

076-187-5003.PAP

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER(S)**

**ANDA 76-187/S-003**

**Trade Name:** Levothyroxine sodium Tablets, USP

**Generic Name(s):**

**Sponsor:** Mylan Pharmaceuticals, Inc.

**Agent:**

**Approval Date:** July 13, 2004

**Indication:** Provides for the agency to make a determination that the drug approved is "AB" rated to Levoxyl Tablets of Jones Pharma Inc.

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RESEARCH

APPLICATION NUMBER:

ANDA 76-187/s-003

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LEVOTHYROXINE SODIUM TABLETS

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**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**ANDA 76-187/S-003**

**Approval Letter(s)**

JUL 13 2004

Mylan Pharmaceuticals, Inc.  
Attention: S. Wayne Talton  
781 Chestnut Ridge Road  
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your supplemental new drug application dated June 24, 2004, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Levothyroxine Sodium Tablets USP, 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.1 mg, 0.112 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.2mg, and 0.3mg.

Reference is also made to your new drug application (ANDA 76-647) dated December 5, 2002. The content and data provided in that ANDA has been incorporated into this supplemental application.

The supplemental application, submitted as "Prior Approval Supplement", provides for the agency to make a determination that Mylan's Levothyroxine Sodium Tablets, USP approved under ANDA 76-187 are "AB"-rated to Levoxyl Tablets of Jones Pharma Inc.

We have completed the review of the supplemental application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the supplemental application is approved. The Division of Bioequivalence has determined each strength of your Levothyroxine Sodium Tablets, USP to be bioequivalent and, therefore, therapeutically equivalent to the respective strength of Levoxyl Tablets of Jones Pharma Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

We remind you that you must comply with the requirements for an approved abbreviated application described in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any changes in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns under this supplemental application. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

[

]

/ Gary Buehler

7/13/04

Director

Office of Generic Drugs

Center for Drug Evaluation and Research

cc: ANDA 76-187/S-003  
ANDA DUP  
Division File  
FIELD COPY  
HFD-610/RWest

Endorsements:

HFD-625/A.Pendse ✓

*/S/ 7/1/04*

HFD-625/M.Smela, TL

*/S/ 7/1/04 \**

HFD-617/P.Chen, PM

*/S/ 7/1/04*

HFD-613/A.Payne

HFD-613/J.Grace *per OCC recommendation* ✓ */S/ 7-1-04*

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F/T by

APPROVAL

*\* CMC adequate per review dated 4/4/03  
and addenda dated 1/13 and 5/6/04 when  
this submission was considered ANDA 76647*

*/S/ 7/1/04*

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**ANDA 76-187/S-003**

**Chemistry Review(s)**

ANDA 76-647 (Levothyroxine Sodium Tablets, Mylan Pharmaceuticals, Inc.)  
Gratuitous amendment: 3/29/04  
Addendum 2 to Chemist Review #1

This amendment provides for a change in the manufacturing process for Levothyroxine Sodium Tablets, USP to be consistent with the process currently approved in ANDA 76-187. Please note that the chemistry, manufacturing and controls information in ANDA 76-647 is incorporated by reference to their approved ANDA 76-187.

Firm is proposing the addition of [redacted] of the drug product. Additionally, the revised production batch records included a correction to the calculation used to adjust the amounts of the excipients [redacted] the Levothyroxine Sodium [redacted] to produce the theoretical batch size. Firm submitted a Supplement Changes Being Effected in 30 days to ANDA 76-187 (S-002) on August 20, 2003 which provided for a revision in the manufacturing process for all strengths of Levothyroxine Sodium Tablets, USP. Firm subsequently received approval of the supplemental application on December 18, 2003. A copy of the approval letter is in Attachment A.

To support the addition of this [redacted] Mylan has submitted revised Master Batch Records for all strengths.

Conclusion: The ANDA remains approvable.

cc: ANDA76-647  
ANDA DUP  
DIV FILE  
Field Copy

Endorsements (Draft and Final with Dates):

HFD-625/APendse/Review chemist/5/6/04  
HFD-625/ MSmela/Team leader/5/6/04

F/T by

V:\FIRMSAMMYLANLTRS&REV\76-647 CR1addendum 2

Handwritten notes and signatures: "15/1" (twice), "5/6/04" (twice), and "576104".

ANDA 76-647 (Levothyroxine Sodium Tablets, Mylan Pharmaceuticals, Inc.)  
Addendum to Chemist Review #1

1. Firm submitted the labeling amendment on 4/22/2003, it was found acceptable by Payne/Grace on 4/29/2003
2. EER is acceptable on 22-May-2003 by Fergusson.
3. Various Patent amendments have been submitted since Chemistry Review 1 (CR1). Mylan has been sued.
4. No new CMC information has been submitted since completion of CR1.
5. Bioequivalence review is acceptable by Makary/Singh on 5/6/2003 and it was determined that Mylan should use the USP dissolution test.

NOTE: Firm confirmed that the bioequivalency batches were manufactured and controlled under the same conditions as those in ANDA 76-187. It is evident from the C of As on pages 29-59 of the 1/29/03 amendment that Mylan is using USP Dissolution Test 1 for this product which is the same as recommended by the DBE.

Conclusion: The ANDA is approvable.

cc: ANDA76-647  
ANDA DUP  
DIV FILE  
Field Copy

Endorsements (Draft and Final with Dates):

HFD-625/APendse/Review chemist/1/6/04 ✓  
HFD-625/MSmela/Team leader/1/6/04  
HFD/617/PChen/Project manager/1/6/04

1/9/04

1/13/04

1/4/04

F/T by

V:\FIRMSAM\MYLAN\LTRS&REV\76-647 CR1addendum



Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : TCM OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-MAY-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

-----  
Establishment : CFN :                      FEI :                     

DMF No:                      AADA:                     

Responsibilities:

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : CTL OAI Status: NONE  
 Last Milestone: OC RECOMMENDATION  
 Milestone Date: 12-FEB-03  
 Decision : ACCEPTABLE  
 Reason : BASED ON PROFILE

Establishment : CFN :            FEI :           

DMF No:            AADA:

Responsibilities:           

Profile : CSN OAI Status: NONE  
 Last Milestone: OC RECOMMENDATION  
 Milestone Date: 12-FEB-03  
 Decision : ACCEPTABLE  
 Reason : BASED ON PROFILE

Establishment : CFN :            FEI :           

DMF No: AADA:

Responsibilities:           

Profile : CTL OAI Status: NONE  
 Last Milestone: OC RECOMMENDATION  
 Milestone Date: 12-FEB-03  
 Decision : ACCEPTABLE  
 Reason : BASED ON PROFILE

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**ANDA 76-187/S-003**

**BIOEQUIVALENCE REVIEW(S)**

**OFFICE OF GENERIC DRUGS  
DIVISION OF BIOEQUIVALENCE**

ANDA #: 76-187 — ), originally submitted as 76-647 on 12/5/2002  
 SPONSOR: Mylan Pharmaceuticals  
 DRUG AND DOSAGE FORM: Levothyroxine Sodium Tablets USP  
 STRENGTH(S) : 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg,  
 0.125 mg, 0.150 mg, 0.175 mg, 0.200 mg and 0.300 mg  
 TYPES OF STUDIES: Fasting SD Study (for 0.300 mg)  
 CINICAL STUDY SITE(S)  3  
 ANALYTICAL SITE(S):  3

STUDY SUMMARY: Acceptable  
 DISSOLUTION: Acceptable  
 WAIVER REQUEST: Waivers for the 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg,  
 0.100 mg, 0.112 mg, 0.125 mg, 0.150 mg, 0.175 mg and 0.200 mg strengths are  
 granted.

**DSI INSPECTION STATUS**

Inspection needed: NO	Inspection status:	Inspection results:
First Generic <u>YES</u>	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

For PRIMARY REVIEWER : Moheb H. Makary, Ph.D.      BRANCH : IV  
 INITIAL : MS      DATE : 6/28/04

TEAM LEADER : Kuldeep R. Dhariwal, Ph.D.      BRANCH : IV  
 INITIAL : MS      DATE : 6/28/04

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.  
 INITIAL : MS      DATE : 6/28/04

**Redacted** 3

**page(s) of trade secret.**

**and/or confidential**

**commercial information**

~~(b4)~~

(b5)

## DIVISION OF BIOEQUIVALENCE REVIEW

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<b>ANDA No.</b>	76-187 — (Originally submitted as ANDA 76-647)
<b>Drug Product Name</b>	Levothyroxine Sodium Tablets USP
<b>Strength</b>	0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.200 mg and 0.300 mg
<b>Applicant Name</b>	Mylan Pharmaceuticals Inc.
<b>Address</b>	Morgantown, WV
<b>Submission Date(s)</b>	December 5, 2002
<b>Reviewer</b>	Moheb H. Makary
<b>File Location</b>	V:\FIRMSAMMYLAN\LTRS&REV\76187S1202.doc

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## Review of Supplement for ANDA 76-187

**Executive Summary**

Mylan is transferring ANDA 76-647 (originally submitted on December 5, 2002) to be a supplement for ANDA 76-187 with therapeutic equivalence for Levoxyl<sup>®</sup>.

