

076187-AB-APPROVAL-6-23-04-PRG

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER(S)**

**ANDA 76-187**

**(\*originally approved under ANDA 76-764)**

**Trade Name:**

**Generic Name(s):**      Levothyroxine Sodium Tablets

**Sponsor:**              Mylan Pharmaceuticals, Inc.

**Agent:**

**Approval Date:**        June 6, 2004

**Indication:** Demonstrates bioequivalence between  
Levothyroxine and Synthroid in order to obtain an AB rating

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER:**

**ANDA 76-187**

**(\*originally approved under ANDA 76-764)**

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**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**ANDA 76-187**

**(\*originally approved under ANDA 76-764)**

**Approval Letter(s)**

ANDA 76-764

JUN 23 2004

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

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated June 16, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (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, 0.15 mg, 0.175 mg, 0.2 mg, and 0.3 mg.

Reference is also made to your amendments dated August 27, and September 11, 2003; and January 22, and January 30, 2004.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Levothyroxine Sodium Tablets USP, to be bioequivalent and, therefore, therapeutically equivalent to the corresponding strength of the listed drug (Synthroid<sup>®</sup> Tablets of Abbott Laboratories). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

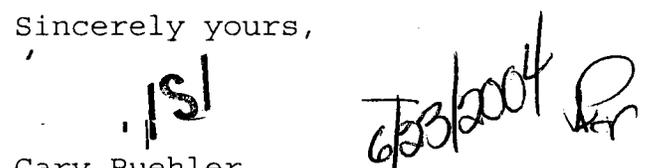
Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change 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. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the 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  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**ANDA 76-187**

**(\* originally approved under ANDA 76-764)**

**Chemistry Review(s)**



**ANDA 76-764**

**Levothyroxine Sodium Tablets, USP**

**Mylan Pharmaceuticals, Inc.**

**Eugene L. Schaefer, Ph.D.  
Chemistry Division I**

**Review #1  
Addendum**



# Chemistry Review Data Sheet

1. ANDA 76-764
2. REVIEW #: 1 Addendum
3. REVIEW DATE: 10-FEB-2004
4. REVIEWER: Eugene L. Schaefer, Ph.D.

## 5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Volumes</u>	<u>Document Date</u>
Original ANDA (for 25, 50, 75, 88, 100, 112, 125, 150, 175 and 200 mcg)	B1.1 and A1.4 (A1.2 and A1.3 are Bio only)	16-JUN-2003
Major amendment (to add 300 mcg strength)	A2.1 and A2.4 (A2.2 and A2.3 are Bio only)	27-AUG-2003
Labeling amendment	A2.1	11-SEP-2003

## 6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Volumes</u>	<u>Document Date</u>
Labeling amendment	A3.1	22-JAN-2004
Bio amendment	<del>A4.1</del> 3 A4.1	✗ 30-JAN-2004



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

12. STRENGTH/POTENCY: 25, 50, 75, 88, 100, 112, 125, 150, 175, 200 and 300 mcg

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER (LoA Date)	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	II		Levothyroxine Sodium, USP	4	N/A		
	ANDA 76-764 is cross-referenced to approved ANDA 76-187 for CMC. Any significant changes to DMF [redacted] will require a supplement to ANDA 76-187. Therefore, there is no need to review DMF [redacted] support of ANDA 76-764.						
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
30. Microbiology	N/A for tablets		
31. Methods Validation	N/A for USP DS and DP		
32. Labeling	Approved	02-FEB-2004	A. Payne
33. EES	Acceptable	22-JUL-2003	S. Ferguson
	Still acceptable	As of 10-FEB-2004	
34. Bioequivalence	Acceptable	20-JAN-2004	Devvrat Patel
	Mylan is using the Dissolution method that DBE recommends.		
35. EA	Exclusion granted	30-SEP-2003	Eugene Schaefer
Radiopharmaceutical	N/A		

# The Chemistry Review for ANDA 76-764

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

ANDA 76-764 is ready to be approved.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None identified at this time.

**APPEARS THIS WAY  
ON ORIGINAL**

cc: ANDA 76-764  
ANANDA DUP  
DIV FILE  
Field Copy

Endorsements (Draft and Final with Dates):

HFD-625/ELSchaefer, Chemist/2/10/04

HFD-625/MSmela, Team Leader/2/11/04

*IS/ 2/12/04*

*IS/ ^ , 2/12/04*

F/T by :ard/2/11/04

V:\FIRMSAMMYLAN\LTRS&REV\76764N00R01ADD.doc

**TYPE OF LETTER: APPROVAL**



**ANDA 76-764**

**Levothyroxine Sodium Tablets, USP**

**Mylan Pharmaceuticals, Inc.**

**Eugene L. Schaefer, Ph.D.  
Chemistry Division I**

**Review #1**



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# Chemistry Review Data Sheet

1. ANDA 76-764
2. REVIEW #: 1
3. REVIEW DATE: 30-SEP-2003
4. REVIEWER: Eugene L. Schaefer, Ph.D.

## 5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Volumes</u>	<u>Document Date</u>
None		

## 6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Volumes</u>	<u>Document Date</u>
Original ANDA (for 25, 50, 75, 88, 100, 112, 125, 150, 175 and 200 mcg)	B1.1 and A1.4 (A1.2 and A1.3 are Bio only)	16-JUN-2003
Major amendment (to add 300 mcg strength)	A2.1 and A2.4 (A2.2 and A2.3 are Bio only)	27-AUG-2003
Labeling amendment	A2.1	11-SEP-2003

## 7. NAME & ADDRESS OF APPLICANT:

Name: Mylan Pharmaceuticals Inc.



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

781 Chestnut Ridge Road  
Address: P.O. Box 4310  
Morgantown, WV 26504-4310  
Representative: S. Wayne Talton  
Telephone: 304-599-2595 Ext. 6551  
Fax: 304-285-6407

#### 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: None  
b) Non-Proprietary Name (USAN): Levothyroxine Sodium USP

#### 9. LEGAL BASIS FOR SUBMISSION:

RLD is Synthroid® Tablets (Abbott Pharmaceuticals, Inc.), NDA 21-402

10. PHARMACOLOGIC CATEGORY: Hormone

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 25, 50, 75, 88, 100, 112, 125, 150, 175, 200 and  
300 mcg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

#### 15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

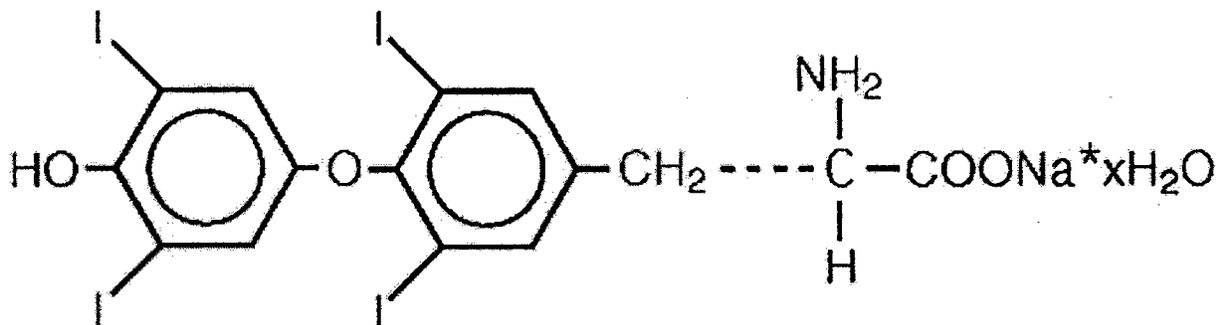
SPOTS product – Form Completed

Not a SPOTS product

## Chemistry Review Data Sheet

**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

L-3,3',5,5'-tetraiodothyronine sodium salt [levothyroxine ( $T_4$ ) sodium].  
 Levothyroxine ( $T_4$ ) sodium has an empirical formula of  $C_{15}H_{10}I_4N NaO_4 \cdot H_2O$ ,  
 molecular weight of 798.86 g/mol (anhydrous)


**17. RELATED/SUPPORTING DOCUMENTS:**
**A. DMFs:**

DMF #	TYPE	HOLDER (LoA Date)	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	II			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
30. Microbiology	N/A for tablets		
31. Methods Validation	N/A for USP DS and DP		
32. Labeling	Pending		
33. EES	Acceptable	22-JUL-2003	S. Ferguson
34. Bioequivalence	Pending		
35. EA	Exclusion granted	30-SEP-2003	Eugene Schaefer
Radiopharmaceutical	N/A		

### 19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.  Yes  No If no, explain reason(s) below:



# The Chemistry Review for ANDA 76-764

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

ANDA 76-764 is ready to be approved on the basis of CMC. However, reviews of bioequivalence and labeling are pending. I recommend a CHEMISTRY CLOSE.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None identified at this time.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

The 200 mcg and 300 mcg Bio batches were commercial production batches of [ ] tablets each.

#### B. Description of How the Drug Product is Intended to be Used

Each strength is supplied in bottles of 100 tablets. The recommended dose depends on a variety of factors including the patient's age, body weight, cardiovascular status, concomitant medical conditions including pregnancy, concomitant medications, and the condition being treated. Doses greater than 200 mcg/day are seldom required. The expiration dating period is 18 months and the label storage condition is 20-25°C.

#### C. Basis for Approvability or Not-Approval Recommendation

Labeling and bioequivalence have not been completed.

### III. Administrative

#### A. Reviewer's Signature

#### B. Endorsement Block

ChemistName: ELSchaefer

ChemistryTeamLeaderName: MSmela

**Redacted** 4

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

**and/or confidential**

**commercial information**

**(b4)**

**35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:** **Satisfactory**

The applicant requests a categorical exclusion, and certifies compliance with all known Federal, State and Local environmental regulations.

**36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT**

None

cc: ANDA 76-764  
ANANDA DUP  
DIV FILE  
Field Copy

Endorsements (Draft and Final with Dates):

HFD-625/ELSchaefter, Chemist/

HFD-625/MSmela, Team Leader/

~~HFD-617/PChen, Project Manager/~~

ISI 9/30/03  
ISI 10/6/03

F/T by /

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**TYPE OF LETTER:** CHEMISTRY CLOSE pending Bio and labeling

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**ANDA 76-187**

**(\*originally approved under ANDA 76-764)**

**BIOEQUIVALENCE REVIEW(S)**

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-764

APPLICANT: Mylan Pharmaceuticals Inc.

DRUG PRODUCT: Levothyroxine Sodium Tablet, 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

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 27.

Please note that the bioequivalence 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 bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

*Jr*

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

CC: ANDA 76-764  
ANDA DUPLICATE  
DIVISION FILE  
HFD-651/ Bio Drug File  
HFD-655/ Patel

Printed in final on 01/20/2004  
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Endorsements: (Final with Dates)

HFD-655/ Patel */S/* 1/20/04

HFD-655/ Nerurkar

HFD-650/ D. Conner */S/* 1/20/04

BIOEQUIVALENCE - ACCEPTABLE

Submission date: 06/16/2003  
08/27/2003

1. FASTING STUDY (STF)

Clinical: L  
Analytical: L

Strength: 0.3 mg

✓ Outcome: AC

1

1

2. FASTING STUDY (STF)

Clinical: L  
Analytical: L

Strength: 0.2 mg

✓ Outcome: AC

1

1

3. DISSOLUTION WAIVER (DIW)

Strength: 0.025 mg

✓ Outcome: AC

4. DISSOLUTION WAIVER (DIW)

Strength: 0.050 mg

✓ Outcome: AC

5. DISSOLUTION WAIVER (DIW)

Strength: 0.075 mg

✓ Outcome: AC

6. DISSOLUTION WAIVER (DIW)

Strength: 0.088 mg

✓ Outcome: AC

7. DISSOLUTION WAIVER (DIW)

Strength: 0.100 mg

✓ Outcome: AC

8. DISSOLUTION WAIVER (DIW)

Strength: 0.112 mg

✓ Outcome: AC

9. DISSOLUTION WAIVER (DIW)

Strength: 0.125 mg

✓ Outcome: AC

10. DISSOLUTION WAIVER (DIW)

Strength: 0.150 mg

✓ Outcome: AC

11. DISSOLUTION WAIVER (DIW)

Strength: 0.175 mg

✓ Outcome: AC

Outcome Decisions: AC - Acceptable  
IC - Incomplete

**OFFICE OF GENERIC DRUGS  
DIVISION OF BIOEQUIVALENCE**

JAN 20 2004

ANDA #: 76-764

SPONSOR: Mylan Pharmaceuticals Inc.

DRUG AND DOSAGE FORM: Levothyroxine Sodium Tablet, 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 study on levothyroxine sodium 0.2 mg tablet  
Fasting study on levothyroxine sodium 0.3 mg tablet

CLINICAL STUDY SITE(S):  1

ANALYTICAL SITE(S):  1

STUDY SUMMARY: Fasting studies are acceptable.

DISSOLUTION: The dissolution testing is acceptable. The dissolution testing should be conducted in 500 mL of 0.01 N HCl containing 0.2% sodium lauryl sulfate using USP Apparatus 2 (paddle) at 50 rpm. The test products should meet the following specifications: NLT 70% (Q) of the labeled amount of levothyroxine in the dosage form is dissolved in 45 minutes. Waivers of *in vivo* bioequivalence study requirements for 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.125 mg, 0.150 mg and 0.175 mg strength tablets are granted.

**DSI INSPECTION STATUS**

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

PRIMARY REVIEWER: Devvrat Patel, Pharm.D.

BRANCH: II

INITIAL: DSI

DATE: 1/20/2004

TEAM LEADER: S. Narkar, Ph.D.

