequences for patients. *Id.* at 15-17; *see also infra* at section IV.D. (discussing FDA’s confidential analysis of the clinical risks of nine percent or smaller dosing differences in levothyroxine patients).

As for relief, Abbott sought formal review of the Division Letter and a joint meeting of the ACPS and the EMDAC. Finally, Abbott requested a full explanation of the reasoning behind the Division Letter, to allow for a productive advisory committee review process. *Id.* at 19-20.

E. The Response to Abbott’s Request for Dispute Resolution

On March 7, 2003, the Director of ODE II (Dr. Robert Meyer) responded to Abbott’s request for dispute resolution. Tab 4. The Office Letter affirmed the decision to adopt a three pre-dose baseline correction method and denied Abbott’s request for a joint advisory committee meeting. The Office Letter asserts that Abbott’s data – showing that the pre-dose correction method cannot distinguish a 450 mcg dose of levothyroxine from a 400 mcg dose – are invalid. These doses are, according to the letter, too close to baseline to assure accurate measurement. According to Dr. Meyer,

⁷ The facts and analysis in Abbott’s February 12 appeal of the Division Letter will not be repeated here, but are incorporated in full by reference. Tab 2 at 5-19.

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at the 450 and 400 mcg doses, baseline “noise” drowns out dose “signal.” The letter, however, cites no data, literature, or analysis to support this assertion. *Id.* at 56.

With respect to Abbott’s request for a joint clinical/biopharmaceutics advisory committee meeting, Dr. Meyer denied the request. According to the Office Letter, the clinical issues are well understood: “I believe the clinical importance of levothyroxine and having the correct dosage is very clear to the Agency’s own medical experts” *Id.* As to the biopharmaceutics issues, Dr. Meyer assured Abbott that these would be covered during an “upcoming” March 13, 2003, ACPS meeting. *Id.* at 57 (“[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”).

Unfortunately, the Office Letter (postmarked March 10) did not arrive at Abbott’s headquarters until March 13 – the day of the ACPS meeting. Abbott had requested an explanation of the Division Letter “to make for a more productive advisory committee meeting” Tab 2 at 4. While Dr. Meyer prepared such an explanation, it was not shared with Abbott in advance of the ACPS meeting (*e.g.*, by sending a courtesy copy by facsimile, overnight delivery, or e-mail).

Along the same lines, the slide deck presented by FDA at the March 13 meeting, critiquing Abbott’s data, was not made available to Abbott in advance of the meeting. Nor was the agency’s slide deck made a part of the ACPS briefing package. The agency also posed no questions to the advisory committee on Abbott’s data and solicited no specific recommendations from the committee. Indeed, just prior to the ACPS meeting, the agency announced that:

Abbott has raised with FDA some issues related to the impact of their study results on the bioequivalence assessment of levothyroxine. This is not a topic for discussion at this ACPS meeting.

Tab 6 at 71 (emphasis in original). In short, Dr. Meyer’s conclusion that the ACPS meeting would be “sufficient” (Tab 4 at 57) was proven wrong. The agency made no serious effort to engage ACPS members in a discussion of Abbott’s data or the related clinical issues; rather, the agency’s analysis was not shared with Abbott and the ACPS until FDA’s actual presentation on the afternoon of March 13.

As with the Division Letter, the Office Letter closes with an invitation to appeal the decision to the next supervisory level in CDER. *Id.* Given the factual and analytical gaps to date, and the mounting legal and procedural concerns, Abbott is compelled to continue its appeal.

III. THE GOVERNING LEGAL STANDARD

The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. No. 98-417) created section 505(j) of the FDCA, which established the current generic drug approval process. 21 USC 355(j). An abbreviated new drug application (“ANDA”) must demonstrate, among other things, that the proposed drug product is bioequivalent to a reference listed drug. *Id.* at 355(j)(2)(A)(iv).

A generic drug is considered bioequivalent if “the rate and extent of absorption of the drug [*i.e.*, its bioavailability] do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses” *Id.* at 355(j)(8)(B)(i). The method used to show bioequivalence must, by regulation, be the “most accurate, sensitive, and reproducible approach available” 21 CFR 320.24(a). A methodology that cannot detect significant, known differences between two drug products does not meet the agency’s statutory or regulatory standards.

The agency’s decision to adopt a three pre-dose connection method for evaluating the bioequivalence of levothyroxine products must also be reviewed against the standards ordinarily applied to agency decisions. 5 USC 706(2)(A). That is, the decision must be set aside if CDER officials failed to consider an important aspect of the problem or provided an explanation that runs counter to the evidence or to sound reasoning. *See Motor Vehicle Mfrs. Ass’n v. State Farm Mut. Auto. Ins. Co.*, 463 US 29, 43 (1983) (The agency must “examine the relevant data and articulate a satisfactory explanation for its action including a rational connection between the facts found and the choice made.” (quotation omitted)).⁸

⁸ For example, in *Whitaker v. Thompson*, 2002 WL 32059742 (D.D.C. Dec. 24, 2002) (memorandum opinion), the court concluded that FDA’s scientific findings were unreasonable because FDA failed to follow its own criteria when it disregarded a number of studies supporting a dietary supplement health claim and gave undue emphasis to other studies. *Id.* at *11. Similarly, FDA is not entitled to deference when it fails to provide a rational, coherent explanation of its decision. *See id.* at *9 (“The deference due to an agency’s expert evaluation of scientific data does not negate the duty of [the] court to ensure that an agency . . . conduct[s] a process of reasoned decision making.” (quotation

The decision to deny Abbott's request for advisory committee review also must be well reasoned and consistent with agency standards and practice. While FDA enjoys discretion on the use of advisory committees, CDER must give interested persons a reasonable opportunity to have scientific disputes vetted before outside experts. 21 USC 355(n), 360bbb-1; 21 CFR 10.75(b)(2).

Finally, FDA's decision must be reversed if CDER failed to follow required procedures for developing and announcing agency policy. See 21 CFR 10.115. Again, while FDA enjoys wide discretion in setting scientific standards, that discretion is not without boundaries. At the direction of Congress, FDA is required to develop important scientific policies through an open, public process. 21 USC 371(h).

IV. ANALYSIS

The decision to adopt a BE methodology, including a pre-dose baseline correction method, fails to meet these basic standards for agency decisions. There is, apparently, no record in support of the decision, let alone a well-reasoned explanation. The Division Letter itself contains no analysis. While it acknowledges Abbott's clinical data, the letter offers no response to the showing that a three pre-dose correction method cannot distinguish among products that differ by 12.5 percent. The Division Letter also violated the agency's procedural regulations; it announced final guidance or, more precisely, it substantively amended the agency's existing guidance on levothyroxine products, without following the agency's good guidance practice regulations ("GGPs").

The Office Letter is similarly flawed. It provides a *post hoc* explanation in support of the Division Letter without any evidence that FDA probed the data or the related clinical issues. As discussed below, the Office Letter attempts to explain FDA's rejection of clinical data showing that the agency's recommended BE methodology cannot reliably distinguish a 450 mcg dose of levothyroxine from a 400 mcg dose. That explanation, however, is void of logical and scientific support. The Office Letter also perpetuates the procedural missteps of the Division Letter. The

and emphasis omitted)); *Pearson v. Shalala*, 164 F.3d 650, 660 (D.C. Cir. 1999) (FDA failed to explain the "significant scientific agreement" standard, and in turn, why the proposed health claims did not meet that standard); *A.L. Pharma v. Shalala*, 62 F.3d-1484, 1492 (D.C. Cir. 1995) ("The FDA has made no attempt to 'cogently explain' . . . why A.L. is mistaken when it contends that a single-dosage study unaccompanied by blood level comparisons cannot prove bioequivalency." (citation omitted)).

Office Letter describes the agency's recommended baseline correction method as if the appropriate public process for issuing guidance had, in fact, been followed. Moreover, Dr. Meyer's explanation for rejecting Abbott's request for an advisory committee meeting is based on several factual errors (*see supra* at section II.E.). Dr. Meyer does not take into account the 1997 amendment to the FDCA that provides an opportunity for interested persons to request an advisory committee to help resolve scientific disputes; there is no evidence in the Office Letter that CDER gave Abbott's request serious consideration consistent with this statutory change.

In sum, the Division and Office Letters, and the underlying decisions, do not meet basic standards of administrative law. The selection of the three pre-dose baseline correction method should be set aside. In its place, the agency should convene an appropriate joint advisory committee meeting and initiate a public process committed to the development of a sound BE methodology for levothyroxine products. Until that process is completed, any further review of levothyroxine products based on a showing of bioequivalence should be halted.

A. CDER's Basis for Adopting a Pre-Dose Correction Method is Scientifically Unsound

Study M02-417 demonstrates that without baseline correction, a 600 mcg dose of levothyroxine is indistinguishable from either a 450 or 400 mcg dose. Tab 2 at 48. The agency agrees and, on this basis, has adopted a three pre-dose correction method (closely tracking Correction Method One in Study M02-417). Tab 1 at 1. Study M02-417 also shows, however, that a pre-dose correction cannot distinguish products that differ by 12.5 percent (*i.e.*, 450 *versus* 400 mcg). According to the Office Letter, this 450 to 400 mcg comparison is unpersuasive because the "signal-to-noise" at these doses is too low to yield accurate measurements. Tab 4 at 56. The Office Letter therefore rejects Abbott's data to the extent it shows that the agency's pre-dose correction method is flawed. This explanation fails on several grounds.

1. The 450 to 400 mcg comparison is valid

The Office Letter is internally inconsistent. If the measures taken from the 450 and 400 mcg arms of the study are valid when compared against the 600 mcg arm, then they are equally valid when compared against each other. There is no logical support for CDER's mistaken use of the data from Study M02-417, given FDA's acceptance of it in support of baseline correction generally.

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Nor is there scientific support for CDER's mistaken use of the data in Study M02-417. The Office Letter argues that the showing of bioequivalence in the 450 *versus* 400 mcg comparison in Study M02-417 is invalid because the doses were too close to baseline T4 levels. As Dr. Meyer states, "we would not expect this study and test-method to distinguish differences of exposure when doses significantly below 600 mcg are compared." Tab 4 at 56. In fact, the showing of bioequivalence between the 450 and 400 mcg arms of the study is significant, for the precise reason given by the agency.

The statistical analysis used to determine whether two products may be declared bioequivalent is performed on the logarithm of the peak concentration ("C_{max}") and the logarithm of the area under the plasma/serum concentration-time curve ("AUC"). The two basic factors that determine whether products will be declared bioequivalent are: (1) The relative bioavailability of the products, based on the ratios of the C_{max} and AUC geometric means; and (2) the variability of the logarithms of C_{max} and AUC. The less variability in the data, the more likely it is that two products will be found bioequivalent.

Here, with lower doses of levothyroxine (and less "signal-to-noise"), the likelihood of showing bioequivalence should also decrease. Indeed, the variability of the data from the 600 mcg arm of Study M02-417 was *smaller* than the variability for the 450 and 400 mcg doses.⁹ Thus, two levothyroxine products that differ by 12.5 percent are more likely to be found bioequivalent in a study with 600 mcg doses than in a study with 450 and 400 mcg doses. If, as Dr. Meyer argues, the noise level at 450 and 400 mcg is high (relative to signal), that would *decrease* the likelihood of two inequivalent formulations being declared equivalent. The fact that Study M02-417 was able to find bioequivalence at 450 and 400 mcg is remarkable for the very reason cited by Dr. Meyer.

This point is further validated by the fact that the 450 and 400 mcg doses passed bioequivalence with a relatively tight confidence interval. Tab 2 at 50. The width of the confidence intervals in Study M02-417 for the 450 *versus* 400 mcg comparison under Correction Method One ranged from 0.14 to 0.25, relative to a

⁹ The variances of the logarithms of C_{max} and AUC for the three dosing levels (*i.e.*, 600, 450, and 400 mcg) with the three pre-dose correction method were estimated, taking into account gender, dosing period, and unequal carryover effects. The estimates of the variances for the 600 mcg dose (0.0356 and 0.0336 for C_{max} and AUC, respectively) were smaller than for the 450 mcg dose (0.0563 and 0.0799) and the 400 mcg dose (0.0459 and 0.0574).

permissible width of 0.45 (*i.e.*, from 0.80 to 1.25), in spite of what Dr. Meyer argues was a low signal-to-noise ratio.

2. The Office Letter does not show that 600 mcg dosing is needed to assure valid results

The Office Letter hinges on the self-evident point that the ratio of exogenous “signal” to endogenous “noise” decreases as the size of the test dose decreases. Test doses that are “significantly below 600 mcg” will, according to the Office Letter, result in too little “signal” and too much “noise” to yield accurate measurements. Tab 4 at 56. The Office Letter, however, begs two key questions: (1) What is the scientific support for a 600 mcg dose; and (2) on what basis did the agency determine that 450 and 400 mcg doses are “significantly below” the level needed to yield accurate measurements? Without answers to both questions, the agency’s position on this critical health issue remains unsupportable.

The only basis cited in the Office Letter for requiring a 600 mcg dose is the agency’s levothyroxine BA Guidance. *Id.* There, the agency simply stated that “*several times the normal dose* should be given to raise the levels of the drug significantly above baseline to allow measurement.” Tab 5 at 63 (emphasis added). Later in the guidance, the agency recommended 600 mcg (*i.e.*, twice the *highest* available strength) as a suitable test dose. There was, however, no scientific showing by the agency that 600 mcg represented a critical threshold. No data were cited and no attempt was made to quantify or explain 600 mcg as the minimum necessary test dose.

Indeed, under the BA Guidance, much lower doses would be suitable. According to the labeling for this class of products, the average full dose of levothyroxine is approximately 1.7 mcg/kilogram (“kg”), or 100-125 mcg for a 70 kg adult. FDA Approved Labeling, *Dosage and Administration* (2002).¹⁰ A test dose of 300 to 375 mcg would, then, be “several times the normal dose.” In short, for Dr. Meyer to assert that 600 mcg is better because it is higher, or that 400 mcg is unacceptable because it is “too low,” does not represent careful scientific analysis.¹¹

¹⁰ See also IMS Health, *National Prescription Audit Plus* (Full Year 2002) (reporting that 100-125 mcg tablets represent approximately 40 percent of all prescriptions).

¹¹ The agency cannot require Abbott to demonstrate why the 450 and 400 mcg arms of Study M02-417 are valid, when the agency itself has not shown why a 600 mcg dose is necessary. Nor can the agency rely on the 600 mcg dose as a *de facto* minimum standard. See, *e.g.*, *Hector v. United States*

Next, the Office Letter's reliance on the 600 mcg dose, in the context of baseline corrected data, is misplaced. The agency originally recommended a 600 mcg dose in its BA Guidance for use *in lieu of* baseline correction. Tab 5 at 63. The large dose is intended to raise the level of the drug sufficiently above baseline to allow for valid measurement. *Id.* In the Office Letter, CDER fails to recognize that Abbott's study showed that the 450 and 400 mcg doses could not be distinguished, even *after* the data were corrected for baseline (using the correction method now being recommended by FDA). The Office Letter continues to rely on the 600 mcg dose as critical, not recognizing that with baseline correction, the original basis for such a dose has otherwise been addressed.