The original submission of December 5, 2002 consisted of one fasting bioequivalence (BE) study and dissolution data on all strengths of the test and reference products. The BE study is a two-way, crossover study in normal males and females (n=23) on the 0.300 mg strength comparing it with Levoxyl<sup>®</sup> 0.300 mg tablets, of Jones Pharma. Statistical analyses of the serum concentration data for L-thyroxine (T<sub>4</sub>) demonstrate bioequivalence. T<sub>4</sub> results based on baseline correction are (point estimate, 90% CI): LAUC<sub>0-48</sub> of 102, 95.5-108.4% and LC<sub>max</sub> of 99, 93.7-105.9%. The Division of Bioequivalence (DBE) does not recommend measurement of L-triiodothyronine (T<sub>3</sub>) of this product. The product meets the FDA dissolution specifications. Waivers of in vivo study requirements are granted for all strengths. The application is acceptable with no deficiencies.

**I. Recommendations**

1. The ANDA 76-647 is transferred to be a supplement for 76-187 with therapeutic equivalence for Levoxyl<sup>®</sup>.

No further action is needed.

for Moheb Makary, Ph.D. 18/28/04  
Review Branch IV

Kuldeep R. Dhariwal, Ph. D. 18/ Date 6/28/04  
Team Leader, Review Branch IV

Concur: 18/ 2 Date: 6/28/04  
Dale P. Connet, Pharm.D.  
Director  
Division of Bioequivalence

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**DIVISION OF BIOEQUIVALENCE REVIEW**

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<b>ANDA No.</b>	76-647
<b>Drug Product Name</b>	Levothyroxine Sodium Tablets USP
<b>Strength</b>	0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.200 mg and 0.300 mg
<b>Applicant Name</b>	Mylan Pharmaceuticals Inc.
<b>Address</b>	Morgantown, WV
<b>Submission Date(s)</b>	December 5, 2002
<b>Reviewer</b>	Moheb H. Makary
<b>File Location</b>	V:\FIRMSAMMYLAN\LTRS&REV\76647N1202.doc

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**Executive Summary**

This submission consisted of one fasting BE study and dissolution data on all strengths of the test and reference products. The BE study is a two-way, crossover study in normal males and females (n=23) on the 0.300 mg strength comparing it with Levoxy<sup>®</sup> tablets, 0.300 mg, of Jones Pharma. Statistical analyses of the serum concentration data for L-thyroxine (T<sub>4</sub>) demonstrate bioequivalence. T<sub>4</sub> results based on baseline correction are (point estimate, 90% CI): LAUC<sub>0-48</sub> of 102, 95.5-108.4% and LCmax of 99, 93.7-105.9%. DBE does not recommend measurement of L-triiodothyronine (T<sub>3</sub>) of this product. The product meets the FDA dissolution specifications. Waivers of in vivo study requirements are granted for all strengths. The application is acceptable with no deficiencies.

**APPEARS THIS WAY  
ON ORIGINAL**

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## III. Submission Summary

### A. Drug Product Information

#### Test Product:

The test product used in this application (ANDA #76647), Mylan's levothyroxine sodium tablets USP, 0.300 mg, lot #R1H0708, was from the same lot used to demonstrate bioequivalence to the reference listed drug, Unithroid<sup>®</sup> tablets, in the bioequivalence studies provided in Mylan's original ANDA #76187 for its levothyroxine sodium tablets USP, 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.200 mg and 0.300 mg. Mylan's generic levothyroxine sodium tablets USP are currently approved under ANDA #76187 and AB rated to the reference listed drug, Unithroid<sup>®</sup> (levothyroxine sodium tablets USP) manufactured by Jerome-Stevens (June 5, 2002).

#### Reference Product:

Levoxyl<sup>®</sup> (levothyroxine sodium) tablets, 0.300 mg, of Jones Pharma was approved under NDA #21301 on May 25, 2001. Other available strengths of Levoxyl<sup>®</sup> (levothyroxine sodium) tablets are 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.125 mg, 0.137, 0.150 mg, 0.175 mg, 0.200 mg strengths. Lot #7000 of the Levoxyl<sup>®</sup> tablet was used in the BE study.

Synthroid<sup>®</sup>, Levo-T<sup>®</sup>, Unithroid<sup>®</sup>, Novothyrox<sup>®</sup> and Thyro-Tabs<sup>®</sup> tablets, 0.300 mg, manufactured by Abbott Laboratories, Mova, Jerome Stevens Pharmaceuticals, Genpharm and Lloyd, respectively, are listed as RLDs in the Orange Book (23<sup>rd</sup> Edition 2003).

The data submitted in this application is to support bioequivalence of the test product with Levoxyl<sup>®</sup> (levothyroxine sodium) tablets.

**Indication:**

Orally administered levothyroxine sodium is used as replacement therapy in conditions characterized by diminished or absent thyroid function such as cretinism, myxedema, nontoxic goiter, or hypothyroidism. Levothyroxine sodium may also be used for replacement or supplemental therapy in patients with secondary (pituitary) or tertiary (hypothalamic) hypothyroidism.

**PK/PD Information**

**Bioavailability:** The relative bioavailability compared to an equal nominal dose of oral levothyroxine sodium solution, is approximately 99%.

**Metabolism:** The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately eighty-percent of circulating T<sub>3</sub> is derived from peripheral T<sub>4</sub> by monodeiodination.

**Half Life:** 6-9 days

**Tmax:** 3 hours

**Excretion:** Thyroid hormones are primarily eliminated by the kidneys. A portion of the conjugated hormone reaches the colon unchanged and is eliminated in the feces. Approximately 20% of T<sub>4</sub> is eliminated in the stool.

**Food Effect:** T<sub>4</sub> absorption is increased by fasting, and decreased in malabsorption syndromes and by certain foods such as soybean infant formula. Dietary fiber decreases bioavailability of T<sub>4</sub>. Absorption may also decrease with age. In addition, many drugs and foods affect T<sub>4</sub> absorption.

**Relevant DBE History:**

The DBE requests only a single-dose fasting *in vivo* bioequivalence study be conducted comparing the 0.300 mg strength of the test product to the RLD product. Only levothyroxine (T<sub>4</sub>) after correction for baseline is recommended for quantitation. Biowaiver requests for all of the lower strengths may be accepted based on (1) acceptable bioequivalence study of the 0.300 mg strength, (2) acceptable *in vitro* dissolution testing for all strengths, and (3) proportional similarity in the formulations of all strengths.

**B. Contents of Submission**

		How many?
Single-dose fasting study	Yes	1
Single-dose fed study	No	0
Steady-state study	No	0
In vitro dissolution testing	Yes	11
Waiver requests	No	10
BCS data	No	
Vasoconstrictor studies	No	
Clinical endpoints	No	

Failed studies No  
 Amendments No

**C. Bioanalytical Method Validation (Pre-Study, Vol.1.2, Pages 376)**

Both L-Thyroxine (T<sub>4</sub>) and L-Triiodothyronine (T<sub>3</sub>) were measured. However, only T<sub>4</sub> data are requested and reviewed.

Number of analytes	1
Analyte name	T <sub>4</sub>
Internal Standard	N/A
Method description	[ ]
QC range	[ ]
Standard curve range	[ ]
Limit of quantitation	[ ] ng/mL
Average recovery of Drug (%)	N/A
Average Recovery of Int. Std (%)	N/A
Interday precision range for QC (%)	[ ]
Interday accuracy range for QC (%)	[ ]
Interday precision range for stds (%)	[ ]
Interday accuracy range for stds (%)	[ ]
Dilution Integrity accuracy(%)	[ ]
Dilution Integrity precision (%)	[ ]
Bench-top stability (hrs)	[ ]
Autosampler stability (hrs)	N/A
Freeze-thaw stability (cycles)	—
Long-term storage stability (days)	[ ]
Specificity	Yes
SOPs submitted	Yes
Bioanalytical method is acceptable	Yes
[ ] included	N/A

Comments on the Analytical Method: The analytical method and data are acceptable.

**D. In Vivo Study**

1. Single-dose Fasting Bioequivalence Study

Study No.	#LEVO-0193
Study Design:	A single-dose, two-period, two-treatment, two-sequence crossover
No. of subjects enrolled	25
No. of subjects completing	23
No. of subjects analyzed	23
Sex(es) included (how many?)	Male (19) Female (6)
Test product	Levothyroxine Sodium tablets USP, 0.300 mg, manufactured by Mylan Pharmaceuticals Inc.
Reference product	Levoxyl <sup>R</sup> tablet, 0.300 mg, Jones Pharma

Strength tested 0.300 mg  
Dose 2 x 0.300 mg tablets

**Summary of Statistical Analysis submitted by the firm based on uncorrected baseline**

(T<sub>4</sub>) Uncorrected baseline

Parameter	Point Estimate	90% Confidence Interval
LnAUCt(0-48)	0.99	96 – 101
LnCmax	0.98	95 – 102

The reviewer calculated the pharmacokinetic parameters based on baseline corrected. The pre-dose baseline value on the day of dosing was subtracted from each post-dose concentration. The pre-dose baseline value was calculated as the average of the three concentrations at -0.5, -0.25 and 0 hours prior to dosing in each period. Negative data resulting from baseline correction were designated as zero (0).

**Summary of Statistical Analysis based on baseline correction for all subjects**

(T<sub>4</sub>)

Parameter	Point Estimate	90% Confidence Interval
LnAUCt(0-48)	1.02	95.5 – 108.4
LnCmax	0.99	93.7 – 105.9

After subtracting the baseline value from each post-dose concentration and 0 hour time point for each subject, subjects #2, 3, 13 and 14 had measurable drug concentrations at 0 hr which were more the 5% of their Cmax values. After excluding these subjects from the statistical analysis of the study, the 90% confidence intervals are shown below:

**Summary of Statistical Analysis based on corrected baseline after excluding subject Nos. 2, 3, 13 and 14**

(T<sub>4</sub>)

Parameter	Point Estimate	90% Confidence Interval
LnAUCt(0-48)	1.01	94.8 – 108.2
LnCmax	0.98	90.9 – 104.9

The study is acceptable. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUCt(0-48) and Cmax for T<sub>4</sub> based on uncorrected and corrected baselines.