BRANCH: II

INITIAL: DSI

DATE: 1/20/2004

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm. D.

INITIAL: DSI

DATE: 1/20/04

CC: ANDA 76-764  
ANDA DUPLICATE  
DIVISION FILE  
HFD-651/ Bio Drug File  
HFD-655/ Patel

Printed in final on 01/20/2004  
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Endorsements: */S/* Final with Dates)

HFD-655/ Patel */S/* 1/20/04

HFD-655/ Nerurkar

HFD-650/ D. Conner */S/* 1/20/04

*/S/* 1/20/04

BIOEQUIVALENCE - ACCEPTABLE

Submission date: 06/16/2003

08/27/2003

- |                              |                    |
|------------------------------|--------------------|
| 1. FASTING STUDY (STF)       | Strength: 0.3 mg   |
| Clinical: L                  | ✓ Outcome: AC      |
| Analytical: L                | 1                  |
| 2. FASTING STUDY (STF)       | Strength: 0.2 mg   |
| Clinical: L                  | ✓ Outcome: AC      |
| Analytical: L                | 1                  |
| 3. DISSOLUTION WAIVER (DIW)  | Strength: 0.025 mg |
| 4. DISSOLUTION WAIVER (DIW)  | ✓ Outcome: AC      |
| 5. DISSOLUTION WAIVER (DIW)  | Strength: 0.050 mg |
| 6. DISSOLUTION WAIVER (DIW)  | ✓ Outcome: AC      |
| 7. DISSOLUTION WAIVER (DIW)  | Strength: 0.075 mg |
| 8. DISSOLUTION WAIVER (DIW)  | ✓ Outcome: AC      |
| 9. DISSOLUTION WAIVER (DIW)  | Strength: 0.088 mg |
| 10. DISSOLUTION WAIVER (DIW) | ✓ Outcome: AC      |
| 11. DISSOLUTION WAIVER (DIW) | Strength: 0.100 mg |
|                              | ✓ Outcome: AC      |
|                              | Strength: 0.112 mg |
|                              | ✓ Outcome: AC      |
|                              | Strength: 0.125 mg |
|                              | ✓ Outcome: AC      |
|                              | Strength: 0.150 mg |
|                              | ✓ Outcome: AC      |
|                              | Strength: 0.175 mg |
|                              | ✓ Outcome: AC      |

Outcome Decisions: AC - Acceptable  
IC - Incomplete

**DIVISION OF BIOEQUIVALENCE REVIEW**

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<b>ANDA No.</b>	76-764
<b>Drug Product Name</b>	Levothyroxine Sodium Tablet, USP
<b>Strengths</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>	781 Chestnut Ridge Road, Morgantown, WV 26504
<b>Submission Date(s)</b>	June 16, 2003
<b>Amendment Date(s)</b>	August 27, 2003
<b>Reviewer</b>	Devvrat Patel
<b>First Generic</b>	No
<b>File Location</b>	V:\firmsam\mylan\ltrs&rev\76764N0603.doc

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**I. Executive Summary**

The original application references Synthroid<sup>®</sup> 0.2 mg tablet and includes one fasting bioequivalence study. The fasting study was a single-dose, two-way crossover study in normal healthy male and female subjects (n=29) given a dose of 0.6 mg (3 x 0.2 mg tablets). 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-t</sub> 1.04, 96.89-111.25% and LC<sub>max</sub> 1.01, 92.83-109.49%. Seven subjects had measurable baseline corrected total L-thyroxine concentrations at 0 hour which were more than the 5% of their C<sub>max</sub> values. The reviewer excluded these subjects from the statistical analysis and the 90% confidence intervals remained within acceptable limits (LAUC<sub>0-t</sub> 94.79-112.15, LC<sub>max</sub> 89.90-110.69). The Division of Bioequivalence (DBE) does not recommend measurement of L-triiodothyronine (T<sub>3</sub>) of this product. The proposed test products meet the USP dissolution specifications, and the dissolution testing (500 mL of 0.01 N HCl containing 0.2% SLS, paddle at 50 rpm) is acceptable. The formulations of levothyroxine sodium 0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.1 mg, 0.112 mg, 0.125 mg, 0.15 mg and 0.175 mg strength tablets are proportionally similar to levothyroxine 0.2 mg tablet, which underwent acceptable *in vivo* bioequivalence testing. Waivers of *in vivo* bioequivalence study requirements for above mentioned lower strength tablets are granted.

The firm submitted the amendment (08/27/2003) to the original submission to provide for addition of levothyroxine sodium 0.3 mg strength tablet. In support of this amendment, the firm conducted a fasting bioequivalence study comparing levothyroxine sodium 0.3 mg tablet to Synthroid<sup>®</sup> 0.3 mg tablet. The fasting study was a single-dose, two-way crossover study in normal healthy male and female subjects (n=29) given a dose of 0.6 mg (2 x 0.3 mg tablets). Statistical analyses of the serum concentration data for L-thyroxine demonstrate bioequivalence. T<sub>4</sub> results based on baseline correction are (point estimate, 90% CI): LAUC<sub>0-t</sub> 1.09, 102.85-114.56% and LC<sub>max</sub> 1.05, 100.59-110.59%. Eight subjects had measurable baseline corrected total L-thyroxine concentrations at 0

hour which were more than the 5% of their  $C_{max}$  values. The reviewer excluded these subjects from the statistical analysis and the 90% confidence intervals remained within acceptable limits (LAUC<sub>0-t</sub> 101.12-114.27, LC<sub>max</sub> 101.09-114.23). The proposed test product meets the USP dissolution specifications, and the dissolution testing is acceptable. The application is acceptable with no deficiencies.

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### III. Submission Summary

#### A. Drug Product Information

<b>Test Product</b>	Levothyroxine Sodium Tablet
<b>Reference Product</b>	Synthroid <sup>®</sup> Tablet
<b>RLD Manufacturer</b>	Abbott
<b>NDA No.</b>	21-402
<b>RLD Approval Date</b>	July 24, 2002
<b>Indication</b>	Levothyroxine sodium is the sodium salt of the levo isomer of the thyroid hormone thyroxine (T <sub>4</sub> ). It is indicated for 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.

#### B. PK/PD Information

<b>Bioavailability</b>	Absorption of T <sub>4</sub> from the GI tract varies from 48% to 80% of the dose administered.
<b>Food Effect</b>	The extent of absorption is increased in the fasting state and decreased in malabsorption syndromes. Dietary fiber decreases bioavailability of T <sub>4</sub> . Absorption may also decrease with age.
<b>T<sub>max</sub></b>	2-4 hours
<b>Metabolism</b>	The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately 80% of the daily dose of T <sub>4</sub> is deiodinated to yield equal amount of T <sub>3</sub> and reverse T <sub>3</sub> (rT <sub>3</sub> ). T <sub>3</sub> and reverse T <sub>3</sub> are further deiodinated to diiodothyronine.
<b>Excretion</b>	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.
<b>Half-life</b>	T <sub>4</sub> is eliminated slowly from the body, with a half-life of 4 to 7 days.

**Relevant OGD or DBE  
History**

The DBE recommends single-dose fasting *in vivo* bioequivalence study comparing the 0.300 mg strength of the test product to the reference listed drug (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 granted 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.

The dissolution testing should be conducted in 500 mL of 0.01 N HCl containing 0.2% sodium lauryl sulfate at 37 °C using apparatus 2 (paddle) at 50 rpm with following USP specifications: NLT 70% (Q) dissolved in 45 minutes.

The DBE has reviewed following ANDAs on levothyroxine sodium tablets:

ANDA 76-187, Mylan, submission date: 6/5/2001. The firm submitted three single-dose fasting studies on the 0.300 mg, 0.125 mg and 0.75 mg strength tablets, and requested a waiver for other strengths. Unithroid<sup>®</sup> (Jerome Stevens Pharmaceuticals) was designated as the RLD. This ANDA was approved on 06/05/2002.

ANDA 76-647, Mylan, submission date: 12/5/2002. The firm submitted one single-dose fasting study on the 0.300 mg strength tablet. Levoxyl<sup>®</sup> (Jones Pharma) was designated as the RLD.

The DBE has reviewed following control documents on levothyroxine sodium tablets: 00-349 (URL, 8/24/2000), 00-472 (Mylan, 11/2/2000), 01-094 (C 2/15/2001) and 01-159 (Bioassay, 3/16/2001).

**Agency Guidance**

The Agency has issued the Guidance for Industry –  
Levothyroxine Sodium Tablets – In Vivo  
Pharmacokinetic and Bioavailability Studies and In  
Vitro Dissolution Testing (12/2000).

**Drug Specific Issues (if any)**

None

**C. Contents of Submission**

<b>Study Types</b>	<b>Yes/No?</b>	<b>How many?</b>
<b>Single-dose fasting</b>	Yes	2
<b>Single-dose fed</b>	No	
<b>Steady-state</b>	No	
<b>In vitro dissolution</b>	Yes	11
<b>Waiver requests</b>	Yes	9
<b>BCS Waivers</b>	No	
<b>Vasoconstrictor Studies</b>	No	
<b>Clinical Endpoints</b>	No	
<b>Failed Studies</b>	No	
<b>Amendments</b>	Yes	1

In the original submission (06/16/2003), the firm conducted a fasting bioequivalence study comparing levothyroxine sodium 0.3 mg tablet to the RLD, Synthroid® 0.2 mg tablet. Pursuant to 21 CFR 320.22(d)(2), the firm requested a waiver of the *in vivo* bioequivalence testing requirements for levothyroxine sodium tablets, 0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.1 mg, 0.112 mg, 0.125 mg, 0.15 mg and 0.175 mg.

The firm submitted the amendment (08/27/2003) to the original submission to provide for addition of levothyroxine sodium 0.3 mg strength tablet. In support of this amendment, the firm conducted a fasting bioequivalence study comparing levothyroxine sodium 0.3 mg tablet to the RLD, Synthroid® 0.3 mg tablet.

**APPEARS THIS WAY  
ON ORIGINAL**

#### D. Pre-Study Bioanalytical Method Validation

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.

	L-thyroxine (T <sub>4</sub> )
Analyte name	L-thyroxine (T <sub>4</sub> )
Internal Standard	N/A
Method description	[ ]
QC range	[ ]
Standard curve range	[ ]: ng/mL
Limit of quantitation	[ ] ng/mL
Average recovery of Drug (%)	N/A
Average Recovery of Int. Std (%)	N/A
Intraday precision range (%CV)	[ ]
Intraday accuracy range (%)	[ ]
Interday precision range (%CV)	[ ]
Interday accuracy range (%)	[ ]
Bench-top stability (hrs)	[ ] hours at room temp
Stock stability (days)	N/A
Processed stability (hrs)	N/A
Freeze-thaw stability (cycles)	[ ]
Long-term storage stability (days)	[ ]
Dilution integrity	[ ]
Specificity	Yes
SOPs submitted	No <sup>1</sup>
Bioanalytical method is acceptable	Yes
[ ] included (Y/N)	N/A
Random Selection of Serial [ ]	N/A

<sup>1</sup> The firm did not provide the SOP No. IA-M-4661-00 (Quantitative Determination of Total T<sub>4</sub> (L-Thyroxine) in [ ]). Since in this submission, the firm used the same bioanalytical method validation procedures as used in ANDA 76-187 (approved on 06/05/2002), review of the SOP is not necessary.

## E. In Vivo Studies

### 1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	LEVO-02144
Study Design	Randomized, Single dose, Two way, Crossover
No. of subjects enrolled	32
No. of subjects completing	29
No. of subjects analyzed	29
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 19      Female: 10
Test product	Levothyroxine Sodium Tablet
Reference product	Synthroid <sup>®</sup> Tablet
Strength tested	0.2 mg
Dose	0.6 mg (3 x 0.2 mg tablet)

Summary of Statistical Analysis Additional Information in Appendix, Table 7 and Table 8		
Parameter	Point Estimate	90% Confidence Interval
LAUC <sub>0-t</sub>	1.04	96.89 – 111.25
LAUC <sub>0-∞</sub>	N/A	N/A
LC <sub>max</sub>	1.01	92.83 – 109.49

Reanalysis of Study Samples Additional information in Appendix, Table 6								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays <sup>1</sup>		Actual number		% of total assays <sup>1</sup>	
	T	R	T	R	T	R	T	R
Analytical repeats	0	2	0	0.2	0	2	0	0.2
Pharmacokinetic repeats	0	0	0	0	0	0	0	0
<b>Total</b>	<b>0</b>	<b>2</b>	<b>0</b>	<b>0.2</b>	<b>0</b>	<b>2</b>	<b>0</b>	<b>0.2</b>

<sup>1</sup> Based on total number of samples analyzed: 985

Did use of recalculated serum concentration data change study outcome? No.

**Comments on Fasting Study:** The study is acceptable.

## 2. Single-dose Fasting Bioequivalence Study (Amendment)

<b>Study No.</b>	LEVO-0323
<b>Study Design</b>	Randomized, Single dose, Two way, Crossover
<b>No. of subjects enrolled</b>	30
<b>No. of subjects completing</b>	29
<b>No. of subjects analyzed</b>	29
<b>Subjects (Normal/Patients?)</b>	Normal
<b>Sex(es) included (how many?)</b>	Male: 16 Female: 13
<b>Test product</b>	Levothyroxine Sodium Tablets
<b>Reference product</b>	Synthroid <sup>®</sup> Tablets
<b>Strength tested</b>	0.6 mg
<b>Dose</b>	2 x 0.3 mg tablet

Summary of Statistical Analysis Additional Information in Appendix, Table 17 and Table 18		
Parameter	Point Estimate	90% Confidence Interval
LAUC <sub>0-t</sub>	1.09	102.85 – 114.56
LAUC <sub>0-∞</sub>	N/A	N/A
LC <sub>max</sub>	1.05	100.59 – 110.59

Reanalysis of Study Samples Additional information in Appendix, Table 16								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays <sup>1</sup>		Actual number		% of total assays <sup>1</sup>	
	T	R	T	R	T	R	T	R
Analytical repeats	0	0	0	0	0	0	0	0
Pharmacokinetic repeats	0	0	0	0	0	0	0	0
<b>Total</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>

<sup>1</sup> Based on total number of samples analyzed: 985

Did use of recalculated serum concentration data change study outcome? No  
The firm did not reassy any samples.

