021210_5003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

21-210/S-003

Trade Name: Unithroid Tablets

Generic Name(s): (levothyroxine sodium, USP)

Sponsor: Jerome Stevens Pharmaceuticals, Inc.

Agent:

Approval Date: December 13, 2004

Indication: Provides for demonstrating bioequivalence between Unithroid and Synthroid in order to obtain an AB rating

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-210/S-003

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-210/S-003

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-210/S-003

Jerome Stevens Pharmaceuticals, Inc.
Attention: Ronald Steinlauf
Vice President
60 DaVinci Drive
Bohemia, N.Y. 11716

Dear Mr. Steinlauf:

Please refer to your supplemental new drug application dated March 26, 2003, received March 27, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Unithroid (levothyroxine sodium tablets, USP).

We acknowledge receipt of your submissions dated August 11 and October 8, 2004.

Your October 8, 2004, submission constituted a complete response to our June 23, 2004, action letter.

This supplemental new drug application proposes to demonstrate bioequivalence between Unithroid and Synthroid in order to obtain an AB rating.

We have determined your Unithroid (levothyroxine sodium tablets, USP) 25, 50, 75, 88, 100, 112, 125, 150, 175, 200, and 300 mcg tablets to be bioequivalent and therapeutically equivalent to the listed drug Synthroid (levothyroxine sodium tablets, USP) 25, 50, 75, 88, 100, 112, 125, 150, 175, 200, and 300 mcg tablets.

Our review concludes that the data establish bioequivalence between these products, and this supplement is approved. However, your supplement requested an "AB" rating for interchangeability between Unithroid and Synthroid. That decision will be made by the Office of Generic Drugs, and any change in the rating of this product will be listed in the next monthly supplement to the "Approved Drug Products with Therapeutic Equivalence Evaluations" list (the "Orange Book") published by the Agency.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Holly Wieland, R.N., M.P.H., Regulatory Project Manager, at (301) 827-6410.

Sincerely,

{See appended electronic signature page}

/S/

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

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/s/

David Orloff
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-210/S-003

Approvable Letter (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-210/S-003

6|23|04

Jerome Stevens Pharmaceuticals, Inc.
Attention: Ronald Steinlauf
Vice President
60 DaVinci Drive
Bohemia, N.Y. 11716

Dear Mr. Steinlauf:

Please refer to your March 26, 2003, supplemental new drug application (NDA) for Unithroid (levothyroxine sodium tablets, USP) which 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").

In a letter dated May 13, 2003, this Division refused to file (RTF) the supplemental application, because the Synthroid reference material (Lot # 0000339726) was not the subject of an approved new drug application.

We also refer to your correspondence received May 23, 2003, which requested a meeting and appealed the RTF decision to Dr. Robert Meyer, Director of 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 Dr. Meyer's October 3, 2003, correspondence, which upheld the Division's RTF decision.

On November 20, 2003, you requested reconsideration by the Office of New Drugs Immediate Office (OND-IO) of the Division's RTF decision and the subsequent affirmation by ODE II. In response, the OND immediate office (OND-IO) issued a letter dated December 19, 2003, granting you a meeting which was held on January 23, 2004.

In addition, on January 30, 2004, in a telephone communication, you notified us of a new bioequivalence study comparing Unithroid to an approved batch of Synthroid. The data from this study were submitted to the application and received on February 13, 2004.

We also refer to the February 20, 2004, letter issued by Dr. John Jenkins, which stated that we have filed this application over protest as of July 22, 2003, pursuant to 21 CFR 314.101(a)(3) (60 days after the May 23, 2003, request for a conference on the RTF decision.)

We have completed our review and find the information presented is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

The data package submitted in support of a claim of bioequivalence of Unithroid to Synthroid includes several components. The first is a two-period crossover study (not yet formally reviewed by FDA) that, although apparently showing bioequivalence to pre-approved Synthroid (which contained a stability overage), did not use the appropriate Synthroid reference product. Thus, this study does not demonstrate that Unithroid is therapeutically equivalent to the approved Synthroid product (which does not contain a stability overage).

The application contains additional data submitted on February 13, 2004, from what was originally proposed and designed as a parallel-group study. The results of the parallel design study failed to demonstrate bioequivalence of Unithroid to approved Synthroid.

The application also contains data from an extension of the parallel design study that was not pre-specified and that involved retesting only some of the original participants in the parallel design study. This extension was an attempt to convert the study into a crossover study that might show bioequivalence. However, the decision by Jerome Stevens Pharmaceuticals (JSP) to extend the parallel group study into a crossover study is procedurally unacceptable. JSP failed to specify the appropriate statistical methods for this attempted conversion to a crossover study before JSP received the information from the parallel design study on treatment outcomes and determined treatment assignments. This deviation from the prespecified trial procedures is unacceptable. The results of this crossover study are statistically uninterpretable, and thus do not demonstrate that Unithroid is bioequivalent to the approved Synthroid product.

In conclusion, a new, stand-alone, bioequivalence study is needed to provide support for a claim of therapeutic equivalence of Unithroid to Synthroid. The division recommends that such a study be conducted as a randomized, two-period, single-dose crossover study in normal volunteers, as recommended in FDA's guidance on *Levothyroxine Sodium Tablets — In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing.*

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Oluchi Elekwachi, Pharm.D., M.P.H., Regulatory Project Manager, at (301) 827-6381.

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

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/s/

David Orloff
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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-210/S-003

Medical Review(s)

MEMO TO FILE

NDA:	21-210/SE4/003
Sponsor:	Jerome Stevens Pharmaceuticals
Drug Name:	Unithroid
Date of Submission:	February 13, 2004
Subject:	Review of Financial Disclosure Information

In compliance with 21 CFR 54.2, the sponsor has submitted financial disclosure information for all clinical investigators participating in clinical studies whose results are relied upon for the approval of this supplement.

I have reviewed the documents submitted and all investigators have provided statements denying the following:

- entering into any financial arrangements with the sponsor of the clinical trial
- receiving significant payments of other sorts
- holding proprietary interest in the tested product
- having significant equity interest in the sponsor of the clinical trial

The sponsor has provided sufficient information for this reviewer to conclude that there are no financial conflicts of interest on the part of the investigator(s) to question the integrity of the data submitted.

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/s/

Mary Parks
6/15/04 01:01:32 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Ronald Steinlauf	Vice President
FIRM / ORGANIZATION	
Jerome Stevens Pharmaceuticals, Inc.	
SIGNATURE	DATE
Ronald Steinlauf	10/8/04

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-210/S003

Statistical Review(s)

Statistical Consult for the Office of Clinical Pharmacology and Biopharmaceutics

NDA:	21-210
Submission Date(s):	26-MAR-2003, 1-MAY-2003, 13-FEB-2004
Brand Name	Unithroid™
Generic Name	Levothyroxine sodium tablets, USP
OCPB Reviewer	Sang M. Chung, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPE-2
OND Division	Metabolic and Endocrine (HFD-510)
OB Statistical Reviewer	Donald J. Schuirmann, MS
OB Staff	Quantitative Methods and Research Staff (HFD-705)
Sponsor	Jerome Stevens Pharmaceuticals, Inc.
Submission Type	Supplement (S-003) for AB rating to Synthroid™
Strength(s)	25, 50, 75, 88, 100, 112, 125, 150,175, 200, and 300 mcg tablets
Indication	Hypothyroidism and suppression of thyroid-stimulating hormone

Background

The Sponsor conducted a randomized parallel design study to demonstrate the Bioequivalence of Unithroid™ (test product) and Synthroid® (reference product) manufactured by Abbott Laboratories. Each arm (reference and test) consisted of 30 volunteers (total 60 volunteers). The study failed to meet BE requirements. Without additional communication to the Agency, the sponsor extended this study by recalling as many of these 60 volunteers as possible (n=37) for study on the treatment alternate to their previous one. The Sponsor treated this as a crossover study and submitted results from the crossover design as a major amendment on 13-FEB-2004. Twenty volunteers who had received the test product in the parallel study received the reference product, while 17 who received the reference in the parallel received the test.

OCPB sent a consult to OB/QMRS for comments on the statistical implications of such a strategy.

Discussion

The unplanned sequential study.

The sponsor initially carried out a parallel group comparison of 30 subjects on each treatment (A and B), for a total of 60 subjects. When the analysis of this parallel group study did not appear to support a conclusion of bioequivalence, they brought 37 of the original 60 subjects back and gave them the treatment alternate to the one they previously had received. The study conduct is summarized in the following table:

Period 1	Period 2
Group 1a: subjects (n=20) who received treatment **A** in period 1 and went on to period 2	Group 1a subjects (n=20) received treatment **B**
Group 1b: subjects (n=10) who received treatment **A** in period 1 and did not participate in period 2	NA
Group 2a: subjects (n=17) who received treatment **B** in period 1 and went on to period 2	Group 2a subjects (n=17) received treatment **A**
Group 2b: subjects (n=13) who received treatment **B** in period 1 and did not participate in period 2	NA

A major concern here is that, in doing this, the Sponsor conducted an unplanned modification of the design of the study, apparently after having analyzed the period 1 data and observing that the results did not support BE. Such a strategy runs counter to the recommendations of the ICH E9 Guidance, discussed below.

Another concern is as follows: in the past, the Agency has accepted a new BE study conducted after a failed one. Perhaps even some of the same volunteers participated in both studies, but they would have been re-randomized to treatment in the 2nd study. In the present situation, a problem arises from the desire on the part of the firm to use the data from the original parallel group study twice – in other words, the parallel study and the crossover study are not separate. Also, the treatment to be received in the 2nd period was not randomly assigned, it was determined by the randomization for period 1.

The September 1998 ICH Guidance Document "Guidance for Industry – E9 Statistical Principles for Clinical Trials" discusses interim analysis in several places, for example section III.D (Trial Design Considerations – Group Sequential Designs), IV.A (Trial Conduct Considerations – Trial Monitoring and Interim Analysis), and IV.E (Trial Conduct Considerations – Interim Analysis and Early Stopping.) Relevant passages from this guidance regarding breaking of the blind, interim analysis, and potential early stopping include the following: in section III.D:

> "The statistical methods should be fully specified in advance of the availability of information on treatment outcomes and subject treatment assignments (i.e. blind breaking, see section IV.E)."

in section IV.E

> "An interim analysis is any analysis intended to compare treatment arms with respect to efficacy or safety at any time prior to formal completion of a trial. Because the number, methods, and consequences of these comparisons affect the interpretation of the trial, all interim analyses should be carefully planned in advance and described in the protocol. Special circumstances may dictate the need for an interim analysis that was not defined at the start of a trial. In these cases, a protocol amendment describing the interim analysis should be completed prior to unblinded access to treatment comparison data."

and later in section IV.E

> "... Deviations from the planned procedure always bear the potential of invalidating the trial results. If it becomes necessary to make changes to the trial, any consequent changes to the statistical procedures should be specified in an amendment to the protocol at the earliest opportunity, especially discussing the impact on any analysis and inferences that such changes may cause. The procedures selected should always ensure that the overall probability of Type I error is controlled."

An argument could be made for using a trial strategy such as the Sponsor did, and this would be a sequential study. However, the design should be planned in advance, and the sizes of the tests (α-levels) should be pre-specified for the first analysis at the end of the parallel study phase and the second at the end of the crossover study. Since the overall α-level has to be maintained (see the Guidance) at the chosen level, in the present case 0.05, the levels of the 2 separate tests need to be adjusted and would be more stringent, that is, each α would be less than 0.05. This was not done, and the Sponsor apparently "spent up" the α-level of 0.05 at the end of the first stage. The Sponsor conducted an unplanned sequential study, without appropriate adjustment of the level of significance. Moreover, comment from the Agency was not sought before the study extension was carried out.

Analyses comparing the two treatments.

