

021216 - S-002 . PAP

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

21-210/S-002

Trade Name: Unithroid Tablets

Generic Name(s): (levothyroxine sodium)

Sponsor: Jerome Stevens Pharmaceuticals,
Inc.

Agent:

Approval Date: June 23, 2004

Indication: Demonstrates bioequivalence between
Unithroid and Levoxyl in order to obtain an AB rating

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RESEARCH**

APPLICATION NUMBER:

21-210/s-002

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Reviews / Information Included in this NDA Review.

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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-210/S-002

Approval Letter(s)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-210/S-002

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 submission dated May 1, 2003.

This supplemental new drug application proposes to demonstrate bioequivalence between Unithroid and Levoxyl 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 Levoxyl (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 Levoxyl. 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

NDA 21-210/S-002

Page 2

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 Oluchi Elekwachi, Pharm.D., M.P.H., Regulatory Project Manager, at (301) 827-6381.

Sincerely,

/s/
{See attached 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-002

Medical Review(s)

MEMO TO FILE

NDA: 21-210/SE4-002
Sponsor: Jerome Stevens Pharmaceuticals
Drug Name: Unithroid
Date of Submission: March 26, 2003
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 02:28:18 PM
MEDICAL OFFICER

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

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	L	1	

- (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 Ronald Steinlauf	TITLE Vice President
FIRM / ORGANIZATION Jerome Stevens Pharmaceuticals, Inc.	
SIGNATURE 	DATE 3/26/03

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

PROTOCOL -- Bioequivalence of levothyroxine sodium tablets

OBJECTIVE: The 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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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-210/S-002

**Clinical Pharmacology and Biopharmaceutics
Review**

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW**

NDA:	21-210
Submission Date(s):	26-March- 2003, 1-May-2003
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-002) for AB rating
Strength(s)	25, 50, 75, 88, 100, 112, 125, 137, 150, 200, and 300 mcg tablets
Indication	Hypothyroidism and suppression of thyroid-stimulating hormone

1 Executive Summary

The sponsor submitted this supplement to demonstrate interchangeability for Unithroid™ (test) with Levoxyl® (reference) manufactured by Jones Pharma (table 1). The tablet of 0.3mg Levoxyl® is listed as one of reference listed drugs in the Electronic Orange Book as of July 2003.

Table 1 Information on test and reference products

	Test	Reference
Name	Unithroid™ 0.3 mg tablet	Levoxyl® 0.3 mg tablet
Lot No.	006701	7483
Exp. Date	6/2003	9/2003
Assay*	96.3%	90.1%
Content Uniformity* (mean of 10 tablets)	95.43%	93.41%

*: Specification was $\pm 5\%$ and $\pm 5\%$ for the assay and the content uniformity (each tablet), respectively.

A comparative bioavailability between two formulations was assessed in an open-label, single dose, crossover study in healthy volunteers (Protocol P1CK02003). Oral doses of 0.6mg (two 0.3mg tablets) were administered under fasting condition and twenty blood samples were obtained including three pre-dose samples for baseline adjustment. There was 49 days washout period between the treatment periods.

Baseline was corrected with the average of the three concentrations at -0.5, -0.25, and 0 hour prior to dosing in each period. Negative values after the correction were set to zero. AUC₀₋₄₈ and C_{max} ratio (test/reference) and 90% confidence interval (CI) were calculated with the corrected concentrations based on the current recommendation on statistical methods in Guidance for Industry**

- **:
1. Guidance for Industry, Bioavailability and Bioequivalence 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 *in vivo* study results (n=24) met the current statistical criteria for the BE between the test (Unithroid) and the reference (Levoxyl) formulation with AUC₀₋₄₈ (CI) and C_{max} (CI) ratios of 102.7 (96.2-109.7) and 108.1 (97.4-120.0), respectively. Results of statistical analyses are summarized in the figure 1 and table 2.