**Comments on fasting study:** The study is acceptable.

### F. Formulation

Location in appendix	Section B, Page 31
Inactive ingredients within IIG Limits (yes or no)	Yes
If no, list ingredients outside of limits	N/A
If a tablet, is the product scored? (yes or no)	Yes
If yes, which strengths are scored?	0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.1 mg, 0.112 mg, 0.125 mg, 0.15 mg, 0.175 mg, 0.2 mg and 0.3 mg tablets
Is scoring of RLD the same as test? (yes or no)	Yes
Formulation is acceptable (yes or no)	Yes
If not acceptable, why?	

### G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	USP
Medium	0.01 N HCl containing 0.2% Sodium Lauryl Sulfate
Volume (mL)	500 mL
USP Apparatus type	Apparatus 2 (Paddle)
Rotation (rpm)	50 rpm
Firm's proposed specifications	NLT 70% (Q) of the labeled amount of levothyroxine dissolved in 45 minutes
FDA-recommended specifications	NLT 70% (Q) of the labeled amount of levothyroxine dissolved in 45 minutes
F2 metric calculated (yes or no)	Yes
If no, reason why F2 not calculated	N/A
Method is acceptable (yes or no)	Yes

F2 Metric, Other Strengths Compared to Biostudy Strength			
Low strength	Highest strength	F2 metric for test	F2 metric for RLD
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

F2 Metric, Test Compared to Reference	
Strength	F2 metric
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

#### H. Waiver Request(s)

Strengths for which waivers requested	0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.1 mg, 0.112 mg, 0.125 mg, 0.15 mg and 0.175 mg tablets
Regulation cited	21 CFR 320.22(d)(2)
Proportional to strength tested in vivo (yes or no)	Yes
Dissolution is acceptable (yes or no)	Yes
Waiver granted (yes or no)	Yes

#### I. Deficiency Comments

None

#### J. Recommendations

1. The *in vivo* bioequivalence study conducted under fasting conditions by Mylan on its levothyroxine sodium 0.2 mg tablet, comparing it to the reference product, Synthroid<sup>®</sup> 0.2 mg tablet (Abbott), is acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, Mylan's levothyroxine sodium 0.2 mg tablet is bioequivalent to the reference product, Synthroid<sup>®</sup> 0.2 mg tablet, manufactured by Abbott.
2. The *in vivo* bioequivalence study conducted under fasting conditions by Mylan on its levothyroxine sodium 0.3 mg tablet, comparing it to the reference product, Synthroid<sup>®</sup> 0.3 mg tablet (Abbott), is acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, Mylan's levothyroxine sodium 0.3 mg tablet is bioequivalent to the reference product, Synthroid<sup>®</sup> 0.3 mg tablet, manufactured by Abbott.

3. The dissolution testing conducted by Mylan on its levothyroxine sodium tablets, 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 formulations of 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.125 mg, 0.150 mg and 0.175 mg tablet strengths are proportionally similar to the 0.200 mg tablet, which underwent bioequivalence testing. Waivers of *in vivo* bioequivalence study requirements 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 and 0.175 mg tablets are granted per 21 CFR 320.22(d)(2). Levothyroxine sodium 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.125 mg, 0.150 mg and 0.175 mg tablets are therefore deemed bioequivalent to the corresponding strengths of Synthroid® tablets, 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.125 mg, 0.150 mg and 0.175 mg, manufactured by Abbott.
4. The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 500 mL of 0.01 N HCl containing 0.2% sodium lauryl sulfate at 37 °C using USP 26 apparatus 2 (paddle) at 50rpm. The test product should meet the following USP specifications:
- Not less than 70% (Q) of the labeled amount of levothyroxine in the dosage form is dissolved in 45 minutes.
5. The firm has met the requirements for *in vivo* bioequivalence and *in vitro* dissolution testing and the application is acceptable.

/S/

1/20/2004

Devvrat Patel, Pharm.D.

Date Signed

Division of Bioequivalence, Branch II

/S/

1/20/2004

Shriniwas Nerurkar, Ph.D.

Date Signed

Team Leader, Division of Bioequivalence, Branch II

/S/

1/20/04

for Dale P. Conner, Pharm. D.

Director, Division of Bioequivalence

Office of Generic Drugs

#### IV. Appendix

##### A. Individual Study Reviews

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

Study Information	
Study Number	LEVO-02144
Study Title	Single-Dose Fasting In Vivo Bioequivalence Study of Levothyroxine Sodium Tablets (200 µg; Mylan) to Synthroid® Tablets (200 µg; Abbott) in Healthy Volunteers
Clinical Site	1
Principal Investigator	1
Study/Dosing Dates	01/17/2003 to 03/03/2003 Dosing Dates: Period 1: 01/18/2003; Period 2: 03/01/2003
Analytical Site	1
Analytical Director	1
Analysis Dates	L-thyroxine (T <sub>4</sub> ): 03/14/2003 to 04/10/2003
Storage Period (no. of days from first sample to final analysis)	82 days

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Levothyroxine sodium	Synthroid® Tablets
Manufacturer	Mylan	Abbott
Batch/Lot No.	1K3174	0000340923
Manufacture Date	08/27/2002	N/A
Expiration Date	N/A	09/01/2003
Strength	0.2 mg	0.2 mg
Dosage Form	Tablet	Tablet
Batch Size	1 tablets	N/A
Production Batch Size	1 tablets	N/A
Potency	100.2%	98.6%
Content Uniformity	Average: 102.2%; %CV: 1.4	Average: 100.2%; %CV: 1.2
Formulation	See Appendix Section B	
Dose Administered	3 x 0.2 mg tablets	3 x 0.2 mg tablets
Route of Administration	Oral	

<b>No. of Sequences</b>	2
<b>No. of Periods</b>	2
<b>No. of Treatments</b>	2
<b>No. of Groups</b>	1
<b>Washout Period</b>	42 days
<b>Randomization Scheme</b>	AB: 1, 2, 6, 8, 9, 12, 13, 15, 18, 21, 23, 24, 26, 28, 29, 32  BA: 3, 4, 5, 7, 10, 11, 14, 16, 17, 19, 20, 22, 25, 27, 30, 31
<b>Blood Sampling Times</b>	-0.5, -0.25, 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24 and 48 hours post-dose
<b>Blood Volume Collected/Sample</b>	14 mL (2 x 7 mL)
<b>Blood Sample Processing/Storage</b>	Blood samples were collected in non-heparinized vacutainers. The whole blood samples were allowed to clot at room temperature for 30 minutes, and then centrifuged for 15 minutes. The separated serum was placed into duplicate 1.5 mL tubes and stored at -80 °C until analyzed.
<b>IRB Approval</b>	Yes
<b>Informed Consent</b>	Yes
<b>Subjects Demographics</b>	See Table 1
<b>Length of Fasting</b>	Subjects fasted overnight for at least 10 hours before dosing and for at least 4 hours post-dose.
<b>Length of Confinement</b>	Subjects were confined to the clinic for at least 14 hours prior to drug administration until 24 hours post-dose. Subjects returned to the clinic for blood collection scheduled at 48 hours post-dose.
<b>Safety Monitoring</b>	Vital signs (including blood pressures, pulse and respiration rates) were measured prior to drug administration and at 1, 2, 4, 8, 12, 24 and 48 hours after dosing. Subjects were monitored throughout confinement for adverse reactions. Physical examination and laboratory evaluations were done during screening and after completion of the study.

**Table 1 Demographics of Study Subjects**

Age (years)		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	N (%)	Category	%
N	29	N	29	<18	0.0			Caucasian	100.0
Mean	26.2	Mean	73.9	18-40	82.8	Male	19 (65.5)	Afr. Amer.	0.0
SD	9.8	SD	9.0	41-64	17.2	Female	10 (34.5)	Hispanic	0.0
Min	18	Min	57.2	65-75	0.0			Asian	0.0
Max	47	Max	91.7	>75	0.0			Others	0.0

**Study Results****Table 2 Dropout Information**

**Subject No** 9  
**Reason** Voluntarily withdrew from the study  
**Period** Prior to period 2 dosing  
**Replacement** None

**Subject No** 13  
**Reason** Voluntarily withdrew from the study  
**Period** Prior to period 2 dosing  
**Replacement** None

**Subject No** 26  
**Reason** Voluntarily withdrew from the study  
**Period** Prior to period 2 dosing  
**Replacement** None

**Was there a difference in side effects for the test versus the reference? No**

**Table 3 Study Adverse Events**

Adverse Event Description	# in Test Group	# in Reference Group
Asthenia	0	1
Dizziness	0	1
Fatigue	2	2
Headache	1	1
Malaise	0	1
Partially torn ligament in right thumb	1	0
Pharyngitis	0	1
Stomatitis ulcerative	1	0
<b>Total:</b>	<b>5</b>	<b>7</b>

**Comments: (on adverse events)**

Twelve adverse events were experienced by nine subjects. All adverse events were listed as mild in severity. Seven adverse events were listed as not study drug related, three adverse events were listed as possibly study drug related and two adverse events were listed as remotely study drug related. No serious adverse events occurred during the conduct of the study.

**Was there a difference in protocol deviations for the test versus the reference? No**

**Table 4 Protocol Deviations**

Type	Subject #s (Test)	Subject #s (Reference)
There were 10 sampling time deviations. The sampling time deviations ranged from 2 minutes to 5.7 hours. The 5.7 hour deviation was for the blood sample scheduled at 48 hours post-dose.	7, 14, 19, 29	7, 9, 11, 13, 15, 18, 19, 26, 30
There were 10 deviations from the protocol instructions of no medications within 30 days of period 1 dose administration (multivitamin tablet, Midol tablet, ibuprofen tablet). The medication use was considered unremarkable by the clinical investigator.	1, 6, 15, 18	3, 14, 22, 30

**Comments: (protocol deviations)**

The firm's calculated pharmacokinetic parameters (using the actual sampling times) were similar to the reviewer's calculated parameters (using the scheduled sample collection times). The sampling time deviations did not have any impact on the pharmacokinetic profile of the drug.

Protocol deviations did not compromise the integrity of the study.

**Table 5 Assay Validation – Within Study**

QC Conc. (ng/mL)	Parent					Metabolite				
	L					N/A				
Inter day Precision (%CV)	9.5	5.1	16.8							
Inter day Accuracy (% Accuracy)	88.0	86.7	104.1							
Cal. Standards Conc. (ng/mL)	9.964	16.606	24.909	39.855	59.782	79.710	119.564	199.274	298.911	
Inter day Precision (%CV)	8.3	8.1	6.1	3.6	3.0	3.4	4.7	6.1	8.2	
Inter day Accuracy (%)	96.5	100.4	99.7	101.2	99.2	99.6	98.6	112.4	88.5	

Linearity Range (range of R <sup>2</sup> values)	Not provided
--------------------------------------------------	--------------

**Chromatograms:** Any interfering peaks? N/A

**Table 6 SOP's dealing with analytical repeats of study samples**

SOP No.	Date of SOP	SOP Title
SL-R-8745-03	Not provided	Generation, Checking and Disposition of Raw Data, Calculations and Derived Data

The firm referenced the above mentioned SOP in the analytical report. However, the firm did not provide the SOP in the submission.

**Comments on Repeat Assays:**

Repeat analysis were conducted on 2 samples due to analytical abnormalities. There were no pharmacokinetic repeats.

Re-assayed samples represented 2 of the total 7 samples assayed. The firm stated that the samples were reanalyzed and reported according to the SOP.

**Comments on Within-Study Validation:**

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.

There was 1 SOP deviation. Contrary to SOP IA-G-4021-A: Quantitative Immunoassay Method Validation section 5.3: Lower and Upper Limit of Quantitation, which states that the LLOQ of the method is established as the lowest concentration that has a demonstrated inter and intra-assay precision of ≤ 25% and an accuracy within ± 25%. The %CV of the LLOQ (n=6) in one of the three runs was 27%.

The firm explained that the reason was that the %CV in the first 2 runs were acceptable; the third run was not within 25% due to 1 particular value of 27%. Since this value was extrapolated so far from the lowest standard, an unknown technical error was suspected.

Since the %CV for all LLQC (n=18) values within all 3 runs was 27%, it demonstrated an acceptable precision for intra-assay within all runs. In addition, the %CV was only 27 between 3 batches which demonstrated an acceptable inter-precision.