We examined the assessment of BE in several subsets of the data, with these results:

Data set 1: Groups 1a, 1b, 2a, and 2b, period 1 only, as a parallel group design (30 subjects received treatment A, 30 subjects received treatment B)

endpoint	point estimate	90% confidence interval
AUC24	114.07%	103.95% , 125.18%
AUC48	110.68%	101.22% , 121.02%
Cmax	119.78%	109.48% , 131.04%

Data set 2. Groups 1a and 2a, both period 1 and period 2, as a crossover design (20 subjects received treatment A in period 1, 17 subjects received treatment B in period 1)

endpoint	point estimate	90% confidence interval
AUC24	107.30%	101.53% , 113.41%
AUC48	105.55%	100.15% , 111.23%
Cmax	112.55%	107.08% , 118.29%

Data set 3. Groups 1a and 2a, period 1 only, as a parallel group design (20 subjects received treatment A, 17 subjects received treatment B)

endpoint	point estimate	90% confidence interval
AUC24	107.80%	95.66% , 121.49%
AUC48	107.39%	96.10% , 120.00%
Cmax	115.26%	103.44% , 128.44%

Data set 4. Groups 1a and 2a, period 2 only, as a parallel group design (17 subjects received treatment A, 20 subjects received treatment B)

endpoint	point estimate	90% confidence interval
AUC24	106.79%	95.33% , 119.62%
AUC48	103.73%	91.58% , 117.48%
Cmax	109.90%	98.16% , 123.03%

The analysis of data set 1 is the sponsor's original analysis of the parallel study, which did not result in acceptable confidence intervals for Cmax (or for AUC24, for that matter). This led them to obtain the period 2 data. The analysis of data set 2 is their analysis of the data from periods 1 and 2 from those subjects who participated in both periods. As described above, studies 1 and 2 are not separate studies, and because the design was not planned in advance, with suitably adjusted significance levels, according to the ICH E9 guidance, the analysis of data set 2 is uninterpretable.

Consideration of possible underpowering of the parallel study.

I would note that the reason that the analysis of data set 1 apparently failed to support a conclusion of bioequivalence is **not** because the parallel study was "under-powered". The estimated standard deviations for the three log-transformed pharmacokinetic (PK) endpoints (log(AUC24), log(AUC48), and log(Cmax)) from the analysis of data set 1 were 0.215298, 0.206891, and 0.208294, respectively, each based on 58 degrees-of-freedom. If we take the largest of these, 0.215298 (for log(AUC24)), and assume that it represents the true standard deviation, we find that if the product population geometric means had been identical, the power of the study would have been 98.0%. Even if we calculate a 95% upper confidence bound for the true standard deviation based on the estimate of 0.215298 and 58 degrees-of-freedom, we get a standard deviation of 0.254550, for which the power of the parallel group study would have been 91.3%, once again assuming that the population geometric means were identical. It is because the population geometric means of these two products are apparently *not* identical that the parallel group study may have failed to support a conclusion of bioequivalence.

Analyzing period 2 (data set 4) as a standalone study

In looking at the analysis of data set 4 above, it may be seen that the results from period 2 of the study, by themselves, support a conclusion of bioequivalence according to the standard criteria. Since the period 2 data are distinct from the original period 1 data, can they be regarded as representing a separate study?

There are two arguments against this interpretation. The first is that of possible bias owing to the fact that not all of the subjects from the original study were brought back for period 2. It may be seen by comparing the results of the analysis of data set 3 to those of data set 1 that the former are closer to supporting a conclusion of bioequivalence, though the test is not passed for Cmax. The point estimates from the analysis of data set 3, which comprised only subjects who went on to period 2, are closer to 100% for each of the three PK endpoints. The sponsor claims to have made every effort to bring back all 60 subjects from the original period 1, and this may well be the case, but it is not possible to know. But could there have been something about having unusually high or low blood levels that correlated with availability for the second period? For each of the two treatments and each of the three log-transformed PK parameters from period 1, the difference between the subjects who went on to period 2 and the subjects who did not was not statistically significant, though it was close ($p = 0.0541$) for log(AUC24) and Treatment B. I would say that there is no strong empirical evidence of bias, but that the issue should still be considered.

The second argument against considering the period 2 data to be a separate study from the period 1 data is the lack of independent randomization. If the 37 subjects (out of the original 60 subjects) who were brought back for period 2 had been re-randomized to receive either treatment A or treatment B, then the two periods could, in my opinion,

certainly be interpreted as two parallel group studies (I am not aware of any restriction against using the same subjects in more than one study.) But in fact the subjects who were brought back for period 2 received whichever treatment they did not receive in period 1. Thus the randomization was the same (in a complementary sense) as that for period 1. To the extent that randomization is the basis for inference, this may argue against regarding period 1 and period 2 as separate parallel group studies.

Conclusions

1. The procedure followed by the sponsor - in which they extended their study to a crossover study for 37 of the original 60 subjects, but only after the analysis of the original parallel group (period 1) data failed to support a conclusion of bioequivalence - constituted an unplanned two-stage sequential study without appropriate adjustments to the levels of significance used to analyze each of the two stages. It is therefore unacceptable based on the ICH E9 Guidance document, in my opinion.

2. The sponsor's period 2 data, if analyzed separately, appear to support a conclusion of bioequivalence. If the period 2 data may be regarded as a separate study from the period 1 data, then their period 2 data may be submitted in support of a bioequivalence claim. However, before period 2 is regarded as a separate study from period 1, the questions of potential bias and lack of independent randomization, as discussed above, should be considered by CDER scientists.

/S/

Donald J. Schuirmann, M.S.
Expert Mathematical Statistician
QMR Staff, Office of Biostatistics, CDER

/S/

Stella G. Machado, Ph.D.
Director, QMR Staff
Office of Biostatistics, CDER

cc:
HFD-870/Henry Malinowski/Hae-Young Ahn/Sang Chung
HFD-003/Solomon Sobel
HFD-510/Oluchi Elekwachi/Enid Galliers
HFD-650/Dale Conner/Barbara Davit
HFD-705/Donald Schuirmann/Stella Machado
HFD-705/Chron

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for supervisory concurrence

Stella Machado
5/12/04 03:54:23 PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-210/S-003

Clinical Pharmacology and Biopharmaceutics Review

12.07.04

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-210
Submission Date(s):	October 28, 2004
Brand Name	Unithroid™
Generic Name	Levothyroxine sodium tablets, USP
Reviewer	Sang M. Chung, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPE-2
OND division	Metabolic and Endocrine (HFD-510)
Sponsor	Jerome Stevens Pharmaceuticals, Inc.
Submission Type	Supplement (SE4-003) for AB rating to Synthroid™
Strength(s)	25, 50, 75, 88, 100, 112, 125, 150,175, 200, and 300 mcg tablets
Indication	Hypothyroidism and suppression of thyroid-stimulating hormone

1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE-2) reviewed the supplement to NDA 21-210 / SE4-003 and finds it acceptable. This recommendation should be sent to the sponsor as appropriate.

2 CPB findings

The sponsor submitted this supplement to demonstrate interchangeability for Unithroid™ (test) with Synthroid® (reference) manufactured by Abbott Laboratories. The 0.3mg Synthroid® tablet is listed as one of Reference Listed Drugs in the Electronic Orange Book as of July 2003.

The original supplement was submitted on March 26, 2003. However, the sponsor used a batch of the reference drug manufactured before NDA approval and thus the Agency issued a letter for refusal to file (May 2003) based on the Code of Federal Regulations (21 CFR 320.25(e)(3)).

The sponsor subsequently submitted results of new study as an amendment on February 13, 2004, and the Agency concluded that the study design and the statistical analyses were not acceptable.

In this supplement, the sponsor submitted a randomized, crossover BE study results (Protocol P1CK04001) using the reference product from the batch manufactured after NDA approval.

Information on the test and reference products is summarized in Table 1

Table 1 **Information on test and reference products**

	Test	Reference
Name	Unithroid™ 0.3 mg tablet	Synthroid® 0.3 mg tablet
Lot No.	006003	000346335P
Manufactured Date	July 2003	
Exp. Date	July 2005	April 2005
Assay*	97.1%	96.4%
Content Uniformity* (mean of 10 tablets)	100.7% (range ———)	96.2% (range —— .

*: Specification was —— % and —— % for the assay and the content uniformity (each tablet), respectively.

Brief summary on the two way crossover study is as follows:

Twenty six subjects were enrolled and completed the study (Note: The study was designed for 24 subjects and tow more subjects were recruited in case of drop-out.). Oral doses of 0.6mg (two 0.3mg tablets of Unithroid® and Synthroid®) were administered under overnight fasting condition.

Total of 18 blood samples were collected in each period (i.e., -0.5, -0.25, 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 18, 24, and 48 hours post-dose). Baseline was calculated as the average of 3 pre-dose serum concentrations (i.e., -0.5, -0.25, and 0 nominal sampling times). The post-dose concentration-time profiles were adjusted by the baselines. Negative values after the correction were set to zero. There was 5 weeks (35 days) washout period between treatments. Ratios (test/reference) of AUCs (i.e., AUC_{0-24}, and AUC_{0-48}) and C_{max}, and 90% confidence interval (CI) were calculated with the adjusted serum concentrations based on the current recommendation on statistical methods in Guidance for Industry**.

**: 1. Guidance for Industry, Bioavailability and Bioequivalance Studies for Orally Administered Drug Products-General Considerations.

2. Guidance for Industry; Levothyroxine sodium tablets – *In vivo* pharmacokinetic and bioavailability studies and in vitro dissolution testing

The first enrollment was on July 23, 2004 and the clinical study was completed on August 30, 2004. Of total 26 subjects completed the study, statistical analyses were performed using the pharmacokinetic data from the first 24 subjects and results were

summarized in table 2. The results from the crossover study design showed that the two products were BE.

Table 2 Statistical results for BE assessment based on the baseline corrected data (n=24)

Parameter	Ratio of T/R (%)	90% CI
AUC_{0-24} (ng h/ml)	101.0	95.9-106.3
AUC_{0-48} (ng h/ml)	103.0	95.1-111.6
C_{max} (ng/ml)	104.4	99.1-109.9

The serum total levothyroxine (T4) levels were measured using the radioimmunoassay (RIA) with a validated range of [redacted] ng/ml. Four nominal concentrations for QC were [redacted] (QC1), [redacted] (QC2), [redacted] (QC3), and [redacted] (QC4) ng/ml. Between-batch accuracy (%nominal) and precision (%CV) are summarized in table 4.

Table 3 Between-batch precision and accuracy from 12 QC samples

QC (ng/ml)	[redacted]			
% nominal	[redacted]			
% CV	5.57	4.04	4.91	4.80

The sponsor requested a waiver of *in vivo* bioequivalence (BE) studies for the 25, 50, 75, 88, 100, 112, 125, 150, 175, and 200 microgram strengths by referencing to dosage form equivalence and comparative dissolution data. The review of the original NDA concluded that dosage form equivalence was established among 50, 100, and 300 microgram strengths, dissolution profiles were comparable among all the strengths, and all the strengths are compositionally proportional in its active and inactive ingredients. In conclusion, the request of biowaiver can be granted.

Dissolution profiles of 300 microgram tablets (n=12) for Unithroid® and Synthroid® were included as part of formulation data (Table 4, mean % dissolved).

Table 4 Summary of percent dissolved (mean percent dissolved, n=12)

Time	Unithroid	Synthroid
10	56.4	62.9
20	84.3	90.0
30	90.3	95.1
45	93.6	96.4

Dissolution conditions were USP apparatus II (paddle) at 50 rpm in 500 ml of 0.01 N HCl containing 0.2% sodium lauryl sulfate. Dissolution specification was NLT 70% of levothyroxine sodium dissolved in 45 minutes.