Finally, a 450 or 400 mcg dose of levothyroxine represents a three to four fold increase over the most-prescribed clinical doses (*see supra*). It is a several fold increase above the normal dose and, according to the criteria in the BA Guidance, is large enough to ensure accurate measurement. *Id.* (describing baseline levels of levothyroxine as "naturally present in *minute quantities* in the blood" (emphasis added)). The agency has cited to no data in support of the need for a 600 mcg dose, and no data to counter the measurements taken by Abbott in the 450 and 400 mcg arms of the study.¹²

Dep't of Agriculture, 82 F.3d 165, 170-71 (7th Cir. 1996) ("When agencies base rules on arbitrary choices they are legislating, and so these rules are legislative or substantive and require notice and comment rulemaking . . ."). In *Hoctor*, the court invalidated a Department of Agriculture policy that perimeter fences around facilities housing dangerous animals should be at least eight-feet high. The court recognized the futility of trying to rebut a standardless numerical determination that the agency had adopted without explanation. As Judge Posner explained, "[t]here is no way to reason to an eight-foot perimeter-fence rule as opposed to a seven-and-a-half foot fence or a nine-foot fence or a ten-foot fence." *Id.* at 170. Also, to the extent CDER has rejected Abbott's 450 and 400 mcg data, simply because those doses fell below the 600 mcg dosing level recommended in the BA Guidance, CDER is applying the BA Guidance as if it were a rule. Rules must be issued through a notice-and-comment process prescribed by law (5 USC 553); the application of a guidance, as if it were a rule, is a clear violation of the Administrative Procedure Act.

¹² To be clear, Abbott is not arguing that the agency may or should recommend any particular test dose for BA or BE purposes. That decision is within the agency's discretion. Rather, Abbott is only arguing that the 450 and 400 mcg data from Study M02-417, used to test the sensitivity of various means of evaluating the equivalence of levothyroxine products, are valid and sound.

3. The absence of an alternative BE study design does not support CDER's adoption of a flawed method

The remaining reason given in the Office Letter for adopting the pre-dose correction method is that Abbott failed to show that an alternative BE method would enhance sensitivity or add validity. Tab 4 at 56. According to the letter, Abbott recommended the use of individuals without functioning thyroid glands in levothyroxine BE studies but "provided no data to support this assertion . . ." *Id.*

In fact, nowhere in Abbott's appeal of the Division Letter did we recommend the use of athyreotic patients in BE studies. When we originally submitted Study M02-417 to FDA, Abbott suggested in the study report that bioequivalence studies in athyreotic patients might help address the confounding influence of baseline T4. Abbott did not, however, raise this issue in its appeal of the Division Letter.

Again, the focus of the appeal is on the validity of *the agency's recommended baseline correction method*. We believe the clinical data in Study M02-417 (along with Abbott's simulation study) show that the agency's methodology has a fundamental flaw; it will allow products that differ by clinically meaningful amounts to be considered bioequivalent and, in turn, therapeutically equivalent.

With that said, we believe the issue of alternative study designs – including the possibility of requiring studies in athyreotic patients – is an additional reason why the agency should refer this matter to a joint ACPS/EMDAC advisory committee meeting (*see infra* at section IV.B.). Studies in such individuals could utilize therapeutic doses of the drug and, because these patients have no endogenous hormone, would not require *any* baseline correction method or attention to the effect on T4 homeostasis. Furthermore, tens of thousands of new thyroid cancer patients are diagnosed each year. Terminal destruction of the thyroid gland, followed by levothyroxine therapy, is a highly successful treatment resulting in a large athyreotic population in which to study.¹³ Abbott would welcome the idea of including the issue of alternative study designs on the agenda for the meeting we have requested.

¹³ At the March 13 advisory committee meeting, an agency official, when asked about the possibility of BE studies in athyreotic patients, stated that it was "unrealistic" due to recruiting difficulties and the lack of enough subjects. To the contrary, numerous studies have been conducted in this population, including several BE studies. *See, e.g.,* Shapiro, et al., *Minimal Cardiac Effects in Asymptomatic Athyreotic Patients Chronically Treated with Thyrotropin-Suppressive Doses of L-Thyroxine*, *J. Clin. Endocrinol. Metab.*, vol. 82 (1997) at 2592 (involving 17 patients); Gottwald et al.,

B. The Agency Erred in Denying Abbott's Request for a Joint Advisory Committee Meeting

The Food and Drug Administration Modernization Act of 1997 ("FDAMA") provided sponsors a statutory right to request advisory committee review of scientific disputes. 21 USC 360bbb-1; see H. Rep. 105-310 (Oct. 7, 1997) at 73 ("Neither the current law nor existing regulations provides an adequate basis for resolving scientific and medical disputes that arise in the course of FDA implementation of the law.").

In response, FDA amended its internal review regulation, adding the opportunity for a sponsor to request review of a "scientific controversy by an appropriate scientific advisory panel . . . or an advisory committee . . ." 21 CFR 10.75(b)(2). As outlined in guidance, disputes involving "technical expertise that require some specialized education, training, or experience" generally should be referred to a committee, while issues involving fraud, bias, or jurisdiction should not. FDR Guidance at 7.

Abbott's dispute over baseline correction and BE criteria is precisely the type of issue that should be presented to an advisory committee for review. Also, because it involves both clinical issues (regarding the need to define the extent to which interchangeable products may differ in potency) and technical issues (regarding the design of a sufficiently sensitive BE study), the dispute requires joint review before the relevant clinical experts (the EMDAC) and biopharmaceutics experts (the ACPS).

Dr. Meyer denied Abbott's request. He concluded that EMDAC participation is unnecessary because the clinical issues are already "very clear to the Agency's own medical experts as evidenced by the BA Guidance" on levothyroxine products. Tab 4 at 56. He also concluded that the March 13 ACPS meeting would be sufficient with respect to any outstanding technical issues. *Id.* at 57.

Bioequivalence of Two Commercially Available Levothyroxine-Na Preparations in Athyreotic Patients, Meth. Find. Exp. Clin. Pharmacol., vol. 16 (1994) at 645-50 (24 patients); Trantow, et al., *A New Method for the Determination of the Bioavailability of Thyroid Hormone Preparations*, Meth. Find. Exp. Clin. Pharmacol., vol. 16 (1994) at 133 (24 patients); Mechelany, et al., *TRIAC has Parallel Effects at the Pituitary and Peripheral Tissue Levels in Thyroid Cancer Patients Treated with L-Thyroxine*, Clinical Endocrinology, vol. 35 (1991) at 123 (22 patients).

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In fact, the BA Guidance on which Dr. Meyer relied does not raise the clinical issues implicated by the substitution of levothyroxine products. The background section of that document discusses generally the need for precise dosing, but does not address how closely matched interchangeable levothyroxine products must be. Tab 5 at 63. As shown in Abbott's February 12 FDR Submission, there is a pressing need to consider this issue specifically in the context of BE studies for products that will be considered fully interchangeable. Tab 2 at 15-17. This point is aptly illustrated by FDA's own discussion in the Confidential Appendix to the agency's April 26, 2001, Petition Response on the regulatory status of Synthroid® (Docket No. 97N-0314). Tab 7. As the agency explains,

The 9 percent difference discussed in this passage would, likewise, not be detected by the agency's recommended BE methodology. As shown in Study M02-417, FDA's methodology cannot reliably distinguish products that differ by 12.5 percent, let alone by 9 percent or less. The exact percentage difference that can be tolerated in active ingredient overages or bioavailability without negatively impacting patients is best determined by first obtaining advice from a joint meeting of the ACPS and the EMDAC.

Finally, Dr. Meyer's reliance on the March 13 ACPS meeting was, in retrospect, misplaced. Tab 4 at 57 ("[T]he session planned at the March 13, 2003, meeting with the ACPS is sufficient . . ."). On March 4, 2003, FDA published a revised advisory committee agenda that *withdrew* the topic of levothyroxine bioequivalence from the March 13 agenda. *Compare* 68 FR 5297, 5298 (Feb. 3, 2003) (listing item 4 on the agenda as "discuss and provide comments on levothyroxine bioequivalence") *with* 68 FR 10254 (Mar. 4, 2003) (listing "discuss and provide comments on bioequivalence/bioavailability of endogenous drugs"). Several days later, FDA posted a public notice stating that the issue of Abbott's study and its impact on levothyroxine BE standards "is not a topic for discussion at this ACPS meeting." Tab 6 at 71 (emphasis in original). Neither Dr. Meyer's analysis nor the agency's slides discussing the analysis were provided in advance to Abbott or to the members of the ACPS. The agency did not even present any questions to the ACPS on the issue or solicit any recommendations.

Such an approach to the advisory committee review process is contrary to Congress's directive in FDAMA and FDA's requirement to exercise its discretion in a rational manner. *See* 63 FR 63978, 63980 (Nov. 18, 1998) ("[21 CFR] 10.75 includes a general mandate that requests for section 404 reviews shall not be unreasonably denied."). Accordingly, Abbott should be granted the opportunity to have its concerns addressed in a reasonable way, with a full session before a joint ACPS/EMDAC advisory committee.

C. The Agency Erred in Failing to Follow Good Guidance Practice Requirements

Both Congress and FDA have recognized the importance of consistent and transparent processes in the development of agency guidance, particularly with respect to complex scientific or highly controversial issues. In amending the FDCA, Congress articulated the procedural steps FDA must follow prior to issuing guidance

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documents and required the agency to issue regulations consistent with that practice. 21 USC 371(h); *see* 21 CFR 10.115.¹⁴

FDA's adoption of a BE methodology for levothyroxine products qualifies as agency guidance. Guidance documents are defined as those "prepared for FDA staff, applicants/sponsors, and the public that describe the agency's interpretation of or policy on a regulatory issue." 21 CFR 10.115(b)(1); *see also id.* at 10.115(b)(2) (including documents relating to the testing of products and the evaluation of submissions). Both in letters to Abbott and in presentations made at the advisory committee meeting, FDA made clear its new regulatory interpretation with respect to levothyroxine BE testing.

In the Division Letter, the agency wrote that it "*will recommend to sponsors* seeking to obtain an AB rating of their product with respect to a reference listed levothyroxine sodium tablet product the following: *It will be necessary to conduct a . . . study . . . using a . . . baseline subtraction method . . .*" Tab 1 at 1 (emphasis added). And in the Office Letter, "FDA plans on recommending the three pre-dose baseline subtraction method to sponsors wishing to do BE testing." Tab 4 at 56. Similarly, the agency's comments at the advisory committee meeting demonstrate that it has adopted a levothyroxine BE methodology for products.¹⁵

Given the concerns motivating FDA to issue other guidance documents on levothyroxine products, a similar process should have been followed prior to adoption of the baseline correction method. Since FDA began regulating levothyroxine products in 1997, it has treated them as a class and issued numerous documents addressing their unique attributes (*see supra* at section II.A.). As Dr. Steven Johnson stated at

¹⁴ These regulations, of course, carry the force and effect of law, and FDA, like private parties, is bound to follow them. *Cherokee Nation of Oklahoma v. Babbitt*, 117 F.3d 1489, 1499 (D.C. Cir. 1997) ("An agency is required to follow its own regulations.").

¹⁵ *See* FDA Advisory Committee Meeting Transcript (Mar. 13, 2003) at 180 ("[T]his part of the presentation will now focus on the FDA's *current recommendation* for evaluating levothyroxine sodium bioequivalence." (emphasis added)), at www.fda.gov/ohrms/dockets/ac/03/transcripts/3926T2.pdf (the Transcript"); *see also id.* at 180 ("This data was confirmatory and very useful when the FDA *decided to adopt* a baseline correction method for evaluating levothyroxine sodium tablet bioequivalence." (emphasis added)); 181 ("Now on to the bioequivalence design. This is the current study protocol that *we're recommending to sponsors seeking [AB] ratings.*" (emphasis added)); 184 ("Now, when the agency *decided to adopt a baseline correction method* for bioequivalence, we went back to data from the six original NDA applications." (emphasis added)).

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the recent advisory committee meeting, "the FDA recognized, in part due to the large number of manufacturers of this product, that we needed to come up with a consistent set of guidelines for this product and so a guidance for industry was put together." Transcript, *supra* note 15, at 164. Nevertheless, FDA adopted the baseline correction method by *ad hoc* means. By issuing its BE methodology without following GGP's, FDA deprived itself of the benefit of public input; in doing so, the agency appears to have adopted a scientifically flawed approach. See 21 CFR 10.115(e) (FDA is prohibited from using means other than a guidance document "to informally communicate new or different regulatory expectations to a broad public audience for the first time."); see also 21 USC 371(h)(1)(C) (requiring that FDA provide for public participation *prior to the implementation* of guidance concerning "complex scientific" or "highly controversial" issues).

The issue of levothyroxine BE qualifies as "Level 1" guidance. 21 CFR 10.115(c). The question of the interchangeability of oral levothyroxine products has existed, unresolved, for many years. Nevertheless, the agency issued a key recommendation on this subject, without engaging the public regarding data indicating its methodology can declare clinically different products equivalent. The agency should now halt the review of any applications based on this unlawful guidance and initiate a public process designed to develop a BE methodology that will ensure the safety and effectiveness of this class of products.

V. PROPOSED RESOLUTION

Abbott urges CDER to initiate a process that is designed to fully and objectively address the scientific issues raised by Study M02-417. This process should include a joint ACPS and EMDAC advisory committee meeting, devoted specifically to the issue of developing a valid BE methodology for levothyroxine drug products. Abbott expects to support whatever appropriate, scientific solution is developed by this expert advisory committee, provided that the process includes the opportunity for objective discussion, takes into account clinical impact, and reflects technical rigor.

VI. CONCLUSION

For the reasons stated above, we respectfully request you set aside the decision made in the Division Letter and decline to approve ANDAs and 505(b)(2) applications until the agency presents the issue to a joint meeting of the EMDAC and ACPS, and develops an accurate, sensitive, and clinically appropriate BE methodology.

John Jenkins, M.D.
April 14, 2003
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Thank you for your careful attention to this matter. Please call me should you have any questions or wish to discuss any aspect of this request.

Sincerely,



Douglas L. Sporn, Divisional Vice President
Regulatory Affairs,
Global Pharmaceutical Research and
Development

Attachments

cc: Gary Buehler, R.Ph.
Director, Office of Generic Drugs, HFD-600

Kim Colangelo
Formal Dispute Resolution Project Manager, HFD-002

Lawrence Lesko, Ph.D.,
Director, Office of Pharmacology and Biopharmaceutics, HFD-850

Robert Meyer, M.D.,
Director, Office of Drug Evaluation II, HFD-102

David Orloff, M.D.,
Director, Division of Metabolic and Endocrine Drug Products, HFD-510

Helen Winkle
Director, Office of Pharmaceutical Science, HFD-003



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857**CONFIDENTIAL**

IND 62,720

Abbott Laboratories
Attention: Douglas Sporn
Divisional Vice President, Corporate Regulatory Affairs
D-387, AP6C-1
100 Abbott Park Road
Abbott Park, IL 60064-6091

Dear Mr. Sporn:

We received your October 10, 2002, correspondence on October 11, 2002 requesting a meeting to discuss the suitability of the current bioequivalence requirements for levothyroxine sodium tablets. We apologize for the delay in responding to your request. We considered your request and concluded the meeting is unnecessary.

We have carefully evaluated your data and the issues you raised based on the results of Study M02-417, which were included in your meeting request. We agree that a baseline correction method should be used when evaluating levothyroxine sodium tablet products for an AB rating. We concluded that the Agency will recommend to sponsors seeking to obtain an AB rating of their product with respect to a reference listed levothyroxine sodium tablet product the following: It will be necessary to conduct a two-way crossover study in healthy subjects under fasting conditions using a three pre-dose baseline subtraction method to evaluate total thyroxine.