**Conclusion:** Analytical method is acceptable.

**Table 7 Arithmetic Mean Pharmacokinetic Parameters**

Mean serum concentrations are presented in Table 10 and Figure 1  
(Single dose fasting study on 0.2 mg tablet)

PARAMETER	UNITS	TEST		REFERENCE		RATIO T/R
		MEAN1	%CV	MEAN2	%CV	
AUCT	ng-hr/mL	1746.45	22.71	1655.37	18.13	1.06
C <sub>MAX</sub>	ng/mL	67.22	22.19	66.06	19.05	1.02
LAUCT	ng-hr/mL	1703.75	0.01	1629.18	0.01	1.05
LC <sub>MAX</sub>	ng/mL	65.65	0.34	64.92	0.29	1.01
T <sub>MAX</sub>	hour	3.03	58.08	2.47	54.18	1.23

**Table 8 Least Square Geometric Means and 90% Confidence Intervals**

(Single dose fasting study on 0.2 mg tablet)

PARAMETER	TEST	REFERENCE	RATIO T/R	90 % CI	
	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
AUCT	1745.72	1667.14	1.05	97.54	111.89
C <sub>MAX</sub>	66.86	65.96	1.01	93.29	109.44
LAUCT	1703.74	1641.03	1.04	96.89	111.25
LC <sub>MAX</sub>	65.30	64.77	1.01	92.83	109.49

Note: Log-transformed data were converted to anti-log in the table

**Table 9 Additional Study Information**

Root mean square error, AUC <sub>0-t</sub>	0.154	
Root mean square error, AUC <sub>0-∞</sub>	N/A	
Root mean square error, C <sub>max</sub>	0.183	
mean ratio AUC <sub>0-t</sub> /AUC <sub>0-∞</sub>	T = N/A	R = N/A
Range of values, ratio AUC <sub>0-t</sub> /AUC <sub>0-∞</sub>	T = N/A	R = N/A

**Comments:** (on pharmacokinetic analysis)

- The firm assayed the serum samples for total L-thyroxine and L-triiodothyronine. The firm calculated the pharmacokinetic parameters for baseline corrected total L-thyroxine and non-baseline corrected total L-triiodothyronine. Since the DBE recommends quantitation of only L-thyroxine after correction for baseline, the reviewer did not review the L-triiodothyronine data.
- The firm performed the statistical analysis and provided the 90% confidence intervals for baseline corrected L-thyroxine data. However, the firm provided the serum concentration profiles without the adjustment of baseline levels.
- The reviewer determined the serum concentrations after correction for baseline for each subject. The pre-dose (baseline) concentration was obtained by averaging the concentration values at -0.5 hours, -0.25 hours and 0 hours before dosing. This baseline concentration value for the subject was then subtracted from each of their serum concentrations from the serum profile for that particular period for L-thyroxine. Negative data resulting from baseline correction were designated as zero (0). Pharmacokinetic parameters for baseline corrected total L-thyroxine were calculated.
- The reviewer calculated 90% confidence intervals for the test to reference ratio for the natural log transformed parameters,  $LAUC_{0-t}$  and  $LC_{max}$ , using the baseline corrected total L-thyroxine levels are in agreement with the firm's reported values and are within acceptable limits of 80%-125%.
- After subtracting the baseline value from each post-dose concentrations and 0 hour time point for each subject, following subjects had pre-dose L-thyroxine concentrations greater than zero:

Period 1: 2, 3, 7, 8, 11, 12, 14, 17, 18, 19, 20, 23, 25, 27, 29, 30 and 32

Period 2: 3, 4, 5, 6, 8, 10, 14, 15, 16, 19, 20, 21, 22, 23, 25, 28 and 32

Subjects 4 (period 2), 11 (period 1), 18 (period 1), 20 (period 1), 23 (period 1), 27 (period 1) and 30 (period 1) had measurable drug concentrations at 0 hour which were more than the 5% of their  $C_{max}$  values. These subjects were excluded from the statistical analysis and the 90% confidence intervals for the test to reference ratio for the natural log transformed parameters,  $LAUC_{0-t}$  and  $LC_{max}$ , using the baseline corrected total L-thyroxine levels remained within acceptable limits of 80%-125% ( $LAUC_{0-t}$  94.79-112.15,  $LC_{max}$  89.90-110.69). Since the pre-dose values for other subjects were less than 5% of their  $C_{max}$  values, they should not influence the bioequivalence assessment; these subjects' data were included in the analysis.

- The period and sequence effects were not statistically significant for any of the pharmacokinetic parameters.

- $K_{el}$  and  $AUC_{0-inf}$  were not determined.
- Number of subjects with the following:
  - a. Measurable drug concentrations at 0 hr: 26
  - b. First scheduled post-dose sampling time as  $T_{max}$ : None
  - c. First measurable drug concentration as  $C_{max}$ : None

**Conclusion:** The single-dose fasting bioequivalence study is acceptable.

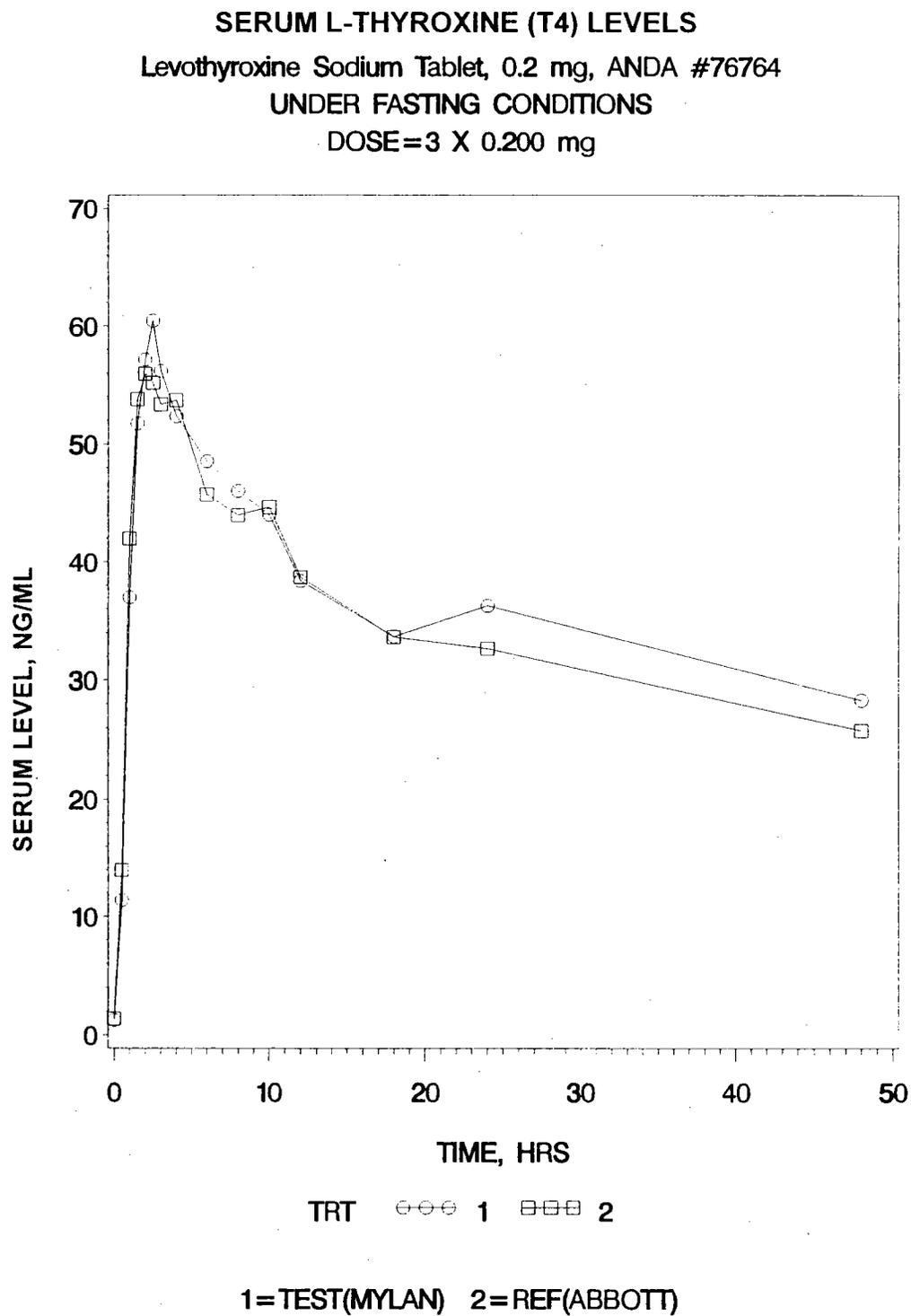
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**Table 10 Mean Serum Concentrations<sup>1</sup>, Single-Dose Fasting Bioequivalence Study**

TIME (HR)	TEST (N=29)		REFERENCE (N=29)		RATIO T/R
	MEAN1 (ng/mL)	%CV	MEAN2 (ng/mL)	%CV	
0	1.26	159.42	1.37	151.64	0.92
0.5	11.40	80.15	13.95	68.32	0.82
1.00	36.98	51.95	41.97	45.49	0.88
1.50	51.75	33.54	53.79	31.32	0.96
2.00	57.16	26.99	55.94	26.83	1.02
2.50	60.44	22.38	55.16	24.15	1.10
3.00	56.18	28.65	53.35	25.93	1.05
4.00	52.36	22.72	53.70	24.11	0.97
6.00	48.56	26.77	45.73	23.86	1.06
8.00	46.04	30.94	43.98	22.25	1.05
10.00	44.00	23.72	44.66	20.61	0.99
12.00	38.36	26.81	38.68	20.46	0.99
18.00	33.68	32.01	33.64	28.45	1.00
24.00	36.28	29.41	32.64	19.37	1.11
48.00	28.33	34.58	25.79	32.76	1.10

<sup>1</sup> Serum concentration levels were adjusted based on pre-dose baseline levels.

Figure 1 Mean Serum Concentrations, Single-Dose Fasting Bioequivalence Study



## 2. Single-dose Fasting Bioequivalence Study (Amendment)

Study Information	
Study Number	LEVO-0323
Study Title	Single-Dose Fasting In Vivo Bioequivalence Study of Levothyroxine Sodium Tablets (300 µg; Mylan) to Synthroid® Tablets (300 µg; Abbott) in Healthy Volunteers.
Clinical Site	1
Principal Investigator	1
Study/Dosing Dates	05/09/2003 to 06/16/2003 Dosing Dates: Period 1: 05/10/2003; Period 2: 06/14/2003
Analytical Site	1
Analytical Director	1
Analysis Dates	L-thyroxine: 06/19/2003 to 07/04/2003
Storage Period (no. of days from first sample to final analysis)	55 days

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Levothyroxine sodium	Synthroid® Tablets
Manufacturer	Mylan	Abbott
Batch/Lot No.	1K3321	0000341461
Manufacture Date	08/24/2002	N/A
Expiration Date	N/A	11/01/2003
Strength	0.3 mg	0.3 mg
Dosage Form	Tablet	Tablet
Batch Size	1 tablets	N/A
Production Batch Size	1 tablets	N/A
Potency	101.1%	95.9%
Content Uniformity	Average: 100.5%; %CV: 1.4	Average: 97.5; %CV: 1.1
Formulation	See Appendix Section B	
Dose Administered	2 x 0.3 mg tablets	2 x 0.3 mg tablets
Route of Administration	Oral	
No. of Sequences	2	
No. of Periods	2	
No. of Treatments	2	
No. of Groups	1	
Washout Period	35 days	

<b>Randomization Scheme</b>	AB: 2, 3, 4, 6, 9, 14, 15, 16, 17, 19, 21, 22, 27, 28, 29 BA: 1, 5, 7, 8, 10, 11, 12, 13, 18, 20, 23, 24, 25, 26, 30
<b>Blood Sampling Times</b>	-0.5, -0.25, 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24 and 48 hours post-dose
<b>Blood Volume Collected/Sample</b>	14 mL (2 x 7 mL)
<b>Blood Sample Processing/Storage</b>	Blood samples were collected in non-heparinized vacutainers. The whole blood samples were allowed to clot at room temperature for 30 minutes, and then centrifuged for 15 minutes. The separated serum was placed into duplicate $\text{C}_{10000}$ tubes and stored at $-80^{\circ}\text{C}$ until analyzed.
<b>IRB Approval</b>	Yes
<b>Informed Consent</b>	Yes
<b>Subjects Demographics</b>	See Table 11
<b>Length of Fasting</b>	Subjects fasted overnight for at least 10 hours before dosing and for at least 4 hours post-dose.
<b>Length of Confinement</b>	Subjects were confined to the clinic for at least 14 hours prior to drug administration until 24 hours post-dose. Subjects returned to the clinic for blood collection scheduled at 48 hours post-dose.
<b>Safety Monitoring</b>	Vital signs (including blood pressures, pulse and respiration rates) were measured prior to drug administration and at 1, 2, 4, 8, 12, 24 and 48 hours after dosing. Subjects were monitored throughout confinement for adverse reactions. Physical examination and laboratory evaluations were done during screening and after completion of the study.

**Table 11 Demographics of Study Subjects**

Age (years)		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	N (%)	Category	%
N	29	N	29	<18	0.0			Caucasian	96.6
Mean	25.6	Mean	73.0	18-40	89.7	Male	16 (55.2)	Afr. Amer.	0.0
SD	8.6	SD	11.8	41-64	10.3	Female	13 (44.8)	Hispanic	3.4
Min	19	Min	50.5	65-75	0.0			Asian	0.0
Max	49	Max	99.1	>75	0.0			Others	0.0

## Study Results

**Table 12 Dropout Information**

<b>Subject No</b>	29
<b>Reason</b>	Voluntarily withdrew from the study
<b>Period</b>	Prior to period 2 dosing
<b>Replacement</b>	None

**Was there a difference in side effects for the test versus the reference? No**

**Table 13 Study Adverse Events**

<b>Adverse Event Description</b>	<b># in Test Group</b>	<b># in Reference Group</b>
Dizziness	2	1
Fever	1	0
Headache	4	3
Lower right backache	1	0
Malaise	0	1
Nausea	0	1
Pharyngitis	1	0
Purpura	1	0
Rash	0	1
Vomiting	3	1
<b>Total:</b>	<b>13</b>	<b>8</b>

**Comments:** *(on adverse events)*

Twenty-one adverse events were experienced by 11 subjects. Seventeen adverse events were listed as mild in severity and four were listed as moderate in severity. Twelve adverse events were listed as not study drug related, seven adverse events were listed as probably study drug related and two adverse events were listed as remotely study drug related. No serious adverse events occurred during the conduct of the study.