The test products (Unithroid™) do not include the 137 microgram strength but the reference products (Synthroid®) have the 137 microgram strength. However, it is concluded that the absence of the 137microgram strength is not a regulatory issue based on the informal consult to OGD.

Studies were conducted at the following facilities:

- Clinical study
  - [redacted]
- Analytical study
  - [redacted]
- Statistical analysis
  - [redacted]

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/s/

Sang Chung
12/6/04 03:36:40 PM
PHARMACOLOGIST

Hae-Young Ahn
12/7/04 05:16:07 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-210
Submission Date(s):	26-MAR-2003, 1-MAY-2003, 13-FEB-2004
Brand Name	Unithroid™
Generic Name	Levothyroxine sodium tablets, USP
Reviewer	Sang M. Chung, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPE-2
OND division	Metabolic and Endocrine (HFD-510)
Sponsor	Jerome Stevens Pharmaceuticals, Inc.
Submission Type	Supplement (S-003) for AB rating to Synthroid™
Strength(s)	25, 50, 75, 88, 100, 112, 125, 150,175, 200, and 300 mcg tablets
Indication	Hypothyroidism and suppression of thyroid-stimulating hormone

1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE-2) reviewed the supplemental NDA 21-210 S003 and finds it not acceptable. This recommendation should be sent to the sponsor as appropriate.

2 CPB findings

The sponsor submitted this supplement to demonstrate interchangeability for Unithroid™ (test) with Synthroid® (reference) manufactured by Abbott Laboratories. The tablet of 0.3mg Synthroid® has been listed as one of reference listed drugs in the Electronic Orange Book as of July 2003.

The original supplement was submitted on 26-MAR-2003. However, the sponsor used a batch of the reference formulation before NDA approval and thus the Agency issued a letter for refusal to file (May-2003) based on the Code of Federal Regulations:

21 CFR 320.25(e)(3): *"reference material should be taken from a current batch of a drug product that is the subject of an approved new drug application and that contains the same active drug ingredient or therapeutic moiety"*

The sponsor proposed a parallel design for a new BE study during a teleconference meeting on 2-SEP-2003 and the Agency accepted the alternative study design with emphasis on the sufficient number of subjects for the statistical power to detect a difference between products.

The sponsor conducted a randomized, parallel BE study (Protocol P1CK03001) in which each arm (reference and test) consisted of 30 volunteers (total 60 volunteers). The study failed to meet BE requirements based on the analyses done by this reviewer (table 1).

Table 1 **Statistical results for BE assessment based on the baseline corrected data (n=60)**

	Parallel study (n=60)	
Parameter	Ratio of T/R (%)	90% CI
AUC_{0-48}	110.68	101.22-121.02
C_{max}	119.78	109.48-131.05

Without additional communications to the Agency, the sponsor extended it to a crossover design (Protocol P1CK03001A, n=37) and submitted results from the crossover design as a major amendment on 13-FEB-2004. According to the amendment, the sponsor made every attempt for the crossover study to include as many of the subjects who participated in the parallel study as possible.

An official consult for issues in statistics was sent to the Office of Biostatistics on March, 2004 and the review is currently pending.

Brief summary on the crossover study is as follows:

Twenty volunteers who had received the test in the parallel study received the reference, and 17 who received the reference in the parallel study received the test. Oral doses of 0.6mg (two 0.3mg tablets) were administered under overnight fasting condition.

Total of 18 blood samples were collected at each period (i.e., -0.5, -0.25, 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 18, 24, and 48 hours post-dose). Baseline was calculated as the average of 3 pre-dose serum concentrations (i.e., -0.5, -0.25, and 0 nominal sampling times). The post-dose concentration-time profiles were adjusted by the baselines. Negative values after the correction were set to zero. There was about a 90 days washout period between the treatment periods: the first treatment from 21st to the 23rd of September 2003, and the second treatment from 20th to the 22nd of December, 2003. Ratios (test/reference) of AUCs (i.e., AUC_{0-24}, and AUC_{0-48}) and C_{max}, and 90%

confidence interval (CI) were calculated with the adjusted serum concentrations based on the current recommendation on statistical methods in Guidance for Industry**.

**: 1. Guidance for Industry, Bioavailability and Bioequivalance Studies for Orally Administered Drug Products-General Considerations.

2. Guidance for Industry; Levothyroxine sodium tablets – *In vivo* pharmacokinetic and bioavailability studies and in vitro dissolution testing

Total 37 subjects completed the study and statistical analyses were performed using the pharmacokinetic data from the all subjects and results were summarized in table 2. The results from the crossover study design showed that the two products were BE.

Table 2 **Statistical results for BE assessment based on the baseline corrected data (n=37)**

Parameter	Ratio of T/R (%)	90% CI
AUC_{0-24}	107.3	101.6-113.4
AUC_{0-48}	105.5	100.2-111.2
C_{max}	112.5	107.1-118.3

Information for the test and reference products is summarized in table 3

Table 3 **Information on test and reference products**

	Test	Reference
Name	Unithroid™ 0.3 mg tablet	Synthroid® 0.3 mg tablet
Lot No.	006003	0000341462
Manufactured Date	July 2003	
Exp. Date	July 2005	May 2004
Assay*	97.1%	97.4%
Content Uniformity* (mean of 10 tablets)	100.7% (range —	98.0% (range —

*: Specification was — % and — % for the assay and the content uniformity (each tablet), respectively.

The serum total levothyroxine (T4) was analyzed using the [redacted] with a validated range of — ng/ml. Four nominal concentrations for QC were —(QC1), — (QC2), — (QC3), and — (QC4) ng/ml. Between-batch accuracy (%nominal) and precision (%CV) are summarized in table 4.

Table 4 **Between-batch precision and accuracy from 12 QC samples**

QC (ng/ml)	QC1 —	QC2 —	QC3 —	QC4 —
% nominal	[redacted]			
% CV	5.87	3.44	3.80	4.03

The sponsor requested a waiver of *in vivo* bioequivalence (BE) studies for the 25, 50, 75, 88, 100, 112, 125, 150, 175, and 200 microgram strengths by referencing to dosage form equivalence and comparative dissolution data. The review of the original NDA concluded that dosage form equivalence was established among 50, 100, and 300 microgram strengths and dissolution profiles were comparable among all the strengths with proportionality in its active and inactive ingredients. In conclusion, the request of biowaiver can be granted.

Dissolution profiles of 300 microgram tablets (n=12) for Unithroid® and Synthroid® were included as part of formulation data as follows (mean % dissolved):

Time	Unithroid	Synthroid
10	56.4	69.6
20	84.3	88.9
30	90.3	92.0
45	93.6	95.9

Dissolution conditions were USP apparatus II (paddle) at 50 rpm in 500 ml of 0.01 N HCl containing 0.2% sodium lauryl sulfate. Dissolution specification was that NLT 70% of levothyroxine sodium was dissolved in 45 minutes.

The test product (Unithroid™) does not include 137 microgram strength that reference product (Synthroid®) includes. However, the absence of the 137microgram strength is acceptable based on the informal consult to OGD.

Studies were conducted at the following facilities:

- Clinical study
  - (
- Analytical study and statistical analysis
  - (

An optional Inter-Division CPB briefing was held on 28-APR-2004 at 13B45 (Attendee: Drs. Henry Malinowski, Dale Conner, Barbara Davit, Stella Machado, Don Schuirmann, Solomon Sobel, Kati Johnson, Hae-Young Ahn and Sang M. Chung) and it was concluded that the results were not acceptable and the sponsor may need to conduct another BE study. According to the current practice of the Office of Generic Drugs, the sponsors are not allowed to analyze results in the middle of studies and Jerome Stevens violated the rule. In addition, the sponsor spent all of level of significance (alpha) at the

end of parallel study design and thus no alpha was left on the crossover study design (refer to the review from the Office of Biostatistics).

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/s/

Sang Chung
5/5/04 05:59:24 PM
PHARMACOLOGIST

Hae-Young Ahn
5/5/04 06:05:27 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-210/S-003

Administrative/Correspondence Reviews

EXCLUSIVITY SUMMARY FOR NDA # __21-210_____ SUPPL #__003

Trade Name __Unithroid Talets_ Generic Name:levothyroxine sodium Tablets (11 strengths)

Applicant Name _Jerome Stevens Pharmaceuticals HFD # __510__

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /__X_/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

_____SE4____ 505(B)(1)_____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /___/ NO /__X_/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

THE APPLICANT AND THE DIVISION AGREE THAT THIS SUPPLEMENT IS BASED ON A BIOEQUIVALENCE STUDY.

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to

question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

Signature Enid Galliers Date 12/09/2004
Title: CPMS, DMEDP, ODE II, CDER

Signature of David G. Orloff, MD
Director, DMEDP, ODE II, CDER

Date: *See attached electronic signature page*

Form OGD-011347 Revised 05/10/2004

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/s/

David Orloff
12/10/04 03:49:11 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-210 **Supplement Type (e.g. SE5):** SE4 **Supplement Number:** S-003

Stamp Date:_____ **Action Date:**

HFD-510__ **Trade and generic names/dosage form:** Unithroid (levothyroxine sodium tablets) (11 strengths)

Applicant: Jerome Stevens Pharmaceuticals, Inc. **Therapeutic Class:** Thyroid

Indication(s) previously approved: thyroid replacement in children and adults

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 0 Not applicable

Indication #1: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA 21-210/S-003
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

'ection D: Completed Studies

Age/weight range of completed studies:

Min ____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**
Max____	**kg____**	**mo.____**	**yr.____**	**Tanner Stage____**

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

cc: **NDA ##-###**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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/s/

Enid Galliers
12/10/04 01:25:19 PM

Jerome Stevens Pharmaceuticals, Inc.
60 DaVinci Drive
Bohemia, NY
USA 11716

DEBARMENT CERTIFICATION

I certify that Jerome Stevens Pharmaceuticals, Inc. did not and will not use the services of any person debarred under Section 306(a) or (b) of the Federal Food, Drug, and Cosmetic Act, in connection with the development of this drug product and the preparation of this Supplemental New Drug Application Amendment.

I further certify that neither Jerome Stevens Pharmaceuticals, Inc. nor any affiliated person responsible in any capacity for providing services or generating information for this Supplemental New Drug Application Amendment for UNITHROID Tablets USP (levothyroxine sodium tablets: 25, 50, 75, 88, 100, 112, 125, 150, 175, 200, and 300 μg) has been convicted of any offense required to be listed under Section 306(k)(2) of the Federal Food, Drug and Cosmetic Act during the past five years.

At this time Jerome Stevens Pharmaceuticals, Inc. has no person to list who have been convicted during the last five years of any offense required to be listed under Section 306(k)(2) of the Federal Food, Drug and Cosmetic Act.

Ronald Steinlauf
Vice President

10/8/04
Date

GENERIC DRUG ENFORCEMENT ACT OF 1992 CERTIFICATION

Re: **Levothyroxine, 0.3 mg**

Protocol Title: **COMPARATIVE BIOAVAILABILITY STUDY OF LEVOTHYROXINE 0.3 MG TABLETS (JEROME STEVENS PHARMACEUTICALS, NY, USA) VS. SYNTHROID® 0.3 MG TABLETS (ABBOTT LABORATORIES, IL, USA) IN HEALTHY MALE AND/OR FEMALE VOLUNTEERS; UNDER FASTING CONDITIONS – P1CK04001**

Section 306 (k) (1) Requirement

In accordance with section 306 (a) or (b) of the Generic Drug Enforcement Act of 1992, [ ] did not use in any capacity the services of any person debarred under subsections 306 (a) or (b), in connection with such application.

Section 306 (k) (2) Requirement

[ ] has no relevant convictions to report under 306 (a) and (b) for any persons (including contracted affiliations) responsible for the development of data or other information used to support this application.