If you disagree with our decision regarding your meeting request, you may discuss the matter with Enid Galliers, Chief, Project Management Staff, at (301) 827-6429. If the issue cannot be resolved at the division level, you may formally request reconsideration according to our guidance for industry titled *Formal Dispute Resolution: Appeals Above the Division Level* (February 2000). The guidance can be found at <http://www.fda.gov/cder/guidance/2740fn1.htm>.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
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/

David Orloff
1/14/03 03:55:36 PM

ABBOTT LABORATORIES
Global Pharmaceutical Research and Development
Regulatory Affairs and Life Cycle Management

Douglas L. Sporn
Divisional Vice President
GPRD Regulatory Affairs and
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February 12, 2003

BY HAND DELIVERY

Janet Woodcock, M.D.
Director, HFD-001
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont Complex II
1451 Rockville Pike
Rockville, Maryland 20852

Re: FORMAL DISPUTE RESOLUTION REQUEST
Synthroid® (levothyroxine sodium tablets, USP) 1/
IND 62,720

Dear Dr. Woodcock:

I am writing on behalf of Abbott Laboratories ("Abbott") to initiate formal dispute resolution based on the January 14, 2003, decision issued by the Division of Metabolic and Endocrine Drug Products (the "Division") with regard to bioequivalence ("BE") testing of levothyroxine sodium drug products. See Tab 1. 2/ As decided, the Food and Drug Administration ("FDA") will recommend the use of a three pre-dose baseline subtraction method to correct for endogenous hormone when applicants seek approval of "A" rated levothyroxine sodium products. Abbott believes that, with this recommendation, the agency has accepted a scientifically flawed test methodology that cannot distinguish between two levothyroxine dosing regimens, *i.e.*, 400 mcg and 450mcg, that differ by 50 mcg or, on a relative basis, 12.5 percent.

1/ This document (including attachments) contains confidential commercial and/or trade secret information and is being designated as exempt from disclosure under 21 CFR 20.61(d).

2/ The January 14 letter was not transmitted to us until January 24, 2003. We will, however, refer to the letter by the date it was signed, *i.e.*, the "January 14 letter."

Janet Woodcock, M.D.
February 12, 2003
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The January 14 letter specifically invited Abbott to request formal reconsideration of FDA's decision in this matter. *See id.*; *see also* 21 USC 360bbb-1; 21 CFR 10.75, 312.48, 314.103; Guidance for Industry: *Formal Dispute Resolution: Appeals Above the Division Level* (Feb. 2000) (the "Dispute Resolution Guidance"). The regulations and guidance recommend seeking the resolution of disputes at each supervisory level. Here, the decision on which we seek dispute resolution was made by the Director of the Division of Metabolic and Endocrine Drug Products, the Director of the Office of Clinical Pharmacology and Biopharmaceutics, and the Director of the Office of Generic Drugs. The Division is within the Center for Drug Evaluation and Research ("CDER") review management hierarchy; the Offices are within CDER's pharmaceutical science hierarchy. Given this posture, we believe it is appropriate to appeal this issue directly to the Center Director. *See* 21 CFR 10.75(c)(1). We also believe that important policy and clinical matters are at issue that warrant review by the Center Director. *See* 21 CFR 10.75(c)(2)-(3). Finally, the record that has been presented to the Division and Office Directors is complete; no new materials are needed for you to address our dispute.

This matter is central to public health. Levothyroxine sodium is used by approximately 13 million Americans (nearly 1 out of every 19). The drug product is effective within a narrow therapeutic range. The substitution of levothyroxine sodium products that differ by only a small margin can result in toxic manifestations such as palpitation and arrhythmia. In patients with coronary heart disease, and in pediatric patients, a small and unexpected increase in dose presents a serious hazard. Consequently, approximately 20 percent of titrations for Synthroid® are for doses that differ by only 12 or 13 mcg. The methodology outlined in the January 14 letter, however, is not sufficiently sensitive to ensure that patients who receive "A" rated products will receive the same dose to which they have been carefully titrated.

For the reasons discussed below, we request immediate review of the decision made in the January 14 letter. As part of this review, we seek a full advisory committee meeting on the subject, with joint representation from both the Advisory Committee for Pharmaceutical Science and the Endocrinologic and Metabolic Drugs Advisory Committee. Granting our request would bring together FDA, the appropriate independent experts, as well as the Abbott representatives most knowledgeable about the data, to develop appropriate test criteria. Finally, to make for a more productive advisory committee meeting, we request an explanation of the reasoning in support of the agency's January 14, 2003, decision. Proceeding in this

manner, with public participation, will help ensure that the agency arrives at a valid methodology for determining BE and assigning therapeutic equivalence ("TE") ratings for levothyroxine sodium products.

I. BACKGROUND

A. The Levothyroxine Guidance Document

As part of the process for bringing levothyroxine sodium products within the new drug application ("NDA") framework, FDA issued a series of guidance documents, including a document on the design of bioavailability ("BA") studies for levothyroxine sodium tablets. See *Guidance for Industry: Levothyroxine Sodium Tablets – In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing* (Feb. 2001) (the "Levothyroxine Guidance" or "the guidance").^{3/} The guidance advises sponsors to conduct both a single-dose bioavailability study and a dosage form proportionality study. The single-dose study described in the guidance is a two-treatment, two-sequence crossover design. The dosage-form proportionality study is a single-dose, three-treatment (six-sequence crossover) design.

The primary confounding factor in conducting studies of levothyroxine sodium products is the presence of baseline levels of endogenous thyroid hormone ("T₄"). A secondary confounding factor is the effect that administration of exogenous levothyroxine has on the production and metabolism of endogenous hormone. As the agency stated in the Levothyroxine Guidance, "[i]t is a challenge to determine the bioavailability of levothyroxine sodium products because levothyroxine is naturally present in minute quantities in the blood, with the total levels reaching 5.0-12.0 [mcg]/dl and free (or unbound) levels reaching 0.8-2.7 [mcg]/dl in a healthy adult." Levothyroxine Guidance at 2. The agency also recognizes the inherent variability in endogenous levothyroxine concentrations in study subjects. Thus, FDA recommends against the "adjustment of baseline levels since endogenous levothyroxine concentrations are unpredictable during the course of the study." *Id.* at 4.

In an effort to address these problems, the guidance simply recommends the use of several times the normal dose of levothyroxine. The inflated dose is

^{3/} See also *Guidance for Industry: Levothyroxine Sodium Products Enforcement of August 14, 2001 – Compliance Date and Submission of New Applications* (July 2001) and *Guidance for Industry: Levothyroxine Sodium Questions and Answers* (Feb. 2001).

intended to drown out the relative impact of baseline hormone levels. The guidance also recommends at least a 35-day washout period, to allow endogenous hormone levels to return to baseline before the next dose is administered.

B. The Abbott Clinical Study Program

Evaluation of the pharmacokinetic curves generated for levothyroxine sodium products led Abbott to question the sensitivity of bioavailability studies conducted according to the guidance. On February 28, 2002, Abbott notified the Division of Metabolic and Endocrine Drug Products in CDER that the company intended to conduct an additional study to evaluate the overall impact of various methods for correcting for baseline endogenous T₄. See Tab 2. On May 8, 2002, Abbott requested a formal meeting to discuss the agency's approach to assessing the bioequivalence of levothyroxine sodium products with the Division Director (David Orloff, M.D.), the Director of the Office of Clinical Pharmacology and Biopharmaceutics (Lawrence Lesko, Ph.D.), and the Director of the Office of Generic Drugs (Gary Buehler, R.Ph.). See Tab 3. Abbott had by then completed a simulation study, based on *in vivo* data collected from its Synthroid® NDA studies; Abbott intended to present the results of the study to Drs. Orloff and Lesko and Mr. Buehler. *Id.*

On May 20, 2002, Dr. Orloff informed Abbott that the meeting request was denied because the company's study was still ongoing. Dr. Orloff stated that the request would be reconsidered after Abbott submitted the final study report. See Tab 4. Abbott kept the agency apprised of the study (see Tab 5), and on October 10, 2002, the company formally submitted the results of its study. See Tab 6. With the submission, Abbott also renewed its request for a meeting with Drs. Orloff and Lesko and Mr. Buehler. *Id.*

The October 10 submission consisted of the final report of Study M02-417, titled "Evaluating the Impact of Correcting for Endogenous T₄ Baseline on the Bioequivalence of Levothyroxine Sodium Formulations in Healthy Volunteers" (the "Clinical Study Report"). ^{4/} As summarized in the cover letter accompanying the

^{4/} The Clinical Study Report referenced here is a lengthy document, and was submitted to IND 62,270 (Serial No. 020) on October 10, 2002. We have not attached a copy of the Report because of its length, however it is available from the review division, and is wholly incorporated herein. The Clinical Study Report Synopsis is attached. See Tab 7.

Clinical Study Report, the results of the study call into question the scientific validity of the Levothyroxine Guidance. Based on the study, Abbott concluded that the methodology recommended in the Levothyroxine Guidance is very likely to yield inaccurate and misleading results if applied in the context of BE testing of levothyroxine sodium drug products.

Study M02-417 used a single-dose design with a three-period crossover. Based on the guidance, one arm (Regimen A) received 600 mcg of levothyroxine sodium. In addition, another (Regimen B) received 450 mcg, and a third (Regimen C) received 400 mcg. Blood samples were collected as per the guidance, with additional samples taken to assess baseline endogenous T₄. In addition, blood samples were collected for 24 hours prior to, and up to 96 hours after, the study dose.

Also, as recommended in the guidance, the relevant pharmacokinetic ("PK") measures (C_{max}, T_{max}, and AUC₄₈, plus AUC₇₂ and AUC₉₆) were analyzed without baseline correction. As shown in Table 1, below, the data show that without baseline correction, each PK measure is consistent with a finding of bioequivalence, even though the test and reference doses differed by as much as 33 percent (400 mcg *versus* 600 mcg). Regimen B (450 mcg dose) and Regimen C (400 mcg dose) would both be declared bioequivalent to Regimen A (600 mcg dose) because the 90 percent confidence intervals for evaluating bioequivalence without correction were contained within the 80 to 125 percent range. Considering the margin by which the conditions for declaring bioequivalence were passed in this study, products that differ by more than 33 percent would also have a high likelihood of being declared bioequivalent.

TABLE 1

Bioequivalence and Relative Bioavailability—Uncorrected Levothyroxine (T₄) 5/

Regimens		Relative Bioavailability			
Test vs.	Pharmacokinetic	Central Value*		Point	90% Confidence
Reference	Parameter	Test	Reference	Estimate ⁺	Interval
450 mcg vs. 600 mcg	C _{max}	13.0	14.0	0.928	0.890 – 0.968
	AUC ₄₈	481.7	504.8	0.954	0.927 – 0.982
	AUC ₇₂	694.9	721.9	0.963	0.936 – 0.990
	AUC ₉₆	896.2	925.6	0.968	0.941 – 0.996
400 mcg vs. 600 mcg	C _{max}	12.9	14.0	0.921	0.883 – 0.960
	AUC ₄₈	469.6	504.8	0.930	0.904 – 0.958
	AUC ₇₂	670.4	721.9	0.929	0.903 – 0.955
	AUC ₉₆	865.7	925.6	0.935	0.909 – 0.962
450 mcg vs. 400 mcg	C _{max}	13.0	12.9	1.007	0.967 – 1.050
	AUC ₄₈	481.7	469.6	1.026	0.997 – 1.055
	AUC ₇₂	694.9	670.4	1.037	1.009 – 1.065
	AUC ₉₆	896.2	865.7	1.035	1.007 – 1.064

* Antilogarithm of the least squares means for logarithms.

+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

5/ See Clinical Study Report Synopsis (Tab 7) at v.

Abbott then compared the data to measurements analyzed with each of three baseline correction methods to determine whether the BE methodology could be refined to adequately distinguish bioinequivalent products. The methods analyzed by Abbott were:

Method 1: The pre-dose baseline value on the day of dosing was subtracted from each post-dose concentration. The pre-dose baseline value was calculated as the average of three concentrations (at 0.5, 0.25, and 0 hours) prior to dosing in each period. (This method assumes no suppression of endogenous T₄ production.)

Method 2: For each time of post-dose sampling, the observed concentration was corrected assuming that the endogenous T₄ baseline level at 0 hours declined according to a half-life of 7 days. (This method assumes equal and complete suppression of endogenous T₄ production for all regimens.)

Method 3: The T₄ concentration for each time of post-dose sampling was corrected by the concentration observed at the same time of day during the 24 hours preceding the dose. (This method assumes a diurnal hormone cycle that is not changed by the administration of the 600 mcg dose.)

As shown in Tables 2, 3, and 4, below, the use of baseline corrected data would reduce the likelihood that two products differing by 25 to 33 percent would be found BE. However, none of the three methods is sufficiently sensitive to distinguish products that differ by as much as 12.5 percent. ^{6/} Even after correcting for endogenous levothyroxine using each of the three correction methods, Regimen B (450 mcg dose) would continue to be declared bioequivalent to Regimen C (400 mcg dose); the 90 percent confidence intervals for evaluating the BE of Regimens B and C were still contained within the 80 to 125 percent range (for all but one of the PK measures).

^{6/} The 12.5 percent figure represents the relative difference between the 400 mcg and 450 mcg dosing regimens used in Study M02-417. Abbott has not sought to make the same demonstration at doses commonly used in patients for hormone replacement therapy (usually 100-150 mcg). Extrapolation of the 12.5 percent relative difference to these lower dosing regimens assumes pharmacokinetic linearity from 100 mcg to 450 mcg. This assumption is appropriate, given FDA's direction to use a 600 mcg dosing regimen in the current guidance.

TABLE 2

Bioequivalence and Relative Bioavailability for T₄ (Correction Method 1) 7/

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value*		Relative Bioavailability	
		Test	Reference	Point Estimate ⁺	90% Confidence Interval
		450 mcg vs. 600 mcg	C _{max}	5.4	6.9
	AUC ₄₈	119.7	167.3	0.715	0.658 – 0.778
	AUC ₇₂	151.4	215.7	0.702	0.636 – 0.774
	AUC ₉₆	170.2	250.2	0.680	0.602 – 0.768
400 mcg vs. 600 mcg	C _{max}	5.6	6.9	0.803	0.745 – 0.865
	AUC ₄₈	118.9	167.3	0.711	0.653 – 0.773
	AUC ₇₂	144.9	215.7	0.672	0.609 – 0.741
	AUC ₉₆	165.1	250.2	0.660	0.584 – 0.746
450 mcg vs. 400 mcg	C _{max}	5.4	5.6	0.975	0.906 – 1.049
	AUC ₄₈	119.7	118.9	1.007	0.926 – 1.094
	AUC ₇₂	151.4	144.9	1.044	0.948 – 1.150
	AUC ₉₆	170.2	165.1	1.031	0.914 – 1.163

* Antilogarithm of the least squares means for logarithms.

+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

7/ See Clinical Study Report Synopsis (Tab 7) at vii.