Subjects 5 (1 episode) and 19 (2 episodes) reported vomiting between study periods 1 and 2. Subject 30 reported vomiting at approximately 14.5 hours after period 2 dose administration.

Was there a difference in protocol deviations for the test versus the reference? No

**Table 14 Protocol Deviations**

Type	Subject #s (Test)	Subject #s (Reference)
There were 19 sampling time deviations. The sampling time deviations ranged from 3 minutes to 36 minutes.	16, 19, 25, 29, 30	3, 17, 23, 25, 28, 29, 30
Subjects 14, 19 and 30 reported taking ibuprofen 200 mg tablets for headache and fever over the course of the study.	--	--

**Comments:** (protocol deviations)

Protocol deviations did not compromise the integrity of the study.

**Table 15 Assay Validation – Within Study**

QC Conc. (ng/mL)	Parent				Metabolite					
	L			1	N/A					
<b>Inter day Precision (%CV)</b>	8.4	4.9	5.1							
<b>Inter day Accuracy (% Accuracy)</b>	88.2	91.8	99.8							
<b>Cal. Standards Conc. (ng/mL)</b>	10.039	16.731	25.097	40.155	60.233	80.311	120.466	200.776	301.165	
<b>Inter day Precision (%CV)</b>	6.0	6.8	3.9	2.4	2.1	1.3	1.7	2.9	4.0	
<b>Inter day Accuracy (%)</b>	108.0	96.7	95.6	103.3	101.9	98.8	98.1	96.7	108.4	
<b>Linearity Range (range of R<sup>2</sup> values)</b>	Not provided									

**Chromatograms:** Any interfering peaks? N/A

**Table 16 SOP's dealing with analytical repeats**

SOP No.	Date of SOP	SOP Title
SL-R-8745-03	Not provided	Generation, Checking and Disposition of Raw Data, Calculations and Derived Data

The firm referenced the above mentioned SOP in the analytical report. However, the firm did not provide the SOP in the submission. Since there were no reassays, the review of the SOP is not necessary.

**Comments on Repeat Assays:**

There were no reassays in this study.

**Comments on Within-Study Validation:** None

**Conclusion:** Analytical method is acceptable.

**Table 17 Arithmetic Mean Pharmacokinetic Parameters**

Mean serum concentrations are presented in Table 20 and Figure 2

(Single dose fasting study on 0.3 mg tablet)

PARAMETER	UNITS	TEST		REFERENCE		RATIO T/R
		MEAN1	%CV	MEAN2	%CV	
AUCT	ng-hr/mL	1630.08	18.47	1507.27	20.67	1.08
C <sub>MAX</sub>	ng/mL	60.02	21.10	56.65	17.92	1.06
LAUCT	ng-hr/mL	1603.58	0.01	1476.67	0.01	1.09
LC <sub>MAX</sub>	ng/mL	58.72	0.37	55.77	0.32	1.05
T <sub>MAX</sub>	hour	2.84	39.61	2.57	38.48	1.11

**Table 18 Geometric Means and 90% Confidence Intervals**

(Single dose fasting study on 0.3 mg tablet)

PARAMETER	TEST	REFERENCE	RATIO T/R	90 % CI	
	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
AUCT	1630.28	1508.71	1.08	102.41	113.70
C <sub>MAX</sub>	60.12	56.65	1.06	101.11	111.14
LAUCT	1604.15	1477.84	1.09	102.85	114.56
LC <sub>MAX</sub>	58.82	55.77	1.05	100.59	110.59

Note: Log-transformed data were converted to anti-log in the table

**Table 19 Additional Study Information**

Root mean square error, AUC <sub>0-t</sub>	0.120	
Root mean square error, AUC <sub>0-∞</sub>	N/A	
Root mean square error, C <sub>max</sub>	0.106	
mean ratio AUC <sub>0-t</sub> /AUC <sub>0-∞</sub>	T = N/A	R = N/A
Range of values, ratio AUC <sub>0-t</sub> /AUC <sub>0-∞</sub>	T = N/A	R = N/A

**Comments:** (on pharmacokinetic analysis)

- The firm assayed the serum samples for total L-thyroxine and L-triiodothyronine. The firm calculated the pharmacokinetic parameters for baseline corrected total L-thyroxine and non-baseline corrected total L-triiodothyronine. Since the DBE recommends quantitation of only L-thyroxine after correction for baseline, the reviewer did not review the L-triiodothyronine data.
- The firm performed the statistical analysis and provided the 90% confidence intervals for baseline corrected L-thyroxine data. However, the firm provided the serum concentration profiles without the adjustment of baseline levels.
- The reviewer determined the serum concentrations after correction for baseline for each subject. The pre-dose (baseline) concentration was obtained by averaging the concentration values at -0.5 hours, -0.25 hours and 0 hours before dosing. This baseline concentration value for the subject was then subtracted from each of their serum concentrations from the serum profile for that particular period for L-thyroxine. Negative data resulting from baseline correction were designated as zero (0). Pharmacokinetic parameters for baseline corrected total L-thyroxine were calculated.
- The reviewer calculated 90% confidence intervals for the test to reference ratio for the natural log transformed parameters,  $LAUC_{0-t}$  and  $LC_{max}$ , using the baseline corrected total L-thyroxine levels are in agreement with the firm's reported values and are within acceptable limits of 80%-125%.
- After subtracting the baseline value from each post-dose concentrations and 0 hour time point for each subject, following subjects had pre-dose L-thyroxine concentrations greater than zero:

Period 1: 1, 3, 4, 7, 8, 9, 10, 11, 12, 13, 15, 16, 17, 18, 20, 22, 23, 27, 28 and 30  
 Period 2: 6, 8, 9, 10, 11, 13, 14, 16, 17, 18, 21, 22, 25, 26 and 28

Subjects 1 (period 1), 8 (period 1), 11 (period 2), 13 (period 1), 14 (period 2), 17 (period 1), 18 (period 1) and 27 (period 1) had measurable drug concentrations at 0 hour which were more than the 5% of their  $C_{max}$  values. These subjects were excluded from the statistical analysis and the 90% confidence intervals for the test to reference ratio for the natural log transformed parameters,  $LAUC_{0-t}$  and  $LC_{max}$ , using the baseline corrected total L-thyroxine levels remained within acceptable limits of 80%-125% ( $LAUC_{0-t}$  101.12-114.27,  $LC_{max}$  101.09-114.23). Since the pre-dose values for other subjects were less than 5% of their  $C_{max}$  values, they should not influence the bioequivalence assessment; these subjects' data were included in the analysis.

- The period and sequence effects were not statistically significant for any of the pharmacokinetic parameters. The treatment effect was statistically significant for  $LAUC_{0-t}$ .
- $K_{el}$  and  $AUC_{0-inf}$  were not determined.
- Number of subjects with the following:
  - a. Measurable drug concentrations at 0 hr: 25
  - b. First scheduled post-dose sampling time as  $T_{max}$ : None
  - c. First measurable drug concentration as  $C_{max}$ : None
- Subject 30 reported vomiting at approximately 14.5 hours after period 2 dose administration. Since the  $T_{max}$  for this subject was 2.5 hours, data for this subject were included in the analysis.

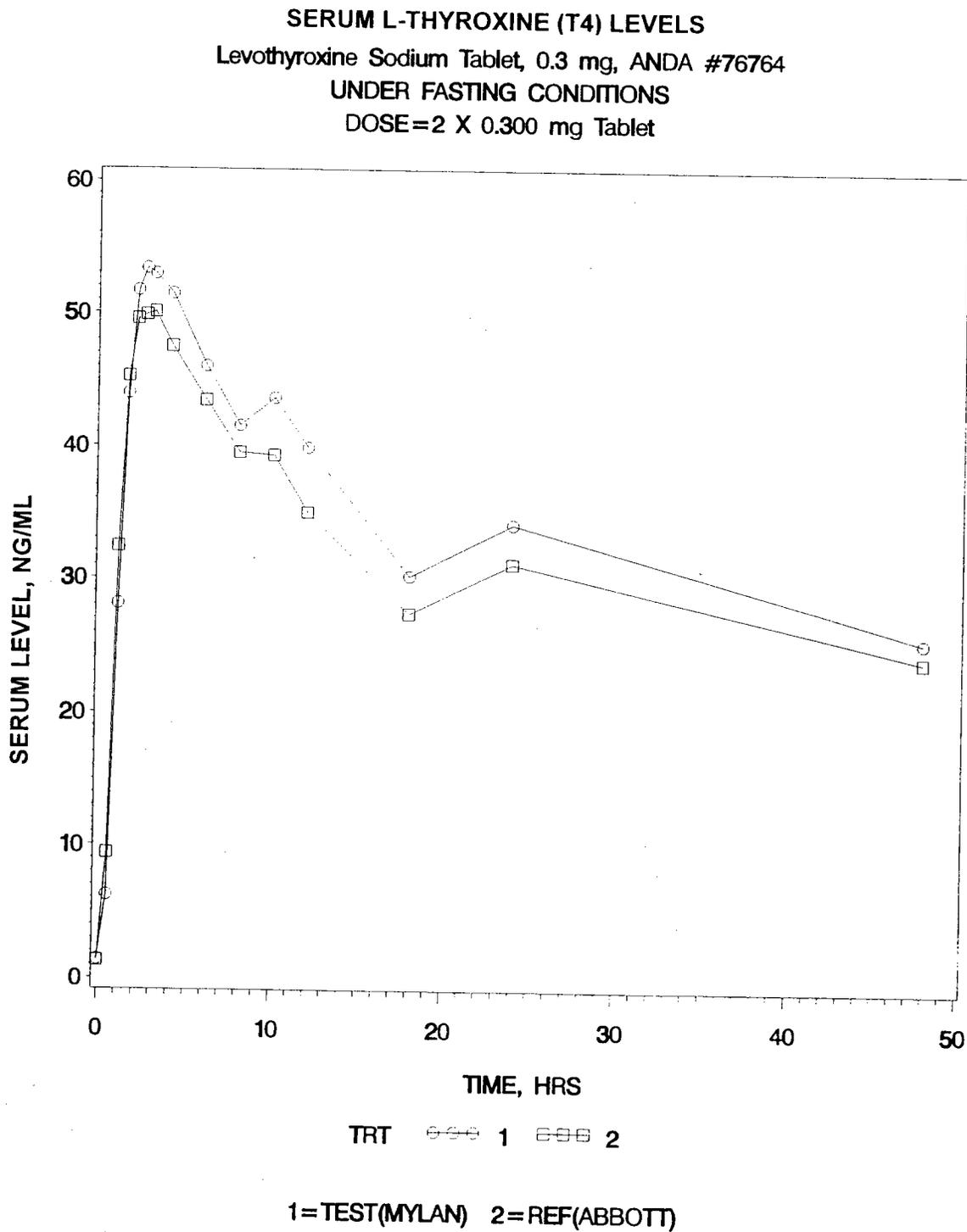
**Conclusion:** The single-dose fasting bioequivalence study is acceptable.

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**Table 20 Mean Serum Concentrations, Single-Dose Fasting Bioequivalence Study**

TIME (HR)	TEST (N=29)		REFERENCE (N=29)		RATIO T/R
	MEAN1 (ng/mL)	%CV	MEAN2 (ng/mL)	%CV	
0	1.36	115.80	1.29	119.56	1.05
0.5	6.20	81.29	9.38	80.03	0.66
1.00	28.09	50.04	32.35	39.51	0.87
1.50	43.97	38.71	45.26	30.60	0.97
2.00	51.68	33.56	49.55	27.78	1.04
2.50	53.32	27.64	49.85	23.40	1.07
3.00	52.92	22.03	50.07	21.82	1.06
4.00	51.43	20.87	47.49	18.76	1.08
6.00	46.03	18.35	43.46	24.52	1.06
8.00	41.56	21.48	39.52	24.83	1.05
10.00	43.63	17.54	39.32	21.36	1.11
12.00	39.91	19.58	34.97	25.28	1.14
18.00	30.21	21.82	27.43	30.74	1.10
24.00	34.14	20.63	31.16	20.10	1.10
48.00	25.50	32.36	24.07	31.93	1.06

Figure 2 Mean Serum Concentrations, Single-Dose Fasting Bioequivalence Study



**B. Formulation Data**

Comparison of Formulation of Levethroxine Sodium Tablets, 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

INGREDIENTS	0.025 mg Tablet		0.050 mg Tablet		0.075 mg Tablet		0.088 mg Tablet		0.100 mg Tablet		0.112 mg Tablet	
	mg/Tab	%(w/w)										
ACTIVE COMPONENT												
Levethroxine Sodium, USP	0.025	—	0.050	—	0.075	—	0.088	—	0.100	—	0.112	—
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												
FD&C Blue #2 Lake												
FD&C Red #40 Lake												
FD&C Blue #1 Lake												
D&C Yellow #10 Lake												
D&C Red #27 Lake												
D&C Red #30 Lake												
FD&C Red #40 Lake												
TOTAL THEORETICAL WEIGHT	130.0	100.0	130.0	100.0	130.0	100.0	130.0	100.0	130.0	100.0	130.0	100.0

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Formulation Data (Continued)

INGREDIENTS	0.125 mg Tablet		0.150 mg Tablet		0.175 mg Tablet		0.200 mg Tablet		0.300 mg Tablet	
	mg/Tab	%(w/w)								
<b>ACTIVE COMPONENT</b>										
Levothroxine Sodium, USP	0.125	—	0.150	—	0.175	—	0.200	—	0.300	—
<b>INACTIVE COMPONENTS</b>										
Mannitol USP,										
Sucrose, NF										
Butylated Hydroxyanisole, NF										
Povidone, NF										
Alcohol, USP (Ethyl Alcohol,										
Microcrystalline Cellulose, NF										
Croscovidone, NF										
Magnesium Stearate/Sodium Lauryl Sulfate										
Colloidal Silicon Dioxide, NF										
FD&C Yellow #6 Lake										
FD&C Blue #2 Lake										
FD&C Red #40 Lake										
FD&C Blue #1 Lake										
D&C Yellow #10 Lake										
D&C Red #27 Lake										
D&C Red #30 Lake										
FD&C Red #40 Lake										
<b>TOTAL THEORETICAL WEIGHT</b>	<b>130.0</b>	<b>100.0</b>								

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## Product Description

**Test Products:** Levothyroxine sodium tablets are available as caplet-shaped, biconvex tablets that are debossed with an M on one side of the tablet. The other side of each tablet is debossed with an L to the left of the score and an individual tablet identification to the right of the score as described below.