**E. Formulation**

The test product formulations are shown in Table 1 of the Appendix.

Inactive Ingredients within IIG limits Yes

The formulation is acceptable Yes

The formulations are proportionally similar by definition 2 of the current general BA/BE guidance.

#### **F. In Vitro Dissolution**

The firm used the USP method for its dissolution testing (Table 2). The dissolution testing conducted by Mylan Pharmaceuticals Inc. on its levothyroxine sodium tablets USP, 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.200 mg and 0.300 mg, is acceptable. The test and reference products meet the USP specification of NLT 70% (Q) of the labeled amount of levothyroxine dissolved in 45 minutes. Similarity Factor F2 calculated between the highest strength and other strengths was acceptable (greater than 50). The dissolution data are acceptable.

#### **G. Waiver Requests**

The applicant requests a waiver of in vivo bioequivalence testing under 21 CFR 320.22(d)(2) for the 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.125 mg, 0.150 mg, 0.175 mg and 0.200 mg tablets.

The formulations are proportionally similar to that of the strength which underwent acceptable in vivo testing.

Acceptable dissolution testing, all strengths: **Yes**

**H. Deficiency Comment** **None**

#### **I. Recommendations**

1. The single-dose, fasting bioequivalence study conducted by Mylan on the test product, levothyroxine sodium tablets, 0.300 mg, lot # R1H0708, comparing it with the reference product, Jones Pharma's LevoxyI<sup>R</sup> tablets, 0.300 mg, lot #7000, has been found acceptable by the Division of Bioequivalence. The study demonstrates that the test product, Mylan's levothyroxine sodium tablets, 0.300 mg, is bioequivalent to the reference product, Jones Pharma's levothyroxine sodium tablets, 0.300 mg, under fasting conditions.

2. The dissolution testing conducted by Mylan on its levothyroxine sodium tablets, 0.300 mg, 0.200 mg, 0.175 mg, 0.150 mg, 0.125 mg, 0.112 mg, 0.100 mg, 0.088 mg, 0.075 mg, 0.050 mg and 0.025 mg, lot Nos. R1H0708, R1H0753, R1H0752, R1H0751, R1H0750, R1H0749, R1H0707, R1H0748, R1H0747, R1H0746 and R1H0854, has been found acceptable by the Division of Bioequivalence. The formulations for the 0.200 mg, 0.175 mg, 0.150 mg, 0.125 mg, 0.112 mg, 0.100 mg, 0.088 mg, 0.075 mg, 0.050 mg and 0.025 mg tablet strengths are proportionally similar to that of the 0.300 mg levothyroxine sodium tablet of the test product, which underwent acceptable bioequivalency testing. Waivers of in-vivo bioequivalence study requirements for the 0.200 mg, 0.175 mg, 0.150 mg, 0.125 mg, 0.112 mg, 0.100 mg, 0.088 mg, 0.075 mg, 0.050 mg and 0.025 mg tablets of levothyroxine sodium are granted per 21 CFR 320.22(d)(2). The 0.200 mg, 0.175 mg, 0.150 mg, 0.125 mg, 0.112 mg, 0.100 mg, 0.088 mg, 0.075 mg, 0.050 mg and 0.025 mg tablets of test product are therefore deemed bioequivalent to the corresponding strengths 0.200 mg, 0.175 mg, 0.150 mg, 0.125 mg,

0.112 mg, 0.100 mg, 0.088 mg, 0.075 mg, 0.050 mg and 0.025 mg of Levoxyl<sup>R</sup> tablets, manufactured by Jones Pharma.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of 0.01 N HCl containing 0.2% SLS at 37°C using USP 26 apparatus II (paddle) at 50 rpm. The test product should meet the following USP specifications:

Not less than 70% (Q) of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

The firm should be informed of the above recommendations.

Moheb H. Makary, Ph.D.  
Division of Bioequivalence  
Review Branch III

RD INITIALLED  
FT INITIALLED GJP SINGH \_\_\_\_\_ Date

Concur: \_\_\_\_\_

Date:

Dale P. Conner, Pharm.D.  
Director  
Division of Bioequivalence

Mmakary/ 4-15-03, 4-16-03, 76647N1202.doc

cc: ANDA #76-647, original, HFD-658 (Makary), Drug File, Division File.

#### IV. Appendix

##### A. Individual Study Reviews

##### 1. Single-dose Fasting Bioequivalence Study

###### Study Information

Study Number: #LEVO-0193  
 Clinical Site: [ ]  
 Dosing Dates: period I: 1/27/2002  
 period II: 3/3/2002  
 Analytical Site: [ ]  
 Analysis Dates: 4/18/2002-4/25/2002  
 Storage Period: 88 days

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Levothyroxine Sodium tablets	Levoxy® tablets
Manufacturer:	Mylan Pharmaceuticals Inc.	Jones Pharma
Manufacture Date:	3/17/2000	N/A
Expiration Date:	N/A	11/2002
Strength	0.300 mg	0.300 mg
Dosage Form	Tablet	Tablet
Bio Batch Size:	[ ] Tablets	N/A
Batch/Lot Number:	R1H0708	7000
Potency:	100.1%	96.2%
Content Uniformity:	101.1%	96.8%
Formulation	See Table #1	N/A
Dose Administered:	2x0.3 mg Tablets	2x0.300 mg Tablets
Route of Administration	Oral	Oral
Study Condition:	Fasting	Fasting
No. of Sequences	2	
No. of Periods	2	
No. of Treatments	2	
Washout Period	5 weeks	
Randomization Scheme	AB for subjects #1, 2, 6, 7, 10, 11, 14, 16, 19, 20, 21, 22, 25 and BA for the rest of subjects.	
Blood Sampling Times	-0.50, -0.25, 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24 and 48 hours	
Blood Volume Collected/Sample	7 mL	
Blood Sample Processing/Storage	Under conditions with minimal UV exposure	
IRB Approval	Yes, on 1/10/2002	
Informed Consent	Yes, same as above.	
Subjects Demographics	See Table #3	
Length of Fasting:	10 hours pre-dose and 4 hours post-dose.	



## Pharmacokinetic/Statistical Analysis

Mean Serum Concentrations	Table #4, Figure #1
---------------------------	---------------------

### Mean Pharmacokinetic Parameters and 90% Confidence Intervals:

#### a. Arithmetic Mean Pharmacokinetic Parameters (based on data uncorrected for baseline)

PK Parameter	Test Treatment A	Reference Treatment B	T/R
AUC <sub>t</sub> (0-28) [ng-hr/mL]	4700 (12%)	4750 (12%)	0.99
C <sub>max</sub> [ng/mL]	120.0 (16%)	122.1 (15%)	0.98
T <sub>max</sub> [hr]	2.39	2.13	

#### b. 90% Confidence Intervals (based on data uncorrected for baseline)

Parameter	RMSE	Point Estimate	90% Confidence Interval
LnAUC <sub>t</sub>	0.050	0.99	96 – 101
LnC <sub>max</sub>	0.066	0.98	95 – 102

### Summary of Statistical Analysis based on data corrected for baseline (all subjects)

(T<sub>4</sub>)

Parameter	Point Estimate	90% Confidence Interval
LnAUC <sub>t</sub> (0-48)	1.02	95.5 – 108.4
LnC <sub>max</sub>	0.99	93.7 – 105.9

After subtracting the baseline value from each post-dose concentration and 0 hour time point for each subject, subjects #2, 3, 13 and 14 had measurable drug concentrations at 0 hr which were more the 5% of their C<sub>max</sub> values. After excluding these subjects from the statistical analysis of the study, the 90% confidence intervals are shown below:

### Summary of Statistical Analysis based on data corrected for baseline (after excluding subject Nos. 2, 3, 13 and 14)

(T<sub>4</sub>)

Parameter	Point Estimate	90% Confidence Interval
LnAUC <sub>t</sub> (0-48)	1.01	94.8 – 108.2
LnC <sub>max</sub>	0.98	90.9 – 104.9