TABLE 3

Bioequivalence and Relative Bioavailability for T₄ (Correction Method 2) 8/

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value*		Relative Bioavailability	
		Test	Reference	Point Estimate ⁺	90% Confidence Interval
		450 mcg vs. 600 mcg	C _{max}	5.6	7.0
	AUC ₄₈	154.5	199.1	0.776	0.721 – 0.835
	AUC ₇₂	227.5	284.9	0.799	0.729 – 0.875
	AUC ₉₆	301.6	369.5	0.816	0.743 – 0.897
400 mcg vs. 600 mcg	C _{max}	5.7	7.0	0.807	0.753 – 0.866
	AUC ₄₈	148.4	199.1	0.745	0.693 – 0.802
	AUC ₇₂	207.9	284.9	0.730	0.666 – 0.800
	AUC ₉₆	277.3	369.5	0.750	0.683 – 0.824
450 mcg vs. 400 mcg	C _{max}	5.6	5.7	0.982	0.916 – 1.051
	AUC ₄₈	154.5	148.4	1.041	0.969 – 1.119
	AUC ₇₂	227.5	207.9	1.094	1.001 – 1.197
	AUC ₉₆	301.6	277.3	1.088	0.992 – 1.192

* Antilogarithm of the least squares means for logarithms.

+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

TABLE 4

Bioequivalence and Relative Bioavailability for T₄ (Correction Method 3) ^{9/}

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value*		Relative Bioavailability	
		Test	Reference	Point Estimate ⁺	90% Confidence Interval
450 mcg vs. 600 mcg	C _{max}	5.7	6.9	0.820	0.757 – 0.888
	AUC ₄₈	125.1	172.9	0.723	0.672 – 0.779
	AUC ₇₂	158.7	222.0	0.715	0.645 – 0.792
	AUC ₉₆	177.7	256.6	0.693	0.631 – 0.760
400 mcg vs. 600 mcg	C _{max}	5.3	6.9	0.775	0.715 – 0.839
	AUC ₄₈	115.4	172.9	0.667	0.620 – 0.718
	AUC ₇₂	135.9	222.0	0.612	0.553 – 0.678
	AUC ₉₆	164.0	256.6	0.639	0.582 – 0.702
450 mcg vs. 400 mcg	C _{max}	5.7	5.3	1.058	0.979 – 1.145
	AUC ₄₈	125.1	115.4	1.084	1.008 – 1.165
	AUC ₇₂	158.9	135.9	1.168	1.057 – 1.291
	AUC ₉₆	177.7	164.0	1.084	0.989 – 1.188

* Antilogarithm of the least squares means for logarithms.

+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

^{9/} See Clinical Study Report Synopsis (Tab 7) at viii.

Finally, as discussed in the study report, these correction methods do not account for the fact that endogenous hormone levels fluctuate on a diurnal cycle. Clinical Study Report at 67-68. There is also evidence of a significant carryover from one dosing period to subsequent periods even with washout periods of up to 53 days. *Id.* at 85-86.

In short, Abbott's October 10, 2002, submission shows serious flaws in the design and analysis of single-dose crossover studies in healthy volunteers to assess the BE of levothyroxine sodium products. Given the need for precise dosing of levothyroxine (*see* discussion below), and given the data, it is incongruent that the current guidance describes a methodology that cannot distinguish between two preparations that differ by 33 percent and, in all likelihood, even greater amounts.

C. The Agency's January 14 Response to Abbott

Based on the results of its study, Abbott made two requests in the October 10 submission to Drs. Orloff and Lesko and Mr. Buehler. First, Abbott requested that FDA examine the data from Study M02-417 and take appropriate action with respect to the agency's BE methodology for levothyroxine products. Second, Abbott renewed its request for a meeting with CDER officials to discuss the data.

On the issue of methodology, the January 14 letter states that FDA has evaluated the data from Study M02-417 and concluded that baseline correction is needed when evaluating levothyroxine sodium products for BE and TE purposes. The January 14 letter goes on to state that FDA will recommend the use of a two-way crossover study in healthy subjects with "a three pre-dose baseline subtraction method to evaluate total thyroxine" to correct for baseline levels of endogenous hormone.

The correction method described in the January 14 letter closely tracks "Correction Method 1" discussed and analyzed in Study M02-417 and summarized above. The study demonstrates that this type of correction method will nevertheless result in a finding of bioequivalence between two dosing regimens (400 mcg and 450 mcg) that differ in total drug content by 12.5 percent. Clinical Study Report at 88. As the Clinical Study Report recognizes, this method does not account for suppression of endogenous hormone production when exogenous levothyroxine is given to healthy subjects. *Id.* at 82. And, as further recognized in the Clinical Study Report, this

correction method fails to account for diurnal variation of hormone levels, a well-established confounding factor. *Id.* at 67.

On the issue of a meeting, CDER likewise denied our request. Having reached a substantive decision, the Division and Office Directors apparently determined that there was no need for a *post hoc* meeting to discuss the data.

D. The Upcoming Advisory Committee Meeting

Separate from our request for a meeting (*see* Tab 6), we also raised with FDA the possibility of bringing the issues raised by Study M02-417 to an appropriate advisory committee. On January 14, 2003, the same date that CDER finalized its substantive decision, FDA publicly announced through its telephone information line that levothyroxine bioequivalence would be discussed at the March 12-13, 2003, meeting of the Advisory Committee for Pharmaceutical Science. Abbott was granted time to make a presentation of its data at that meeting, however the issue is scheduled for less than two hours of discussion. Moreover, in light of the January 14 letter, CDER appears to have already decided the matter.

II. ABBOTT'S REQUEST FOR FORMAL DISPUTE RESOLUTION

Based on the January 14 letter, CDER has effectively decided to amend the guidance to include a baseline correction method. ^{10/} The method chosen, however, will not resolve the underlying issue. In addition, CDER made this decision without the benefit of a meeting with Abbott, without the benefit of advisory committee review, and without even explaining its underlying rationale. CDER's issuance of a substantive decision on the same day that CDER also scheduled advisory committee time to discuss the issue is of great concern; it appears that CDER officials have prejudged this matter before hearing from the advisory committee.

^{10/} The January 14 FDA letter states that "[w]e agree that a baseline correction method should be used when evaluating levothyroxine sodium tablet products for an AB rating. We concluded that the Agency will recommend to sponsors seeking to obtain an AB rating of their product with respect to a reference listed levothyroxine sodium tablet product the following: It will be necessary to conduct a two-way crossover study in healthy subjects under fasting conditions using a three pre-dose baseline subtraction method to evaluate total thyroxine." Tab 1.

A. The Agency's BE Methodology Must be Sufficiently Sensitive to Detect Clinically Significant Differences

As discussed below, FDA has repeatedly recognized the clinical significance of dosing increments as low as 12 mcg for levothyroxine sodium products. This recognition is grounded in sound science. For example, the class labeling that CDER has developed for levothyroxine sodium tablets recommends 12.5-25 mcg dosing increments based on extensive support in the medical literature. As further discussed below, the clinical concerns regarding small variations in the amount of active ingredient in and among levothyroxine products formed the basis for FDA's decision to require NDAs for all levothyroxine sodium products including, ultimately, Synthroid®. See 62 FR 43535 (Aug. 14, 1997).

Orally administered levothyroxine sodium products are widely used in the treatment of hypothyroidism. The drug has a narrow therapeutic range and must be precisely and consistently dosed for it to be safe and effective. According to the agency,

If a drug product of lesser potency or bioavailability is substituted in the regimen of a patient who has been controlled on one product, a suboptimal response and hypothyroidism could result. Conversely, substitution of a drug product of greater potency or bioavailability could result in toxic manifestations of hyperthyroidism such as cardiac pain, palpitations, or cardiac arrhythmias. In patients with coronary heart disease, even a small increase in the dose of levothyroxine sodium may be hazardous.

Id. at 43536. Thus, maintenance of a euthyroid state – with avoidance of both over- and under-dosing – is critical to the health and well being of the patient. See FDA Petition Response at 8 (April 26, 2001) (FDA Docket No. 97N-0314) (the “Petition Response”) (“Because of the serious consequences of too much or too little circulating thyroxine, it is very important that patients receive the dose of levothyroxine sodium determined by their physicians to be optimal to replace the amount of hormone that would have been present naturally.”).

This fact was central to the agency's 1997 decision to require new drug approval of levothyroxine sodium tablets. 62 FR at 43535. In support of that decision, the agency cited instances in which variations in dose resulted in adverse drug

experiences, including 58 reports in which patients who received either too little or too much drug suffered serious adverse events. *Id.* at 43536.

The agency also raised clinical concerns associated with the use of overages in levothyroxine sodium products. *Id.* at 43536, 43537 (discussing the potential for overages to cause superpotency which, in turn, may lead to “toxic manifestations of hyperthyroidism such as cardiac pain, palpitations, or cardiac arrhythmias”); *see also* Petition Response at 8 (“Superpotent tablets of levothyroxine sodium pose safety risks. Patients who inadvertently receive more levothyroxine than is necessary to control their condition may experience angina, tachycardia, or arrhythmias.”). The relative size of the overages that have raised concerns for the agency with respect to Synthroid®, however, are smaller than the differences that would be allowed under FDA’s BE methodology for levothyroxine products. 11/

Further to this point, the agency has approved levothyroxine sodium dosing increments of 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg. According to the agency, these increments are clinically necessary “to allow for fine adjustments of dose” in light of levothyroxine sodium’s narrow therapeutic range. Petition Response at 8. Moreover, in class labeling that has been used with approved levothyroxine sodium products, dosing adjustments of 12.5 to 25 mcg are recommended for elderly patients with underlying cardiac disease, and patients with severe hypothyroidism. *See Synthroid® Approved Labeling, “Dosage and Administration”* (2002) (“The levothyroxine sodium dose is generally adjusted in 12.5-25 mcg increments until the patient with primary hypothyroidism is clinically euthyroid and the serum TSH has normalized.”).

As FDA stated in its review of Unithroid, “a 25 mcg dosage strength that meets chemistry and biopharm criteria for approval, *is essential for proper labeling of the product for safe and effective use* given that in certain clinical situations, levothyroxine sodium dosing is initiated at 12.5-25 mcg/day and increased in 12.5-25 mcg dosing increments.” Unithroid Medical Review at 45-46 (July 21, 2000) (emphasis added). 12/ This conclusion is likewise supported by the medical literature on which

11/ The entire Synthroid® NDA and the review documents are available from the review division and are wholly incorporated herein.

12/ Class labeling being used for levothyroxine sodium products instructs practitioners to dose in 12.5 mcg increments. *See Synthroid® Approved Labeling, “Dosage and Administration”* (2002). We note, however, that in the conclusion to the final medical review of Synthroid®, the agency for an unexplained

FDA based its decision to approve Synthroid® and other levothyroxine sodium tablets, which uniformly emphasizes the clinical need for fine dosing increments. *See, e.g., id.* at 10-12, 46-52 (citing, for example, Munson, *Principles of Pharmacology: Basic Concepts and Clinical Applications* (1996) (discussing dose increments of 12.5-25 mcg); Brent and Larsen, *Werner and Ingbar's The Thyroid* (7th ed. 1996) (dose for elderly patients should be no more than 50 mcg/day, with increments of 25 mcg); Martindale, *The Extra Pharmacopoeia/Martindale* (20th ed. 1993) (starting dose for patients with severe hypothyroidism should be 12.5-25 mcg/day with increments of 25-50 mcg); Becker, *Principles and Practice of Endocrinology and Metabolism* (1990) (starting dose of 12.5-25 mcg/day in patients with severe hypothyroidism or underlying heart disease and in elderly patients); Williams, *Textbook of Endocrinology* (8th ed. 1992) (starting dose for elderly patients with heart disease of 12.5-25 mcg/day); Mazzaferri, *et al.*, *Am. J. Obstet. Gyn.* 176:507-14 (1997) (starting dose of 12.5-25 mcg/day in patients with a history of cardiovascular disease or the frail elderly, with increments of 12.5-25 mcg)).

There is, in effect, no difference between FDA's prior concern regarding the inconsistent potency of brand name levothyroxine sodium products and the potential for inconsistent potency between levothyroxine products deemed bioequivalent under the current guidance or the corrected test method, as discussed in the January 14 letter. The range of variation is comparable, and the certainty of substitution between a brand name product and an "A" rated product means that the risk of under- or over-treatment is the same. Moreover, the likelihood of there being more than one "A" rated product to each brand name product adds yet another level of potential variation. The determination of therapeutic equivalence for a levothyroxine sodium product must signify that, under all circumstances, the tested product is truly interchangeable for the reference product, without the need for clinical monitoring, retesting, and retitration. Based on Study M02-417, however, it is unlikely that the methodology described in the January 14 letter could distinguish between products that differ by as much as 12.5 percent.

reason whited-out references to the 12.5 mcg dose. Synthroid® Medical Review at 12 (Apr. 18, 2002). This redaction is anomalous as all other posted levothyroxine sodium reviews retain the references to 12.5 mcg dosing.

B. The Review of Levothyroxine BE Issues Should Occur Before an Appropriate Panel of Experts

On February 3, 2003, FDA published a notice in the *Federal Register* of the agenda for the March 12-13, 2003, meeting of CDER's Advisory Committee for Pharmaceutical Science. There are five agenda items on the calendar for the second day of the meeting, including "discuss and provide comments on levothyroxine bioequivalence." 68 FR 5297, 5298 (Feb. 3, 2003).

Abbott first suggested a joint meeting of the Endocrine and Metabolic Advisory Committee and the Advisory Committee for Pharmaceutical Science on December 27, 2002. On January 10, 2003, Abbott learned that levothyroxine BE standards would be discussed at the Advisory Committee for Pharmaceutical Science only, because the Endocrine and Metabolic Committee already had a full agenda. This was only four days before the agency's January 14 letter. We have since been advised that less than two hours of the Committee's time over the two days will be devoted to the issue. The allotted time is inadequate to properly address the significant underlying medical and scientific issues. The issue of baseline correction, and the confounding effect of exogenous levothyroxine administration, is a complex subject that requires full and objective advisory committee review. We are also concerned that the Committee, while expert in areas of pharmacology, lacks the necessary clinical expertise with the use of levothyroxine sodium products for hormone replacement therapy and the treatment of patients with thyroid cancer. None of the current members of the Committee is an expert in endocrinology. Precedent exists, which the agency should follow in this case, for joint advisory committee meetings convened to consider challenging bioequivalence issues with clinical implications. 13/

Finally, we are concerned that this meeting will occur after a letter has been issued that, on its face, purports to be the agency's decision on the very issue set

13/ For example, the Advisory Committee for Pharmaceutical Science and the Dermatologic and Ophthalmic Drugs Advisory Committee met jointly twice to discuss bioequivalence in topical products and the DRAFT Guidance for Industry: *Topical Dermatological Drug Product NDAs and ANDAs - In Vivo Bioavailability, Bioequivalence, In Vitro Release and Associated Studies* (June 1998). See 67 FR 35122 (May 17, 2002) (withdrawing the guidance document and citing the joint meetings). Similarly, the Advisory Committee for Pharmaceutical Science and the Pulmonary and Allergy Drugs Advisory Committee met jointly to discuss bioequivalence in metered dose inhalers. See 61 FR 38453, 38454 (July 24, 1996) (notice).

for discussion on March 13. Based on the January 14 letter, CDER appears to have accepted the proposition that baseline correction is needed when assigning TE ratings to levothyroxine sodium preparations. That decision represents a significant – and much needed – departure from the guidance. However, the letter goes one step further, adopting a correction method that the agency will immediately begin recommending to applicants seeking to obtain an “A” rating of their product with respect to a reference listed levothyroxine sodium tablet. *See* Tab 1. As discussed above, the method selected by the agency cannot itself distinguish among products that differ by as much as 12.5 percent. In the most common dosage range and clinical setting, this means an 88 mcg dose may be indistinguishable from a 100 mcg dose, a 100 mcg tablet from a 112.5 mcg dose, and so on.

