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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."

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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	C _{max}	13.0	14.0	0.928	0.890 – 0.968
vs.	AUC ₄₈	481.7	504.8	0.954	0.927 – 0.982
600 mcg	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	C _{max}	12.9	14.0	0.921	0.883 – 0.960
vs.	AUC ₄₈	469.6	504.8	0.930	0.904 – 0.958
600 mcg	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	C _{max}	13.0	12.9	1.007	0.967 – 1.050
vs.	AUC ₄₈	481.7	469.6	1.026	0.997 – 1.055
400 mcg	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 bioequivalent 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	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
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		Central Value*		Relative Bioavailability	
Test vs.	Pharmacokinetic	Central Value*		Point	90% Confidence
Reference	Parameter	Test	Reference	Estimate ⁺	Interval
450 mcg	C _{max}	5.6	7.0	0.793	0.739 – 0.850
vs.	AUC ₄₈	154.5	199.1	0.776	0.721 – 0.835
600 mcg	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	C _{max}	5.7	7.0	0.807	0.753 – 0.866
vs.	AUC ₄₈	148.4	199.1	0.745	0.693 – 0.802
600 mcg	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	C _{max}	5.6	5.7	0.982	0.916 – 1.051
vs.	AUC ₄₈	154.5	148.4	1.041	0.969 – 1.119
400 mcg	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		Relative Bioavailability			
Test vs.	Pharmacokinetic	Central Value*		Point	90% Confidence
Reference	Parameter	Test	Reference	Estimate ⁺	Interval
450 mcg	C _{max}	5.7	6.9	0.820	0.757 – 0.888
vs.	AUC ₄₈	125.1	172.9	0.723	0.672 – 0.779
600 mcg	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	C _{max}	5.3	6.9	0.775	0.715 – 0.839
vs.	AUC ₄₈	115.4	172.9	0.667	0.620 – 0.718
600 mcg	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	C _{max}	5.7	5.3	1.058	0.979 – 1.145
vs.	AUC ₄₈	125.1	115.4	1.084	1.008 – 1.165
400 mcg	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
Page 18

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,

A handwritten signature in cursive script that reads "Douglas L. Sporn" followed by a date "1/03".

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
Food and Drug Administration
Parklawn Building
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

Janet Woodcock, M.D.
February 12, 2003
Page 19

Lawrence J. Lesko, Ph.D.
Director, Office of Pharmacology and Biopharmaceutics, HFD-850
Center for Drug Evaluation and Research
Food and Drug Administration
Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20857

David Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
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Rockville, Maryland 20857

Helen Winkle
Acting Director, Office of Pharmaceutical Science, HFD-003
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont Complex II
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



ABBOTT

Pharmaceutical Products Division

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

February 28, 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

Re: Synthroid®
(levothyroxine sodium tablets, USP)
IND 62,720
Serial No. 014

Amendment:
New Protocol (M02-417)

Dear Dr. Orloff:

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 312.30(a).

Reference is made to the FDA December 2000 Guidance for Industry entitled: "Levothyroxine Sodium Tablets -In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing." The guidance recommends that two bioavailability studies be conducted. The first recommended study is a single-dose bioavailability study. The second recommended study is a dosage form proportionality study. Both of the studies were conducted by Abbott Laboratories in accordance with the above cited guidance, and were submitted to the Division of Metabolic and Endocrine Drug Products on November 20, 2001, to NDA 21-402 for Synthroid® (levothyroxine sodium tablets, USP).

The sponsor, Abbott Laboratories, is pursuing an additional bioavailability study in order to evaluate the overall impact of various methods for correcting for endogenous T₄ baseline on the bioequivalence of levothyroxine sodium formulations in healthy volunteers. The purpose of this submission is to provide the requisite documents to initiate study M02-417, entitled: "Evaluating the Impact of Correcting for Endogenous T₄ Baseline on the Bioequivalence of Levothyroxine Sodium Formulations in Healthy Volunteers." Clinical Study M02-417 is a Phase I, single-dose, open-label, randomized study that will be conducted in 36 adult male and female subjects according to a three



David Orloff, M.D., Director
Food and Drug Administration
IND No. 62,720
February 28, 2002
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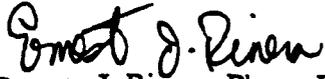
period crossover design. The total dose given will be 600 micrograms of levothyroxine for Regimen A, 450 micrograms levothyroxine sodium for Regimen B, and 400 micrograms levothyroxine sodium tablets for regimen C. A washout interval of at least 42 days will separate the doses of the three study groups.

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
Fax: (847) 937-8002

Desk copy of this submission to:
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



ABBOTT

FA LRF

Pharmaceutical Products Division

Abbott Laboratories
200 Abbott Park Road
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May 08, 2002

David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products, HFD-510
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Lawrence J. Lesko, Ph.D., Director
Office of Clinical Pharmacology and Biopharmaceutics, HFD-850
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Food and Drug Administration
Woodmont Office Complex 2
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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 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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Page 2

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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Page 4

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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Food and Drug Administration
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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.

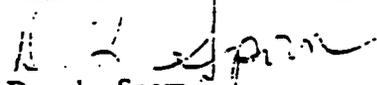
Accordingly, submitted herein is the following information:

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
IND No. 62,720
Serial No. 017
Page 10

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.

2

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
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October 10, 2002

David Orloff, M.D., Director
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Food and Drug Administration
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Lawrence J. Lesko, Ph.D., Director
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Center for Drug Evaluation and Research
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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).

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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 T_4 so true bioequivalence may be established.

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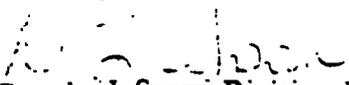
With this letter we are also requesting a meeting with FDA in accordance with our previous submission to this IND 62,720 (May 8, 2002, Serial No. 017). Reference is made to your May 20, 2002 response to our initial May 8, 2002 (Serial No. 017) submission requesting a meeting to discuss the suitability 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
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Copy of this cover letter to:
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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 [‡]		
	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* ⁺

‡ 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 [£]		
	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*

£ 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 athyreotic 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.

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