22 JUL 04
Date

(Debarment Certification Statement/18Oct02)

6 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: December 10, 2004

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-210/S-003

AND: Gary Buehler
Director, Office of Generic Drugs

SUBJECT: NDA 21-210/S-003
Unithroid (levothyroxine sodium) tablets
Jerome Stevens Pharmaceuticals
Proposal for AB rating with Synthroid (Abbott)
sNDA review issues and recommended action

History of NDA 21-210/S-003

Original bioequivalence study against "pre-approval" Synthroid

Jerome Stevens Pharmaceuticals (JSP) submitted a supplemental NDA (sNDA) on March 26, 2003, including a bioequivalence (BE) study comparing its Unithroid product to Abbott Laboratories' Synthroid. JSP was seeking to have its product AB-rated to Synthroid. The division responded with a letter dated May 13, 2003, refusing to file the application because the Synthroid used in the single dose, two-way crossover BE study had been manufactured prior to the approval of the Synthroid NDA. The division had knowledge that the formulation for Synthroid had been altered to support approval of the NDA. Specifically, "pre-approval" Synthroid included a "stability" overage of active ingredient (levothyroxine) targeting active drug content at release in substantial excess of nominal dosage strength in order to permit a favorable shelf life for the final product. It is worth noting that the refuse-to-file (RTF) decision was consistent with an earlier decision by the Office of Generic Drugs (OGD) to refuse to accept as valid for a determination of therapeutic equivalence a BE study submitted by Mylan Pharmaceuticals comparing its levothyroxine sodium product to pre-approval Synthroid because Mylan used pre-approval Synthroid in its BE study.

JSP appealed the division's RTF decision to Dr. Robert Meyer, Director, Office of Drug Evaluation II. In a letter to JSP dated October 3, 2003, Dr. Meyer upheld the division's RTF decision, citing JSP's failure to meet the regulatory requirement of using the "appropriate reference material" in its bioequivalence study.

On November 20, 2003, JSP sent a request to the Agency that the RTF decision again be reconsidered. This request was handled according to CDER's formal dispute resolution policy and procedures and ultimately led to a meeting with Dr. Jenkins, Director, Office of New Drugs, and other FDA officials on January 23, 2004. At that meeting, JSP and its consultants and

counsel made scientific, legal, and regulatory arguments why FDA should accept the data from the BE study for review. No other bioequivalence data were discussed at the meeting. However, it is important to note that on September 2, 2003, the division (Office of Clinical Pharmacology and Biopharmaceutics (OCPB) team) had a telephone conference with JSP, its legal counsel, and Dr. [ ], the CRO that conducted JSP's BE study). JSP requested the conference to discuss the protocol for a new BE study comparing Unithroid to Synthroid. JSP asked for comment on a parallel-group BE study (not the design recommended by FDA according to guidance on levothyroxine bioequivalence studies, previously conveyed to JSP by letter dated January 16, 2003, from the division in response to a letter from the firm dated September 11, 2002). In the telephone conference of September 2, 2003, the division agreed in principle to the parallel group design. However, the division emphasized that the study would require adequate sample size and statistical power. On November 11, 2003, the project manager had a telephone conversation with JSP counsel concerning JSP's plans to submit the results of the previously discussed parallel group study.

After the meeting with Dr. Jenkins and others on January 23, 2004, Dr. Jenkins sent a letter to JSP on February 20, 2004, informing the company that the Agency was filing the original sNDA over protest as of July 22, 2003, with a user-fee goal date of March 23, 2004. The letter also noted a January 30, 2004, telephone conference with JSP at which FDA was notified of JSP's intent to submit the results of the new BE study of Unithroid to approved Synthroid and the subsequent submission of those data on February 13, 2004. The letter also explained the designation of this study submission as a major amendment, and the resulting decision to extend the user-fee date to June 23, 2004. Of further note, JSP also had a telephone conference with Dr. Meyer on February 2, 2004, addressing, among other items, the firm's position that an audit of the new study by the Division of Scientific Investigations was not necessary because JSP deemed the study merely "supportive" of its previously submitted BE study.

Study P1CK03001

Study P1CK03001 was submitted on February 13, 2004, and was reviewed by OCPB and by the Office of Biostatistics. The results of the parallel group study of 30 normal volunteers per treatment group failed to support bioequivalence of Unithroid to Synthroid because the upper limit of the 90% confidence interval (CI) for the ratio of Cmax for Unithroid to Cmax for Synthroid was 1.31.

JSP and its investigators sought to "salvage" the failed parallel design study by extending it into a crossover study. In order to do this, JSP enrolled a total of 37 out of the original 60 volunteers (20 who had received Unithroid, 17 who had received Synthroid) into what became the second period of a two-way crossover study. Without considering whether the study is scientifically valid, the *prima facie* analysis of the data for the 37 patients supports bioequivalence of Unithroid to Synthroid, with the 90% confidence intervals for the ratios of levothyroxine AUC (0-24), AUC (0-48), and Cmax for Unithroid to Synthroid all within the range of 0.8 to 1.25.

The biometrics reviewer concluded that the study was not scientifically valid for a number of reasons, with which the division concurred. The study failed to specify fully the appropriate statistical methods in advance of JSP's receiving information on treatment outcomes and determining treatment assignments. Instead, it appears that JSP conducted an unplanned interim

analysis of the period 1 data from the parallel group study. Based on this analysis, JSP then made a deviation from the prespecified trial procedures by adding a second period to create a crossover study. Because of these deviations from proper scientific procedure in the conduct and analysis of bioequivalence studies, the results of the "crossover study" are statistically uninterpretable.

On June 23, 2004, the division took a "Not Approvable" action on the amended application. Up to that point, the data package submitted in support of a claim of bioequivalence of Unithroid to Synthroid included several components. The first was a two-period crossover study (not formally reviewed by FDA) that, although reportedly showing bioequivalence to pre-approved Synthroid, did not use the appropriate Synthroid reference product. Thus, this study could not support a conclusion that Unithroid is therapeutically equivalent to the approved Synthroid product.

The application also contained additional data submitted on February 13, 2004, from what was originally proposed and designed as a parallel-group study. The results of the parallel design study failed to demonstrate bioequivalence of Unithroid to approved Synthroid.

The application also contained data from a non-prespecified extension of the parallel design study that involved retesting in a crossover "second period" only some of the original participants in the parallel design study. This extension was an attempt to convert the study into a crossover study that might show bioequivalence. JSP's decision to extend the parallel group study into a crossover study was deemed procedurally unacceptable. The results of that crossover study were thus statistically uninterpretable, and thus could not support a conclusion that Unithroid was bioequivalent to the approved Synthroid product.

Study P1CK04001

On October 28, 2004, JSP amended their application with the submission of the results of another comparative bioavailability study of Synthroid and Unithroid. This has been reviewed by OCPB and the results are summarized briefly here.

This was a two-period, two-way, double-blind, randomized, single-dose crossover study in 26 normal healthy subjects. For each of the two periods, the 0.6 mg dose of levothyroxine was administered as two 0.3 mg tablets after an overnight fast. Eighteen blood samples were collected from baseline to 48 hours. The data were corrected for baseline total T4 concentration based on current guidance for industry on levothyroxine bioequivalence testing. Statistical analysis was conducted on the first 24 patients (enrollment of 26 patients was a contingency for potential dropouts or unevaluable subjects).

The data, as summarized in table 2 of Dr. Chung's review, show that for AUC (0-24) and AUC (0-48), the ratios of test to reference were 1.01 and 1.03, respectively, with 95% confidence intervals well within the criterion 0.8-1.25 range. Specifically, for AUC (0-48), the upper limit of the 95% CI for the ratio of test to reference was 1.116. For Cmax, the ratio of test to reference was 1.044, with 95% CI 0.991-1.099.

Based on comparative bioavailability studies of 600 mcg total doses of the 50, 100, and 300 mcg strengths of the product, establishing dose proportionality, comparable dissolution profiles across the entire dosage range, and compositional proportionality for active and inactive ingredients, the sponsor requested a waiver of the *in vivo* bioequivalence requirement for the doses other than the 300 mcg dose studied, and this is granted by the division.

We note that Unithroid does not include a 137 mcg dosage strength, while Synthroid does, though this is not deemed a meaningful difference in the utility of the two products and certainly does not impact substitutability across the dosage strengths in common between the two products.

Based on the data from this trial, Unithroid is deemed therapeutically equivalent to Synthroid.

Financial disclosure

The financial disclosure information is in order. The sponsor has submitted form 3454 (Certification: Financial Interests and arrangements of clinical investigators). The applicant certifies that the listed clinical investigators 1) did not participate in any financial arrangement with the sponsor of the study whereby the value of the compensation to the investigator for conducting the study could be affecting by the outcome of the study, 2) had no proprietary interest in the product or equity interest in the JSP, and 3) were not the recipients of significant payment of other sorts.

Summary and conclusions

In conclusion, JSP has now submitted the results of a new, stand-alone, bioequivalence study to support a claim of therapeutic equivalence of Unithroid to Synthroid. This was a randomized, blinded, two-period, single-dose crossover study in normal volunteers as recommended by FDA. The analysis included a correction of the levothyroxine data using baseline serum levothyroxine concentration according to Agency guidance. The results of the trial indicate bioequivalence according to Agency criteria, and the overall comparative analyses of Unithroid to Synthroid leads to a conclusion that the two products are therapeutically equivalent.

DMEDP will approve this sNDA and recommends that OGD grant an AB rating of Unithroid to Synthroid.

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/s/

David Orloff
12/13/04 05:11:25 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: June 21, 2004

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: Gary Buehler
Director, Office of Generic Drugs

SUBJECT: NDA 21-210/S-003
Unithroid (levothyroxine sodium) tablets
Jerome Stevens Pharmaceuticals
Proposal for AB rating with Synthroid (Abbott)
sNDA review issues and recommended action

Background

Jerome Stevens Pharmaceuticals (JSP) submitted a supplemental NDA (sNDA) on March 26, 2003, including a bioequivalence (BE) study comparing its Unithroid product to Abbott Laboratories' Synthroid. JSP was seeking to have its product AB-rated to Synthroid. The division responded with a letter dated May 13, 2003, refusing to file the application because the Synthroid used in the single dose, two-way crossover BE study had been manufactured prior to the approval of the Synthroid NDA. The division had knowledge that the batch formula for Synthroid had been altered to support approval of the NDA. Specifically, "pre-approval" Synthroid included a clinically significant "stability" overage of active ingredient (levothyroxine) targeting active drug content at release in substantial excess of nominal dosage strength in order to permit a favorable shelf life for the final product. It is worth noting that the refuse-to-file (RTF) decision was consistent with an earlier decision by the Office of Generic Drugs (OGD) to refuse to accept as valid for a determination of therapeutic equivalence a BE study submitted by Mylan Pharmaceuticals comparing its levothyroxine sodium product to pre-approval Synthroid because Mylan used pre-approval Synthroid in its BE study.

JSP appealed the division's RTF decision to Dr. Robert Meyer, Director, Office of Drug Evaluation II. In a letter to JSP dated October 3, 2003, Dr. Meyer upheld the division's RTF decision, citing JSP's failure to meet the regulatory requirement of using the "appropriate reference material" in its bioequivalence study.

On November 20, 2003, JSP sent a request to the Agency that the RTF decision again be reconsidered. This request was handled according to CDER's formal dispute resolution policy and procedures and ultimately led to a meeting with Dr. Jenkins, Director, Office of New Drugs, and other FDA officials on January 23, 2004. At that meeting, JSP and its consultants and counsel made scientific, legal, and regulatory arguments why FDA should accept the data from

the BE study for review. No other bioequivalence data were discussed at the meeting. However, it is important to note that on September 2, 2003, the division (Office of Clinical Pharmacology and Biopharmaceutics (OCPB) team) had a telephone conference with JSP, its legal counsel, and Dr. [ ] the CRO that conducted JSP's BE study). JSP requested the conference to discuss the protocol for a new BE study comparing Unithroid to Synthroid. JSP asked for comment on a parallel-group BE study (not the design recommended by FDA according to guidance on levothyroxine bioequivalence studies, previously conveyed to JSP on January 16, 2003, in response to a letter from the firm dated September 11, 2002). In the telephone conference of September 2, 2003, the division agreed in principle to the parallel group design. However, the division emphasized that the study would require adequate sample size and statistical power. On November 11, 2003, the project manager had a telephone conversation with JSP counsel concerning JSP's plans to submit the results of the previously discussed parallel group study.