**Reference Products:** Synthroid® tablets are round, color coded, scored and debossed with "SYNTHROID" on one side and potency on the other side as described below.

Strength (mcg)	Levothyroxine Sodium Tablets (Mylan)		Synthroid® Tablets (Abbott)	
	Color	Identification Information debossed on scored side of tablet	Color	Information debossed on scored side of tablet
25	Orange	L   4	Orange	25
50	White	L   5	White	50
75	Violet	L   6	Violet	75
88	Olive	L   7	Olive	88
100	Yellow	L   8	Yellow	100
112	Rose	L   9	Rose	112
125	Gray	L   10	Brown	125
150	Blue	L   11	Blue	150
175	Lilac	L   12	Lilac	175
200	Pink	L   13	Pink	200
300	Green	L   14	Green	300

## Comments (Formulation)

The formulations of the test products are the same as the formulations of the test products submitted in Mylan's ANDA 76-187, which was approved on 06/05/2002.

All inactive ingredients in the formulations of all strengths are within the acceptable oral ranges cited in the FDA Inactive Ingredient Guide. The formulations are proportionally similar.

### C. Dissolution Data

Method: USP  
 Medium: 0.01 N HCl containing 0.2% Sodium Lauryl Sulfate  
 at 37 °C ± 0.5 °C  
 Volume: 500 mL  
 Apparatus: 2 (paddle) at 50 rpm  
 Specifications: NLT 70% (Q) of the labeled amount of levothyroxine dissolved  
 in 45 minutes

Table 1

Sampling Time (min)	Levothyroxine Sodium Tablet Strength: 0.025 mg Lot No. 1K3161			Synthroid® Tablet Strength: 0.025 mg Lot No. 0000340914		
	Mean (%)	%CV	Range (%)	Mean (%)	%CV	Range (%)
10	60	18.4	—	73	10.46	—
20	76	7.6	—	96	2.97	—
30	82	7.0	—	98	1.13	—
45	85	5.7	—	99	1.27	—

Table 2

Sampling Time (min)	Levothyroxine Sodium Tablet Strength: 0.05 mg Lot No. 1K3016			Synthroid® Tablet Strength: 0.05 mg Lot No. 0000340850		
	Mean (%)	%CV	Range (%)	Mean (%)	%CV	Range (%)
10	73	13.1	—	73	4.87	—
20	83	6.9	—	91	2.09	—
30	85	5.1	—	93	2.08	—
45	86	5.2	—	95	2.38	—

Table 3

Sampling Time (min)	Levothyroxine Sodium Tablet Strength: 0.075 mg Lot No. 1K3041			Synthroid® Tablet Strength: 0.075 mg Lot No. 0000340591		
	Mean (%)	%CV	Range (%)	Mean (%)	%CV	Range (%)
10	50	20.0	—	66	9.32	—
20	69	10.7	—	87	2.72	—
30	73	8.6	—	91	1.86	—
45	78	7.6	—	93	2.11	—

Table 4

Sampling Time (min)	Levothyroxine Sodium Tablet Strength: 0.088 mg Lot No. 1K3164			Synthroid® Tablet Strength: 0.088 mg Lot No. 0000341004		
	Mean (%)	%CV	Range (%)	Mean (%)	%CV	Range (%)
10	51	12.6		70	9.32	
20	76	6.1		92	3.24	
30	80	6.6		95	3.02	
45	85	5.7		97	2.81	

Table 5

Sampling Time (min)	Levothyroxine Sodium Tablet Strength: 0.1 mg Lot No. 1K3048			Synthroid® Tablet Strength: 0.1 mg Lot No. 0000340654		
	Mean (%)	%CV	Range (%)	Mean (%)	%CV	Range (%)
10	66	13.9		69	8.25	
20	73	7.9		88	2.31	
30	77	7.5		91	2.09	
45	80	6.7		93	2.40	

Table 6

Sampling Time (min)	Levothyroxine Sodium Tablet Strength: 0.112 mg Lot No. 1K3167			Synthroid® Tablet Strength: 0.112 mg Lot No. 0000340595		
	Mean (%)	%CV	Range (%)	Mean (%)	%CV	Range (%)
10	69	13.1		67	11.18	
20	83	6.9		88	3.91	
30	88	6.6		91	3.13	
45	90	5.0		94	2.55	

Table 7

Sampling Time (min)	Levothyroxine Sodium Tablet Strength: 0.125 mg Lot No. 1K3052			Synthroid® Tablet Strength: 0.125 mg Lot No. 0000340598		
	Mean (%)	%CV	Range (%)	Mean (%)	%CV	Range (%)
10	59	13.8		69	9.08	
20	83	6.6		90	2.93	
30	85	6.0		93	1.81	
45	87	5.8		96	1.64	

Table 8

Sampling Time (min)	Levothyroxine Sodium Tablet Strength: 0.150 mg Lot No. 1K3054			Synthroid® Tablet Strength: 0.150 mg Lot No. 0000340594		
	Mean (%)	%CV	Range (%)	Mean (%)	%CV	Range (%)
10	52	20.3		66	9.82	
20	72	7.3		89	3.17	
30	74	4.9		93	1.93	
45	78	5.0		95	1.62	

Table 9

Sampling Time (min)	Levothyroxine Sodium Tablet Strength: 0.175 mg Lot No. 1K3170			Synthroid® Tablet Strength: 0.175 mg Lot No. 0000340593		
	Mean (%)	%CV	Range (%)	Mean (%)	%CV	Range (%)
10	63	11.0		67	9.61	
20	75	5.6		85	3.92	
30	77	4.0		87	3.02	
45	80	3.1		89	2.87	

Table 10

Sampling Time (min)	Levothyroxine Sodium Tablet Strength: 0.2 mg Lot No. 1K3174			Synthroid® Tablet Strength: 0.2 mg Lot No. 0000340923		
	Mean (%)	%CV	Range (%)	Mean (%)	%CV	Range (%)
10	65	17.66		66	7.26	
20	76	7.05		87	3.25	
30	80	6.09		91	2.43	
45	83	5.75		92	2.71	

Table 11

Sampling Time (min)	Levothyroxine Sodium Tablet Strength: 0.3 mg Lot No. 1K3321			Synthroid® Tablet Strength: 0.3 mg Lot No. 0000341461		
	Mean (%)	%CV	Range (%)	Mean (%)	%CV	Range (%)
10	63	13.07		72	12.36	
20	83	5.41		88	5.90	
30	87	5.75		93	4.27	
45	89	7.05		96	3.30	

**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.

**Redacted** 6

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

**and/or confidential**

**commercial information**

**(b4)**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**ANDA 76-187**

**(\*originally approved under ANDA 76-764)**

**Administrative/Correspondence Reviews**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

ANDA 76-764

Food and Drug Administration  
Rockville MD 20857

JUL 26 2004

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

Dear Mr. Talton:

This is in reference to your abbreviated new drug application (ANDA 76-764) dated June 16, 2003, and approved on June 23, 2004. This application was submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (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, 0.15 mg, 0.175 mg, 0.2 mg, and 0.3 mg. In addition, this application established that your product is therapeutically equivalent to Synthroid® (Levothyroxine Sodium) Tablets, approved under NDA 21-402, held by Abbott Laboratories.

We are incorporating by reference all of the information in ANDA 76-764 into your ANDA 76-187 for levothyroxine sodium tablets. The labeling for your drug product should be the same as the labeling that is approved in your original ANDA 76-187. All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field reports, annual reports, supplements, and other submissions should be addressed to the original ANDA 76-187 for this drug product, not to ANDA 76-764. In the future do not make submissions to ANDA 76-764.

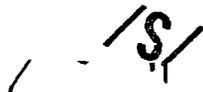
Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change 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. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the 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,

A handwritten signature in black ink, appearing to be 'G. Buehler', written over a horizontal line.

Gary Buehler  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research



# MYLAN PHARMACEUTICALS INC

31

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

January 30, 2004

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

**ORIG AMENDMENT**

*N/AS  
MC*

## **BIOEQUIVALENCE AMENDMENT (BIOEQUIVALENCE INFORMATION ENCLOSED)**

RE: LEVOTHYROXINE SODIUM TABLETS USP, 25MCG, 50MCG, 75MCG, 88MCG, 100MCG, 112MCG, 125MCG, 150MCG, 175MCG, 200MCG AND 300MCG  
ANDA 76-764  
(RESPONSE TO AGENCY CORRESPONDENCE DATED JANUARY 29, 2004)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the Bioequivalence comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated January 29, 2004 (refer to Attachment 1). In response to the October 31<sup>st</sup> comments from the Division of Bioequivalence, Mylan wishes to amend this application as follows:

**FDA COMMENT 1:** 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 27.

Please note that the bioequivalence 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 bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

**MYLAN RESPONSE:** As acknowledged by the Division of Bioequivalence, the recommended dissolution testing requirements as specified in USP 27 for Levothyroxine Sodium Tablets USP, 25mcg, 50mcg, 75mcg, 88mcg, 100mcg, 112mcg, 125mcg, 150mcg, 175mcg, 200mcg and 300mcg has been incorporated into Mylan's stability and quality control programs.

Mylan acknowledges that the bioequivalence comments provided in the January 29, 2004 communication are preliminary and that these comments may be revised after review of the entire application.

**RECEIVED**

**FEB 02 2004**

G:\PROJECT\ANDA\LEVOTHYROXINE\SYNTHROID\BIO-LETTER-DATED-012904.doc

Department—Fax Numbers		Information Systems	(304) 285-6404
Accounting	(304) 285-6403	Label Control	(800) 848-0463
Administration	(304) 599-7284	Legal Services	(304) 598-5408
Business Development	(304) 598-5419	Maintenance & Engineering	(304) 598-5411
Corporate Services	(304) 598-5404	Medical Unit	(304) 598-5445
Human Resources	(304) 598-5406	Product Development	(304) 285-6411

Purchasing	(304) 598-5401
Quality Assurance	(304) 598-5407
Quality Control	(304) 598-5409
Regulatory Affairs	(304) 285-6407
Research & Development	(304) 285-6409
Sales & Marketing	(304) 598-3232

**OGD/CDER**

Gary J. Buehler  
Page 2 of 2

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

Sincerely,

A handwritten signature in black ink, appearing to read "S. Wayne Talton". The signature is written in a cursive style with a long horizontal stroke at the end. There are some small marks above the first part of the signature.

S. Wayne Talton  
Executive Director  
Regulatory Affairs

SWT/dn

Enclosures

**APPROVAL SUMMARY (minor)**  
**REVIEW OF PROFESSIONAL LABELING**  
**DIVISION OF LABELING AND PROGRAM SUPPORT**  
**LABELING REVIEW BRANCH**

---

**ANDA Number** 76-764  
**Date of Submission** Jan. 22, 2004  
**Applicant** Mylan Pharmaceuticals Inc.  
**Drug Name** Levothyroxine Sodium Tablets USP  
**Strength(s)** 0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.1 mg, 0.112 mg, 0.125 mg, 0.15 mg, 0.175 mg, 0.2 mg, 0.3 mg

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**FPL Approval Summary**

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**Container Labels** 100s EDR- FPL document  
 0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.1 mg, 0.112 mg, 0.125 mg, 0.15 mg, 0.175 mg, 0.2 mg, 0.3 mg  
 Jan. 22, 2004 EDR

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**Package Insert Labeling** #SLVTX:R1 Jan. 22, 2004 EDR

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**BASIS OF APPROVAL:**

**Patent Data for NDA 21-402: No unexpired patents**

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact

**Exclusivity Data For NDA: No unexpired exclusivity**

Code/sup	Expiration	Use Code	Description	Labeling Impact

---

**Reference Listed Drug**

RLD on the 356(h) form Synthroid  
 NDA Number 21-402  
 RLD established name Levothyroxine sodium tablets USP  
 Firm Abbott  
 Currently approved PI N-000  
 AP Date 7/24/2002

Note: Mylan wanted a Bio rating to a third RLD. They were instructed by OGD to submit this new request as an original application. Mylan's approved application ANDA 76-187 used Unithyroid as the RLD. Mylan ANDA 76-647 use levoxy and while ANDA 76-764 use synthroid as the RLDs.