III. REQUEST FOR RELIEF

For the reasons discussed, we wish to initiate formal dispute resolution of the decision to adopt an inadequate correction method to address concerns associated with establishing the BE of levothyroxine sodium drug products. *See* 21 CFR 10.75, 312.48, and 314.103. We have twice requested a meeting to discuss our data, and have twice been rejected. This, and the issuance by CDER of a decision with no explanation, are particularly discouraging given that Abbott believes its data offers the agency the chance to mitigate a situation that otherwise presents a public health issue.

Because the Division Director and Office Directors appear already to have made an important policy and clinical decision that we believe is in error, we seek through this appeal to have the final decision on the proper BE methodology made at the Center Director level. *See* 21 CFR 10.75(c)(1)-(3). As part of this review, and pursuant to 21 USC 360bbb-1 and 21 CFR 10.75, 312.48, and 314.103, we request that you convene a full, joint meeting of the Advisory Committee for Pharmaceutical Science and the Endocrinologic and Metabolic Drugs Advisory Committee to review the agency’s BE assessment criteria, and its clinical relevance, for levothyroxine sodium products. This request follows CDER’s stated position that advisory committee review should be granted when “technical expertise . . . requir[ing] some specialized education, training, or experience [is needed] to understand and resolve” the topic at issue. Dispute Resolution Guidance at 7. A joint advisory committee will bring together FDA, the appropriate independent experts, as well as the Abbott representatives most knowledgeable about the data and levothyroxine bioequivalence issues, to review the development of appropriate test criteria. Proceeding in this manner, with public participation, will help ensure that the agency arrives at a valid

Janet Woodcock, M.D.
February 12, 2003
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methodology for determining BE and assigning TE ratings for levothyroxine products. Finally, we request a prompt explanation of the reasoning underlying the January 14 letter. We believe that having CDER's rationale will make for a more productive advisory committee review process.

As always, we thank you for your careful attention and, should you have any questions or wish to discuss this matter, please do not hesitate to call.

Sincerely,



Douglas L. Sporn, Divisional Vice President
Global Pharmaceutical Research and
Development and Life Cycle Management

Attachments

cc: Formal Dispute Resolution Project Manager, HFD-002
Center for Drug Evaluation and Research
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5600 Fishers Lane
Rockville, Maryland 20857

Gary J. Buehler, R.Ph.
Director, Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

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Lawrence J. Lesko, Ph.D.
Director, Office of Pharmacology and Biopharmaceutics, HFD-850
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Food and Drug Administration
Parklawn Building
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Rockville, Maryland 20857

David Orloff, M.D.
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Helen Winkle
Acting Director, Office of Pharmaceutical Science, HFD-003
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Food and Drug Administration
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1451 Rockville Pike
Rockville, Maryland 20852



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857**CONFIDENTIAL**

IND 62,720

Abbott Laboratories
Attention: Douglas Sporn
Divisional Vice President, Corporate Regulatory Affairs
D-387, AP6C-1
100 Abbott Park Road
Abbott Park, IL 60064-6091

Dear Mr. Sporn:

We received your October 10, 2002, correspondence on October 11, 2002 requesting a meeting to discuss the suitability of the current bioequivalence requirements for levothyroxine sodium tablets. We apologize for the delay in responding to your request. We considered your request and concluded the meeting is unnecessary.

We have carefully evaluated your data and the issues you raised based on the results of Study M02-417, which were included in your meeting request. We agree that a baseline correction method should be used when evaluating levothyroxine sodium tablet products for an AB rating. We concluded that the Agency will recommend to sponsors seeking to obtain an AB rating of their product with respect to a reference listed levothyroxine sodium tablet product the following: It will be necessary to conduct a two-way crossover study in healthy subjects under fasting conditions using a three pre-dose baseline subtraction method to evaluate total thyroxine.

If you disagree with our decision regarding your meeting request, you may discuss the matter with Enid Galliers, Chief, Project Management Staff, at (301) 827-6429. If the issue cannot be resolved at the division level, you may formally request reconsideration according to our guidance for industry titled *Formal Dispute Resolution: Appeals Above the Division Level* (February 2000). The guidance can be found at <http://www.fda.gov/cder/guidance/2740fn1.htm>.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
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/

David Orloff
1/14/03 03:55:36 PM



David Orloff, M.D., Director
Food and Drug Administration
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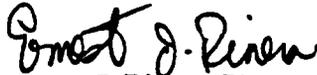
period crossover design. The total dose given will be 600 micrograms of levothyroxine for Regimen A, 450 micrograms levothyroxine sodium for Regimen B, and 400 micrograms levothyroxine sodium tablets for regimen C. A washout interval of at least 42 days will separate the doses of the three study groups.

Accordingly, the following documents are submitted herein:

Tab	Title	Page Number
I	Protocol M02-417, entitled: "Evaluating the Impact of Correcting for Endogenous T ₄ Baseline on the Bioequivalence of Levothyroxine Sodium Formulations in Healthy Volunteers."	002
II	Case Report Forms	070
III	Principal Investigator Documents (FDA Form 1572 and Curriculum Vitae)	113
IV	Chemistry, Manufacturing, and Controls Summary	121

If there are any questions regarding this submission, please contact me at the telephone number listed below.

Sincerely,
ABBOTT LABORATORIES


Ernesto J. Rivera, Pharm.D.
Regulatory Affairs Project Manager
Telephone: (847) 937-7847
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Desk copy of this submission to:
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ABBOTT

FR L18

Pharmaceutical Products Division

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May 08, 2002

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**Re: Synthroid
(levothyroxine sodium tablets, USP)
IND No. 62,720
Serial No. 017**

**General Correspondence:
Request for a Meeting**

Dear Drs. Orloff, Lesko, and Mr. Buehler:

The purpose of this correspondence is to request a meeting in accordance with the FDA's February 2000 Guidance for Industry, "Formal Meetings with Sponsors and Applicants for PDUFA Products." Specifically, the purpose of this request is to discuss the suitability of the current bioequivalence requirements for levothyroxine sodium tablets, and its potential impact on public health and patient care. Thomas M. Ludden Ph.D., Vice President, Pharmacometric R&D, GloboMax®, LLC, will present an overview of a

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simulation study, based on in-vivo data collected from healthy human volunteers who participated in two clinical pharmacokinetic studies (M01-324 and M01-323) previously conducted under this IND and submitted to our NDA 21-402. The simulation study assesses alternative bioavailability calculations, study designs and acceptance criteria for determining the bioequivalence of levothyroxine sodium tablets. Dr. Ludden will explain the factors he explored in designing, developing, and executing this scientific approach. In addition, Abbott Laboratories will present an overview of our clinical development program, which focuses on validating the conclusions of Dr. Ludden's work.

Rationale for the Meeting

The Food and Drug Administration (FDA) issued a guidance document related to pharmacokinetic and bioavailability studies associated with Levothyroxine Sodium Tablets in December of 2000 ("Levothyroxine Sodium Tablets - In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing"). This guidance document provided instructions for analyzing plasma/serum profile data generated from (i) a single dose bioavailability study and (ii) a dosage-form proportionality study. A key component of the data analysis required that values obtained from plasma/serum profiles be presented without adjustment of baseline endogenous levothyroxine levels, since these levels were "unpredictable during the course of the study." The FDA has also recommended that the use of baseline uncorrected data be employed when assessing the bioequivalence of ANDA's.

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The availability and the impact of data from our two pharmacokinetic studies (M01-324, M01-323) prompted us to host two meetings; one in December of 2001¹ and a second meeting in April of 2002², with nationally recognized experts in the areas of biopharmaceutics and endocrinology to discuss FDA's criteria related to the bioequivalence that would be applied to all levothyroxine sodium containing products. The following is a list of attendees from the expert panel:

Gordon Amidon, Ph.D.¹
Professor, College of Pharmacy
University of Michigan.

Leslie DeGroot, M.D.¹
Professor of Medicine & Radiology
Section of Endocrinology
University of Chicago Medical Center

Thomas Ludden, Ph.D.^{1,2}
Vice President, Pharmacometric Research & Development
GloboMax, LLC

Carl Peck, M.D.¹
Professor of Pharmacology & Medicine at Georgetown University
Director of the Center for Drug Development Science
Georgetown University

Leonard Wartofsky, M.D.^{1,2}
Professor of Medicine and Physiology
Uniformed Services University of Health Sciences
Bethesda, Maryland
Clinical Professor of Medicine
Georgetown, Howard, Maryland and George Washington Universities
Chairman, Department of Medicine
Washington Hospital Center
Washington, DC

¹ Attended the December, 2001 meeting.

² Attended the April, 2002 meeting.

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List of attendees from the expert panel continued:

William H. Barr, Pharm D., Ph.D.²
Professor and Executive Director
Center for Drug Studies
School of Pharmacy
Virginia Commonwealth University
Richmond, Virginia

Paul W. Ladenson, M.D.²
Professor of Medicine, Pathology and International Health
John Eager Howard Professor of Medicine
The Johns Hopkins University School of Medicine
Director, The Johns Hopkins Thyroid Tumor Center
The Johns Hopkins Medical Institutions
Baltimore, Maryland

E. Chester Ridgway, M.D.²
Professor of Medicine
Senior Associate Den of Academic Affairs
University of Colorado School of Medicine
Head, Division of Endocrinology, Metabolism and Diabetes
University of Colorado Health Sciences Center
Denver, Colorado

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The expert panel unanimously concluded that the current December 2000 FDA Guidance is not adequate and could result in the erroneous conclusion that two different levothyroxine sodium tablets preparations were therapeutically equivalent when in fact, they are not. The consequences of physicians and pharmacists substituting non-therapeutically equivalent products without concomitant re-titration could result in hypothyroidism or hyperthyroidism.

In order to scientifically validate this conclusion, Abbott is conducting an extensive clinical development program. Three key components of the program are summarized below.

- 1. Simulation Study to Assess Alternative Bioavailability Calculations, Study Designs and Acceptance Criteria for Determining the Bioequivalence of Levothyroxine Sodium Tablets**

Dr. Thomas M. Ludden, Ph.D. of GloboMax LLC conducted a simulation using data obtained from Abbott's single-dose bioavailability study (M01-324) and a dosage-form proportionality study (M01-323), which were conducted in support of SYNTHROID[®], NDA 21-402 (submitted as an amendment to the NDA, dated November 20, 2001). In the simulation, the investigators compared uncorrected baseline data to data that were corrected using either of two methods to estimate the contribution of the endogenous levothyroxine pool to the specified pharmacokinetic parameter.

Evaluation of the simulation model suggests that products that differ up to 35% in the extent of absorption are likely to be declared bioequivalent if the usual criterion for bioequivalence assessment (evaluation of uncorrected C_{max} and AUC_{0-48h} by 90% confidence intervals with acceptance range 80-125% of the reference) is used. However, if the endogenous pool of levothyroxine is accounted for by either baseline correction method, the predicted pass rates revert to the expected nominal range, when the true difference in extent of absorption is -20 to +25%.

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This simulation clearly highlights the potential for declaring two products bioequivalent under the current guidance when, in fact, they are not. This is a consequence of the relatively large contribution of endogenous levothyroxine to the total *in vivo* levothyroxine measured after a 600 mcg exogenous dose. The endogenous hormone pool can mask significant pharmacokinetic differences in exogenous levothyroxine products, which can result in erroneous conclusions regarding bioequivalence. Due to the complexity of the simulation, it is proposed that Dr. Ludden explain the factors he explored in designing, developing, and executing this scientific approach and provide FDA an opportunity to discuss the assumptions and interpretations of the simulation study.

2. Clinical Pharmacokinetic Study in Healthy Subjects with Correction of Endogenous Levothyroxine Levels

In addition to conducting a simulation using data from our bioavailability studies, Abbott initiated a clinical pharmacokinetic study to confirm the simulation predictions and more rigorously examine the bioequivalence criteria for levothyroxine sodium products.

Abbott submitted Clinical Study Protocol M02-417 to FDA on February 28, 2002 (IND 62,720, Serial 014). The study was designed as a three-period crossover in normal subjects. Regimen A consisted of a 600 mcg total dose, Regimen B consisted of a 450 mcg total dose and Regimen C consisted of a 400 mcg total dose. Based on the data obtained from the simulation analysis, the doses administered in the three regimens could potentially be considered bioequivalent using the current bioequivalence criteria. This clinical study was designed to clearly illustrate the consequence of not adjusting for the endogenous levothyroxine pool and to propose an adjustment method that appropriately distinguishes between products with different pharmacokinetic properties.

The study was designed as per the FDA guideline, with the addition of data collected at supplemental intervals (i.e., beyond the prescribed intervals outlined in FDA's December 2000 guidance document) for assessing *in vivo* levothyroxine levels. The protocol requires additional sample collection for a sufficient time period prior to the pharmacokinetic dose. These intervals were added to (i) more rigorously assess baseline levothyroxine values, and (ii) account for the possibility of a circadian pattern in *in vivo* levothyroxine levels.

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Study Timeline

The clinical pharmacokinetic study is nearly complete. The following table summarizes the list of significant milestones associated with Clinical Study Protocol M02-417.

Milestone	Status
Study Start Date	March 5, 2002
Period 2	April 16-22, 2002
Period 3	June 8-14, 2002
Final Report	August 15, 2002

3. Synopsis of Proposed Clinical Studies in Athyreotic Patients

The goal of the proposed clinical study in patients is to determine if replacement doses of levothyroxine sodium that differ from the steady-state euthyroid replacement dose by up to 25% are therapeutically equivalent.

The study population includes athyreotic subjects maintained on replacement doses of levothyroxine sodium to a euthyroid state (e.g. TSH levels in the low range of normal). These are subjects who have received definitive therapy (e.g. thyroidectomy and radioiodine ablation) and have had two consecutive radioiodine surveillance images revealing no uptake in the thyroid bed or ectopic sites.

Replacement doses of levothyroxine sodium that are up to 25% lower than the replacement dose that results in the euthyroid state will be administered to patients. A control group will be maintained on their euthyroid replacement dose.

Clinical end-points will include an assessment of the therapeutic response by measuring the serum TSH levels at steady-state and bioequivalence by measuring the AUC for free levothyroxine and total levothyroxine in response to the steady state dose of levothyroxine sodium.

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Purpose of the Meeting

Abbott is requesting a meeting with FDA for the following reasons:

1. To provide FDA an opportunity to discuss the tenets, assumptions and interpretation of the simulation study conducted by Dr. Ludden.
2. To discuss the status of Abbott's clinical development program to assess the bioequivalence criteria for levothyroxine sodium.