After the meeting with Dr. Jenkins and others on January 23, 2004, Dr. Jenkins sent a letter to JSP on February 20, 2004, informing the company that the Agency was filing the original sNDA over protest as of July 22, 2003, with a user-fee goal date of March 23, 2004. The letter also noted a January 30, 2004, telephone conference with JSP at which FDA was notified of JSP's intent to submit the results of the new BE study of Unithroid to approved Synthroid and the subsequent submission of those data on February 13, 2004. The letter also explained the designation of this study submission as a major amendment, and the resulting decision to extend the user-fee date to June 23, 2004. Of further note, JSP also had a telephone conference with Dr. Meyer on February 2, 2004, addressing, among other items, the firm's position that an audit of the new study by the Division of Scientific Investigations was not necessary because JSP deemed the study merely "supportive" of its previously submitted BE study.

Review of new BE study

Study P1CK03001 was reviewed by OCPB and by the Office of Biostatistics. The results of the parallel group study of 30 normal volunteers per treatment group failed to support bioequivalence of Unithroid to Synthroid because the upper limit of the 90% confidence interval (CI) for the ratio of Cmax for Unithroid to Cmax for Synthroid was 1.31.

JSP and its investigators sought to "salvage" the failed parallel design study by extending it into a crossover study. In order to do this, JSP enrolled a total of 37 out of the original 60 volunteers (20 who had received Unithroid, 17 who had received Synthroid) into what became the second period of a two-way crossover study. Without considering whether the study is scientifically valid, the *prima facie* analysis of the data for the 37 patients supports bioequivalence of Unithroid to Synthroid, with the 90% confidence intervals for the ratios of levothyroxine AUC(0-24), AUC(0-48), and Cmax for Unithroid to Synthroid all within the range of 0.8 to 1.25.

The biometrics reviewer concluded that the study is not scientifically valid for a number of reasons, with which the division concurs. First, the study failed to specify fully the appropriate statistical methods in advance of JSP's receiving information on treatment outcomes and determining treatment assignments. Instead, it appears that JSP conducted an unplanned interim analysis of the period 1 data from the parallel group study. Based on this analysis, JSP then

made a deviation from the prespecified trial procedures by adding a second period to create a crossover study. Because of these deviations from proper scientific procedure in the conduct and analysis of bioequivalence studies, the results of the "crossover study" are statistically uninterpretable.

Summary and conclusions

In sum, the data package submitted in support of a claim of bioequivalence of Unithroid to Synthroid includes several components. The first is a two-period crossover study (not yet formally reviewed by FDA) that, although apparently showing bioequivalence to pre-approved Synthroid, did not use the appropriate Synthroid reference product. Thus, this study does not demonstrate that Unithroid is therapeutically equivalent to the approved Synthroid product (which does not contain a stability overage as does pre-approved Synthroid).

The application contains additional data submitted on February 13, 2004, from what was originally proposed and designed as a parallel-group study. The results of the parallel design study failed to demonstrate bioequivalence of Unithroid to approved Synthroid.

The application also contains data from an extension of the parallel design study that was not pre-specified and involved retesting only some of the original participants in the parallel design study. This extension was an attempt to convert the study into a crossover study that might show bioequivalence. JSP's decision to extend the parallel group study into a crossover study is procedurally unacceptable. The results of that crossover study are statistically uninterpretable, and thus do not demonstrate that Unithroid is bioequivalent to the approved Synthroid product.

In conclusion, a new, stand-alone, bioequivalence study is needed to provide support for a claim of therapeutic equivalence of Unithroid to Synthroid. The division intends to recommend strongly that such a study be conducted as a randomized, two-period, single-dose crossover study in normal volunteers as recommended in FDA's guidance on *Levothyroxine Sodium Tablets — In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing.*

Recommendation

The sNDA should not be approved. A new study is required to provide conclusive evidence that Unithroid and approved Synthroid are the same with regard to rate and extent of absorption of levothyroxine.

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/s/

David Orloff
6/22/04 06:18:45 PM
MEDICAL OFFICER

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

12/12/04

NDA 21-210	Efficacy Supplement Type SE-4	Supplement Number S-003	
Drug: Unithroid (levothyroxine sodium tablets) 11 strengths		Applicant: Jerome Stevens Pharms.	
RPM: Elekwachi & Galliers		HFD- 510	Phone # 817-6429

Application Type: (x) 505(b)(1) ( ) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** (x) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	(x) Standard ( ) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
User Fee Goal Dates	April 28, 2005
❖ Special programs (indicate all that apply)	(x) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	( ) Paid UF ID number N/A
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)

Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (x) No
• This application is on the AIP	( ) Yes (x) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	( ) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified **N/A** 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).*	( ) Yes ( ) No ( ) Yes ( ) No

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	( ) Yes ( ) No
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).*	( ) Yes ( ) No
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	Not Applicable; BIOAVAILABILITY STUDIES ONLY
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ **(x)** No
Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	5/24/03;

Version: 6/16/2004

Actions	
• Proposed action	(x) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	RF 5/13/03; NA 6/23/04
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (x) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(x) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	NONE
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	NONE
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	
• Reviews	
❖ Post-marketing commitments	NONE
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other RF, FDR(x2), GUID.	
❖ Advisory Committee Meeting	NONE
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	NONE

Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	DivDir 12/ /04
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	N/A
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	N/A
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	12.10.04
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	5/12/04
❖ Biopharmaceutical review(s) *(indicate date for each review)*	5/12/04; 12/07/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	6/17/04
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	N/A
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: **N/A** ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed **N/A** ( ) Requested ( ) Not yet requested
Nonclinical Pharmacology/Toxicology	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	N/A

11.24.04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-210/S-003

Jerome Stevens Pharmaceuticals
Attention: James P. Rathvon
Piper Rudnick
1200 Nineteenth Street, N.W.
Washington, DC 20036-2412

Dear Mr. Rathvon:

We refer to the New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Unithroid® (levothyroxine sodium tablets, USP).

We also refer to your August 11, 2004, request for formal dispute resolution received on August 12, 2004. In your request for formal dispute resolution, you appeal the not approvable letter issued by Dr. David Orloff, Director, Division of Metabolic and Endocrine Drug Products (the "Division"), to Jerome Stevens Pharmaceuticals (JSP) on June 23, 2004. This letter stated that the Division was not approving JSP's NDA seeking an "AB" rating in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (referred to as the "Orange Book") for its Unithroid product to Abbott Laboratories' (Abbott's) Synthroid®. This letter cited deficiencies in the design of two clinical bioequivalence (BE) trials submitted to support a determination of bioequivalence between Unithroid and Synthroid. Your appeal requests the review of the following two issues that you assert are the basis of the Division's not approvable decision:

1. The sufficiency of JSP's first BE study of Unithroid-Synthroid to support an equivalence determination by FDA despite the use of a pre-NDA sample of Synthroid.
2. The sufficiency of JSP's second BE study of Unithroid-Synthroid using a post-NDA sample to support an equivalence determination by FDA since the anomalies of the parallel study were investigated and explained.

In our October 18, 2004, letter we granted your request for a meeting, held October 26, 2004, (minutes attached). On October 29, 2004, in a telephone communication between you and Kevin Fain, Office of Chief Counsel, you informed us that a third BE study had been completed using a post-NDA sample of Synthroid in a cross-over study design and had been submitted to the supplement. You had not mentioned the existence of the study during the meeting three days earlier. The study was submitted to FDA on October 28, 2004.

This submission constitutes a complete response to the June 23, 2004, not approvable letter and is currently under review by the Division. The PDUFA goal date for this submission is April 28, 2005. This submission provides critical information supporting your request for a determination of bioequivalence between Unithroid and Synthroid. If your submission meets the requirements for a determination of bioequivalence between Unithroid and Synthroid, this dispute resolution request will

be moot. Therefore, we do not intend to address the merits of this dispute at this time. If, after reviewing the study, we determine that it does not show bioequivalence, you may then appeal that determination and the agency can address the merits of your current dispute at that time.

If you have any questions regarding this supplemental application, please contact Oluchi Elekwachi, Regulatory Project Manager at (301) 827-6381. Questions regarding formal dispute resolution should be directed to Kim Colangelo, Associate Director for Regulatory Affairs, at (301) 594-3937.

Sincerely,

{See appended electronic signature page}

/S/

Steven Galson, M.D., M.P.H.
Acting Director
Center for Drug Evaluation and Research

11.17.04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-210/S-003

Jerome Stevens Pharmaceuticals, Inc.
Attn: Ronald Steinlauf
Vice President
60 DaVinci Drive
Bohemia, N.Y. 11716

Dear Mr. Steinlauf:

We acknowledge receipt on October 28, 2004, of your October 8, 2004, resubmission to your supplemental new drug application for Unithroid (levothyroxine sodium tablets, USP).

We consider this a complete, class 2 response to our June 23, 2004, action letter. Therefore, the user fee goal date is April 28, 2005.

If you have any question, call me at (301) 827-6381.

Sincerely,

/S/

{See appended electronic signature page}

Oluchi Elekwachi, PharmD, MPH
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 26, 2004
TIME: 9:00 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
MEETING CHAIR: Steven Galson, M.D.
MEETING RECORDER: Kim Colangelo

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Name of FDA Attendee	Title	Division Name & HFD#
Dr. Steven Galson	Director	FDA/CDER (HFD-001)
Ms. Terry Martin	Regulatory Project Manager	FDA/OEP (HFD-006)
Ms. Kim Colangelo	Associate Director for Regulatory Affairs	FDA/OND (HFD-020)
Mr. Matthew Bacho	Regulatory Project Manager	FDA/OND (HFD-020)
Dr. Robert Meyer	Director	FDA/OND/ODE II (HFD-102)
Mr. Gary Buehler	Director	FDA/OGD (HFD-600)
Mr. Kevin Fain	Regulatory Counsel	FDA/OC/OCC (GCF-1)

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Title	Sponsor/Firm Name
Mr. Jerome Steinlauf	President	Jerome Stevens Pharmaceuticals
Mr. Ronald Steinlauf	Vice President	Jerome Stevens Pharmaceuticals
Dr. [ ]	[ ]	[ ]
Mr. Marc J. Scheineson	Counsel	Alston & Bird
Mr. James Rathvon	Counsel	Piper Rudnick

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").

In a letter dated May 13, 2003, the Division of Metabolic and Endocrine Drug Products (the "Division") refused to file (RTF) the supplemental application under 21 CFR 320.25(e)(3), because the Synthroid reference material was not the subject of an approved new drug application (i.e., was a pre-approval batch). 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 October 3,

2003, correspondence from ODE II upholding the Division's RTF decision. ODE II based its decision on the conclusion that pre-approval batches of Synthroid was not an "appropriate reference material" under 21 CFR 320.26(a)(1).

On November 20, 2003, JSP requested formal dispute resolution and a reconsideration by the OND Immediate Office of the Division's RTF decision and the subsequent affirmation by ODE II. A meeting was held on January 23, 2004, to discuss this appeal. On January 30, 2004, JSP notified Dr. John Jenkins, Director, OND, that a new bioequivalence (BE) study had been conducted comparing Unithroid to an approved batch of Synthroid. This information was submitted to the supplement and received February 13, 2004. On June 23, 2004, the Division issued a not approvable letter for that supplement due to deficiencies in the trial design of the two studies submitted to support the bioequivalence determination between Unithroid and Synthroid.