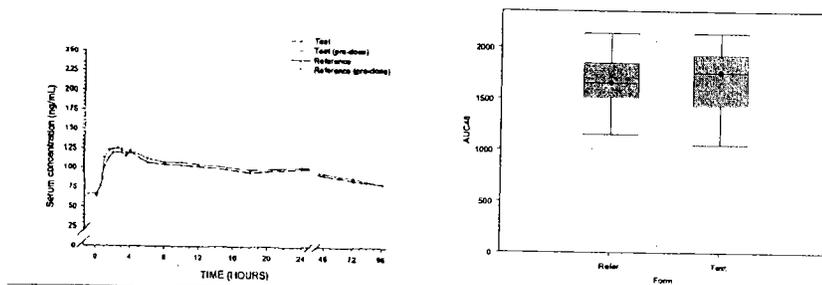


Figure 1 Mean plasma concentration-time profiles of uncorrected data (left) and box plot of untransformed AUC₀₋₄₈ of baseline corrected data (Closed circle, box, and bracket are for median, 1st quartile, and 3rd quartile, respectively.)

Table 2 Statistical results for BE assessment based on the baseline corrected data

Parameter	Ratio of T/R (%)	90% CI
AUC ₂₄	103.4	97.3-109.9
AUC ₄₈	102.7	96.2-109.7
AUC _t	101.0	93.2-109.5
C _{max}	108.1	97.4-120.0

The serum total levothyroxine (T4) was analyzed using the L with lower and upper limit of quantitation of L 3 ng/ml (%CV; \pm 1) and L 3 ng/ml

(%CV; ≤ 1), respectively. Representative calibration curve in human plasma is shown in figure 3.

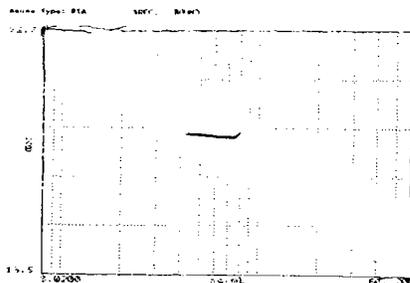


Figure 3 Representative calibration curve of Levothyroxine in human plasma ($r=0.9996$).

In addition, the sponsor requested a waiver of *in vivo* bioequivalence (BE) studies for the 25, 50, 75, 88, 100, 112, 125, 137, 150, and 200 microgram strengths by referencing the original NDA for 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 these regards, the request of waiver can be granted based on the original NDA data and review.

The test product (Unithroid™) is not included 175 microgram strength compared to strengths in the reference product (Levoxyl®). However, this does not raise a regulatory issue on the waiver request according to the informal OGD consult of current practice.

The Division of Scientific Investigations (DSI) conducted audits of clinical study site and analytical study site, and recommended accepting the data from the study. The transmittal memo from DSI is in the attachment 2.

Studies were conducted at the following facilities:

- Clinical study

○ []

- Analytical study

○ []

- Statistical analysis

○ []

Optional Intra-Division CPB briefing was held on 3 December, 2003 at 13B17 (Attendee: Drs. Henry Malinowski, John Hunt, Hae-Young Ahn, Solomon Sobel, Sam Haidar, Robert Lionberger, and Sang M. Chung) and it was concluded that there was no major regulatory issues.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE-2) reviewed the supplemental NDA 21-210 S002 and finds it acceptable. This recommendation should be sent to the sponsor as appropriate.

List of Attachments

1. Synopsis
2. Transmittal memo from DSI

Attachment starts here.

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1. Synopsis

REF: 000003

BASELINE-CORRECTED RESULTS
PROJECT CODE: P1CK02003
REV. 0, 28-APR-03

SYNOPSIS

This report was prepared to provide additional results requested by the Sponsor. In the original analysis, bioequivalence was assessed on the basis of C_{max} , T_{max} and AUC_t using the data uncorrected for the levothyroxine baseline values. In addition to these parameters, the Sponsor requested to also provide the area under the serum concentration-time curve calculated from time zero to 24 hours (AUC_{24}) as well as from time zero to 48 hours (AUC_{48}) and to carry out the baseline correction. Parameters related to concentrations and the various AUC's were also transformed to their natural logarithm. Details of the study and the original pharmacokinetic and statistical report can be found in the previous final report (P1CK02003, REV 0, 12-MAR-03).

The serum levothyroxine baseline concentration was calculated as the average of the available pre-dose concentrations (-1, -0.5 and 0 hour). For all subjects and periods, individual baseline values were subtracted from all subsequent serum concentrations and negative values were set to zero. In the following tables, AUC_t represents the area under the serum concentration-time curve calculated from time zero to 96 hours. The details of the additional analysis are presented in Appendices 1 through 10.