**Comments: (on pharmacokinetic analysis)**

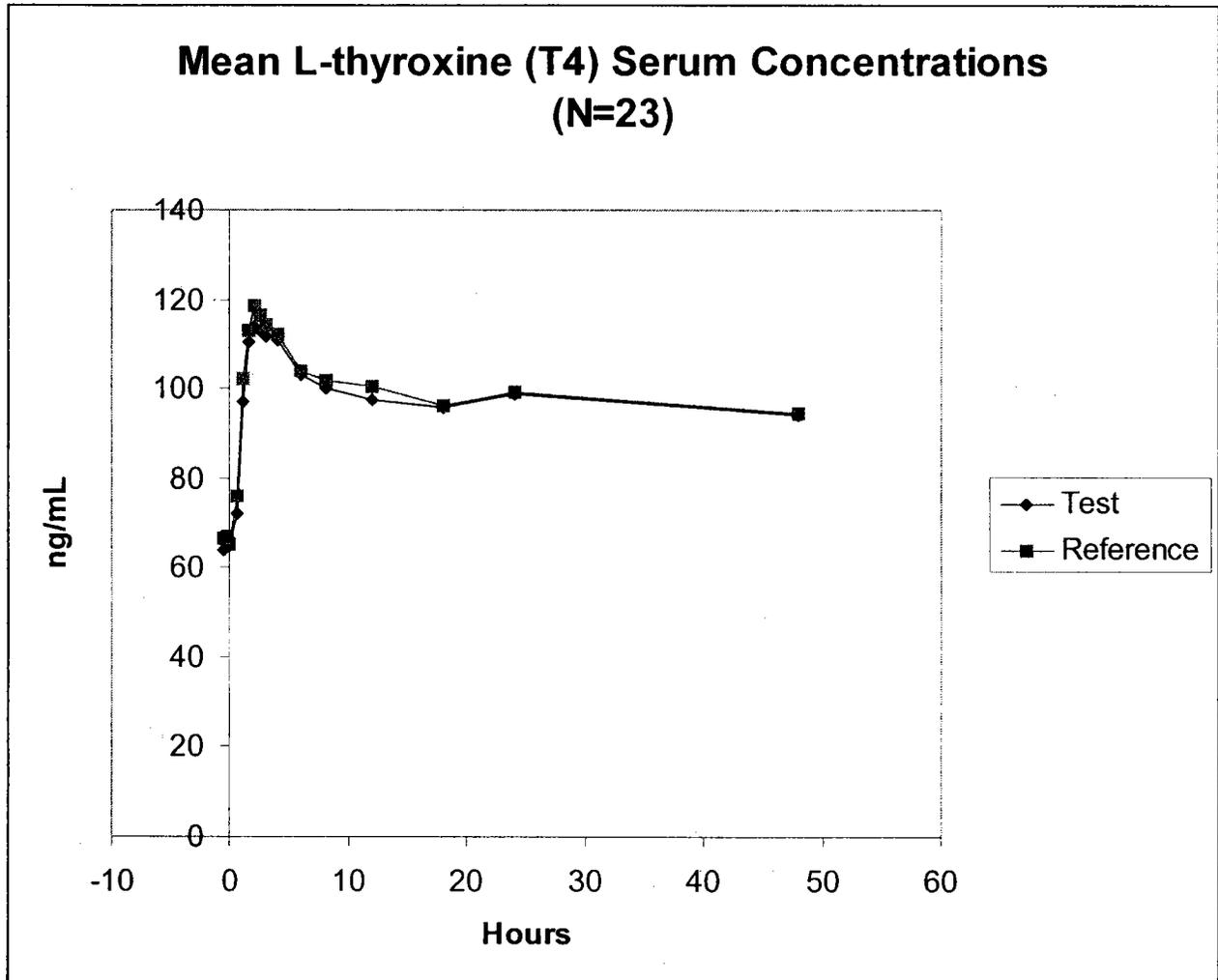
- Measurable drug concentrations at 0 hr: 4 based on correction for baseline
- First scheduled post-dose sampling time as Tmax: None
- First measurable drug concentration as Cmax: None
- Pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations.
- The 90% confidence intervals for AUC<sub>t</sub>, C<sub>max</sub> are within the acceptable limits of 80-125% for corrected and uncorrected baselines.

**Conclusion:**

The single-dose fasting bioequivalence study is acceptable.

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ON ORIGINAL**

B. Attachments  
Fig 1



**Table I**

**COMPARATIVE QUANTITATIVE COMPOSITIONS**

LEVOTHYROXINE SODIUM TABLETS USP, 0.025mg, 0.050mg, 0.075mg, 0.088mg, 0.100mg, 0.112mg, 0.125mg, 0.15mg, 0.175mg, 0.200mg AND 0.300mg

	0.025mg Tablet	0.05mg Tablet	0.075mg Tablet	0.088mg Tablet	0.1mg Tablet	0.112mg Tablet
Levothyroxine Sodium, USP	0.025mg	0.05mg	0.075mg	0.088mg	0.1mg	0.112mg
INACTIVE COMPONENTS						
Mannitol USP, [						
Sucrose, NF						
Butylated Hydroxyanisole, NF						
Povidone, NF [						
[						
Alcohol, USP (Ethyl Alcohol) [						
Microcrystalline Cellulose, NF [						
Crospovidone, NF [						
Magnesium Stearate/Sodium Lauryl Sulfate [						
Colloidal Silicon Dioxide, NF						
FD&C Yellow #6 Lake HT						
FD&C Blue #2 Lake HT						
FD&C Red #40 Lake HT						
FD&C Blue #1 Lake HT						
D&C Yellow #10 Lake HT						
D&C Red #27 Lake HT						
D&C Red #30 Lake HT						
FD&C Red #40 Lake HT						
<b>TOTAL THEORETICAL WEIGHT</b>	<b>130</b>	<b>130</b>	<b>130</b>	<b>130</b>	<b>130</b>	<b>130</b>

**COMPARATIVE QUANTITATIVE COMPOSITIONS (continued)**

LEVOTHYROXINE SODIUM TABLETS USP, 25MCG, 50MCG, 75MCG, 88MCG, 100MCG, 112MCG, 125MCG, 150MCG, 175MCG, 200MCG AND 300MCG

	0.125mg Tablet	0.15mg Tablet	0.175mg Tablet	0.2mg Tablet	0.3mg Tablet
Levothyroxine Sodium, USP	0.125mg	0.15mg	0.175mg	0.2mg	0.3mg
INACTIVE COMPONENTS					
Mannitol USP, [					
Sucrose, NF					
Butylated Hydroxyanisole, NF					
Povidone, NF [					
[					
Alcohol, USP (Ethyl Alcohol) [					
Microcrystalline Cellulose, NF [					
Crospovidone, NF [					
Magnesium Stearate/Sodium Lauryl Sulfate					
Colloidal Silicon Dioxide, NF					
FD&C Yellow #6 Lake HT					
FD&C Blue #2 Lake HT					
FD&C Red #40 Lake HT					
FD&C Blue #1 Lake HT					

D&C Yellow #10 Lake HT  
 D&C Red #27 Lake HT  
 D&C Red #30 Lake HT  
 FD&C Red #40 Lake HT  
**TOTAL THEORETICAL WEIGHT**

130 130 130 130 130

**Table II**  
**LEVOTHYROXINE SODIUM TABLETS, USP**  
 0.025mg, 0.050mg, 0.075mg, 0.088mg, 0.100mg, 0.112mg,  
 0.125mg, 0.150mg, 0.175mg, 0.200mg AND 0.300mg

**DISSOLUTION PROFILE SUMMARY**

	10 MINUTES	20 MINUTES	30 MINUTES	45 MINUTES
<b>Mylan Lot R1H0854 (0.025mg)</b>				
Mean	58%	78%	83%	87%
Range	58%	78%	83%	87%
RSD	15.9%	4.2%	3.1%	2.8%
<b>Levoxyll® Lot 7032 (0.025mcg)</b>				
Mean	96%	96%	95%	97%
Range	96%	96%	95%	97%
RSD	3.1%	1.1%	3.0%	1.4%
<b>Mylan Lot R1H0746 (0.050mg)</b>				
Mean	59%	74%	79%	83%
Range	59%	74%	79%	83%
RSD	16.3%	6.3%	4.9%	4.3%
<b>Levoxyll® Lot 7269 (0.050mg)</b>				
Mean	96%	98%	98%	98%
Range	96%	98%	98%	98%
RSD	2.1%	2.0%	2.1%	1.9%
<b>Mylan Lot R1H0747 (0.075mg)</b>				
Mean	70%	78%	82%	85%
Range	70%	78%	82%	85%
RSD	6.7%	5.8%	5.2%	4.9%
<b>Levoxyll® Lot 7194 (0.075mg)</b>				
Mean	98%	98%	97%	96%
Range	98%	98%	97%	96%
RSD	5.6%	1.6%	6.3%	6.0%
<b>Mylan Lot R1H0748 (0.088mg)</b>				
Mean	67%	78%	82%	85%
Range	67%	78%	82%	85%
RSD	11.8%	6.8%	5.7%	5.8%
<b>Levoxyll® Lot 7122 (0.088mg)</b>				
Mean	95%	93%	97%	94%
Range	95%	93%	97%	94%
RSD	2.5%	7.6%	1.6%	5.5%

**CONDITIONS (USP METHOD):**

Dissolution Medium: 0.01 N HCl containing 0.2% Sodium Lauryl Sulfate, 37°C ± 0.5°C, 500 mL

Apparatus: 2 (Paddles)

Speed: 50 rpm

Sample Times: 10, 20, 30 and 45 minutes

Limits: NLT 70% (Q) in 45 minutes

**LEVOTHYROXINE SODIUM TABLETS, USP**  
**0.025mg, 0.050mg, 0.075mg, 0.088mg, 0.100mg, 0.112mg,**  
**0.125mg, 0.150mg, 0.175mg, 0.200mg AND 0.300mg**