List of FDA Staff and Disciplines Requested

In addition to Dr. Orloff, Dr. Lesko and Mr. Buehler, Abbott requests that representatives from the following areas attend the proposed meeting:

- ~~1. The Office of Generic Drugs,~~
2. The Office of Clinical Pharmacology and Biopharmaceutics, and
3. Division of Metabolic and Endocrine Drug Products

List of Abbott Participants

The following list includes Abbott participants and their titles:

Doug Sporn	Division Vice President, Corporate Regulatory Affairs
Vicky Blakesley MD, PhD	Medical Director, Diabetes and Metabolism Venture
Walid Awni, PhD	Director, Department of Clinical Pharmacokinetics
Richard Granneman, PhD	Senior Director, Center for Clinical Assessments
Kathy McFarland, PhD	Division Vice President, SYNTHROID [®] Program Head
Thomas Ludden, PhD	Vice President, Pharmacometrics Research and Development, Globomax, LLC
Leonard Wartofsky, MD	Professor of Medicine, Chairman, Department of Medicine Washington Hospital Center
Ernesto Rivera, PharmD	Regulatory Affairs Project Manager
Todd E. Chermak, MS	Director, Regulatory Affairs, Chemistry, Manufacturing and Controls

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List of Proposed Meeting Dates

In view of the fact that an ANDA for one of the approved levothyroxine sodium products could be approved at any time or two approved NDAs for this drug product could be rated AB to each other, we believe a meeting to review Dr. Luden's findings as well as our ongoing research should take place as soon as possible. We propose the following dates for your consideration: June 13-14, June 17-21 and June 25-28.

Accordingly, submitted herein is the following information:

Attachment	Contents	Page Number
I	Protocol M02-417, entitled: "Evaluating the Impact of Correcting for Endogenous T4 Baseline on the Bioequivalence of Levothyroxine Sodium Formulations in Healthy Volunteers;" submitted on February 28, 2002 (Serial No. 014, IND 62,720).	002
II	S. Riley and T. M. Ludden, GloboMax LLC Report, entitled: "Simulation Study to Assess Alternative Bioavailability Calculations, Study Designs and Acceptance Criteria for Determining the Bioequivalence of Levothyroxine Sodium Tablets."	070

If you have any questions regarding this submission, please contact me at the number below. If I am not available, please contact Todd E. Chermak at (847) 938-3864.

Sincerely,
ABBOTT LABORATORIES


Douglas Sporn
Divisional Vice President
Corporate Regulatory Affairs
Abbott Laboratories
Telephone: (847) 937-7986
Fax: (847) 938-3106

Center for Drug Evaluation and Research
Food and Drug Administration
May 08, 2002
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Desk copy of this cover letter to:

Lawrence E. Roebel, Ph.D.
Divisional Vice President, Pharmaceutical Products Division
Regulatory Affairs and Research Information Center
Abbott Laboratories
Telephone: (847) 937-7495
Fax: (847) 935-2625

Mr. Stephen McCort, Project Manager
Division of Metabolic and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
ATTN: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Enid Galliers, Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
ATTN: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857



IND 62,720

Abbott Laboratories/Pharmaceutical Products Division
Attention: Doug Sporn
Divisional Vice President
Corporate Regulatory Affairs
200 Abbott Park Road
D-491, AP30-1E
Abbott Park, IL 60064-6157

Dear Mr. Sporn:

We received your May 8, 2002, correspondence (S/N-017) on May 9, 2002, requesting a meeting to discuss the suitability of the current bioequivalence requirements for levothyroxine sodium tablets. We considered your request and concluded the meeting is premature.

We would be willing to reconsider a request for a meeting to discuss this subject when the final study report for your ongoing study is available.

If you disagree with our decision, you may discuss the matter with Enid Galliers, Chief, Project Management Staff, at (301) 827-6429. If the issue cannot be resolved at the division level, you may formally request reconsideration according to our guidance for industry titled *Formal Dispute Resolution: Appeals Above the Division Level* (February 2000). The guidance can be found at <http://www.fda.gov/cder/guidance/2740fnl.htm>.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
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/

David Orloff
5/20/02 06:50:13 PM



ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
200 Abbott Park Road
D-491, AP30-1E
Abbott Park, Illinois 60064-6157
August 7, 2002

David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

Lawrence J. Lesko, Ph.D., Director
Office of Clinical Pharmacology and Biopharmaceutics, HFD-850
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont Office Complex 2
1451 Rockville Pike
Rockville, Maryland 20852

Gary J. Buehler, Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Metro Park North 2
Rockville, Maryland 20855

**Re: Synthroid®
(levothyroxine sodium tablets, USP)
IND 62,720
Serial No. 018**

**General Correspondence:
Follow-up to May 8, 2002
Request for a Meeting
to Discuss Bioequivalence
Requirements**

Dear Drs. Orloff, Lesko, and Mr. Buehler:

The sponsor, Abbott Laboratories, submits this amendment to the above Investigational New Drug Application under the provisions of Section 505(i) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 312.

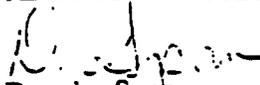
David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products
Food and Drug Administration
IND No. 62,720
August 7, 2002
Serial No. 018
Page 2

Reference is made to the May 8, 2002 submission (Serial No. 017, IND 62,720) regarding a request for a meeting to discuss the suitability of the current bioequivalence requirements for levothyroxine sodium tablets. In that submission, Abbott indicated that the final study results for M02-417 (February 28, 2002, Serial No. 014, IND 62,720), entitled: "Evaluating the Impact of Correcting for Endogenous T4 Baseline on the Bioequivalence of Levothyroxine Sodium Formulations in Healthy Volunteers," would be provided to the FDA on August 15, 2002. However, because of the complexity of the analyses and our desire to provide a more comprehensive scientific and clinical report, Abbott will need additional time to compile and complete the final clinical study report for clinical protocol M02-417.

The purpose of this submission is to inform FDA that the clinical study report will be submitted in mid-September (target date: September 12, 2002). In accordance, with the May 20, 2002, correspondence from FDA, once the results of the trial are available, they will be submitted to this IND and Abbott will again request a meeting to discuss this subject with FDA.

If there are any questions regarding this submission, please contact Ernesto J. Rivera, Pharm.D., (847-937-7847) Regulatory Affairs Project Manager.

Sincerely,
ABBOTT LABORATORIES


Douglas Sporn
Divisional Vice President
Corporate Regulatory Affairs

Copy of this cover letter to:
Enid Galliers, Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

ABBOTT LABORATORIES
Corporate Regulatory

Douglas L. Sporn
Divisional Vice President
Corporate Regulatory Affairs
D-387, AP6C-1
Telephone: (847) 937-7986

100 Abbott Park Road
Abbott Park, Illinois 60064-6091
Facsimile: (847) 938-3106
E-mail: doug.sporn@abbott.com

October 10, 2002

David Orloff, M.D., Director
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Lawrence J. Lesko, Ph.D., Director
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Rockville, Maryland 20857

Gary J. Buehler, R.Ph., Director
Office of Generic Drugs, HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Metro Park North 2, Room 150
Rockville, Maryland 20855

**Re: Synthroid®
(levothyroxine sodium tablets UPS)
IND 62,720
Serial No. 020**

**INFORMATION AMENDMENT:
Clinical Final Study Report
M02-417
Request for a Meeting**

Dear Drs. Orloff, Lesko, and Mr. Buehler:

Abbott Laboratories, submits this amendment to the above Investigational New Drug Application under the provisions of Section 505(i) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 312.31. This amendment contains the final clinical study report (R&D/02/371), for study M02-417 entitled: "Evaluating the Impact of Correcting for Endogenous T₄ Baseline on the Bioequivalence of Levothyroxine Sodium Formulations in Healthy Volunteers" (February 28, 2002, Serial No. 014, IND 62,720).

David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products
Food and Drug Administration
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The report contains the results of an in vivo bioequivalence study that demonstrates that the use of CDER's current guidance in conducting such studies (FDA February 2001, Levothyroxine Sodium Tablets - In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing) can result in the approval of ANDAs that are not therapeutically equivalent to any levothyroxine sodium tablet reference listed drug. Essentially, the study demonstrates that two doses of levothyroxine sodium that differ from the reference dose by 25% and 33%, respectively, could be determined to be bioequivalent based on the current guidance. The Office of Generic Drugs has already approved one ANDA for these reference products and will certainly review other ANDAs. Based on the findings of our study and the fact that all approved NDA levothyroxine sodium products are narrow therapeutic index drugs, we respectfully request that the Agency examine the study results as soon as possible and take appropriate actions to ensure that only truly therapeutically equivalent products are approved.

It is also important to note that any sponsor of an approved NDA levothyroxine sodium tablet product who relies on the Center's bioequivalence recommendations in assuring performance "sameness" after instituting significant formulation or manufacturing process changes may be misled (FDA November 1999 Guidance for Industry, Changes to an Approved NDA or ANDA; FDA November 1995 Guidance for Industry, Immediate Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation).

We would like to assure the Agency that this study was designed, conducted, and analyzed in a robust, scientific manner with input from both Dr. Tom Ludden, former head of the Office of Clinical Pharmacology and Biopharmaceutics, CDER and Dr. Carl Peck, former CDER Director. Abbott is aware through my own experiences in the Office of Generic Drugs that there have been many instances over the years of sponsors petitioning the Agency to change bioequivalence or other review standards in the name of public health. Generally, these petitions were not based on solid, in vivo scientific data and subsequently rejected by the Agency. For that reason and the fact that over 9 million Americans take levothyroxine sodium tablets, Abbott has invested in not only scientifically testing the Center's guidance but also investigating possible options for adjusting for endogenous T₄ so true bioequivalence may be established.

David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products
Food and Drug Administration
IND No. 62,720
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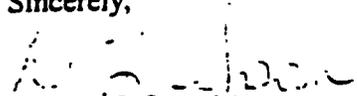
With this letter we are also requesting a meeting with FDA in accordance with our previous submission to this IND 62,720 (May 8, 2002, Serial No. 017). Reference is made to your May 20, 2002 response to our initial May 8, 2002 (Serial No. 017) submission requesting a meeting to discuss the suitability of the current bioequivalence requirements for levothyroxine sodium tablets. In that correspondence you indicated that our request was premature and that FDA would be willing to reconsider a request for a meeting to discuss this subject when the final study report was available. Therefore, we request a meeting and propose the following agenda for discussion:

- Background and rationale for the bioequivalence study submitted
- Overview of the study design
- Study results including methods examined for correcting for endogenous T4
- Future research possibilities for endogenous T4 correction

If the meeting request is granted, Abbott Laboratories will submit potential dates for the meeting, and a list of Abbott representatives. Information in support of the meeting consists of the final study report for M02-417, submitted herein, and the simulation report written by Dr. Thomas Ludden, Vice President, Pharmacometric Research and Development, at GloboMax LLC, entitled: "Simulation Study to Assess Alternative Bioavailability Calculations, Study Designs and Acceptance Criteria for Determining the Bioequivalence of Levothyroxine Sodium Tablets" which was previously submitted to the FDA on May 8, 2002 (Serial No. 017).

If there are any questions regarding this submission, please contact Ernesto J. Rivera, Pharm.D., Regulatory Affairs Project Manager, at 847-937-7847.

Sincerely,


Douglas L. Sporn, Divisional Vice President
Corporate Regulatory Affairs
Abbott Laboratories

David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products
Food and Drug Administration
IND No. 62,720
October 10, 2002
Serial No. 020
Page 4

Copy of this cover letter to:

Enid Galliers, Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Division Document Room, 14B-19
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Rockville, Maryland 20857

Dale Conner, Pharm.D., Director
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7500 Standish Place, Room 150
Metro Park North 2
Rockville, Maryland 20855

Ajaz Hussain, Ph.D., Deputy Director
Office of Pharmaceutical Science, HFD-003
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont Office Complex 2, Room 6009
1451 Rockville Pike
Rockville, Maryland 20852

1.0 Title Page

ABBOTT LABORATORIES Clinical Study Report R&D/02/371

Evaluating the Impact of Correcting for Endogenous T₄ Baseline on the Bioequivalence of Levothyroxine Sodium Formulations in Healthy Volunteers

Levothyroxine Sodium / Protocol M02-417

Development Phase: 1

Investigational Product: Levothyroxine Sodium

Study Design: This was a Phase 1, single-dose, fasting, open-label, randomized, three-period, crossover study in 36 subjects. Doses in the three periods were separated by at least 44 days.

Investigator: Laura A. Williams, MD, MPH
Abbott Clinical Pharmacology Research Unit

Screening Procedures Initiated: 14 February 2002

Date First Subject Dosed: 05 March 2002

Date Last Subject Completed Dosing: 10 June 2002

Date of Last Study Procedure: 14 June 2002

Sponsor Signatory: Vicky Blakesley, Phone: (847) 935-6320
Global Project Head Fax: (847) 937-6224
SYNTHROID®
Dept. R4DM, Bldg. AP30-3
Abbott Laboratories
200 Abbott Park Rd.
Abbott Park, IL 60064-6146

Report Date: 23 September 2002

This study was conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements including the archiving of essential documents.

2.0 Synopsis

Abbott Laboratories	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Study Drug: Levothyroxine Sodium	Volume:	
Name of Active Ingredient: Levothyroxine Sodium	Page:	
Title of Study: Evaluating the Impact of Correcting for Endogenous T ₄ Baseline on the Bioequivalence of Levothyroxine Sodium Formulations in Healthy Volunteers		
Investigator: Laura A. Williams, MD, MPH		
Study Site: Abbott Clinical Pharmacology Research Unit		
Publication (Reference): Not applicable.		
Studied Period: Screening Procedures Initiated: 14 February 2002 Date First Subject Dosed: 05 March 2002 Date Last Subject Completed Dosing: 10 June 2002 Date of Last Study Procedure: 14 June 2002		Phase of Development: 1
Objective: The objective of this study was to evaluate the impact of various methods for correcting for endogenous T ₄ baseline on the bioequivalence of levothyroxine sodium formulations in healthy volunteers.		
<p>Methodology: This Phase 1, single-dose, open-label, study was conducted according to a three-period, randomized crossover design. The total dose given was 600 µg levothyroxine sodium for Regimen A, 450 µg levothyroxine sodium for Regimen B and 400 µg levothyroxine sodium for Regimen C. Subjects were to receive one of six sequences of Regimen A (twelve 50 µg levothyroxine sodium tablets), Regimen B (nine 50 µg levothyroxine sodium tablets) or Regimen C (eight 50 µg levothyroxine sodium tablets) under fasting conditions at approximately 0800 on Study Day 1 of each period; dosing actually occurred at 0830. A washout interval of at least 44 days separated the doses of the three study periods.</p> <p>Blood samples for total levothyroxine (T₄), total triiodothyronine (T₃) and thyroid stimulating hormone (TSH) assay were collected by venipuncture into 5 mL evacuated siliconized collection tubes (red top with no separator gel) as follows:</p> <ul style="list-style-type: none"> • At approximately 0 hours and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 18 hours after the 0-hour collection on Study Day -1 in each study period. • At approximately -30 minutes, -15 minutes and at 0 hours prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, 36, 48, 72 and 96 hours after dosing on Study Day 1 in each study period. <p>Sufficient blood was collected to provide approximately 2 mL serum from each sample.</p> <p>Serum concentrations of T₄ and T₃ were determined using validated radioimmunoassay (RIA) methods at</p>		

PPD Development, Richmond, VA. The lower limit of quantitation of T₄ was 1.00 µg/dL using a 25 µL serum sample. The lower limit of quantitation of T₃ was 0.25 ng/mL using a 100 µL serum sample. Serum concentrations of TSH were determined using a validated IRMA assay at PPD Development, Richmond, VA. The lower limit of quantitation of TSH was 0.250 µIU/mL using a 200 µL sample. Samples were analyzed between the dates of 17 June 2002 and 12 July 2002.