On August 11, 2004, JSP again requested formal dispute resolution and a meeting with and review by the Center Director of the June 23, 2004, not approvable decision. This meeting was granted via telephone communication on September 17, 2004.

MEETING OBJECTIVES:
To review the following issues , raised by JSP in their August 11, 2004 correspondence, that were the basis of the June 23, 2004, not approvable letter:

- The sufficiency of JSP's first BE study of Unithroid-Synthroid to support an equivalence determination by FDA despite the use of a pre-NDA sample of Synthroid.
- The sufficiency of JSP's second BE study of Unithroid-Synthroid using a post-NDA sample to support an equivalence determination by FDA since the anomalies of the parallel study were investigated and explained.

DISCUSSION POINTS:
Dr. Galson opened the meeting by stating that a decision on the appeal would not be provided at this meeting. Dr. Galson stated that he would listen to and consider JSP's position that sufficient information has been provided to support an AB rating for Unithroid to Synthroid and issue his decision within 30 days.

JSP opened the meeting by stating their belief that Unithroid was the most consistently potent and safe levothyroxine product currently on the market. They accused the Agency of being arbitrary and unfair to date regarding our decision-making on the requested AB rating between Unithroid and Synthroid.

Bioequivalence Study 1: Pre-approval Synthroid
JSP reiterated their position that the pre-approval (pre-NDA) batches of Synthroid were the same as the post-approval batches, and met the criteria of sameness as a pharmaceutical equivalent based on meeting compendial standards. The Synthroid purchased for the first BE study tested at 99-103% potency; compendial standards allow for a range of 90-110%. JSP did not ask the Division about the acceptability of using the pre-approval batch of Synthroid to support bioequivalence, nor did the Division advise them that pre-approval batches would not be acceptable prior to study initiation.

Citizen Petition Response
JSP contended that the Agency response to their Citizen Petition regarding the acceptability of using a pre-approval batch was "insulting", and created and answered arguments not made in their Petition. They cited the Agency's decision to allow the Mylan levothyroxine product to receive an AB rating to Unithroid based on a BE study to a pre-approval batch of Unithroid. The Agency responded that we

had determined that pre- and post-approval batches of Unithroid were the same (i.e., did not contain stability overages as in the Synthroid product). In addition, consistent with our position regarding Unithroid, the Agency did not allow the Mylan levothyroxine product to achieve an AB rating to Synthroid when pre-approval batches of Synthroid were used.

Bioequivalence Study 2: Parallel-trial Design Study using Post-approval Synthroid

JSP stated that because the FDA was not willing to accept the pre-approval Synthroid batches to support BE, they conducted and submitted a second BE study using a parallel-trial design. This trial design was utilized due to the lengthy wash-out period necessary for cross-over studies with levothyroxine. The Division had advised that a parallel-trial design would be acceptable if the data showed bioequivalence. When the study failed, JSP added a post-hoc cross-over arm to the study, citing OGD policy to "salvage" data by allowing re-dosing of subjects in BE studies to convert parallel studies to a cross-over design. While Dr. [ ] argued that such a conversion is scientifically robust, the Center generally does not consider such conversions to be statistically valid unless they are pre-specified. The Agency explained that statistical inferential testing generally does not allow for an interim look at the results without a statistical adjustment. Such a departure from our overall policy would require a scientifically robust explanation and justification. JSP countered that this is a unique situation and not "precedent setting".

Scientific support for conversion of trial design

Dr. [ ] gave a brief presentation regarding the scientific validity of the conversion, and the individual steps taken to preserve the integrity of the study. A request for a copy of the slides presented at the meeting was not answered.

Both CDER and JSP attendees noted that the point estimates were not as tight as had been expected based on information provided at the January 23, 2004, meeting. The widening of this range could not be explained. JSP agreed to provide the specifications of the post-approval Synthroid used in this study.

Closing

When asked, Dr. Galson stated that we would review a third BE study as expeditiously as possible, but would not commit to a timeframe shorter than the PDUFA goal for such a submission. A response to this dispute will issue within 30 days of this meeting (by November 25, 2004.)

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/s/

Steven Galson
11/24/04 02:22:22 PM

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/s/

Oluchi Elekwachi
11/17/04 03:42:24 PM

10.18.04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-210/S-003

Jerome Stevens Pharmaceuticals
Attention: Marc J. Scheineson
Alston & Bird LLP
601 Pennsylvania Avenue, N.W.
North Building, 10th Floor
Washington, DC 20004-2601

Dear Mr. Scheineson:

We refer to the New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Unithroid® (levothyroxine sodium tablets, USP).

We also refer to your August 11, 2004, request for formal dispute resolution received on August 12, 2004. In your request for formal dispute resolution, you appeal the not approvable letter issued by Dr. David Orloff, Director, Division of Metabolic and Endocrine Drug Products ("Division"), to Jerome Stevens Pharmaceuticals (JSP) on June 23, 2004. This letter stated that the Division was not approving JSP's NDA seeking an AB rating for its Unithroid product to Abbott Laboratories' (Abbott's) Synthroid®. This letter cited deficiencies in the design of two clinical bioequivalence (BE) trials submitted to support a determination of bioequivalence between Unithroid and Synthroid. Your appeal requests the review of the following two issues that you assert are the basis of the Division's not approvable decision:

1. The sufficiency of JSP's first BE study of Unithroid-Synthroid to support an equivalence determination by FDA despite the use of a pre-NDA sample of Synthroid.
2. The sufficiency of JSP's second BE study of Unithroid-Synthroid using a post-NDA sample to support an equivalence determination by FDA since the anomalies of the parallel study were investigated and explained.

This is to confirm the verbal response to your request given in the September 17, 2004, telephone conversation between Kim Colangelo, Associate Director for Regulatory Affairs, Office of New Drugs, and yourself. The meeting has been scheduled as follows:

Date:	October 26, 2004
Time:	9:00-10:00 AM, EDT
Location:	Rockwall II, Conference Room 1033 5515 Security Lane, Rockville

In addition to myself, representatives from the Office of New Drugs, Office of Drug Evaluation II, Office of Generic Drugs, Office of Regulatory Policy, and the Office of Chief Counsel have been invited to attend. We will respond to the appeal within 30 days of the meeting.

If you have any questions, call Ms. Colangelo, at (301) 443-5374.

Sincerely,

{See appended electronic signature page}

Steven Galson, M.D.
Director
Center for Drug Evaluation and Research

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/s/

Steven Galson
10/18/04 12:43:35 PM

17 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-210/S-003

Jerome Stevens Pharmaceuticals, Inc.
Attention: Ronald J. Steinlauf
Vice President
Sixty DaVinci Drive
Bohemia, NY 11716

3/23/04

Dear Mr. Steinlauf:

Please refer to your March 26, 2003, supplemental new drug application (NDA) for Unithroid (levothyroxine sodium tablets, USP) which 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").

In a letter dated May 13, 2003, this Division refused to file (RTF) the supplemental application, because the Synthroid reference material (Lot # 0000339726) was not the subject of an approved new drug application.

We also refer to your correspondence received May 23, 2003, which requested a meeting and appealed the RTF decision to Dr. Robert Meyer, Director of 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 Dr. Meyer's October 3, 2003, correspondence, which upheld the Division's RTF decision.

On November 20, 2003, you 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) issued a letter dated December 19, 2003, granting you a meeting which was held on January 23, 2004.

In addition, on January 30, 2004, in a telephone communication, you notified us of a new bioequivalence study comparing Unithroid to an approved batch of Synthroid. The data from this study was submitted to the application and received on February 13, 2004.

We also refer to the February 20, 2004, letter issued by Dr. John Jenkins, which stated that we have filed this application over protest. This supplemental application is considered to have been filed over protest as of July 22, 2003, according to 21 CFR 314.101(a)(3) (60 days after the May 23, 2003, request for a conference on the RTF decision.)

The file over protest (FO) user fee goal date was calculated from the May 23, 2003, receipt of your meeting request and it was March 23, 2004. However, your amendment dated and received on February 13, 2004, constitutes a major amendment to this application. The receipt date is

within three months of the user fee goal date. Therefore, we are extending the goal date by three months from the user fee goal date of March 23, 2004, to provide time for a full review of the submission. The extended user fee goal date for this supplemental application is June 23, 2004.

If you have any questions, call Oluchi Elekwachi, Pharm.D., M.P.H., Regulatory Health Project Manager, at 301-827-6381.

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

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/s/

Enid Galliers
3/23/04 09:41:54 AM
Signing for Dr. Orloff.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-210/S-003

2/20/04

Jerome Stevens Pharmaceuticals, Inc.
ReedSmith, agent for Jerome Stevens Pharmaceuticals
Attention: Marc J. Scheineson, Esq.
1301 K Street, N.W.
Suite 1100 – East Tower
Washington, DC 20005-3373

Dear Mr. Scheineson:

We refer to the supplemental New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Unithroid® (levothyroxine sodium tablets, USP).

We refer also to your November 20, 2003, memorandum addressed to Dr. Robert Temple, Director, Office of Medical Policy. This memorandum requested a reevaluation of the Refuse to File (RTF) decision made by Dr. David Orloff, Director, Division of Metabolic and Endocrine Drug Products (DMEDP), that was affirmed by Dr. Robert Meyer, Director, Office of Drug Evaluation II (ODE II). As per our telephone discussion on December 16, 2003, and our letter dated December 19, 2003, we planned to address your request via our established procedures for formal dispute resolution. The RTF action was taken because DMEDP determined that the use of an unapproved batch of Synthroid® was not an "appropriate reference material" to support therapeutic equivalence between Unithroid and Synthroid.

In our December 19, 2003, letter we also granted your request for a meeting, held January 23, 2004 (minutes attached). During that meeting, you presented new scientific and regulatory information (submitted in the background package dated January 20, 2004) that had not been submitted to, or reviewed by, DMEDP or ODE II, in making their determinations. Please note that pursuant to the CDER/CBER Guidance to Industry "Formal Dispute Resolution: Appeals Above the Division Level," no new information should be submitted as part of the request for reconsideration or appeal. In addition, on January 30, 2004, in a telephone communication, you notified us of a new bioequivalence study comparing Unithroid to an approved batch of Synthroid. The data from this study was submitted to the application and received on February 13, 2004.

We believe that the new information submitted January 20, and February 13, 2004, provide sufficient information to support review of your application.

Therefore, this supplemental application will be considered filed as of July 22, 2003, according to 21 CFR 314.101(a)(3) (60 days after the May 23, 2003, request for a conference on the RTF decision.) Your February 13, 2004, amendment constitutes a major amendment to this application. Therefore, the PDUFA goal date for this supplemental application is June 23, 2004. Please be aware that accepting this supplemental application for filing does not guarantee its approval and that all applicable review issues, including inspections, will need to be satisfactorily addressed.

If you have any questions regarding this supplemental application, please contact Oluchi Elekwachi, Regulatory Project Manager, at (301) 827-6381.

Sincerely,

/S/

{See appended electronic signature page}

John K. Jenkins, M.D., F.C.C.P.
Director
Office of New Drugs
Center for Drug Evaluation and Research

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:

Name of FDA Attendee	Title	Division Name & HFD#
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:

External Attendee	Title	Sponsor/Firm Name
Jerome Steinlauf	President	Jerome Stevens Pharmaceuticals
Ronald Steinlauf	Vice President	Jerome Stevens Pharmaceuticals
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
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").

NDA 21-210/S-003

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. [ ] 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

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 to 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. [ ] 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.