**DISSOLUTION PROFILE SUMMARY (continued)**

	10 MINUTES	20 MINUTES	30 MINUTES	45 MINUTES
<b>Mylan Lot R1H0707 (0.100mg)</b>				
Mean	59%	78%	82%	86%
Range	[			]
RSD	14.4%	6.1%	5.5%	5.1%
<b>Levoxyl® Lot 7037 (0.100mg)</b>				
Mean	95%	100%	100%	101%
Range	[			]
RSD	4.4%	1.7%	2.0%	1.6%
<b>Mylan Lot R1H0749 (0.112mg)</b>				
Mean	59%	79%	83%	88%
Range	[			]
RSD	15.4%	5.9%	4.7%	3.9%
<b>Levoxyl® Lot 7145 (0.112mg)</b>				
Mean	99%	100%	102%	102%
Range	[			]
RSD	3.0%	2.5%	1.2%	1.4%
<b>Mylan Lot R1H0750 (0.125mg)</b>				
Mean	63%	76%	80%	83%
Range	[			]
RSD	13.0%	5.1%	4.4%	3.9%
<b>Levoxyl® Lot 7201 (0.125mg)</b>				
Mean	101%	101%	101%	101%
Range	[			]
RSD	1.6%	1.6%	1.5%	1.4%
<b>Mylan Lot R1H0751 (0.150mg)</b>				
Mean	53%	75%	80%	84%
Range	[			]
RSD	10.2%	5.7%	4.3%	4.3%
<b>Levoxyl® Lot 7223 (0.150mg)</b>				
Mean	96%	97%	96%	95%
Range	[			]
RSD	1.5%	1.3%	1.5%	4.2%

**CONDITIONS (USP METHOD):**

Dissolution Medium: 0.01 N HCl containing 0.2% Sodium Lauryl Sulfate,

37°C ± 0.5°C, 500 mL

Apparatus: 2 (Paddles)

Speed: 50 rpm

Sample Times: 10, 20, 30 and 45 minutes

Limits: NLT 70% (Q) in 45 minutes

**LEVOTHYROXINE SODIUM TABLETS, USP**  
**0.025mg, 0.050mg, 0.075mg, 0.088mg, 0.100mg, 0.112mg,**  
**0.125mg, 0.150mg, 0.175mg, 0.200mg AND 0.300mg**

**DISSOLUTION PROFILE SUMMARY (continued)**

	10 MINUTES	20 MINUTES	30 MINUTES	45 MINUTES
<b>Mylan Lot R1H0752 (0.175mg)</b>				
Mean	56%	78%	82%	86%
Range	[			]
RSD	8.1%	3.3%	3.8%	2.8%
<b>Levoxyl® Lot 7138 (0.175mg)</b>				
Mean	96%	96%	95%	95%
Range	[			]
RSD	0.9%	1.0%	2.03%	1.0%
<b>Mylan Lot R1H0753 (0.200mg)</b>				
Mean	58%	79%	83%	86%
Range	[			]
RSD	7.8%	4.5%	4.7%	4.7%
<b>Levoxyl® Lot 7227 (0.200mg)</b>				
Mean	96%	97%	97%	97%
Range	[			]
RSD	1.0%	1.2%	0.8%	0.9%
<b>Mylan Lot R1H0708 (0.300mg)</b>				
Mean	56%	83%	88%	90%
Range	[			]
RSD	10.4%	5.0%	4.6%	3.7%
<b>Mylan Lot R1H0708 (0.300mg)</b>				
Mean	60%	87%	90%	92%
Range	[			]
RSD	15.9%	3.4%	3.3%	2.5%
<b>Levoxyl® Lot 7000 (0.300mg)</b>				
Mean	100%	99%	100%	100%
Range	[			]
RSD	2.3%	2.6%	2.7%	2.4%

**CONDITIONS (USP METHOD):**

Dissolution Medium: 0.01 N HCl containing 0.2% Sodium Lauryl Sulfate,  
37°C ± 0.5°C, 500 mL  
Apparatus: 2 (Paddles)  
Speed: 50 rpm  
Sample Times: 10, 20, 30 and 45 minutes  
Limits: NLT 70% (Q) in 45 minutes

**F<sub>2</sub> Analysis**

**REFERENCE: Levothyroxine Sodium Tablets USP, 300mcg, Lot R1H0708  
(Highest Strength the Lot used in Bioequivalence Study)**

Analysis of Profiles Generated at Initial Release

LOT NUMBER	STRENGTH	TIME (minutes)				f <sub>2</sub>
		10	20	30	45	
R1H0854	0.025mg	58	78	83	87	69.40
R1H0746	0.050mg	59	74	79	83	56.30
R1H0747	0.075mg	70	78	82	85	53.64
R1H0748	0.088mg	67	78	82	85	56.94
R1H0707	0.100mg	59	78	82	86	66.20
R1H0749	0.112mg	59	79	83	88	70.97
R1H0750	0.125mg	63	76	80	83	56.74
R1H0751	0.150mg	53	75	80	84	58.85
R1H0752	0.175mg	56	78	82	86	67.34
R1H0753	0.200mg	58	79	83	86	69.73
R1H0708	300mcg (ref./bio)	56	83	88	90	

**Acceptance Criteria:**  $50 < f_2 < 100$

Similarity Factor F2 calculated between the highest strength and other strengths was acceptable.

	Age		Age Groups		Gender		Race		Weight (lbs)	
			Range	%	Sex	%	Category	%		
			<18	0			Caucasian	80		
Mean	23.2	24-40	100	Male	76.0	Black.	0	Mean	168.4	
SD	4.3	41-64	0	Female	24.0	Asian/Pacific	4	SD	27.9	
Range	19-39	65-75	0			Hispanic	12	Range	110-208	
		>75	0			Other	4			

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**Similarity Factor (F<sub>2</sub>) Calculations:**

<b>F<sub>2</sub> Metric, Other Strengths Compared to Biostudy Strength</b>			
<b>Low strength</b>	<b>Highest strength</b>	<b>F2 metric for test</b>	<b>F2 metric for RLD</b>
0.025 mg	0.2 mg	75.85	55.91
0.050 mg	0.2 mg	60.58	67.21
0.075 mg	0.2 mg	51.39	97.58
0.088 mg	0.2 mg	57.31	66.69
0.100 mg	0.2 mg	77.42	85.65
0.112 mg	0.2 mg	58.55	90.05
0.125 mg	0.2 mg	62.20	74.47
0.150 mg	0.2 mg	55.10	82.00
0.175 mg	0.2 mg	79.27	76.76

<b>F<sub>2</sub> Metric, Test Compared to Reference</b>	
<b>Strength</b>	<b>F2 metric</b>
0.025 mg	39.78
0.050 mg	56.84
0.075 mg	38.70
0.088 mg	40.16
0.100 mg	45.54
0.112 mg	70.97
0.125 mg	53.20
0.150 mg	38.64
0.175 mg	53.09
0.200 mg	52.15
0.300 mg	57.80

**Comments (Dissolution)**

The firm has conducted the dissolution testing using the USP method. The test and reference products meet the USP specifications of NLT 70% (Q) dissolved in 45 minutes. The F<sub>2</sub> value for all of the lower strengths compared to the highest strength of the test product is greater than 50. The dissolution testing is acceptable.

**Table IV**  
**Mean Serum Concentration (ng/mL) of L-thyroxine T<sub>4</sub> – Fasting Study**

<b>Time (Hrs)</b>	<b>Test Treatment A</b>	<b>Test Treatment B</b>	<b>Ratio (A vs B)</b>
-0.5	64.0 (16)	66.39 (18)	0.96
-0.25	64.87 (14)	67.14 (17)	0.97
0.0	64.81 (13)	65.09 (19)	1.00
0.5	72.20 (16)	76.00 (18)	0.95
1.0	97.13 (21)	102.37 (17)	0.95
1.5	110.17 (18)	112.78 (17)	0.98
2.0	113.62 (17)	118.74 (16)	0.96
2.5	112.95 (15)	116.47 (15)	0.97
3.0	111.76 (15)	114.07 (11)	0.98
4.0	110.79 (15)	111.90 (13)	0.99
6.0	102.95 (13)	104.11 (12)	0.99
8.0	100.17 (15)	101.58 (14)	0.99
12.0	97.35 (14)	100.36 (13)	0.97
18.0	95.87 (14)	96.40 (14)	0.99
24.0	98.83 (12)	99.40 (13)	0.99
48.0	94.19 (13)	94.42 (12)	1.00

BIOEQUIVALENCY COMMENTS

ANDA: 76-647

APPLICANT: Mylan Pharmaceuticals

DRUG PRODUCT: Levothyroxine Sodium Tablets USP, 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.200 mg & 0.300 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the dissolution testing has been incorporated into your stability and quality control programs as specified in USP 26.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

*/s/*

Dale P. Conner, Pharm. D.  
Director, Division of Bioequivalence  
Office of Generic Drugs  
Center for Drug Evaluation and Research



**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**ANDA 76-187/S-003**

**Administrative/Correspondence**

**MEMORANDUM****DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE:** July 13, 2004

**FROM:** Gary J. Buehler, Director  
Office of Generic Drugs

**SUBJECT:** Levothyroxine Sodium Tablets  
ANDA 76-187/S-003

**TO THE FILE:** ANDA 76-187/S-003

LSI  
7/13/04

**Background:**

On June 6, 2001, Mylan submitted an ANDA (76-187) for levothyroxine sodium (LS) tablets citing Jerome Steven's Unithroid as a reference listed drug. This ANDA was approved for marketing on June 5, 2002. On August 8, 2002, Mylan submitted a supplement to its ANDA, seeking an FDA determination that its approved and marketed product is also bioequivalent (and thus therapeutically equivalent) to Levoxyl.<sup>1</sup> The supplement was received by FDA on August 9, 2002.