Table 1 summarizes the results of the pharmacokinetic and statistical analysis carried out on the baseline-corrected untransformed pharmacokinetic parameters. Table 2 summarizes the results of the analysis carried out on the baseline-corrected ln-transformed parameters.

Table 1

Summary of the Statistical Analysis for Levothyroxine
Corrected for baseline

Untransformed data

Parameter	Least Square Mean Test	Least Square Mean Reference	Ratio Test/Reference (%)	Intra-subject Variability (%)	90% Confidence Interval		Power (%) *
					Lower	Upper	
AUC_{24} (ng.h/mL)	945	913	103.5	11.0	98.0	109.1	>99.9
AUC_{48} (ng.h/mL)	1686	1634	103.2	12.3	97.0	109.3	99.9
AUC_t (ng.h/mL)	2697	2646	101.9	15.6	94.1	109.7	98.5
C_{max} (ng/mL)	68.93	64.49	106.9	24.6	94.3	119.5	73.9
T_{max} (hours)	2.54	2.54	100.0	29.6	85.3	114.7	60.3

* Power to detect a 20% difference from the Reference mean

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Table 2

Summary of the Statistical Analysis for Levothyroxine
Corrected for baseline

Ln-transformed data

Parameter	Least Square Mean Test	Least Square Mean Reference	Ratio Test/Reference (%)	Intra-subject Variability (%)	90% Confidence Interval		Power (%) *
					Lower	Upper	
AUC ₂₄ (ng.h/mL)	6.8366	6.8032	103.4	12.4	97.3	109.9	>99.9
	931	901					
AUC ₄₈ (ng.h/mL)	7.4129	7.3860	102.7	13.4	96.2	109.7	99.9
	1657	1613					
AUC ₁ (ng.h/mL)	7.8781	7.8678	101.0	16.4	93.2	109.5	99.3
	2639	2612					
C _{max} (ng/mL)	4.2144	4.1362	108.1	21.2	97.4	120.0	93.9
	67.65	62.56					

* The top value represents the least square mean and the bottom value, the geometric mean
* Power to detect a 20% difference from the Reference mean

As described in Tables 1 and 2, the Test/Reference ratio of the geometric mean C_{max} was 108.1% with a 90% confidence interval from 97.4 to 120.0%. The Test/Reference ratios of the geometric mean AUC₂₄, AUC₄₈ and AUC₁ were 103.4, 102.7 and 101.0% respectively. The corresponding 90% confidence intervals were 97.3-109.9, 96.2-109.7 and 93.2-109.5% respectively. Based on the ratios of geometric means and their 90% confidence intervals, it is concluded that Unithroid™ 0.3 mg tablet (Jerome Stevens Pharmaceuticals, NY, USA) is bioequivalent to Levoxy® 0.3 mg tablet (Jones Pharma Incorporated, MO, USA) when administered as a single 0.6-mg oral dose under fasting conditions, based on baseline-corrected results.

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/s/

Sang Chung
4/6/04 03:33:32 PM
PHARMACOLOGIST

Hae-Young Ahn
4/6/04 03:50:28 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-210/S-002

Administrative/Correspondence

EXCLUSIVITY SUMMARY FOR NDA # 21-210 SUPPL # -002

Trade Name: Unithroid Generic Name: levothyroxine sodium tablets, USP

Applicant Name: Jerome Stevens Pharmaceuticals, Inc. 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) 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

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.

 This supplement sought an AB rating to Levoxyl.

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:

 N/A

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 Written 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

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 _____
_____	!	_____
_____	!	_____

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

DA/BLA #: 21-210 Supplement Type (e.g. SE5): SE4 Supplement Number: -002

Stamp Date: March 27, 2003 Action Date: January 27, 2004

HFD 510 Trade and generic names/dosage form: Unithroid (levothyroxine sodium tablets, USP)

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

Indication(s) previously approved: hypothyroidism and suppression of thyroid stimulating hormone

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

Number of indications for this application(s): 2

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: _____

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
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.

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 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)

Unithroid (levothyroxine sodium tablets, USP) sNDA
25, 50, 75, 88, 100, 112, 125, 137, 150, 200 and 300 µg

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.