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:

Item	Responsible Person	Due Date
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

NDA 21-210/S-003

ATTACHMENTS/HANDOUTS:

1. Dr. [redacted]
2. [redacted]

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

MEETING MINUTES

27 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

John Jenkins
2/20/04 04:57:20 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-210/S-003

12/19/03

HH9/03

ReedSmith
Attention: Marc J. Scheineson, Esq.
1301 K Street, N.W.
Suite 1100 – East Tower
Washington, D.C. 20005-3373

Dear Mr. Scheineson:

We refer to the supplemental New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Unithroid (levothyroxine sodium tablets, USP).

We refer also to your memorandum, dated and received on November 20, 2003. This memorandum requests a reevaluation of the Refuse to File (RTF) decision made by Dr. David Orloff, Director, Division of Metabolic and Endocrine Drug Products, that was affirmed by Dr. Robert Meyer, Director, Office of Drug Evaluation II. As discussed with you by telephone on December 16, 2003, we are planning to address your request via our established procedures for formal dispute resolution. This matter has been forwarded for review to Dr. John Jenkins, Director, Office of New Drugs.

This letter serves to confirm the telephone conversation between yourself and Kim Colangelo, Associate Director for Regulatory Affairs, Office of New Drugs, granting your request for a meeting on this matter. The meeting has been scheduled as follows:

Date/Time:	January 23, 2004, 8:30 – 10:00 AM EST
Location:	Rockwall II, Conference Room 1033 5515 Security Lane, Rockville, MD

In addition to Dr. Jenkins, representatives from the following offices have been invited to attend the meeting: Office of Drug Evaluation II, Division of Metabolic and Endocrine Drug Products, Office of Generic Drugs, Office of Regulatory Policy, Office of Medical Policy, and Office of Chief Counsel.

If you have any questions, please call Ms. Colangelo, Formal Dispute Resolution Project Manager, at (301) 443-5374.

Sincerely,

/S/

{See appended electronic signature page}

John K. Jenkins, M.D., F.C.C.P.
Director
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

John Jenkins
12/19/03 02:52:03 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-210/S-003

Jerome Stevens Pharmaceuticals, Inc.
Attention: Mr. Ronald Steinlauf
Vice President
Sixty DaVinci Drive
Bohemia, NY 11716

10/3/03

Dear Mr. Steinlauf:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Unithroid (levothyroxine sodium tablets, USP).

We also refer to your submissions dated May 26 (received May 23), June 30, and July 23 and 25, 2003.

This letter responds to your request that the Food and Drug Administration (FDA) reconsider its May 13, 2003, decision to refuse to file Jerome Stevens' supplemental new drug application (NDA 21-210/S-003) containing a bioequivalence study comparing Unithroid with Synthroid. The purpose of that application was for Unithroid to be rated therapeutically equivalent to Synthroid.

Background

By letter dated May 13, 2003, Dr. David G. Orloff, Director, Division of Metabolic and Endocrine Drug Products (DMEDP), refused to file Jerome Stevens' application because the Synthroid product used in the bioequivalence study (referred to as the "pre-approved Synthroid") was not the subject of an approved application. The letter cited 21 CFR 320.25(e)(3), which states that the "reference material should be taken from a current batch of a drug product that is the subject of an approved new drug application and that contains the same active drug ingredient or therapeutic moiety, if the new formulation . . . is intended to be comparable to or to meet any comparative labeling claims made in relation to the drug product that is the subject of an approved new drug application."

By letter dated May 26, 2003, Jerome Stevens asked Dr. Orloff to reconsider the refuse to file decision and hold an informal conference with Jerome Stevens pursuant to 21 CFR 314.101(a)(3).[1] Jerome Stevens' legal counsel, Jonathan Emord and Andrea Ferrenz, submitted correspondence dated June 30, July 23, and July 25, 2003, to Dan Troy, Chief Counsel, in support of their position. FDA held an informal conference with Jerome Stevens and its legal counsel on July 24, 2003.

[1] The letter is mistakenly dated May 26, 2003, because DMEDP actually received the letter on May 23, 2003.

Analysis

Although Dr. Orloff's letter cited FDA's regulation at 21 CFR 320.25, the regulation that applies more specifically to Jerome Stevens' bioequivalence study is 21 CFR 320.26, titled "Guidelines on the design of a single-dose in vivo bioavailability study or bioequivalence study." The pertinent part of that regulation is 21 CFR 320.26(a)(1), which states: "An in vivo bioavailability and bioequivalence study should be a single-dose comparison of the drug product to be tested and the appropriate reference material conducted in normal adults."

In a bioequivalence study comparing a drug product to Synthroid, the "appropriate reference material" under 21 CFR 320.26(a)(1) is the Synthroid product approved under the NDA and not the pre-NDA Synthroid product.

The Synthroid tablets used by Jerome Stevens in its bioequivalence test contained an overage of levothyroxine sodium at the time of release. The approved Synthroid drug product, however, targets 100% of labeled claim at release. Thus, the batch formulas of the two drug products are different. Because of this difference between pre-NDA and approved Synthroid, pre-NDA Synthroid is not the "appropriate reference material" for a bioequivalence study that is meant to establish therapeutic equivalence between Unithroid and the approved Synthroid product.

The conclusion that pre-NDA Synthroid is not the "appropriate reference material" is further supported by the agency's supplemental application requirements. If Abbott had sought to make this change in the formula amount of active ingredient under a currently approved NDA, the company would have been required to submit a supplement for approval under 21 CFR 314.70(b)(2)(i) (as a change in the composition of the drug product).

Based on this scientific and legal analysis, FDA has concluded the Synthroid tablets used in Jerome Stevens' bioequivalence study were not "the appropriate reference material." Accordingly, I affirm DMEDP's refusal to file Jerome Stevens' supplemental new drug application (NDA 21-210/S-003), because Jerome Stevens failed to use the approved Synthroid drug product as the reference material for its bioequivalence test.

Sincerely,

/S/

{See appended electronic signature page}

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

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/s/

Robert Meyer
10/3/03 05:06:20 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-210/S-003

9/16/03

Jerome Stevens Pharmaceuticals
Attention: Ronald Steinlauf
Vice President
Sixty DaVinci Drive
Bohemia, NY 11716

Dear Mr. Steinlauf:

Please refer to the teleconference between representatives of your firm and FDA on September 2, 2003. The purpose of the meeting was to discuss a draft protocol for a parallel-design, bioequivalence study to compare Abbott Laboratories' approved Synthroid to your approved Unithroid (levothyroxine sodium tablets, USP).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-6429.

Sincerely,

/S/

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 2, 2003

TIME: 11:00 AM

LOCATION: C/R 13B-45

APPLICATION: NDA 21-210/S-003 Unithroid (levothyroxine sodium tablets, USP)

TYPE OF MEETING: TELEPHONE CONFERENCE

MEETING CHAIR: Hae-Young Ahn, Ph.D.

MEETING RECORDER: Enid Galliers

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1. Hae-Young Ahn, Ph.D.	Biopharmaceutics Team Leader	Division of Pharmaceutical Evaluation II (DPE II) (HFD-870), Office of Clinical Pharmacology and Biopharmaceutics, (OCPB)
2. Sang Chung, Ph.D.	Biopharmaceutics Reviewer	DPE II (HFD-870)
3. Oluchi Elekwachi, Pharm.D., M.P.H.	Regulatory Project Manager	Division of Metabolic and Endocrine Drug Products (DMEDP; HFD-510), Office of Drug Evaluation II, CDER
4. Enid Galliers	Chief, Project Management Staff	DMEDP, HFD-510

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Title	Sponsor/Firm Name
1. Ron Steinlauf	Vice President	Jerome Stevens Pharmaceuticals (JSP)
2. Bill Cardone	Scientific Director	JSP
3. [redacted]	[redacted]	[redacted]
4. [redacted]	[redacted]	[redacted]

BACKGROUND: On August 26, 2003, the firm requested a telephone conference (tcon) to discuss the acceptability of a new protocol for a parallel-design, randomized bioequivalence study to compare Unithroid to Synthroid. A copy of the protocol outline was emailed on August 28, 2003.

MEETING OBJECTIVES:

1. To reach consensus on a study design that could meet the Agency's requirements to demonstrate therapeutic equivalence and thus earn an AB rating between Unithroid and Synthroid.

2. The firm wants to obtain written agreement from the Agency to review the results of the proposed study within 45 days after receiving it.

DISCUSSION POINTS AND DECISIONS (AGREEMENTS) REACHED:

1. The Agency requested two minor refinements of the protocol to which Dr. [ ] agreed. One issue involved changing the sampling times for baseline correction from -1, -.5, 0 hrs to -.5, -.25, 0 hrs. The other issue was the absence of a specification for specific AUC calculations; the firm agreed to provide AUC_{24} and AUC_{48}.

2. The Agency agreed in principle that the study protocol (a parallel-design study) was acceptable.

3. The Agency stated clearly it was not certifying that the sample size was adequate nor would the new study be considered a bridging study; i.e., the study would have to stand on its own with adequate statistical power. The firm indicated it understood.

4. There was a brief discussion on FDA's classification of the bioequivalence studies needed for AB ratings as "type 4 efficacy supplements" (i.e., a supplement which contains study results from a comparison of approved products) and their eligibility for standard (10-month) and priority (6 month) review clocks.

5. Mr. Steinlauf requested a written commitment for a 45-day review of the results of the proposed study, and FDA said it could not make that commitment but would pass on the request to management and Office of Chief Counsel (OCC).

6. Mr. Steinlauf said that without such a review commitment he would not do another study (which he still believed to be not necessary and had not been justified by the Agency), and he would pursue other courses of action; e.g., contacting OCC as the first step.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

1. Mr. Steinlauf asked for a written commitment from the Agency to review the proposed study within 45 days after receiving the data.

ACTION ITEMS:

Item	Responsible Person	Due Date
1. Convey JSP request to management and Office of Chief Counsel	Enid Galliers	As soon as possible

Minutes Preparer: /s/ 9.16.03
Enid Galliers, CPMS, DMEDP

Chair Concurrence: /s/ 9.16.03
Hae-Young Ahn, Ph.D.
Biopharmaceutics Team Leader

ATTACHMENTS/HANDOUTS:
Draft protocol outline

MEETING MINUTES

[redacted]	Jerome Stevens
[redacted] Levothyroxine Thyroid hormone	[redacted] Synthroid Abbott 0.3 mg tablet
[redacted] Class A	[redacted] 26-Aug-03
[redacted] Yes	[redacted] 138 ± 20, 135 ± 18, 137 ± 15 and 128 ± 23 ng/mL
[redacted] No	[redacted] Median 2.5 (1-6) hrs
[redacted] N/A	[redacted] Not applicable
[redacted] Single-period, parallel study with two 0.3-mg tablets (total dose of 600 µg)	
[redacted] 18	-1, -0.5, 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 18, 24, 48 hours
[redacted] -10 to 24 hours	[redacted] 1
[redacted] Levothyroxine	
[redacted]	see below see below

[redacted]	40	----
	4	----

[redacted] None

[redacted] None

P1CK02001 = Unithroid vs. Synthroid; P1CK02003 = Unithroid vs. Levoxyl

[redacted]	P1CK02001 Uncorrected	Intrasubject cv of 8.7% for Cmax and 7.1% for AUC-96
	P1CK02001 Corrected	Intrasubject cv of 10.9% for Cmax 14.2, 16.2 and 21.0% for AUC-24, AUC-48 and AUC-96
	P1CK02003 Uncorrected	Intrasubject cv of 10.7% for Cmax and 5.0% for AUC-96
	P1CK02003 Corrected	Intrasubject cv of 21.2% for Cmax 12.4, 13.4 and 16.4% for AUC-24, AUC-48 and AUC-96

[redacted]

Based on the non-baseline corrected data, the calculated effect size was 1.49 and 1.50 for AUCt and Cmax in P1CK02001; and 1.82 and 1.10 for AUCt and Cmax in study P1CK02003.