Number of Subjects:

Planned: 36; Entered: 36; Completed: 31; Evaluated for Safety: 36; Evaluated for Pharmacokinetics: 33

For the 36 subjects (18 males and 18 females) who participated in the study, the mean age was 32.9 years (ranging from 19 to 50 years), the mean weight was 74.5 kg (ranging from 55 to 95 kg) and the mean height was 172.0 cm (ranging from 150 to 196 cm). For the 33 subjects (16 males and 17 females) included in the pharmacokinetic analyses, the mean age was 33.1 years (ranging from 19 to 50 years), the mean weight was 73.5 kg (ranging from 55 to 95 kg) and the mean height was 171.3 cm (ranging from 150 to 196 cm).

Diagnosis and Main Criteria for Inclusion: Subjects were male and female volunteers between 19 and 50 years of age, inclusive. Subjects in the study were judged to be euthyroid and in general good health based on the results of his/her medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG) and laboratory tests. Females were postmenopausal, sterile, or if of childbearing potential, were not pregnant or breast-feeding and were practicing an acceptable method of birth control.

Test Product/Reference Therapy, Dose/Strength/Concentration, Mode of Administration and Lot Numbers:

Dosage Form	Tablet
Formulation	SYNTHROID®
Strength	50 µg
NDC	0048-1040-05
Bulk Product Lot Number	335755
Potency (% of Label Claim)	103.5
Manufacturing Site	Abbott Laboratories – Jayuya, Puerto Rico
Manufacturing Date	November 2001
Batch Size	3798 bottles (1000 count bottles)
Packaging Lot Number	335878
Expiration Date	August 2003

Duration of Treatment: Three single doses of 600 µg, 450 µg or 400 µg levothyroxine sodium were administered on 05 March 2002, 18 April 2002 and 10 June 2002.

Criteria for Evaluation:

Pharmacokinetic: The pharmacokinetic parameter values of total levothyroxine (T₄) and total triiodothyronine (T₃) were estimated using noncompartmental methods. These included: the maximum serum concentration (C_{max}) and time to C_{max} (T_{max}), the area under the serum concentration-time curve (AUC) from time 0 to 48 hours (AUC₄₈), time 0 to 72 hours (AUC₇₂) and time 0 to 96 hours (AUC₉₆).

For T₄, values of these parameters (C_{max}, T_{max}, AUC₄₈, AUC₇₂ and AUC₉₆) were determined without

correction for endogenous T_4 levels and after correcting all post-dose concentrations using each of following three methods:

Correction Method 1: The predose baseline value on the day of dosing was subtracted from each post-dose concentration. The pre-dose baseline value was calculated as the average of the three concentrations at -0.5, -0.25 and 0 hours prior to dosing in each period.

Correction Method 2: For each time of post-dose sampling, the observed concentration was corrected assuming that the endogenous T_4 baseline level at 0 hours declines according to a half-life of 7 days.

Correction Method 3: The T_4 concentration for each time of post-dose sampling was corrected by the concentration observed at the same time of day during the 24 hours preceding the dose.

For all three methods of correction, the corrected 0-hour concentration was assumed to be 0.

Safety: Safety was evaluated based on assessments of adverse events, physical examinations, vital signs and laboratory tests.

Statistical Methods:

Pharmacokinetic: For uncorrected and corrected T_4 , and uncorrected T_3 , an analysis of variance (ANOVA) with fixed effects for sex, sequence, sex-by-sequence interaction, period, regimen and the interaction of sex with each of period and regimen, and with random effects for subjects nested within sex-by-sequence combination was performed for T_{max} , and the natural logarithms of C_{max} , AUC_{48} , AUC_{72} and AUC_{96} . A significance level of 0.05 was used for all tests.

The bioavailability of each of Regimen B (450 μg dose) and Regimen C (400 μg dose) relative to that of Regimen A (600 μg dose) for uncorrected T_4 , corrected T_4 and for uncorrected T_3 was assessed by the two one-sided tests procedure *via* 90% confidence intervals obtained from the analysis of the natural logarithms of AUC_{48} and C_{max} . Bioequivalence was concluded if the 90% confidence intervals from the analyses of the natural logarithms of AUC_{48} and C_{max} were within the 0.80 to 1.25 range. Likewise, the bioavailability of Regimen B relative to that of Regimen C was assessed. The same was done using each of AUC_{72} and AUC_{96} in place of AUC_{48} .

A repeated measures analysis was performed on the T_4 concentration data of Study Day -1 for each period. To investigate the possibility of carryover effects, an ANOVA was performed on the logarithms of the Study Day -1 AUC_{24} .

Safety: The number and percentage of subjects reporting adverse events were tabulated by COSTART V term and body system with a breakdown by regimen. Laboratory test values outside the reference ranges were identified.

Summary/Conclusions:

Pharmacokinetic Results:

Levothyroxine (T_4) Without Correcting for Endogenous T_4 Baseline Concentrations: Mean \pm standard deviation (SD) pharmacokinetic parameters of T_4 after administration of the three regimens without correcting for endogenous T_4 baseline concentrations are listed in the following table.

Pharmacokinetic Parameters (units)	Regimen ^f		
	A: 600 µg Dose (N = 31)	B: 450 µg Dose (N = 33)	C: 400 µg Dose (N = 33)
T _{max} (h)	3.1 ± 2.4	3.2 ± 2.1	3.5 ± 3.3
C _{max} (µg/dL)	14.3 ± 2.14	13.2 ± 2.05*	13.2 ± 2.45*
AUC ₄₈ (µg·h/dL)	518 ± 71.8	493 ± 72.7*	484 ± 73.6*
AUC ₇₂ (µg·h/dL)	741 ± 102	712 ± 108*	691 ± 102* ⁺
AUC ₉₆ (µg·h/dL)	951 ± 133	919 ± 139	892 ± 133* ⁺

f Regimen A: Twelve 50 µg levothyroxine sodium tablets administered under fasting conditions.
 Regimen B: Nine 50 µg levothyroxine sodium tablets administered under fasting conditions.
 Regimen C: Eight 50 µg levothyroxine sodium tablets administered under fasting conditions.

* Statistically significantly different from Regimen A (ANOVA, p < 0.05).
 + Statistically significantly different from Regimen B (ANOVA, p < 0.05).

The bioequivalence/bioavailability results for uncorrected T₄ are listed in the following table.

Regimens I vs. II	Pharmacokinetic Parameter	Central Value [*]		Relative Bioavailability	
		I	II	Point Estimate ⁺	90% Confidence Interval
B vs. A	C _{max}	13.0	14.0	0.928	0.890 – 0.968
	AUC ₄₈	481.7	504.8	0.954	0.927 – 0.982
	AUC ₇₂	694.9	721.9	0.963	0.936 – 0.990
	AUC ₉₆	896.2	925.6	0.968	0.941 – 0.996
C vs. A	C _{max}	12.9	14.0	0.921	0.883 – 0.960
	AUC ₄₈	469.6	504.8	0.930	0.904 – 0.958
	AUC ₇₂	670.4	721.9	0.929	0.903 – 0.955
	AUC ₉₆	865.7	925.6	0.935	0.909 – 0.962
B vs. C	C _{max}	13.0	12.9	1.007	0.967 – 1.050
	AUC ₄₈	481.7	469.6	1.026	0.997 – 1.055
	AUC ₇₂	694.9	670.4	1.037	1.009 – 1.065
	AUC ₉₆	896.2	865.7	1.035	1.007 – 1.064

* Antilogarithm of the least squares means for logarithms.
 + Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

Levothyroxine (T₄) After Correction for Endogenous T₄ Baseline Concentrations: Mean ± SD pharmacokinetic parameters of T₄ after administration of the three regimens after correcting for endogenous T₄ baseline concentrations are listed in the following table.

Pharmacokinetic Parameters (units)	Regimens ^f		
	A: 600 µg Dose (N = 31)	B: 450 µg Dose (N = 33)	C: 400 µg Dose (N = 33)
Correction Method 1			
T _{max} (h)	3.1 ± 2.4	3.2 ± 2.1	3.5 ± 3.3
C _{max} (µg/dL)	7.05 ± 1.66	5.54 ± 1.53*	5.72 ± 1.44*
AUC ₄₈ (µg·h/dL)	172 ± 40.4	126 ± 39.0*	123 ± 45.4*
AUC ₇₂ (µg·h/dL)	222 ± 56.0	161 ± 55.5*	149 ± 68.6*
AUC ₉₆ (µg·h/dL)	259 ± 72.5	184 ± 69.9*	169 ± 92.5*
Correction Method 2			
T _{max} (h)	3.3 ± 2.8	5.8 ± 9.3	3.7 ± 3.5
C _{max} (µg/dL)	7.15 ± 1.64	5.68 ± 1.50*	5.83 ± 1.45*
AUC ₄₈ (µg·h/dL)	204 ± 40.9	160 ± 40.1*	156 ± 43.4*
AUC ₇₂ (µg·h/dL)	292 ± 56.9	235 ± 58.2*	221 ± 62.7*
AUC ₉₆ (µg·h/dL)	379 ± 74.0	312 ± 74.6*	295 ± 82.2*
Correction Method 3			
T _{max} (h)	3.5 ± 3.1	3.6 ± 2.3	3.6 ± 4.0
C _{max} (µg/dL)	7.03 ± 1.64	5.85 ± 1.78*	5.56 ± 1.69*
AUC ₄₈ (µg·h/dL)	176 ± 36.9	131 ± 39.2*	120 ± 28.4*
AUC ₇₂ (µg·h/dL)	226 ± 49.4	166 ± 52.9*	146 ± 45.4* ⁺
AUC ₉₆ (µg·h/dL)	263 ± 64.8	189 ± 65.6*	167 ± 67.2*

^f Regimen A: Twelve 50 µg levothyroxine sodium tablets administered under fasting conditions.

Regimen B: Nine 50 µg levothyroxine sodium tablets administered under fasting conditions.

Regimen C: Eight 50 µg levothyroxine sodium tablets administered under fasting conditions.

* Statistically significantly different from Regimen A (ANOVA, p < 0.05).

+ Statistically significantly different from Regimen B (ANOVA, p < 0.05).

The bioequivalence/bioavailability results for T₄ using Correction Method 1 are listed in the following table.

Regimens I vs. II	Pharmacokinetic Parameter	Central Value*		Relative Bioavailability	
		I	II	Point Estimate ⁺	90% Confidence Interval
B vs. A	C _{max}	5.4	6.9	0.783	0.727 – 0.844
	AUC ₄₈	119.7	167.3	0.715	0.658 – 0.778
	AUC ₇₂	151.4	215.7	0.702	0.636 – 0.774
	AUC ₉₆	170.2	250.2	0.680	0.602 – 0.768
C vs. A	C _{max}	5.6	6.9	0.803	0.745 – 0.865
	AUC ₄₈	118.9	167.3	0.711	0.653 – 0.773
	AUC ₇₂	144.9	215.7	0.672	0.609 – 0.741
	AUC ₉₆	165.1	250.2	0.660	0.584 – 0.746
B vs. C	C _{max}	5.4	5.6	0.975	0.906 – 1.049
	AUC ₄₈	119.7	118.9	1.007	0.926 – 1.094
	AUC ₇₂	151.4	144.9	1.044	0.948 – 1.150
	AUC ₉₆	170.2	165.1	1.031	0.914 – 1.163

* Antilogarithm of the least squares means for logarithms.

+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

The bioequivalence/bioavailability results for T₄ using Correction Method 2 are listed in the following table.

Regimens I vs. II	Pharmacokinetic Parameter	Central Value*		Relative Bioavailability	
		I	II	Point Estimate ⁺	90% Confidence Interval
B vs. A	C _{max}	5.6	7.0	0.793	0.739 – 0.850
	AUC ₄₈	154.5	199.1	0.776	0.721 – 0.835
	AUC ₇₂	227.5	284.9	0.799	0.729 – 0.875
	AUC ₉₆	301.6	369.5	0.816	0.743 – 0.897
C vs. A	C _{max}	5.7	7.0	0.807	0.753 – 0.866
	AUC ₄₈	148.4	199.1	0.745	0.693 – 0.802
	AUC ₇₂	207.9	284.9	0.730	0.666 – 0.800
	AUC ₉₆	277.3	369.5	0.750	0.683 – 0.824
B vs. C	C _{max}	5.6	5.7	0.982	0.916 – 1.051
	AUC ₄₈	154.5	148.4	1.041	0.969 – 1.119
	AUC ₇₂	227.5	207.9	1.094	1.001 – 1.197
	AUC ₉₆	301.6	277.3	1.088	0.992 – 1.192

* Antilogarithm of the least squares means for logarithms.

+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

The bioequivalence/bioavailability results for T₄ using Correction Method 3 are listed in the following table.

Regimens I vs. II	Pharmacokinetic Parameter	Central Value*		Relative Bioavailability	
		I	II	Point Estimate ⁺	90% Confidence Interval
B vs. A	C _{max}	5.7	6.9	0.820	0.757 – 0.888
	AUC ₄₈	125.1	172.9	0.723	0.672 – 0.779
	AUC ₇₂	158.7	222.0	0.715	0.645 – 0.792
	AUC ₉₆	177.7	256.6	0.693	0.631 – 0.760
C vs. A	C _{max}	5.3	6.9	0.775	0.715 – 0.839
	AUC ₄₈	115.4	172.9	0.667	0.620 – 0.718
	AUC ₇₂	135.9	222.0	0.612	0.553 – 0.678
	AUC ₉₆	164.0	256.6	0.639	0.582 – 0.702
B vs. C	C _{max}	5.7	5.3	1.058	0.979 – 1.145
	AUC ₄₈	125.1	115.4	1.084	1.008 – 1.165
	AUC ₇₂	158.9	135.9	1.168	1.057 – 1.291
	AUC ₉₆	177.7	164.0	1.084	0.989 – 1.188

* Antilogarithm of the least squares means for logarithms.

+ Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

Baseline Levothyroxine (T₄) Prior to Dosing (Study Day -1): Analysis of the T₄ concentration data obtained during the 24 hours of Study Day -1 of each period confirmed that T₄ has a diurnal cycle with statistically significant differences across time. Analysis of the 24-hour AUC for Study Day -1 revealed that the regimens (dose levels) had statistically significantly different carryover effects from one period to the next (first-order carryover) and from Period 1 to Period 3 (second-order carryover).

Safety Results: Thirteen (13/36) subjects reported at least one treatment-emergent adverse event (event with onset after the first dose of study drug) during the study. The most commonly reported treatment-emergent adverse events were abdominal pain (three subjects, 8.3%), back pain (three subjects, 8.3%), accidental injury (two subjects, 5.6%) and nausea (two subjects, 5.6%). All remaining treatment-emergent adverse events were reported by at most 2.8% of subjects (one subject).

The majority of the treatment-emergent adverse events were assessed by the investigator as probably not or not related to study drug and mild in severity. Results of other safety analyses including individual subject changes, changes over time and individual clinically significant values for vital signs, ECGs and physical examinations were unremarkable for each treatment group.

No deaths were reported during the study. Subjects 204 and 217 were discontinued from the study due to positive serum pregnancy tests prior to dosing in Periods 2 and 3, respectively. Subject 204 experienced a serious adverse event (elective abortion) during the washout between Periods 1 and 2 that was judged not related to study drug by the investigator. Subject 217 experienced a post-study serious adverse event (elective abortion) 71 days after her last study drug administration in Period 2.