At the time, the Office of Generic Drugs (OGD) believed that Mylan's use of a supplement to its approved ANDA for LS tablets to seek a determination of bioequivalence and therapeutic equivalence to a listed drug different than the one referenced in the initial ANDA could be confusing (i.e., to have the same approved drug product AB rated to multiple listed drugs) and administratively inconvenient. OGD staff expressed concerns about the supplement to Mylan by phone, and, on January 27, 2003, Mylan administratively withdrew its supplement and resubmitted it as a new ANDA. As of January 2003, no patents were listed for Levoxyl so the administrative conversion of the supplement into a stand-alone ANDA did not bring with it patent certification requirements that did not exist when the supplement was first submitted.

<sup>1</sup> Drug products are considered to be therapeutically equivalent if they are pharmaceutically equivalent and bioequivalent. See Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) at viii (available at <http://www.fda.gov/cder/orange/default.htm>). Drug products are pharmaceutical equivalents if they are identical dosage forms that contain identical amounts of the identical active ingredient and meet identical standards of identity, strength, quality, purity, and potency. 21 C.F.R. 320.1(c). Drugs are considered bioequivalent if there is the absence of a significant difference in the rate and extent to which the active ingredient is absorbed and becomes available at the site of drug action. 21 U.S.C. 355(j)(8)(B); 21 C.F.R. 320.1(e). ANDAs with ratings demonstrating therapeutic equivalence to a listed drug ("A" therapeutic equivalence ratings) are generally considered substitutable for those drugs.

Subsequently, on April 29, 2003, King obtained a patent on Levoxyl and timely submitted it to FDA for listing. Because Mylan had, at that time, a pending ANDA seeking approval of a drug product referencing (and bioequivalent to) Levoxyl, Mylan's pending ANDA relied on FDA's previous finding of safety and effectiveness for Levoxyl, as contemplated by 21 U.S.C. 355(j)(2)(A). Accordingly, Mylan was required to certify to Levoxyl's patent. See 21 U.S.C. 355(j)(2)(A)(vii). Mylan certified with a paragraph IV certification on April 30, 2003 and, according to Mylan, was sued for patent infringement within the statutory 45-day period. Mylan's ANDA is subject to a 30-month stay, which is due to expire on November 7, 2005.

Separately, on June 23, 2004, FDA approved supplements to the approved Unithroid and LEVO-T 505(b)(2) applications seeking AB ratings to Synthroid and Levoxyl on June 23, 2004. At the time of those approvals, the agency recognized that, whereas holders of the approved LS NDAs were permitted to obtain therapeutic equivalence determinations by supplementing their approved NDAs, Mylan was told it should obtain such a determination through a separate stand-alone ANDA approval. NDA holders seeking bioequivalence determinations with respect to Levoxyl through supplements had no patent certification obligations because they were not relying on the finding of safety and effectiveness for Levoxyl to establish the safety and effectiveness of their LS drug products; safety and effectiveness had been established by reference to published literature. See King Pharmaceuticals, Inc. v. FDA, Civ. No. 04-1058 (RBW) (Mem. Op. dated July 8, 2004) (upholding determination that patent certifications were not required). By contrast, the Mylan stand-alone ANDA was required to contain certifications to any listed Levoxyl patents, as a new ANDA submitted pursuant to 21 U.S.C. 355(j)(2)(A). In light of this apparent inconsistency, OGD, in consultation with the Office of Chief Counsel (OCC), reviewed the legal basis for the original determination that approved ANDAs seeking to demonstrate therapeutic equivalence to another listed drug should do so through a new stand-alone ANDA rather than through a supplement to an approved ANDA.

#### **Summary of Conclusion and Remedial Actions:**

Upon further consideration of OGD's January 2003 determination, FDA has decided that the administrative conversion of Mylan's supplement into a stand-alone ANDA was not required under either the statute or the regulations. Mylan should have been permitted to file an ANDA supplement as it originally intended. In contrast to a stand-alone ANDA, a supplement to an approved ANDA that merely seeks a determination by FDA that the approved drug is therapeutically equivalent to another approved drug, and does not seek to make any changes to the approved drug product, does not carry patent certification obligations.

As a policy matter, a separate ANDA that describes precisely the same drug product with the same formulation, manufacturing, and labeling as the drug product approved in another ANDA held by the same sponsor could lead to even greater consumer, physician, and pharmacist confusion than a single ANDA for a drug product that is therapeutically equivalent (and thus AB-rated) to two comparators. In addition, requiring separate ANDAs in these circumstances could waste scarce review resources as FDA personnel would be required to re-review sections of the application (such as labeling) that would not require re-review if a supplement were permitted.

FDA promptly informed Mylan of its determination that Mylan could seek an AB rating to Levoxyl through a supplement to its ANDA. On June 25, 2004, at Mylan's request, FDA administratively reimposed the relevant sections of Mylan's ANDA seeking AB rating to Levoxyl into a supplement to its previously approved ANDA.

### Reasons for Conclusion:

#### Levoxyl Is Not a Reference Listed Drug for Mylan's Supplements

FDA has determined that it may approve a supplement to an already approved ANDA when the supplement contains bioequivalence information necessary to establish therapeutic equivalence to a listed drug (other than the reference listed drug relied upon by the ANDA applicant for approval). In these circumstances, the applicant need not submit a stand-alone ANDA and accompanying patent certifications.

Under 21 U.S.C. 355(j)(1), "[a]ny person may file with the Secretary an abbreviated application for approval of a new drug." An ANDA applicant does not conduct safety and effectiveness investigations to support its approval; instead, it establishes safety and effectiveness by referring to a previously approved drug (listed drug) and showing that its proposed product has the same active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics and conditions of use as, and is bioequivalent to that listed drug. 21 U.S.C. 355(j)(2). The listed drug referenced in an ANDA and relied on for approval of that ANDA is known as the "reference listed drug." See 21 C.F.R. 314.3 (defining reference listed drug as "the listed drug identified by FDA as the drug product upon which an applicant relies for approval of its abbreviated application."); 21 C.F.R. 314.94 (stating ANDA must contain name of reference listed drug and information to show proposed product has the same active ingredient, dosage form, strength, route of administration, and labeling as reference listed drug and is bioequivalent to reference listed drug).

As a quid pro quo for the opportunity to rely on a reference listed drug's previous approval to establish its own safety and effectiveness, and to protect the intellectual property relating to the reference listed drug, an applicant seeking approval for an ANDA must certify to patents submitted to FDA and published in the Orange Book as claiming the reference listed drug or an approved use of the reference listed drug. See 21 U.S.C. 355(j)(2)(A)(vii); 21 C.F.R. 314.94(a)(12). Because, by definition, a stand-alone ANDA relies on the finding of safety and effectiveness of the drug to which it compares itself for its own approval, the comparator drug in any stand-alone ANDA (even one that describes a product that has been previously approved in another ANDA) is a reference listed drug. Under the statute and regulations, any stand-alone ANDA applicant must include a certification to the listed patents, if any, on that reference listed drug. Mylan's stand-alone ANDAs complied with this requirement.

By contrast, the holder of an **approved** ANDA, that seeks to **supplement** its approved application to obtain an FDA determination that its drug is therapeutically equivalent to a listed drug other than the reference listed drug relied on for its initial approval, but that does not seek to

change the finished dosage form, its approved labeling, or any other condition of approval, is not "seeking approval for a new drug" within the meaning of 21 U.S.C. 355(j). Moreover, the new comparator is not a new "reference listed drug" as that term is defined and used in FDA's regulations. In contrast to an unapproved stand-alone ANDA, such a supplement does not seek to establish safety and effectiveness of a drug product by "piggybacking" on the finding of safety and effectiveness for a previously approved drug. The safety and effectiveness of the generic drug product as labeled was established by its initial approval under the original ANDA. After the bioequivalence/therapeutic equivalence supplement is approved, the drug product, formulation, manufacturing information, and approved labeling will be the same as the drug product, formulation, manufacturing information and approved labeling that existed before the supplement was approved. The supplement containing the new bioequivalence data merely seeks to provide FDA and the world with one additional piece of information about its previously approved drug product - i.e., that its drug product is therapeutically equivalent (i.e., pharmaceutically equivalent and bioequivalent) to another comparator drug.

Applying these principles to the facts at issue, Mylan's supplement seeking to demonstrate therapeutic equivalence to Levoxyl does not seek to make Levoxyl a reference listed drug and does not carry patent certification obligations.<sup>2</sup> In its supplement, Mylan is not relying on Levoxyl for approval; nor is Mylan seeking to change the conditions of approval based on its comparison to Levoxyl.<sup>3</sup> Mylan's supplement proposes no changes to Mylan's drug product or its approved labeling. Here, Mylan is merely asking FDA to affirm that its LS tablets that have been approved and marketed since August 8, 2002, are also bioequivalent (and, thus, therapeutically equivalent) to Levoxyl. Mylan, itself, conducted the bioequivalence study to support this assertion. Because evaluation of Mylan's bioequivalence study did not require Mylan to change any aspects of its previous approval, Mylan can not be said to have relied on Levoxyl "for approval of its abbreviated application." Because, in its supplement, Mylan does not rely on FDA's previous finding of safety and effectiveness for Levoxyl to establish the safety and

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<sup>2</sup> Because Levoxyl is not a reference listed drug for Mylan's application, section 1101(a)(1)(D)(i) of the Medicare Modernization Act (which states that "[a]n applicant may not amend or supplement an application to seek approval of a drug referring to a different listed drug from the listed drug identified in the application as submitted to the Secretary") is not applicable to these facts. The use of the words "drug referring to a different listed drug" specifically refers to a change in reference listed drugs. In this case, Mylan does not seek to change reference listed drugs - Levoxyl is not a reference listed drug either for its initial approval or for its supplement, nor does Mylan seek to make it one. Instead, Mylan merely seeks to provide FDA and the world with additional information about its previously approved ANDA. The MMA provision was intended to prevent an ANDA applicant from seeking approval for one drug product and later changing its application to seek approval for a different drug product without incurring the possibility of a 30-month stay in conjunction with paragraph IV certifications and resulting patent litigation related to that changed ANDA. It was not intended to limit the information that an ANDA holder can provide to FDA and the public about the ANDA holder's previously approved and unchanged drug product.