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# MYLAN PHARMACEUTICALS INC

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

January 22, 2004

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

ORIG AMENDMENT

N/A/F

## LABELING AMENDMENT (ELECTRONIC LABELING INFORMATION ENCLOSED)

RE: ANDA 76-764; LEVOTHYROXINE SODIUM TABLETS, USP  
25MCG, 50MCG, 75MCG, 88MCG, 100MCG, 112MCG, 125MCG, 150MCG, 175MCG,  
200MCG AND 300MCG  
RESPONSE TO AGENCY'S CORRESPONDENCE DATED OCTOBER 29, 2003

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review and to labeling comments pertaining to this application which were provided to Mylan in a correspondence dated October 29, 2003. The purpose of this Labeling Amendment is to submit final printed labeling in accordance with the Agency's October 29<sup>th</sup> correspondence. Please note that the enclosed container labeling is identical to that approved in ANDA 76-187.

In accordance with the Agency's *Guidances Providing Regulatory Submissions in Electronic Format – ANDAs and Providing Regulatory Submissions in Electronic Format – General Considerations*, we enclose a CD-Rom which contains the following items:

Cover.pdf	Cover Letter
356h.pdf	Signed Form FDA 356h
Letter1.pdf	Copy of the Agency's Letter Dated October 29, 2003
Comp1.pdf	Side-By-Side Comparison of Mylan's Final Printed Outsert (SLVTX:R1; Revised January 2004) To Mylan's Previously Submitted Revised Draft Outsert (SLVTX:RX1)
ProposedOT.pdf	Proposed Outsert (SLVTX:R1)
DraftOT.pdf	Draft Outsert (SLVTX:RX1)
CurrentBL1.pdf	Current Final Printed Bottle Label - 25 mcg (RM1800A1)
CurrentBL2.pdf	Current Final Printed Bottle Label - 50 mcg (RM1803A1)
CurrentBL3.pdf	Current Final Printed Bottle Label - 75 mcg (RM1805A1)
CurrentBL4.pdf	Current Final Printed Bottle Label - 88 mcg (RM1807A1)
CurrentBL5.pdf	Current Final Printed Bottle Label - 100 mcg (RM1809A1)
CurrentBL6.pdf	Current Final Printed Bottle Label - 112 mcg (RM1811A1)
CurrentBL7.pdf	Current Final Printed Bottle Label - 125 mcg (RM1813A1)
CurrentBL8.pdf	Current Final Printed Bottle Label - 150 mcg (RM1815A1)

RECEIVED

JAN 23 2004

OGD/CDER

Department - Form 1085 ANDA LEVOTHYROXINE SODIUM TABLETS AGENCY LETTER DATED OCTOBER 29, 2003 (N/A/F).doc	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Quality Assurance	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5409
Business Development	(304) 598-5419	Maintenance & Engineering	(304) 598-5411
Corporate Services	(304) 598-5404	Medical Unit	(304) 598-5445
Human Resources	(304) 598-5406	Product Development	(304) 285-6411
		Regulatory Affairs	(304) 285-6407
		Research & Development	(304) 285-6409
		Sales & Marketing	(304) 598-3232

Gary Buehler

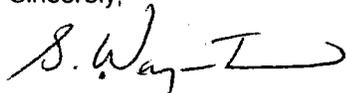
Page 2 of 2

CurrentBL9.pdf	Current Final Printed Bottle Label - 175 mcg (RM1817A1)
CurrentBL10.pdf	Current Final Printed Bottle Label - 200 mcg (RM1819A1)
CurrentBL11.pdf	Current Final Printed Bottle Label - 300 mcg (RM1821A1)

Mylan acknowledges that the Agency may request further changes to the labeling prior to approval. In addition, Mylan may have to revise our labeling pursuant to approved changes for the referenced listed drug. Mylan will monitor FDA's website for any approved labeling changes.

Should you have any questions regarding this supplement, please contact the undersigned by telephone at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,



S. Wayne Talton  
Executive Director  
Regulatory Affairs

SWT/dmy

Enclosures

**REVIEW OF PROFESSIONAL LABELING #1**  
**DIVISION OF LABELING AND PROGRAM SUPPORT**  
**LABELING REVIEW BRANCH**

---

ANDA Number: 76-764

Date of Submission: August 27, 2003 and Sept 11, 2003 NC

Applicant's Name: Mylan Pharmaceuticals

Established Name: Levothyroxine Sodium Tablets USP, 0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.112 mg, 0.125 mg, 0.15 mg, 0.175 mg, 0.1 mg, 0.2 mg, 0.3 mg

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Labeling Deficiencies:

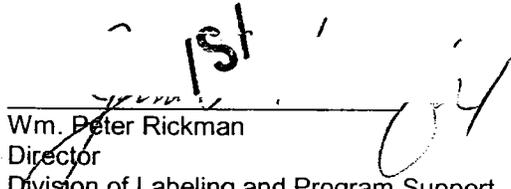
1. CONTAINER - Satisfactory in draft.
2. INSERT LABELING - Satisfactory in draft.

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed container labels and insert labeling.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

<http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

  
\_\_\_\_\_  
Wm. Peter Rickman  
Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

**APPROVAL SUMMARY  
 REVIEW OF PROFESSIONAL LABELING  
 DIVISION OF LABELING AND PROGRAM SUPPORT  
 LABELING REVIEW BRANCH**

---

**ANDA Number** 76-764  
**Date of Submission**  
**Applicant** Mylan Pharmaceuticals Inc.  
**Drug Name** Levothyroxine Sodium Tablets USP  
**Strength(s)** 0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.1 mg, 0.112 mg, 0.125 mg, 0.15 mg, 0.175 mg, 0.2 mg, 0.3 mg

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**FPL Approval Summary**

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**Container Labels**  
 0.025 mg, 0.05 mg, 100s  
 0.075 mg, 0.088 mg,  
 0.1 mg, 0.112 mg,  
 0.125 mg, 0.15 mg,  
 0.175 mg, 0.2 mg, 0.3 mg

---

**Package Insert Labeling**

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**BASIS OF APPROVAL:**

**Patent Data for NDA 21-301: No unexpired patents**

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact

**Exclusivity Data For NDA: No unexpired exclusivity**

Code/sup	Expiration	Use Code	Description		Labeling Impact

---

**Reference Listed Drug**

RLD on the 356(h) form Synthroid  
 NDA Number 21-402  
 RLD established name Levothyroxine sodium tablets USP  
 Firm Abbott  
 Currently approved PI N-000  
 AP Date 7/24/2002

Note: Mylan wanted a Bio rating to a third RLD. They were instructed by OGD to submit this new request as an original application. Mylan's approved application ANDA 76-187 used Unithyroid as the RLD. Mylan ANDA 76-647 use levoxy and while ANDA 76-764 use synthroid as the RLDs.

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## REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
<b>Error Prevention Analysis</b>			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
<b>Packaging</b>			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
<b>Labeling</b>			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
<b>Labeling(continued)</b>			
	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult, Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by..." statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
<b>Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR</b>			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
<b>Inactive Ingredients: (FTR: List page # in application where inactives are listed)</b>			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
<b>USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)</b>			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	

Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
<b>Bioequivalence Issues:</b> (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
<b>Patent/Exclusivity Issues?:</b> FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

**NOTES/QUESTIONS TO THE CHEMIST:**

**FOR THE RECORD:**

- Review based on the labeling of 21-402/ 000 Synthroid; Abbotts' (C<sub>1</sub> absorption) ; { NDA 21-301/S-002; C<sub>1</sub> Jones pharma; NDA 21-210/ S-001, JSP; Unithyroid, ; approved 8/21/01}.
- Patent/ Exclusivities: no unexpired patents or exclusivity, firm file a paragraph PI
- Storage Conditions:  
NDA - 20-25 C (68-77 F) with excursion between 15-30 C ( 59-86 F). protect from light and moisture  
ANDA - store at between 20-25 (68-77F). See USP CRT)  
USP - None
- Dispensing Recommendations:  
NDA - none  
ANDA - Dispense in a tight, light resistant container as defined in UDP. Using a child resistant closure.  
USP - tight light resistant container
- Scoring:  
NDA - partial bisected.  
ANDA - scored  
USP - none
- Product Line:  
The innovator markets their product in bottles of 100s and 1000s  
The applicant proposes to market their product in C<sub>1</sub> bottles of 100s with CRC.
- The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). Yes.
- Inactive Ingredients:  
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page for ANDA 76-764 ( vol 1.2 pag. 1676).
- Mylan, at Morgantown, will perform all operations in the manufacturing package and labeling.  
The Container Labels ANDA 76-187: company used samples from Levotab and thros that are marketed by C<sub>1</sub> since Unithroid is not commercial available.
- The insert labeling follows the levothyroxine sodium tablets template developed by the agency (revised July 9, 2002) except for product specific information. Mylan wanted a Bio rating to a third RLD. They were instructed by OGD to submit this new request as an original application. The approved application 76-187 used Unithyroid as the RLD. Mylan ANDA 76-647 use levoxyl, while ANDA 76-764 use synthroid as the RLD. with no changes to the approved ANDA formulation or container labels. The absorption rate differs amongst the NDAs

Date of Review: 10/22/03

Date of Submission: 8/27/03 and 9/11/03

cc: ANDA: 76-764  
DUP/DIVISION FILE  
HFD-613/Apayne/JGrace (no cc)  
V:firmsam/mylan/lets&revs/76764na2.Lab  
Review

TS - 10/22/03  
12/21/2003

76-764  
V1.1 or 2.1  
w/ACK Hr.

REVIEW OF PROFESSIONAL LABELING #1  
DIVISION OF LABELING AND PROGRAM SUPPORT  
LABELING REVIEW BRANCH

ANDA Number: 76-764

Date of Submission: June 16, 2003

Applicant's Name: Mylan Pharmaceuticals

Established Name: Levothyroxine Sodium Tablets USP, 0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.112 mg, 0.125 mg, 0.15 mg, 0.175 mg, 0.1 mg, 0.2 mg, 0.3 mg

Labeling Deficiencies:

1. CONTAINER - In your storage statement please change — to "store between...". In addition, we encourage you to add protect from moisture and light as does the reference listed drug. This statement could be considered as a dispensing statement to the pharmacist and ultimately to the consumer when the product is place in the home.
2. INSERT LABELING - Satisfactory in draft.

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed container labels and insert labeling.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

<http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

ISI  
Wm. Peter Rickman  
Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

**APPROVAL SUMMARY  
 REVIEW OF PROFESSIONAL LABELING  
 DIVISION OF LABELING AND PROGRAM SUPPORT  
 LABELING REVIEW BRANCH**

---

**ANDA Number** : 76-764  
**Date of Submission**  
**Applicant** Mylan Pharmaceuticals Inc.  
**Drug Name** Levothyroxine Sodium Tablets USP  
**Strength(s)** 0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.112 mg, 0.125 mg, 0.15 mg, 0.175 mg, 0.1 mg, 0.2 mg, 0.3 mg

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**FPL Approval Summary**

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**Container Labels**  
 0.025 mg, 0.05 mg, 100s  
 0.075 mg, 0.088 mg,  
 0.1 mg, 0.112 mg,  
 0.125 mg, 0.15 mg,  
 0.175 mg, 0.2 mg, 0.3 mg

---



---

**Package Insert Labeling**

---

**BASIS OF APPROVAL:**

**Patent Data for NDA 21-301: No unexpired patents**

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact

**Exclusivity Data For NDA: No unexpired exclusivity**

Code/sup	Expiration	Use Code	Description	How Filed	Labeling Impact

---

**Reference Listed Drug**

RLD on the 356(h) form Synthroid  
 NDA Number 21-301  
 RLD established name Levothyroxine sodium tablets USP  
 Firm Abbott  
 Currently approved PI N-000  
 AP Date 7/247/2002

Note: Mylan wanted a Bio rating to a third RLD. They were instructed by OGD to submit this new request as an original application. Mylan's approved application ANDA 76-187 used Unithyroid as the RLD. Mylan ANDA 76-647 use levoxyl and while ANDA 76-764 use synthroid as the RLDs.

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## REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
<b>Error Prevention Analysis</b>			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
<b>Packaging</b>			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
<b>Labeling</b>			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
<b>Labeling(continued)</b>			
	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by..." statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
<b>Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR</b>			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
<b>Inactive Ingredients: (FTR: List page # in application where inactives are listed)</b>			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
<b>USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)</b>			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	

Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
<b>Bioequivalence Issues:</b> (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
<b>Patent/Exclusivity Issues?:</b> FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

**NOTES/QUESTIONS TO THE CHEMIST:**

**FOR THE RECORD:**

- Review based on the labeling of 21-402/ 000 Synthroid; Abbotts' (1 1/2 absorption) ; ( NDA 21-301/S-002; Jones pharma; NDA 21-210/ S-001, JSP; Unithyroid, ; approved 8/21/01).
- Patent/ Exclusivities: no unexpired patents or exclusivity, firm file a paragraph PI
- Storage Conditions:  
NDA - 20-25 C (68-77 F) with excursion between 15-30 C ( 59-86 F). protect from light and moisture  
ANDA - store at between 20-25 (68-77F). See USP CRT  
USP - None
- Dispensing Recommendations:  
NDA - none  
ANDA - Dispense in a tight, light resistant container as defined in UDP. Using a child resistant closure.  
USP - tight light resistant container
- Scoring:  
NDA - partial bisected.  
ANDA - scored  
USP - none
- Product Line:  
The innovator markets their product in bottles of 100s and 1000s  
The applicant proposes to market their product in bottles of 100s with CRC.
- The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). Yes.
- Inactive Ingredients:  
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page for ANDA 76-764 ( vol 1.2 pag. 1676).
- Mylan, at Morgantown, will perform all operations in the manufacturing package and labeling.  
The Container Labels ANDA 76-187: company used samples from Levotab and thros that are marketed by L 1 since Unithroid is not commercial available.
- The insert labeling follows the levothyroxine sodium tablets template developed by the agency (revised July 9, 2002) except for product specific information. Mylan wanted a Bio rating to a third RLD. They were instructed by OGD to submit this new request as an original application. The approved application 76-187 used Unithyroid as the RLD. Mylan ANDA 76-647 use levoxyl, while ANDA 76-764 use synthroid as the RLD. with no changes to the approved ANDA formulation or container labels. The absorption rate differs amongst the NDAs

Date of Review: 8/4/03

Date of Submission: 6/16/03

cc: ANDA: 76-764  
DUP/DIVISION FILE  
HFD-613/Apayne/JGrace (no cc)  
V:firmsam/mylan/lets&revs/76764na1.Lab  
Review

*of me* 8/6/03  
15/1

8/14/2003

# MYLAN PHARMACEUTICALS INC

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

August 27, 2003

## MAJOR AMENDMENT ELECTRONIC DATA ENCLOSED CMC AND BIOEQUIVALENCE DATA ENCLOSED

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

RE: LEVOTHYROXINE SODIUM TABLETS USP, 25MCG, 50MCG, 75MCG, 88MCG,  
100MCG, 112MCG, 125MCG, 150MCG, 175MCG and 200MCG  
ANDA 76-764  
(Amendment to Provide for Addition of 300mcg Strength)

Dear Mr. Buehler:

Mylan wishes to amend the above referenced Abbreviated New Drug Application to provide for Levothyroxine Sodium Tablets USP, 300mcg, as a product line extension to Mylan's ANDA for Levothyroxine Sodium Tablets USP, 25mcg, 50mcg, 75mcg, 88mcg, 100mcg, 112mcg, 125mcg, 150mcg, 175mcg and 200mcg (ANDA 76-764) originally submitted on June 16, 2003.

