



ABBOTT

FR LRF

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May 08, 2002

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Gary J. Buehler, Director
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Center for Drug Evaluation and Research
Food and Drug Administration
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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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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

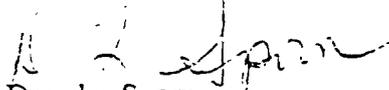
In view of the fact that an ANDA for one of the approved levothyroxine sodium products could be approved at any time or two approved NDAs for this drug product could be rated AB to each other, we believe a meeting to review Dr. Luden's findings as well as our ongoing research should take place as soon 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


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Desk copy of this cover letter to:

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