Moreover, even if that provision were applicable to the facts of this case (and it is not), it is not retroactive and did not apply to applications submitted before December 8, 2003. Mylan initially submitted its application as a supplement on August 8, 2002, before the MMA was effective. But for the decision of OGD to reject that supplement and administratively convert it to a full ANDA, that supplement would have predated the MMA's enactment. For purposes of determining which regulatory scheme applies, Mylan should not be penalized for OGD's initial mistake.

<sup>3</sup> As noted above, the reference listed drug for Mylan's ANDA is Jerome Stevens' Unithroid.

effectiveness of Mylan's drug product, Levoxyl is not a reference listed drug for Mylan's supplement and no obligations to certify to Levoxyl's patents attach.<sup>4</sup>

Accordingly, such an ANDA supplement is on the same footing as an approved 505(b)(2) application (such as Jerome Stevens' Unithroid and Alara's LEVO-T) that seeks to establish therapeutic equivalence to another approved drug product. No patent certifications are required in either case because in neither case is the approved application relying on the safety or effectiveness of another approved application to establish its own safety and effectiveness.

Mylan was not required to seek therapeutic equivalence evaluations in a stand-alone ANDA

Nothing in FDA's statute or regulations requires that therapeutic equivalence evaluations can be made only in stand-alone ANDAs. FDA has made multiple therapeutic equivalence evaluations both in NDA's and supplements.

Moreover, as a policy matter, once someone holds an approved application, FDA believes it is generally inefficient to require a stand-alone ANDA where a supplement (to an NDA or ANDA) would accomplish the same purpose. Although determinations of bioequivalence are necessary for approval of an original stand-alone ANDA, they are not sufficient for such an approval. Review of an original stand-alone ANDA also requires, among other things, review of labeling for compliance with the same labeling requirement. See 21 U.S.C. 355(j)(2)(A)(v) (requiring ANDAs to show that their labeling proposed for the new drug is the same as the labeling approved for the reference listed drug); 21 C.F.R. 314.94(a)(8) (requiring ANDA applicant to submit copies of proposed labeling, statement that its labeling is the same as that of the reference listed drug, and a side by side comparison of ANDA applicant's proposed labeling and labeling of the reference listed drug). Moreover, each separately approved ANDA carries with it separate periodic reporting obligations. See 21 C.F.R. 314.81. By contrast, once an ANDA is approved, a supplement seeking to establish bioequivalence to a second approved drug and seeking to make no other changes does not seek to obtain "approval of a new drug" under 505(j). Such a supplement does not generally require a new labeling review and, once approved, does not carry with it separate periodic reporting obligations that attach to a stand-alone ANDA.

In this case, the finished drug product and labeling for Mylan's product will be exactly the same after approval of the supplement as it was before the approval of the supplement. As a general matter, it would be a waste of government resources to require a new ANDA review and to impose separate reporting requirements in circumstances such as this one where no change to the approved drug product or approved labeling is proposed.

This policy to minimize unnecessary re-review for previously approved drug products (such as re-review of the Mylan data already approved in its original ANDA as part of a review of a new stand-alone ANDA) is also reflected in FDA's refusal to file regulations. FDA's regulation at 21 C.F.R. 314.101(d)(8) permits FDA to refuse to file an NDA or ANDA where "the drug product

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<sup>4</sup> By contrast, if an ANDA supplement proposes a change to an approved ANDA, the ANDA applicant might have to submit new or additional certifications to patents listed for the reference listed drug - in this case, Unithroid.

that is the subject of the submission is already covered by an approved application or abbreviated application and the applicant of the submission (i) [h]as an approved application or abbreviated application for the same drug product." 21 C.F.R. 314.101(d)(8)(i). The policy behind this regulation is the same policy behind permitting Mylan to demonstrate therapeutic equivalence in an ANDA supplement (rather than a stand-alone ANDA) - it is a waste of government resources to re-review a new stand-alone application for a previously approved drug product when a more circumscribed review of the new information regarding the drug product (e.g., bioequivalence data) would suffice. See 57 Fed. Reg. 17950, 17965-17966 ("To permit applicants to force review of a product that is already covered by an approved application would result in a severe drain on FDA resources to review duplicate applications, create duplicate product and patent listings in the Orange Book, and contribute to the agency's accumulation of applications.").

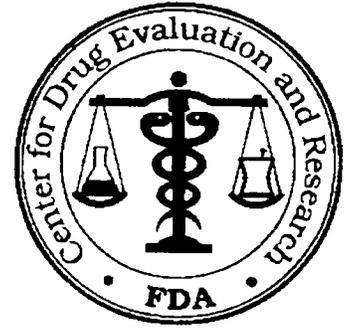
Similarly, FDA's 1998 Guidance for Industry, Variations in Drug Products that May be Included in a Single ANDA ("Variations Guidance") does not suggest that a stand-alone ANDA must be required. By its terms, the Variations Guidance deals with "variations" in a drug product; it is inapplicable to situations, such as this one, where an applicant seeks to have FDA determine that its approved drug product is therapeutically equivalent to a new comparator but seeks to make no changes to the approved drug product. Moreover, the general rule stated in the Variations Guidance is that "when there is a separate NDA as a reference listed drug for a specific drug product there should be a separate abbreviated application for that NDA." Here, Mylan's supplement does not seek to reference a separate reference listed drug - before and after approval of the supplement, the only reference listed drug for the application will be Jerome Stevens' Unithroid. Finally, the purpose of the Variations Guidance is to describe variations that are permitted in a single ANDA in order to minimize the number of situations where separate ANDAs are submitted. Although the Variations Guidance does not explicitly address the situation where, as here, an applicant seeks to compare itself to a second comparator without changing the finished dosage form or approved labeling of the approved drug product, it is consistent with the spirit of the Variations Guidance to permit such a change to be made without requiring a separate application. Here, Mylan does not seek to vary its approved drug product in any way. To require a separate stand-alone application under these circumstances would be inefficient and unnecessary.

For the reasons described above, FDA permits Mylan to supplement its approved ANDA with information purporting to show it is therapeutically equivalent to Levoxyl and has determined that the supplement filed carries no obligations to certify to Levoxyl's patent.

q:\issues\levothyr\levopatcertmem.doc

v:\firmsam\mylan\memos\76-187levopatcert.doc

cc: G. Buehler  
R. West  
C. Parise  
D. Read  
D. Hare  
R. Hassall  
P. Rickman  
M. Shimer  
T. Ames  
P. Chen



## OFFICE OF GENERIC DRUGS

Food and Drug Administration  
HFD-600, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773  
Fax: 301-594-0180

### FAX TRANSMISSION COVER SHEET

APPLICANT: Mylan Pharmaceuticals, Inc. TEL: 304-599-2595  
ATTN: ~~S. Wayne Talton~~ FRANK SISTO FAX: 304-285-6407  
FROM: Peter Chen PROJECT MANAGER: 301-827-5848

Dear Sir:

This facsimile is in reference to your supplemental new drug application dated June 24, 2004, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Levothyroxine Sodium Tablets USP, 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.1 mg, 0.112 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.2 mg, and 0.3 mg.

We are pleased to inform you that this supplemental application is APPROVED!

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

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## West, Robert L

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**From:** Parise, Cecelia M  
**Sent:** Thursday, July 01, 2004 3:09 PM  
**To:** Shimer, Martin; Chen, Peter; Grace, John F; West, Robert L  
**Subject:** RE: levothyroxine

Ok that takes care of it thanks.

Cec

-----Original Message-----

**From:** Shimer, Martin  
**Sent:** Thursday, July 01, 2004 3:08 PM  
**To:** Parise, Cecelia M; Chen, Peter; Grace, John F; West, Robert L  
**Subject:** RE: levothyroxine

Cec,

I'm relatively certain that Mylan did do this in their cover letter requesting conversion to a supplement. After you and I discussed with Wayne what need to be done to convert the ANDA to a supplement he called back and asked for clarification on the labeling issue. I advised that reference to the Levoxyl labeling should be withdrawn.

Marty

-----Original Message-----

**From:** Parise, Cecelia M  
**Sent:** Thursday, July 01, 2004 3:05 PM  
**To:** Parise, Cecelia M; Chen, Peter; Grace, John F; Shimer, Martin; West, Robert L  
**Subject:** RE: levothyroxine

We should request that Mylan withdraw reference to the labeling section of the Levoxyl application.

Cec

-----Original Message-----

**From:** Parise, Cecelia M  
**Sent:** Thursday, July 01, 2004 2:58 PM  
**To:** Chen, Peter; Grace, John F; Shimer, Martin; West, Robert L  
**Subject:** FW: levothyroxine

<< File: 76-187tel02.doc >> << File: 76-187tel01.doc >>

See info below, also please place these two telecons in the approval package.

