

MEMORANDUM OF MEETING MINUTES

MEETING DATE: January 23, 2004
TIME: 8:30 am to 10:00 am
LOCATION: Rockwall Room 1033, 5515 Security Lane, Rockville, MD
APPLICATION: NDA 21-210/S-003; Unithroid® (levothyroxine sodium tablets, USP)
TYPE OF MEETING: Formal Dispute Resolution (Refuse-to-File Appeal)
MEETING CHAIR: John K. Jenkins, M.D.
MEETING RECORDER: James T. Cross, M.S.

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division Name & HFD#</u>
John Jenkins, M.D.	Director	FDA/OND (HFD-020)
Warren Rumble	Ombudsman	FDA/OEP (HFD-006)
Robert Temple, M.D.	Associate Director	FDA/OMP (HFD-040)
Jane Axelrad, J.D.	Associate Director	FDA/ORP (HFD-005)
Gary Buehler	Director	FDA/OGD (HFD-600)
Robert Meyer, M.D.	Director	FDA/OND/ODE-II (HFD-102)
David Orloff, M.D.	Director	FDA/OND/DMEDP (HFD-510)
Dale Conner, Ph.D.	Team Leader	FDA/OGD (HFD-650)
Keven Fain, J.D.	Regulatory Counsel	FDA/OC/OCC (GCF-1)
Laurie Lenkel, J.D.	Regulatory Counsel	FDA/OC (HF-7)
James Cross, M.D.	Regulatory Project Manager	FDA/OND (HFD-020)

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
Jerome Steinlauf	President	Jerome Stevens Pharmaceuticals
Ronald Steinlauf	Vice President	Jerome Stevens Pharmaceuticals
Jake Thiessen, Ph.D.	Professor & Associate Dean	Faculty of Pharmacy, University of Toronto
Betty Cory	Vice President	PDi Regulatory Services
Marc J. Scheineson, Esq.	Partner	Reed Smith, LLP
Areta Kupchyk, Esq.	Counsel	Reed Smith, LLP
William Schultz, Esq.	Partner	Zuckerman, Spader

BACKGROUND:

NDA 21-210/S-003, submitted March 26, 2003, for Unithroid (levothyroxine sodium tablets, USP) proposed to establish that Unithroid is comparable (i.e., therapeutically equivalent) to Synthroid (levothyroxine sodium, USP) manufactured by Abbott Laboratories. This supplemental NDA requested an "AB" rating in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (referred to as the "Orange Book").

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In a letter dated May 13, 2003, the Division of Metabolic and Endocrine Drug Products refused to file (RTF) the supplemental application under 21 CFR 320.25(e)(3), because the Synthroid reference material (Lot # 0000339726) was not the subject of an approved new drug application. JSP's response, dated May 23, 2003, requested a meeting and appealed the RTF decision to the Office of Drug Evaluation II (ODE II). Submissions to FDA's Office of Chief Counsel dated June 30, July 23 and 25, 2003, were also received and considered in the ODE II's October 3, 2003, correspondence, which upheld the Division's RTF decision.

On November 20, 2003, JSP requested reconsideration by the OND Immediate Office of the Division's RTF decision and the subsequent affirmation by ODE-II. In response, the OND immediate office (OND-IO) granted today's meeting with JSP in a letter December 19, 2003. A background package was submitted January 20, 2004, received January 21, 2004, for today's meeting.

MEETING OBJECTIVES:

1. For JSP to present their evidence and rationale as to why the Agency's refuse-to-file (RTF) action was incorrect.
2. For FDA to better understand the sponsor's views regarding the issues in dispute prior to making a decision on the Formal Dispute Resolution.

DISCUSSION POINTS:

After introductions, the Office of New Drugs (OND) explained that the Office of Medical Policy, to which JSP had directed the November 20, 2003, meeting request, was not the deciding office for appeals of a refuse-to-file (RTF) action. OND is the deciding office. OND also noted that no decisions would be made on the Formal Dispute Resolution Request (FDRR) at the meeting. OND stated that, following the meeting, it will consult internally on the scientific, regulatory, and legal issues prior to reaching a decision on the FDRR. That decision will then be communicated to the sponsor in a letter.

Two presentations, one scientific and one regulatory, were given by Jerome Stevens Pharmaceuticals, Inc. to explain why the company believes that the Agency's decision to RTF the application was incorrect. Following the presentations, a discussion of the issues related to the RTF decision and the request for dispute resolution was held between JSP and FDA staff. A brief summary of some of those issues is captured below.

A. Scientific Presentation on Unithroid

JSP affirmed that tablets from a marketed pre-approval batch of Synthroid were used as the reference material for their bioequivalence study. Dr. Thiessen's presentation addressed three scientific issues regarding the RTF decision related to the use of pre-approval Synthroid: (1) differences between pre- and post- approval Synthroid, (2) levothyroxine overage, and (3) degradants. Slides of this presentation are appended for reference.

B. Regulatory/Legal Presentation on Unithroid

The purpose of this presentation, according to JSP, was two-fold: (1) to provide an understanding of the basis for the RTF decision and (2) explain why the reference material used by JSP in their

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bioequivalence trial should be considered acceptable. Slides of this presentation are appended for reference.