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 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

3/26/03

Date

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

Redacted 3

page(s) of trade secret.

and/or confidential

commercial information

~~(b4)~~

(b5)

MEMORANDUM

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

DATE: June 22, 2004

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

TO: NDA 21-210/S-002
Unithroid (levothyroxine sodium) tablets
Jerome Stevens Pharmaceuticals
Bioequivalence to Levoxyl (Jones Pharma)

SUBJECT: NDA review issues and recommended action

Background

This application was submitted on March 26, 2003, and included the results of a bioequivalence study comparing Unithroid to Levoxyl. The sponsor proposed that the results of the study supported bioequivalence and demonstrated interchangeability of Unithroid and Levoxyl.

Biopharmaceutics

Dr. Chung (OCPB) has reviewed the bioequivalence study. It was an open-label, single dose, crossover study in 24 healthy volunteers and conducted in accordance with Agency guidance on levothyroxine bioequivalence. A correction for baseline T4 was conducted according to the method recommended by the Agency (correction with the average of three pre-dose serum T4 with negative values after correction set to zero). Analysis of the data shows that bioequivalence is demonstrated with the 90% confidence intervals for the ratios of levothyroxine AUC (0-24), AUC (0-48), AUC (0-72), and Cmax for Unithroid to Levoxyl are all within the range of 0.8 to 1.25.

The methods validation for the [] was acceptable, and the request for a waiver of the in vivo bioequivalence studies for the dosage strengths other than the 0.3 mg tablet formally tested was granted based on dosage form equivalence and dissolution data submitted and reviewed with the original NDA for Unithroid.

DSI/Data Integrity

DSI conducted audits of the clinical site and of the analytical site found no deficiencies, and recommended that the data be accepted for review.

Financial disclosure

The financial disclosure information is in order. The sponsor has certified that no investigator received outcome payments, that no investigator disclosed a proprietary interest in the product or

NDA # 21-210
Drug: Unithroid (LT4, JSP)
Proposal: BE to Levoxyl
06/22/04

an equity interest in the company, and that no investigator was the recipient of significant payments of other sorts.

OPDRA/nomenclature

Recommendation

In concurrence with the conclusions of the review by OCPB, the Division will approve this sNDA and recommends the granting of AB rating of Unithroid to Levoxyl by the Office of Generic Drugs.

**APPEARS THIS WAY
ON ORIGINAL**

NDA # 21-210
Drug: Unithroid (LT4, JSP)
Proposal: BE to Levoxyl
06/22/04

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

David Orloff
6/22/04 06:07:30 PM
MEDICAL OFFICER

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information

NDA 21-210	Efficacy Supplement Type SE-4	Supplement Number -002
Drug: Unithroid (levothyroxine sodium, USP)		Applicant: Jerome Stevens Pharmaceuticals, Inc.
RPM: Oluchi Elekwachi, Pharm.D., M.P.H.		HFD-510 Phone # 301-827-6381
Application Type: <input checked="" type="checkbox"/> 505(b)(1)		Reference Listed Drug (NDA #, Drug name): NA
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		N/A
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		27JAN04 (as soon as CP issues) 6/23/0
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
User Fee Information		
• User Fee		<input type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input checked="" type="checkbox"/> Other – No Clinical Data
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> 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.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that form FDA-3542a was submitted.		N/A
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.\		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV
• Not (b)(2) – N/A		21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified

Exclusivity (approvals only)	
• Exclusivity summary	
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!</i>	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	5/24/03
General Information	
❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	
• 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))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	N/A
• Original applicant-proposed labeling	N/A
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	N/A
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	N/A
• Reviews	N/A
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A

Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	
Clinical Information	
❖ Clinical review(s) <i>(indicate date for each review)</i>	N/A
❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	N/A
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	N/A
❖ Risk Management Plan review(s) <i>(indicate date/location if incorporated in another rev)</i>	N/A
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	
❖ Demographic Worksheet <i>(NME approvals only)</i>	N/A
❖ Statistical review(s) <i>(indicate date for each review)</i>	N/A
❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i>	4/6/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i>	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	9/22/03
CMC Information	
❖ CMC review(s) <i>(indicate date for each review)</i>	N/A
❖ Environmental Assessment	
• Categorical Exclusion <i>(indicate review date)</i>	N/A
• Review & FONSI <i>(indicate date of review)</i>	N/A
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	N/A
❖ Facilities inspection (provide EER report)	Date completed: N/A () Acceptable () Withhold recommendation
❖ Methods validation	() Completed N/A () Requested () Not yet requested
Nonclinical Pharm Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	N/A
❖ CAC/ECAC report	N/A

5/24/03

NDA REGULATORY FILING REVIEW (Including Memo of Filing Meeting)

NDA # 21-210 Supplement # 002 SE4

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): **30-OCT-2003** User Fee Goal Date: 27-JAN-2004

CHANGE requested: To show comparability between Unithroid and Levoxyl 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?