Based on the baseline-corrected data, the calculated effect size was 0.78, 0.

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/s/

Enid Galliers
9/16/03 02:23:57 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # **21-210** Supplement # **003** SE4

5/24/03

Trade Name: Unithroid
Generic Name: levothyroxine sodium tablets, USP
Strengths: (11) 25, 50, 75, 88, 100, 112, 125, 150, 175, 200, 300 mcg

Applicant: Jerome Stevens Pharmaceuticals, Inc.

Date of Application: March 26, 2003
Date of Receipt: March 27, 2003
Date clock started after UN:
Date of Filing Meeting: April 30, 2003
Filing Date: May 26, 2003
Action Goal Date (optional): User Fee Goal Date: RF

CHANGE requested: To show comparability between Unithroid and Synthroid and obtain an AB rating

Type of Application: Original (b)(1) NDA _____ Original (b)(2) NDA _____
(b)(1) Supplement _____ (b)(2) Supplement ___X_____
[If the Original NDA was a (b)(2), all supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or a (b)(2).]

NOTE: If the application is a 505(b)(2) application, complete the 505(b)(2) section at the end of this summary.

Therapeutic Classification: S ____X____ P _____
Resubmission after a withdrawal? _____ Resubmission after a refuse to file? _____
Chemical Classification: (1,2,3 etc.) ____N/A___
Other (orphan, OTC, etc.) _____

User Fee Status: Paid ___N/A____ Waived (e.g., small business, public health) _____
Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: YES NO
User Fee ID # N/A
Clinical data? YES **NO**, Referenced to NDA # ____**N/A**_____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES **NO**

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? YES **NO**

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

N/A YES NO

Is the application affected by the Application Integrity Policy (AIP)? YES **NO**
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES **NO**

- Does the submission contain an accurate comprehensive index? **YES** NO
- Was form 356h included with an authorized signature? **YES** NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? **YES** NO
  If no, explain:
- If an electronic NDA, does it follow the Guidance? **N/A** YES NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- If in Common Technical Document format, does it follow the guidance? **N/A** YES NO
- Is it an electronic CTD? **N/A** YES NO
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- Patent information included with authorized signature? **YES** NO
- Exclusivity requested? YES, _____years **NO**
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? **YES** NO
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as "To the best of my knowledge . . . ."
- Financial Disclosure information included with authorized signature? **YES** NO
  (Forms 3454 and/or 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES **N/A** NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- **PDUFA** and Action Goal dates correct in COMIS? **YES** NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections. **Y**

- List referenced IND numbers: **None**

- End-of-Phase 2 Meeting(s)? Date(s) _____ **NO**
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____ **NO**
  If yes, distribute minutes before filing meeting.

Project Management

- Package insert consulted to DDMAC? **N/A** YES NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support? **N/A** YES NO

- MedGuide and/or PPI (plus PI) consulted to ODS/Div. of Surveillance, Research and Communication Support?
  N/A YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/ Div. of Surveillance, Research and Communication Support?
  N/A YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? **N/A**
  YES NO

Chemistry

N/A

- Did applicant request categorical exclusion for environmental assessment? YES NO
  If no, did applicant submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO

- If parenteral product, consulted to Microbiology Team (HFD-805)? YES **N/A** NO

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #: **N/A**

- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Requests AB rating to Synthroid

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

YES **NO**

- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

YES **N/A** NO

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

YES **N/A** NO

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

__X__ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

_____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:

  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    YES **NO**

  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    N/A YES NO

  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug? **It compares one approved product to another approved product.**

    N/A YES NO

  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

    N/A YES NO

- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    YES NO

  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    YES NO

  - EITHER
    The number of the applicant's IND under which the studies essential to approval were conducted.

    YES, IND # _____ NO

    OR
    A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

    N/A YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

  YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 30, 2003

BACKGROUND: Unithroid was the first levothyroxine sodium tablets NDA approved. This supplement provides a comparative bioavailability study to obtain an AB rating to Synthroid.

ATTENDEES: Dr. David Orloff, Dr. Hank Malinowski, Dr. Hae-Young Ahn, Dr. Mamta Gautam-Basak, Dr. Sang Chung, Dr. David Lewis, Enid Galliers.

ASSIGNED REVIEWERS:

Discipline		**Reviewer**
Medical:	(Financial Disclosure only)	J. Temeck
Secondary Medical:		
Statistical:		-----
Pharmacology:		-----
Statistical Pharmacology:		-----
Chemist:		-----
Environmental Assessment (if needed):		-----
Biopharmaceutical:		Sang Chung
Microbiology, sterility:		-----
Microbiology, clinical (for antimicrobial products only):		-----
DSI:		Vishwanathan
Regulatory Project Manager:		Enid Galliers
Other Consults:		-----

Per reviewers, are all parts in English or English translation? **YES** NO
If no, explain:

CLINICAL FILE _____ REFUSE TO FILE _____ **N/A**

- Clinical site inspection needed: YES NO
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

  N/A YES NO

CLINICAL MICROBIOLOGY FILE _____ REFUSE TO FILE _____ **N/A**

STATISTICS FILE _____ REFUSE TO FILE _____ **N/A**

BIOPHARMACEUTICS FILE _____ REFUSE TO FILE __X__

- Biopharm. inspection needed: **No, because it is refused to file.** YES NO

PHARMACOLOGY FILE _____ REFUSE TO FILE _____ **N/A**

- GLP inspection needed: YES NO

CHEMISTRY FILE _____ REFUSE TO FILE _____ **N/A**

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:
Any comments: Disks w data were submitted but could not be loaded into the EDR.

REGULATORY CONCLUSIONS/DEFICIENCIES:

__X__ The application is unsuitable for filing. Explain why: **The lot of Synthroid (#0000339726) used for the comparative study was manufactured prior to approval of the Synthroid NDA 21-402, and is therefore not the subject of an approved NDA as required by 21 CFR 320.25(e)(3).**

_____ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER. **RF letter sent 05.13.2003.**
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

Enid Galliers
Chief, Project Management Staff, HFD-510

C:\Data\Wpfiles\FilingSummary2.doc
LRipper/1-13-03

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/s/

Enid Galliers
5/24/03 07:12:07 PM
CSO
Refue to File letter was issued on May 13, 2003.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-210/S-003

5/13/03

Jerome Stevens Pharmaceuticals, Inc.
Attention: Ronald J. Steinlauf
Vice President
Sixty DaVinci Drive
Bohemia, NY 11716

Dear Mr. Steinlauf:

Please refer to your March 26, 2003new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Unithroid (levothyroxine sodium tablets, USP).

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reason:

> In this supplement, you propose to establish that Unithroid is comparable (i.e., therapeutically equivalent) to Synthroid (levothyroxine sodium tablets, USP) manufactured by Abbott Laboratories and request an "AB" rating in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (referred to as the "Orange Book".)
>
> To support this claim, you compared Unithroid to Synthroid (Lot # 0000339726) in a comparative bioavailability study (P1CK02001) in which the reference material, Synthroid tablets, used in your study was not the subject of an approved new drug application.
>
> The Code of Federal Regulations requires that the "reference material should be taken from a current batch of a drug product that is the subject of an approved new drug application and that contains the same active drug ingredient or therapeutic moiety, if the new formulation . . . is intended to be comparable to or to meet any comparative labeling claims made in relation to the drug product that is the subject of an approved new drug application" (21 CFR 320.25(e)(3).

Within 30 days of the date of this letter, you may request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the informal conference, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the informal conference. The application will be considered a new original application for user fee purposes.

If you have any questions, call Enid Galliers, Chief, Project Management Staff, at (301) 827-6429.

Sincerely,

/S/

{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

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/s/

David Orloff
5/13/03 05:41:49 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-210/S-003

PRIOR APPROVAL SUPPLEMENT

5/6/03

Jerome Stephens Pharmaceuticals, Inc.
Attn: Ronald Steinlauf
Vice President
60 DaVinci Drive
Bohemia, NY 11716

Dear Mr. Steinlauf:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Unithroid (levothyroxine sodium tablets, USP)
NDA Number:	21-210
Supplement number:	S-003
Review Priority Classification:	Standard
Date of supplement:	March 26, 2003
Date of receipt:	March 27, 2003

We have administratively separated your submission into two supplements – one for each comparative study.

This supplemental application (Supplement-003) proposes to demonstrate interchangeability between **Unithroid** and the reference product **Synthroid** based on the results of a comparative bioavailability study, **P1CK02001**.

Supplement-002 proposes to demonstrate interchangeability between **Unithroid** and the reference product **Levoxyl** based on the results of a comparative bioavailability study, **P1CK02003**.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 26, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be January 27, 2004.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6429.

Sincerely,

/S/ *{See appended electronic signature page}*

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Enid Galliers
5/6/03 06:52:53 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-210

Jerome Stevens Pharmaceuticals, Inc.
Attention: Ronald J. Steinlauf
Vice President, Regulatory Affairs
Sixty DaVinci Drive
Bohemia, New York 11716

1/16/03

Dear Mr. Steinlauf:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Unithroid (levothyroxine sodium tablets, USP).

We also refer to your September 11, 2002, letter (fax) requesting bioequivalence status for (i.e., an AB rating between) Unithroid to the recently approved Synthroid. In the same letter you inquired whether the firm could achieve bioequivalence status by submission of a supplement to the existing NDA for Unithroid. In addition, if a supplement were required, what appropriate study requirements for the bioequivalence study comparing Unithroid to Synthroid would be necessary.

In response to your request, we agree that the procedure for determining the bioequivalence status of Unithroid versus Synthroid can be accomplished through supplementing your Unithroid NDA with the appropriate studies. We are enclosing a *"Protocol – Bioequivalence of levothyroxine sodium tablets"* to be used as a guide for the submission and conduct of these studies. We recommend that you submit a protocol to your IND and request comments before initiating your study.

If you have any questions, call Steve McCort, Regulatory Project Manager, at (301) 827-6415.

Sincerely,

/S/

{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

ENCLOSURE

PROTOCOL -- Bioequivalence of levothyroxine sodium tablets

OBJECTIVE: The of objective of this study is to determine if bioequivalence can be conferred between Product A and Product B.

METHODOLOGY: Single-dose, two-treatment, two-sequence, crossover design. The total administered dose given for each regimen will be 600 mcg levothyroxine sodium. Subjects will receive one of two sequences of Regimen A (two 300 mcg Product A tablets) and Regimen B (two 300 mcg Product B tablets) under fasting conditions in the morning of study day 1 of each period. A washout interval of at least 35 days will separate the doses in consecutive study periods.

Blood samples for total (free + bound) thyroxine (T_4) assay will be collected at –0.5, -0.25, 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, 36, and 48 hours post dose.

SUBJECTS: Refer to Guidance for Industry: Levothyroxine Sodium Tablets - In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing

EVALUATION:

Pharmacokinetic: The pharmacokinetic parameter values of total thyroxine (T_4) will be estimated using non-compartmental methods. These will include the maximum serum concentration (C_{max}) and time to C_{max} (T_{max}), the area under the concentration-time curve (AUC) from time 0 to 24 hours (AUC_{24}) and time 0 to 48 hours (AUC_{48}).

Values of these parameters (C_{max}, T_{max}, AUC_{24}, and AUC_{48}) will be determined after correcting all post-dose concentrations using the following method:

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

Statistical: Analysis of variance (ANOVA) will be performed for log-transformed C_{max}, AUC_{24}, and AUC_{48}, using the SAS General Linear Models (GLM) procedure. The geometric means and 90% confidence intervals of the geometric mean ratio of C_{max} and AUC_{0-t} will be presented for each pairwise comparison. Bioequivalence is demonstrated if the 90% confidence intervals fall within the 80 – 125 percent range for corrected T_4.

SAFETY: Refer to appropriate *Guidance for Industry* documents.

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/s/

David Orloff
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