C. Sponsor/Agency Discussion

1. AB Rating: Following the two presentations, the Agency stated that pharmaceutical equivalence and bioequivalence of two drug products must be established in order to obtain an AB rating between those two drug products. Pharmaceutical equivalence requires, among other things, a demonstration that the test and reference products contain the same amount of drug substance and that the two products are the same dosage form. The Agency noted that the pre-approval batches of Synthroid were released with a stability overage and that this overage draws into question whether the two products are pharmaceutical equivalents. On behalf of the sponsor, Dr. Thiessen responded that bioequivalence is a test of dosage form performance and that potency correction can account for overage provided that the two products are within the same range of potency. He also noted that at the time of use in the bioequivalence study that the tablets of pre-approval Synthroid were assayed and contained an amount of drug substance very close to the labeled dose. He concluded that the results of the bioequivalence test were therefore informative for how Unithroid would perform in comparison to tablets from a post approval batch of Synthroid, which do not contain a stability overage.

2. Degradation/Overage: The Agency noted that the sponsor was using the fact that levothyroxine degrades over time as a substitute for using pharmaceutically equivalent products in the bioequivalence assay. The Agency noted that stability overages are not allowed for any of the approved levothyroxine products. The Agency reiterated that formulations of new drugs are defined not simply by the list of ingredients, but also by the amount of the drug substance in the product. The Agency has concluded that because of the presence of a stability overage pre-approval and post-approval Synthroid tablets are not pharmaceutically equivalent. JSP countered that FDA did not require a bridging study between pre-approval and post-approval Synthroid and that the Agency did not require re-titration of patients who had previously been treated with pre-approval Synthroid once Synthroid was approved. JSP also noted that the agency had granted an AB rating to Mylan Pharmaceuticals' ANDA levothyroxine product based on a comparison to pre-approval Unithroid. JSP argued that this suggested that a pre-approval product could be used to support an AB rating.

3. Trial Design: The Agency asked the sponsor to specify what issues JSP had sought input on from FDA when designing their bioequivalence trial. JSP stated that they had received general guidance regarding study design but that they had not submitted a detailed protocol to the Agency for review. The Agency specifically asked if JSP had ever contacted the Agency about what constituted an appropriate reference material, i.e., whether pre-approval product would be considered an appropriate reference material. In response, JSP stated that it never sought FDA input on what would be an appropriate reference product. JSP stated that their decision to use tablets from a pre-approval batch of Synthroid for the bioequivalence study was based on the fact that they were unable to purchase Synthroid tablets from a post-approval batch. JSP felt that they could not continue to wait until Synthroid tablets from a post-approval batch were commercially available. JSP also stated that they assumed that tablets from a pre-approval batch would be acceptable since the Agency did not make any public statements that led the firm to believe that their selection of pre-approval product would be unacceptable as a reference.

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4. Regulatory Requirements for Establishing Bioequivalence:

- The Agency and the sponsor discussed the specific citations from the Code of Federal Regulations that had been cited by the Agency as justification for its RTF decision as well as other applicable regulations and Agency guidance documents as they relate to the issue of the selection of an appropriate reference material. JSP argued that, as written, the regulations allowed for Agency flexibility in determining an appropriate reference material and argued that they had provided adequate scientific data to support their view that the pre-approval Synthroid was an appropriate reference material.

The Agency concluded the meeting with a reminder to the sponsor that they should not have introduced new data during the meeting. The Agency noted that, as described in the guidance for industry entitled, *Formal Meetings With Sponsors and Applicants for PDUFA Products*, no new information should be submitted as part of the reconsideration request or appeal. Lastly, the Agency stated that a response to the request for formal dispute resolution would likely take more than 30 days from the meeting date since the Office of Chief Counsel was being solicited for input.

The Agency stated that, according to our procedures, a response to the request for formal dispute resolution would be completed within 30 days from the meeting date unless consultation with the Office of Chief Counsel was necessary, in which case additional time may be required. The Agency noted that given the issues raised by the sponsor in the FDRR it was likely that OCC consultation would be required prior to a final decision.

DECISIONS (AGREEMENTS) REACHED:

The Agency stated that it will respond to the request for formal dispute resolution dated November 20, 2003, after the Office of New Drugs has conferred with the Office of Chief Counsel.

ACTION ITEMS:

<u>Item</u>	<u>Responsible Person</u>	<u>Due Date</u>
Issue response to request for formal dispute resolution	John Jenkins, M.D.	30 days from date of dispute resolution meeting (more than 30 days may be needed when consulting FDA's Office of Chief Counsel)

Minutes Preparer: James Cross
Regulatory Project Manager

Chair Concurrence: *see appended electronic signature page*
John K. Jenkins, M.D.
Director, Office of New Drugs
Center for Drug Evaluation and Research

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ATTACHMENTS/HANDOUTS:

1. Dr. Thiessen's presentation entitled, *A Scientific Perspective on the Bioequivalence of Unithroid and Synthroid*.
2. Areta Kupchyk's presentation entitled, *Unithroid-Synthroid Bioequivalency Legal/Regulatory Overview*.

cc: Original

HFD-510/Div. Files
HFD-510/Meeting Minutes files
HFD-020/RPM, ADRA, and Director
HFD-510/RPM and Attendees
HFD-102/Attendees
HFD-600/Reviewers & Attendees
HFD-005/Attendees
HF-007/Attendees
GCF-001/Attendees

Drafted by: J.Cross/1-26-04

Revised by: G.Buehler/1-27-04; L.Lenkel/1-30-04, 2/17/04; J.Axelrad/2-19-04; J.Cross/2-9-04, 2-20-04; R.Temple 2/18/04; J.Jenkins/2-19-04; K.Colangelo/2-20-04

Initialed by: D.Orloff/2-3-04

Final: J.Jenkins/2-20-04

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