Thanks,

Cec

-----Original Message-----

**From:** Buehler, Gary J  
**Sent:** Thursday, July 01, 2004 11:42 AM  
**To:** Hare, Donald B; Parise, Cecelia M; West, Robert L; Read, David T; Shimer, Martin  
**Subject:** FW:

Folks

This appears to be correct to me. Any comments from anyone on it?

Thanks  
Gary

-----Original Message-----

**Redacted** 2

**page(s) of trade secret.**

**and/or confidential**

**commercial information**

~~(b4)~~

(b5)

Paul, Olive\*

---

**From:** Chen, Peter  
**Sent:** Friday, June 25, 2004 3:52 PM  
**To:** CDER-DDR600; Payne, Angela; Davit, Barbara M  
**Cc:** Conner, Dale P; Grace, John F; Rickman, William P; Shimer, Martin; Smela Jr, Michael  
**Subject:** Conversion of ANDA 76-647 into a supplement for ANDA 76-187

Document Room:

Please convert ANDA 76-647 into a new strength supplement — to ANDA 76-187. Please inform me ASAP once the transfer is completed.

Bio and Labeling:

Bio and labeling reviews were completed for ANDA 76-647. No new labeling review needed. New Bioequivalence signoff review is needed.

Barbara:

ANDA 76-647 was supposed to be AB equivalent for Levoxyl. Mylan is transferring this ANDA to be a supplement for 76-187 with therapeutic equivalence for Levoxyl. Thus a brief and quick bio review probably needs to be completed for the 76-187 supplement.

Thanks,  
Peter Chen

*No additional Bio Review needed.*

*ST*

**APPEARS THIS WAY  
ON ORIGINAL**

-----Original Message-----

**From:** Sanchez, Aida L  
**Sent:** Monday, June 28, 2004 9:19 AM  
**To:** Dhariwal, Kuldeep R; Makary, Moheb H; Fabian-Fritsch, Beth  
**Cc:** Conner, Dale P; Davit, Barbara M  
**Subject:** FW: Conversion of ANDA 76-647 into a supplement for ANDA 76-187

Moheb, Kuldeep and Beth:

See below. The Office has decided to change this ANDA into a supplement of 76-187. I guess they need a short review and biosignoff for the supplement. I guess we can use the same review that you did for 76-647 and change the title to say that is a supplement for 76-187 and that the Mylan product is AB rated to Levoxyl. Thanks,

Lizzie

-----Original Message-----

**From:** Conner, Dale P  
**Sent:** Friday, June 25, 2004 4:23 PM  
**To:** Sanchez, Aida L  
**Subject:** FW: Conversion of ANDA 76-647 into a supplement for ANDA 76-187

-----Original Message-----

**From:** Chen, Peter  
**Sent:** Friday, June 25, 2004 3:52 PM  
**To:** CDER-DDR600; Payne, Angela; Davit, Barbara M  
**Cc:** Conner, Dale P; Grace, John F; Rickman, William P; Shimer, Martin; Smela Jr, Michael  
**Subject:** Conversion of ANDA 76-647 into a supplement for ANDA 76-187

Document Room:

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Please inform me ASAP once the transfer is completed.

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ANDA 76-647 was supposed to be AB equivalent for Levoxyl. Mylan is transferring this ANDA to be a supplement for 76-187 with therapeutic equivalence for Levoxyl. Thus a brief and quick bio review probably needs to be completed for the 76-187 supplement.

Thanks,  
Peter Chen

RECORD OF TELEPHONE CONVERSATION

<p>Wayne Talton of Mylan phoned and wondered if they were going to receive approval of their supplement today. I stated that we had been sued by King and that an approval probably would not happen until the lawsuit was resolved. I suggested that they speak to their lawyers and determine how they wish to proceed.</p> <p align="center"><b>APPEARS THIS WAY ON ORIGINAL</b></p>	<b>DATE</b> 6/28/04
	<b>ANDA NUMBER</b>  76-187 76-647
	<b>IND NUMBER</b>
	<b>TELECON</b>
	<b>INITIATED BY MADE</b> _ APPLICANT/ <input checked="" type="checkbox"/> BY SPONSOR TELE.
	<b>FDA _ IN PERSON</b>
	<b>PRODUCT NAME</b> Levothyroxine SodiumTablets
	<b>FIRM NAME</b> Mylan
	<b>NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD</b> Wayne Talton
	<b>TELEPHONE NUMBER</b> 800-285-6407 x 6551
	<b>SIGNATURE</b> Cecelia M. Parise 6/30/04 V:\firmsam\mylan\76187te 101.doc



# MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

June 24, 2004

## PRIOR APPROVAL SUPPLEMENT

Office of Generic Drugs, CDER, FDA  
Gary J. Buehler, Director  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

NDA NO 76187 REF NO 970-003  
NDA SUPPL FOR New Strength

RE: LEVOTHYROXINE SODIUM TABLETS USP, 25MCG, 50MCG, 75MCG, 88MCG, 100MCG, 112MCG, 125MCG, 150MCG, 175MCG, 200MCG AND 300MCG  
ANDA 76-187  
(Request for Approval of Bioequivalence (AB) Rating to Levoxyt® Tablets)

Dear Mr. Buehler:

Reference is made to the above referenced Abbreviated New Drug Application (ANDA) which received approval on June 5, 2002 and provided for a Bioequivalence (AB) Rating of Mylan's generic Levothyroxine Sodium Tablets, USP to the reference listed drug, Jerome Stevens' Unithroid® (Levothyroxine Sodium Tablets, USP). Reference is also made to a telephone conversation held with Ms. Cecelia Parise and Mr. Martin Shimer, of your Office, on June 24, 2004. Mylan wishes to supplement this ANDA to request approval for a Bioequivalence (AB) Rating of its generic Levothyroxine Sodium Tablet product to Levoxyt® (Levothyroxine Sodium Tablets, USP).

Information to support this supplement has previously been submitted and reviewed under ANDA 76-647 for Levothyroxine Sodium Tablets USP. The purpose of this supplemental application is to incorporate by reference Sections VI (Bioequivalence), VII (Components and Composition), VIII (Raw Materials), IX (Description of Manufacturing Facility), X (Outside Firms), XI (Manufacturing and Processing Instructions), XII (In-process Information), XIII (Packaging Material Controls), XIV (Controls for the Finished Dosage Form), XV (Analytical Controls), XVI (Stability of the Dosage Form), XVIII (Samples) and XX (Generic Drug Enforcement Act) contained within ANDA 76-647 and the Agency's review of this information into a supplemental application to ANDA 76-187 so that approval of this supplement may be granted.

Pursuant to 21 CFR 314.71(b), we certify that a true copy of this supplement, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This supplement is being submitted in duplicate to the above referenced application. Should you require additional information or have any questions regarding this supplement, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton  
Executive Director  
Regulatory Affairs

SWT/dn

Enclosures

RECEIVED

JUN 25 2004

OGD / CDER

Department—Fax Numbers	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	Legal Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Administration	Legal Services	(304) 598-5408	Quality Control	(304) 598-5407
Business Development	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6409
Corporate Services	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6409
Human Resources	Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

RECORD OF TELEPHONE CONVERSATION

<p>John O'Donnell of Mylan Pharmaceuticals had phoned Gary Buehler earlier in the day to determine how the 505(b)(2) applications were approved as bioequivalent to Levoxyl when they could only receive a tentative approval due to a 30 month stay.</p> <p>Gary and I spoke to Mr. O'Donnell. Gary informed them that we had found out a few days earlier that no patent certification was required based upon the fact that the product was already approved and the applicants were not relying upon the King application to obtain approval. Gary also informed them that we had inquired if the same concept could be applied to Mylan's ANDA since it was already approved ANDA and was similarly situated to the 505(b)(2) applications. We informed him that the same pathway was an option for Mylan. Mr. O'Donnell said that he would have either Wayne Talton or Frank Sisto phone me for the details.</p> <p>Later in the day I spoke to Wayne Talton of Mylan and informed him to obtain an AB rating to Levoxyl in the same manner as the 505(b)(2) applications Mylan should submit a supplement to their approved ANDA with the 356h referencing the original basis of their submission, Unithroid, and without a patent certification. He wanted to reference the data in Mylan's ANDA that was already submitted ANDA 76-647 and he wanted to know which sections should be referenced. Marty Shimer and I went through the sections we thought should be referenced.</p> <p>Mr. Talton inquired whether they could have one common package insert because there were minor differences in the labeling and I asked that he should check with labeling but it seemed reasonable. He also asked what would happen to the 180-day exclusivity and I said if they supplemented without the patent certification there would not be 180- day exclusivity. Mr. Talton said would submit a draft then would submit a supplement by Fed-Ex.</p>	<p><b>DATE</b> 6/24/04</p>
	<p><b>ANDA NUMBER</b>  76-187 76-647</p>
	<p><b>IND NUMBER</b></p>
	<p align="center"><b>TELECON</b></p>
	<p><b>INITIATED BY MADE</b> _ APPLICANT/ <u>X</u> BY SPONSOR TELE.</p>
	<p>FDA _ IN PERSON</p>
	<p><b>PRODUCT NAME</b> Levothyroxine Sodium Tablets</p>
	<p><b>FIRM NAME</b> Mylan</p>
	<p><b>NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD</b>  John O'Donnell Wayne Talton</p>
	<p><b>TELEPHONE NUMBER</b> 1-800-826-9526</p>
<p><b>SIGNATURE</b> Cecelia M. Parise 6/30/04 V:\firmsam\mylan\76187te 101.doc</p>	