If yes, explain: YES NO

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

- Did applicant request categorical exclusion for environmental assessment? N/A 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 Levoxyl

- 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)].

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 Levoxyl.

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:

<u>Discipline</u>	<u>Reviewer</u>
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 _____	<u>N/A</u>
• 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 _____	<u>N/A</u>
STATISTICS	FILE _____	REFUSE TO FILE _____	<u>N/A</u>
BIOPHARMACEUTICS	FILE <u>X</u>	REFUSE TO FILE _____	

• Biopharm. inspection needed:	(Consult sent)	<u>YES</u>	NO
PHARMACOLOGY	FILE _____	REFUSE TO FILE _____	<u>N/A</u>
• GLP inspection needed:		YES	NO
CHEMISTRY	FILE _____	REFUSE TO FILE _____	<u>N/A</u>
• 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:

_____ The application is unsuitable for filing. Explain why:

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

X 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.
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. **FI sent 05.19.03**

Enid Galliers
Chief, Project Management Staff, HFD-510

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LRipper/1-13-03

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/s/

Enid Galliers

5/24/03 07:00:28 PM

CSO

FN 05.19.03



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-210/S-002

NO FILING ISSUES IDENTIFIED

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

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on May 26, 2003, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

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
(HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Enid Galliers

5/19/03 12:45:33 PM



Jerome Stevens Pharmaceuticals, Inc.

March 26, 2003

Dr. Hye Young Ahn
Division of Metabolism and Endocrine Drug Products
Center for Drugs and Biologics (HFD-316)
Preclinical Control Room 14B0
500 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-110, Supplement 002
UNITHROID (Levothyroxine Sodium Tablets, USP)
Supplement Date March 26, 2003
Baseline Correction Data

Dr. Ahn

As per agency request enclosed please find Baseline Correction Data for the above referenced NDA supplement.

Jerome Stevens Pharmaceuticals had first requested from the division on September 11, 2002 requirements for supplementing bioequivalence data to approved NDA Unithroid. Jerome Stevens Pharmaceuticals did not receive the requirements until end of January 2003. However, as explained, we began the studies in November 2002 and the process was underway following the guidelines from the original Levothyroxine requirements. As a result, the request of this data was inadvertently overlooked and was not included in the original supplement.

We apologize for any inconvenience that this may have caused. Please contact me should you have further questions.

Sincerely,

Ronald Stemlauf, Vice President
Jerome Stevens Pharmaceuticals, Inc.

RECEIVED

MAY 16 2003

FDR/ODEP

UNRECORDED

This application contains the following items: (Check all that apply)

- 1. Index
- 2. Labeling (check one) Draft Labeling Final Printed Labeling
- 3. Summary (21 CFR 314.50(c))
- 4. Chemistry section
 - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
 - B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
 - C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306(k)(1))
- 17. Field copy certification (21 CFR 314.50(l)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Ronald Steinlauf</i>	TYPED NAME AND TITLE Ronald Steinlauf, Vice President	DATE 4/30/03
ADDRESS (Street, City, State, and ZIP Code) 60 DaVinci Drive Bohemia NY 11716		TELEPHONE NUMBER (613) 567-1113

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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.

**sNDA Amendment Index
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**APPEARS THIS WAY
ON ORIGINAL**

4/7/03



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-210/S-002

PRIOR APPROVAL SUPPLEMENT

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-002
Review Priority Classification:	Standard
Date of supplement:	March 26, 2003
Date of receipt:	March 27, 2003

This supplemental application proposes to demonstrate interchangeability between Unithroid and the two reference products, Synthroid and Levoxyl, based on the results of comparative bioavailability studies.

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

4/7/03 03:08:26 PM

ORIGINAL

NDA NO. 21210 REF NO. 002
NDA SUPPL FOR SE4



Jerome Stevens Pharmaceuticals, Inc.