Conclusions: The results of this study raise multiple important questions concerning the conduct and analysis of bioequivalence studies for levothyroxine sodium products. First, the results indicate that the use of baseline uncorrected T₄ C_{max}, AUC₄₈, AUC₇₂ and AUC₉₆ values would result in declaring two

products bioequivalent when they actually differ by as much as 25% to 33% (450 µg and 400 µg versus 600 µg). Regimens B (450 µg dose) and C (400 µg dose) would both be declared bioequivalent to Regimen A (600 µg dose) because the 90% confidence intervals for evaluating bioequivalence without correction for endogenous T₄ baseline were contained within the 0.80 to 1.25 range. Considering the margin by which the conditions for declaring bioequivalence were passed in this study, products that differ by even more than 33% would also have a high likelihood of being declared bioequivalent.

Second, the results from this study indicate that the use of baseline corrected C_{max}, AUC₄₈, AUC₇₂ and AUC₉₆ values would reduce the likelihood that two products would be declared bioequivalent when they actually differ by 25% to 33%. After correcting for endogenous T₄ levels using each of the three correction methods employed in this study, neither Regimen B (450 µg dose) nor C (400 µg dose) would be declared bioequivalent to Regimen A (600 µg dose) because the 90% confidence intervals for evaluating bioequivalence were not contained within the 0.80 to 1.25 range for C_{max}, AUC₄₈, AUC₇₂ and AUC₉₆.

Third, Regimen B (450 µg dose) would continue to be declared bioequivalent to Regimen C (400 µg dose) utilizing the C_{max}, AUC₄₈, AUC₇₂ and AUC₉₆ values for the uncorrected T₄ data or the baseline corrected T₄ data by any of the three methods of correction except for the AUC₇₂ calculated utilizing Correction Method 3. A 12.5% difference (400 µg versus 450 µg) in levothyroxine sodium products may have a clinically relevant adverse impact on patients. This raises questions concerning the appropriate acceptance range for declaring levothyroxine sodium products to be bioequivalent even after baseline correction. It may well be necessary to use a range that is narrower than the standard, 0.80 to 1.25.

Finally, it is apparent that simple methods of correction for endogenous T₄ concentrations may be inadequate since these concentrations not only fluctuate on a diurnal cycle but may also be differentially affected by products with different rates and extents of absorption. Additionally, there is evidence of significant carryover from one dosing period to subsequent periods even with washout periods up to 53 days. This study illustrates some important flaws in the design and analysis of single-dose crossover studies in healthy volunteers to assess bioequivalence of levothyroxine sodium products, stemming from the significant and complex contribution of endogenous T₄. Better characterization of endogenous T₄ is required to allow proper interpretation of results in healthy volunteer studies. Alternatively, it may be necessary to perform these studies in athyrotic patients.

The regimens tested were generally well tolerated by the subjects. No clinically significant physical examination results, or vital signs or laboratory measurements were observed during the course of the study. No differences were seen among the regimens with respect to adverse event profiles. There were no apparent differences among the regimens with regard to safety.

Date of Report: 23 September 2002

FEB. 20. 2003

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CQA-RA HFD 020

NO. 3657 P. 3 P. 02



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 62,720

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 acknowledge receipt on February 13, 2003, of your February 12, 2003, request for formal dispute resolution concerning the investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Synthroid® (levothyroxine sodium tablets, USP). This request concerns scientific issues related to bioequivalence testing of levothyroxine sodium products, and the recommended method for baseline correction. You are requesting review of this matter by the Center Director, and a full, joint meeting of the Advisory Committee for Pharmaceutical Science and the Endocrinologic and Metabolic Drugs Advisory Committee.

Pursuant to the CDER/CBER Guidance to Industry "Formal Dispute Resolution: Appeals Above the Division Level," we have thirty (30) calendar days from the receipt date of the formal request to respond to the appeal. Therefore, our response to this request is due on or before March 14, 2003.

The decision which you are appealing was communicated to you in correspondence (dated January 14, 2003) signed by Dr. David Orloff, Director, Division of Metabolic and Endocrine Drug Products. Pursuant to the aforementioned guidance document, this matter should be formally reviewed by the next supervisory level, Dr. Robert Meyer, Director, Office of Drug Evaluation II, and therefore, has been forwarded to him. We will contact you should we have any questions or require additional information.

If you have any questions, please contact me at (301) 594-5479.

Sincerely,

(See appended electronic signature page)

Kim M. Colangelo
Formal Dispute Resolution Project Manager
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/

Kim Colangelo
2/20/03 09:07:04 AM

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

IND 62,720

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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

IND 62,720
Page 3

involved in the ascertainment of exogenous exposure, given that such exposure is not readily distinguishable from endogenous LT4. Based on the current circumstances - including Abbott'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
3/7/03 10:01:10 AM

Guidance for Industry

Levothyroxine Sodium Tablets — In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2001
Clinical Medical

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GDL 2

Guidance for Industry

Levothyroxine Sodium Tablets — In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing

*Additional copies are available from:
the Drug Information Branch (HFD-210),
Center for Drug Evaluation and Research (CDER),
5600 Fishers Lane, Rockville, MD 20857 (Tel) 301-827-4573*

Internet at <http://www.fda.gov/cder/guidance/index.htm>

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**February 2001
Clinical Medical**

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GUIDANCE FOR INDUSTRY¹

Levothyroxine Sodium Tablets — In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance is intended to assist sponsors of new drug applications (NDAs) for levothyroxine sodium tablets who wish to conduct in vivo pharmacokinetic and bioavailability studies and in vitro dissolution testing for their products. Information from these studies would generally be submitted in section 6 of an NDA. Sponsors who wish to use approaches other than those recommended in this guidance should discuss their plans with the FDA prior to preparing an NDA.

II. BACKGROUND

Levothyroxine sodium is the sodium salt of the levo isomer of the thyroid hormone thyroxine. Thyroid hormones affect protein, lipid, and carbohydrate metabolism, growth, and development. They stimulate the oxygen consumption of most cells of the body, resulting in increased energy expenditure and heat production, and possess a cardiostimulatory effect that may be the result of a direct action on the heart.

The production of levothyroxine hormone is regulated by the hypothalamus-pituitary axis through a negative feedback system. When hormone levels are inadequate, the hypothalamus secretes thyroid stimulating hormone-releasing hormone (TSH-RH), which stimulates the anterior pituitary to produce thyroid stimulating-hormone (TSH). TSH then stimulates the thyroid gland to produce levothyroxine

¹ This guidance has been prepared by the Division of Pharmaceutical Evaluation II, Office of Clinical Pharmacology and Biopharmaceutics, which operates under the direction of the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA). The guidance has also been reviewed by the Guidances Technical Committee of the Biopharmaceutics Coordinating Committee, as well as the Division of Metabolic and Endocrine Drug Products in CDER.

(T₄) and triiodothyronine (T₃). T₄ is subsequently converted to the highly active T₃ in the peripheral tissues. High levels of T₄ inhibit the production of TSH and (to a lesser degree) TSH-RH. This effect in turn decreases the further production of T₄ (Farwell 1996).

Orally administered levothyroxine sodium is used as replacement therapy in conditions characterized by diminished or absent thyroid function such as cretinism, myxedema, nontoxic goiter, or hypothyroidism. The diminished or absent thyroid function may result from functional deficiency, primary atrophy, partial or complete absence of the thyroid gland, or the effects of surgery, radiation, or antithyroid agents. Levothyroxine sodium may also be used for replacement or supplemental therapy in patients with secondary (pituitary) or tertiary (hypothalamic) hypothyroidism.

Levothyroxine sodium is a compound with a narrow therapeutic range. If a drug product of lesser potency or bioavailability is substituted in the regimen of a patient who has been controlled on another product, a suboptimal response and hypothyroidism could result. Conversely, substitution of a drug product of greater potency or bioavailability could result in toxic manifestation of hyperthyroidism such as cardiac pain, palpitation, or cardiac arrhythmia. In patients with coronary heart disease, even a small increase in the dose of levothyroxine sodium may be hazardous. Hyperthyroidism is a known risk factor for osteoporosis (Paul et al. 1988). To minimize the risk of osteoporosis, it is advisable that levothyroxine sodium be titrated to the lowest effective dose. Because of the risks associated with over- or under-treatment with levothyroxine sodium, it is critical that patients have available to them products that are consistent in potency and bioavailability.

It is a challenge to determine the bioavailability of levothyroxine sodium products because levothyroxine is naturally present in minute quantities in the blood, with the total levels reaching 5.0-12.0 µg/dl and free (or unbound) levels reaching 0.8-2.7 ng/dl in a healthy adult. To assess the bioavailability of levothyroxine sodium after a single dose, several times the normal dose should be given to raise the levels of the drug significantly above baseline to allow measurement. Furthermore, levothyroxine has a long half-life of 6 to 9 days, and therefore, a long washout period is necessary between treatments.

III. PHARMACOKINETIC AND BIOAVAILABILITY STUDIES IN VIVO

Information on the pharmacokinetics (absorption, distribution, metabolism, and excretion) of levothyroxine sodium can be obtained from the literature and/or from original studies. If the studies cited have used levothyroxine sodium formulations other than the formulation intended for marketing, the submission should contain information identifying how those formulations differ from the to-be-marketed formulation.

For sponsors who have a product on the market, we recommend that in vivo bioavailability studies be conducted using the formulation(s) already on the market, assuming that the sponsor intends to keep marketing the formulation(s). The tablets used in the study should be made from a full-scale production batch and should meet all compendial requirements. The formulations used should demonstrate sufficient stability for the length of the study. Stability evaluations should be made for the bio-batch prior

to and after the study. All dissolution, potency, and content uniformity data should be submitted to the NDA for review.

For sponsors who do not have a levothyroxine sodium formulation on the market, the usual approaches to developing pilot-scale batches for bioavailability studies apply.²

A. Inclusion Criteria

For each pharmacokinetic and bioavailability study outlined below, at least 24 volunteers should complete the trial. The subjects should be healthy volunteers, 18 to 50 years of age and within 15 percent of ideal body weight for their height and build. Sponsors should attempt to enroll an equal number of men and women, if possible. Volunteers recruited for the study should have an acceptable medical history, physical examination, and clinical laboratory tests. All thyroid function tests should be within normal limits. Volunteers with any current or past medical condition that might significantly affect their pharmacokinetic or pharmacodynamic response to levothyroxine sodium should be excluded. Female volunteers should be given a pregnancy test prior to beginning the study. Pregnant women should be excluded from the study. Written informed consent should be obtained from all volunteers before they are accepted into the study.

B. Single-Dose Bioavailability Study

Objective: To determine the bioavailability of the to-be-marketed formulation of levothyroxine relative to a reference (oral solution) under fasting conditions.

Design: The study is a single-dose, two-treatment, two-sequence crossover design. An equal number of volunteers should be randomly assigned to each sequence. The washout period between treatments should be at least 35 days.

Tablet Strength and Dose: A multiple of the highest tablet strength to achieve a total dose of 600 µg should be given to detect T₄ above baseline levels.

Procedure: Following a 10-hour overnight fast, volunteers should be administered a single dose of levothyroxine sodium orally with 240-mL water. The treatments should be as follows:

Treatment 1: Multiples of the highest strength of levothyroxine sodium tablets to be marketed.

Treatment 2: Levothyroxine sodium as an oral solution at an equivalent dose with treatment 1. The intravenous formulation can be used as a convenient source of an oral levothyroxine solution.

² See *QIA Stability Testing of New Drug Substances and Products* (59 FR 48754, September 1994).

Volunteers should remain fasted for 4 hours after dosing, with water only allowed after the first hour. Volunteers should be served standardized meals according to the schedule throughout the study.

Blood Sampling: Blood samples should be drawn at -0.5, -0.25, 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, and 48 hours post dose.

Data Analysis: Individual and mean plasma/serum concentration-time profiles of total (bound + free) T_4 and T_3 should be included in the report. The plasma/serum profiles and pharmacokinetic measures should be presented without the adjustment of baseline levels since endogenous levothyroxine concentrations are unpredictable during the course of the study. The following pharmacokinetic measures should be computed:

- Area under the plasma/serum concentration-time curve from time 0 to the last measurable time point (AUC_{0-t})
- Peak concentration (C_{max})
- Time to peak concentration (T_{max})

Analysis of variance (ANOVA) should be performed for both log-transformed AUC_{0-t} and C_{max} using the SAS General Linear Models (GLM) procedure. The oral solution should be used as the reference formulation. The geometric means and 90 percent confidence intervals of the geometric mean ratio (test/reference) in AUC_{0-t} and C_{max} should be presented as evidence of bioavailability.

C. Dosage-Form Proportionality Study

Objective: To determine the dosage-form proportionality among the to-be-marketed tablet strengths of levothyroxine sodium.³

Design: The recommended study is a single-dose, three-treatment, six-sequence crossover design. An equal number of volunteers should be randomly assigned to each sequence. The washout period between treatments should be at least 35 days.

Tablet Strengths and Dose: Three strengths of tablets should be studied that represent the low, middle, and high strength of the formulations to be marketed. Generally, the middle strength studied is the 100- μ g tablet. A multiple of each tablet strength should be given to detect T_4 above baseline levels. The total dose given for each treatment in the study will usually be 600 μ g and should be the same dose for each treatment.

³ Available strengths of levothyroxine sodium tablets from many manufacturers include 25, 50, 75, 88, 100, 112, 125, 137, 150, 200 and 300 μ g.

Procedure: Following a 10-hour overnight fast, volunteers should be given a single dose of levothyroxine sodium orally with 240-mL water. The treatments consisting of equal doses of levothyroxine should be as follows:

Treatment 1: Multiples of the representative low strength tablets (usually 50 µg).

Treatment 2: Multiples of the representative mid-strength tablets. This is normally the 100-µg tablet, and should be considered as the reference for this study.

Treatment 3: Multiples of the representative high strength tablets (usually 300 µg).

Volunteers should fast for an additional 4 hours after dosing, with only water allowed after the first hour. Volunteers should be served standardized meals throughout the study according to the schedule.

Blood Sampling: The blood sampling schedule for this study should be identical to that recommended for the bioavailability study.

Data Analysis: Individual and mean plasma/serum concentration-time profiles of total (bound + free) T₄ and T₃ should be included in the report. The plasma/serum profiles and pharmacokinetic measures should be presented without adjustment of baseline levels since endogenous levothyroxine concentrations are unpredictable during the course of the study.

The pharmacokinetic measures, including AUC_{0-t}, C_{max} and T_{max}, should be computed for both total T₄ and T₃. For the assessment of proportionality between strengths, both log-transformed AUC_{0-t} and C_{max} should be analyzed with ANOVA using the SAS GLM procedure. The geometric means and 90 percent confidence intervals of the geometric mean ratio of AUC_{0-t} and C_{max} should be presented for each pairwise comparison. Dosage-form proportionality is demonstrated if the 90 percent confidence intervals fall within the 80-125 percent range.

For both single-dose bioavailability and dosage-form proportionality studies, the assessment of bioavailability should be based on the measurement of total (bound + free) T₄ and total T₃ levels. The determination of free T₄ and T₃ is not necessary. However, if sufficiently precise and accurate assays are available for free T₄ and T₃, these moieties can be measured as well. Statistical analyses of free T₄ and T₃ should then be performed, with the results used as supportive data. If free T₄ and T₃ are measured, the assays used should be based on the immuno-extraction (two-step) method, rather than the labeled analog (one-step) method. Levels of TSH should be measured as part of the volunteer-screening process as well as post-study examination. These TSH data should be reported in the NDA.