March 26, 2003

RECEIVED

MAR 27 2003

FDR/CDER

Division of Metabolism and Endocrine Drug Products
Center for Drugs and Biologics (HFN-810)
Document Control Room 14B03
5600 Fishers Lane
Rockville, Maryland 20857

Re: sNDA – Drug Name: UNITHROID (levothyroxine sodium tablets, USP)
Company: Jerome Stevens Pharmaceuticals, Inc.
Original NDA: 21-210 (approval received Aug. 21, 2000)

To whom it may concern:

Jerome Stevens Pharmaceuticals, Inc. is hereby submitting an original Supplemental New Drug Application (sNDA) for UNITHROID (levothyroxine sodium tablets, USP) 25, 50, 75, 88, 100, 112, 125, 175, 150, 200 and 300 µg. The original application (NDA 21-210) for UNITHROID received approval August 21, 2000.

This sNDA is compiled in accordance with 21 Code of Federal Regulations Part 314.0, and contains 9 volumes (archival copy) of documentation to demonstrate interchangeability between Unithroid and the two reference products, Synthroid and Levoxyl based on the results of two original comparative bioavailability studies.

↳ S-002

The supplement is composed of one Archival Copy and one Pharmacokinetic Review Copy. The Human Pharmacokinetics and Bioavailability/Bioequivalence section contains results from two new comparative bioavailability studies.

There have been no changes to Chemistry, Manufacturing and Controls since approval of the original NDA (21-210) and thus this section is cross-referenced to the original NDA and no Field Copy or Field Copy Certification have been provided.

Additionally there have been no changes to labeling, the Nonclinical section, or the Clinical section since approval of the original NDA (21-210) and thus these sections have not been provided in the body of the NDA. Cross-reference to the original NDA (21-210) is provided for these sections in the Application Index.

Please note that this application includes electronic data (BA/BE study data) which has been provided on CD immediately following the Guide for Reviewers.

CD's were not loadable



Jerome Stevens Pharmaceuticals, Inc.

UNITHROID is indicated for the treatment of i) hypothyroidism and ii) suppression of thyroid-stimulating hormone.

The correspondent for the sNDA is:

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

Yours sincerely,
Jerome Stevens Pharmaceuticals, Inc.

Ronald Steinlauf
Vice President

1/16/03



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

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,

{See ed 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

Galliers, Enid M

From: Galliers, Enid M
Sent: Tuesday, August 26, 2003 7:27 PM
To: []
Cc: []
Subject: FDA Request for Patent Certification for NDA 21-210/S-002

Dear []

This message confirms my response to your inquiry today on behalf of Jerome Stevens Pharmaceuticals (JSP) regarding my August 6, 2003, email request addressed to Mr. Ronald Steinlauf, Vice President, JSP, to submit a patent certification to pending Supplement-002, which requests an AB rating (therapeutic equivalence) between JSP's Unithroid and Jones Pharmaceuticals' Levoxyl.

Subsequent to your phone call earlier today, []

[] a patent certification is not required when an applicant is seeking to establish equivalence between two approved 505(b)(2) applications.

Therefore, I am rescinding my request for a patent certification and extend my apologies for the inconvenience.

Very truly yours,

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II

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/s/

Enid Galliers
8/26/03 07:50:31 PM
CSO

Galliers, Enid M

From: Galliers, Enid M
Sent: Tuesday, August 26, 2003 7:27 PM
To: [redacted]
Cc: [redacted]
Subject: FDA Request for Patent Certification for NDA 21-210/S-002

Dear [redacted]

This message confirms my response to your inquiry today on behalf of Jerome Stevens Pharmaceuticals (JSP) regarding my August 6, 2003, email request addressed to Mr. Ronald Steinlauf, Vice President, JSP, to submit a patent certification to pending Supplement-002, which requests an AB rating (therapeutic equivalence) between JSP's Unithroid and Jones Pharmaceuticals' Levoxyl.

Subsequent to your phone call earlier today, [redacted] a patent certification is not required when an applicant is seeking to establish equivalence between two approved 505(b)(2) applications. Therefore, I am rescinding my request for a patent certification and extend my apologies for the inconvenience.

Very truly yours,

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II

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/s/

Enid Galliers

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