The proposed strength is qualitatively identical and compositionally proportional to the other strengths of Levothyroxine Sodium Tablets USP, and will be manufactured, tested, packaged, and labeled using procedures and controls similar to those provided in Mylan's ANDA 76-764 submitted on June 16, 2003. In support of this Amendment, Mylan has also conducted a fasting bioequivalence study with Levothyroxine Sodium Tablets USP, 300mcg and the reference listed drug, Synthroid® Tablets, 300mcg, which is included in Section VI this amendment.

This amendment consists of 9 volumes as follows:

Archival Copy - 4 volumes.

Review Copy - 5 volumes.

Technical Section For Chemistry - 2 volumes.

Technical Section For Pharmacokinetics - 3 volumes.

CD-Rom – eCover Letter, e356h, eTOC, and data listings for the bioequivalence study conducted in support of this amendment.

As an aid to the reviewer, this amendment has been assembled according to the traditional ANDA format. Only those documents that have been revised since the original submission and new documents in support of the additional strength are provided in this submission. Details of revisions made to previously submitted documents are provided on the cover page to the appropriate section of this amendment containing the revised documents. The enclosed Table of Contents provides a listing of the information being submitted in support of this amendment.

G:\PROJECT\ANDA\LEVOTHYROXINE\SYNTHROID\300mcg amendment\SECTIONS-01THRU07.doc

Department—Fax Numbers

Accounting (304) 285-6403  
Administration (304) 599-7284  
Business Development (304) 598-5419  
Corporate Services (304) 598-5404  
Human Resources (304) 598-5406

Information Systems

Label Control (800) 848-0463  
Legal Services (304) 598-5408  
Maintenance & Engineering (304) 598-5411  
Medical Unit (304) 598-5445  
Product Development (304) 285-6411

Purchasing

Quality Assurance (304) 598-5407  
Quality Control (304) 598-5409  
Regulatory Affairs (304) 285-6407  
Research & Development (304) 285-6409  
Sales & Marketing (304) 598-3232

Gary J. Buehler  
Page 2 of 2

As required by 21 CFR 314.94(d)(5), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (304) 599-2595, extension 6551 and/or facsimile number (304) 285-6407.

Sincerely,



S. Wayne Talton  
Executive Director  
Regulatory Affairs

SWT/tg

Enclosures



# MYLAN PHARMACEUTICALS INC

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

September 11, 2003

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

## LABELING AMENDMENT

ORIG AMENDMENT

*N/A*

RE: ANDA 76-764; LEVOTHYROXINE SODIUM TABLETS, USP  
25MCG, 50MCG, 75MCG, 88MCG, 100MCG, 112MCG, 125MCG, 150MCG, 175MCG,  
200MCG AND 300MCG  
(Response to Agency Correspondence Dated August 20, 2003)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application identified above for Mylan's Levothyroxine Sodium Tablets, USP which is currently under review. Reference is also made to the Agency's correspondence dated August 20, 2003, requesting that Mylan revise our container labeling in accordance with the Agency's comments. A copy of the Agency's August 20, 2003 correspondence is provided in Attachment 1 for the reviewer's reference.

### FDA COMMENT 1:

CONTAINER – In your storage statement please change [ ] to "store between...". In addition, we encourage you to add protection from moisture and light as does the reference listed drug. This statement could be considered as a dispensing statement to the pharmacist and ultimately to the consumer when the product is placed in the home.

### MYLAN RESPONSE:

Mylan submitted a Major Amendment on August 27, 2003 to provide for the addition of a 300mcg tablet strength. Please note that the labeling contained in the August 27<sup>th</sup> Amendment supercedes the labeling contained in the original ANDA submitted on June 16, 2003.

In accordance with labeling comments received from the Agency on other ANDAs currently under review, Mylan has been consistently updating our standard storage statement to read "Store at 20 to 25°C (68 to 77°F). [See USP for Controlled Room Temperature.]" Since May 2003, the Agency has requested Mylan to adopt this storage statement for the following products:

PRODUCT NAME/ STRENGTH	ANDA #	DATE OF COMMENT LETTER	FDA COMMENT #
		August 14, 2003	1.a.
		June 23, 2003	1.
Metolazone Tablets USP, 2.5mg	76-698	June 23, 2003	1.c.
Metoprolol Tartrate Tablets USP, 50mg and 100mg	76-704	July 18, 2003	1.a.
Famotidine Tablets USP, 20mg and 40mg	75-704	May 14, 2003	--
		May 2, 2003	1.b.

SEP 10 2003

#### Department—Fax Numbers

Accounting (304) 285-6403  
 Administration G:PROJECT AND (304) 598-7881  
 Business Development (304) 598-5419  
 Corporate Services (304) 598-5404  
 Human Resources (304) 598-5406

Information Systems (304) 285-6404  
 Label Control (800) 848-0463  
 Regulatory Affairs (304) 598-5408  
 Maintenance & Engineering (304) 598-5411  
 Medical Unit (304) 598-5445  
 Product Development (304) 285-6411

Purchasing (304) 598-5401  
 Quality Assurance (304) 598-5407  
 Quality Control (304) 598-5409  
 Regulatory Affairs (304) 285-6407  
 Research & Development (304) 285-6409  
 Sales & Marketing (304) 598-3232

Therefore, Mylan wishes to retain our storage statement "Store at 20 to 25°C (68 to 77°F). [See USP for Controlled Room Temperature.]" which has routinely been found acceptable by the Agency.

Regarding the Agency's recommendation to add a protect from moisture and light statement, please note that Mylan's Levothyroxine Sodium Tablets subject of ANDA 76-764 (Reference Listed Drug, Synthroid®) is the same product as that currently approved in ANDA 76-187 (Reference Listed Drug, Unithroid®) and currently pending review in ANDA 76-647 (Reference Listed Drug, Levoxyl®). As demonstrated in Mylan's approved original ANDA 76-187, the additional storage statement of "Protect from Moisture and Light" was not a required labeled storage condition to ensure adequate protection of our product. In addition, the container labeling submitted in ANDA 76-647 which also does not contain a "Protect from Moisture and Light" statement has been found acceptable by the Agency.

The "Protect from Moisture and Light" statement is specific to the Synthroid® brand of Levothyroxine Sodium Tablets, USP as this storage statement does not appear on the other two Reference Listed Drugs, Unithroid® or Levoxyl®, for which Mylan has submitted ANDAs to demonstrate bioequivalence.

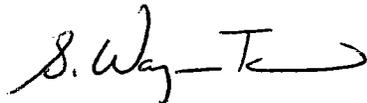
As with all container labeling for Mylan's generic drug products, the bottle labels for Levothyroxine Sodium Tablets, USP do contain the following precautionary dispensing statements:

- "Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure."
- "Keep container tightly closed."

Therefore, Mylan believes that our product contains the appropriate storage statements and wishes to retain the container labeling as submitted in our Amendment dated August 27, 2003. Since our Levothyroxine Sodium Tablets and corresponding container labeling are subject of three separate ANDAs (76-764, 76-187, and 76-647), it is also necessary for Mylan to maintain a single version of the approved container labeling for this product.

This amendment is submitted in duplicate. Should you require additional information or have any questions concerning this amendment, please contact the undersigned by telephone at (304) 599-2595, ext. 6551 or by facsimile at (304) 285-6407.

Sincerely,



S. Wayne Talton  
Executive Director  
Regulatory Affairs

SWT/dn

Enclosures



# MYLAN PHARMACEUTICALS INC

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

**ORIG AMENDMENT**

NIAC

August 27, 2003

**MAJOR AMENDMENT  
ELECTRONIC DATA ENCLOSED  
CMC AND BIOEQUIVALENCE DATA ENCLOSED**

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

RE: LEVOTHYROXINE SODIUM TABLETS USP, 25MCG, 50MCG, 75MCG, 88MCG, 100MCG, 112MCG, 125MCG, 150MCG, 175MCG and 200MCG  
ANDA 76-764  
(Amendment to Provide for Addition of 300mcg Strength)

Dear Mr. Buehler:

Mylan wishes to amend the above referenced Abbreviated New Drug Application to provide for Levothyroxine Sodium Tablets USP, 300mcg, as a product line extension to Mylan's ANDA for Levothyroxine Sodium Tablets USP, 25mcg, 50mcg, 75mcg, 88mcg, 100mcg, 112mcg, 125mcg, 150mcg, 175mcg and 200mcg (ANDA 76-764) originally submitted on June 16, 2003.

The proposed strength is qualitatively identical and compositionally proportional to the other strengths of Levothyroxine Sodium Tablets USP, and will be manufactured, tested, packaged, and labeled using procedures and controls similar to those provided in Mylan's ANDA 76-764 submitted on June 16, 2003. In support of this Amendment, Mylan has also conducted a fasting bioequivalence study with Levothyroxine Sodium Tablets USP, 300mcg and the reference listed drug, Synthroid® Tablets, 300mcg, which is included in Section VI this amendment.

This amendment consists of 9 volumes as follows:

- Archival Copy - 4 volumes.
- Review Copy - 5 volumes.
  - Technical Section For Chemistry - 2 volumes.
  - Technical Section For Pharmacokinetics - 3 volumes.
  - CD-Rom – eCover Letter, e356h, eTOC, and data listings for the bioequivalence study conducted in support of this amendment.

RECEIVED

AUG 28 2003

OGD/CD

As an aid to the reviewer, this amendment has been assembled according to the traditional ANDA format. Only those documents that have been revised since the original submission and new documents in support of the additional strength are provided in this submission. Details of revisions made to previously submitted documents are provided on the cover page to the appropriate section of this amendment containing the revised documents. The enclosed Table of Contents provides a listing of the information being submitted in support of this amendment.

G:\PROJECT\ANDA\LEVOTHYROXINE\SYNTHROID\300mcg amendment\SECTIONS-01THRU07.doc

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
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Corporate Services	(304) 598-5404	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6409
Human Resources	(304) 598-5406	Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

Gary J. Buehler  
Page 2 of 2

As required by 21 CFR 314.94(d)(5), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (304) 599-2595, extension 6551 and/or facsimile number (304) 285-6407.

Sincerely,



S. Wayne Talton  
Executive Director  
Regulatory Affairs

SWT/tg

Enclosures

ANDA 76-764

JUL 17 2003

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

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Levothyroxine Sodium Tablets USP, 0.025 mg,  
0.05 mg, 0.075 mg, 0.088 mg, 0.1 mg, 0.112 mg,  
0.125 mg, 0.15 mg, 0.175 mg and 0.2 mg

DATE OF APPLICATION: June 16, 2003

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 17, 2003

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Peter Chen  
Project Manager  
(301) 827-5848

Sincerely yours,

*/S/* *b for*  
Wm Peter Rickman  
Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research



# MYLAN PHARMACEUTICALS INC

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

June 16, 2003

505(j)(2)(A) 16-Jul-03  
OK ABC  
S/S

ELECTRONIC DATA ENCLOSED  
BIOEQUIVALENCE DATA ENCLOSED

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

RECEIVED

JUN 17 2003

OGD / CDER

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

Dear Mr. Buehler:

Pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.92 and 314.94, we submit the enclosed Abbreviated New Drug Application for:

Proprietary Name: None

Established Name: Levothyroxine Sodium Tablets USP, 25mcg, 50mcg, 75mcg, 88mcg, 100mcg, 112mcg, 125mcg, 150mcg, 175mcg and 200mcg

Reference Listed Drug: Synthroid® Tablets (Abbott Pharmaceuticals, Inc.), NDA 21-402

This application consists of a total of 11 volumes.

Archival Copy - 4 volumes.

Review Copy - 5 volumes.

Technical Section For Chemistry - 2 volumes.

Technical Section For Pharmacokinetics - 3 volumes.

Analytical Methods – Refer to Mylan's ANDA 76-187.

CD-Rom – eCover Letter, e356h, eTOC, and data listings for the bioequivalence study conducted in support of this application.

Reference is made to a telephone discussion held on January 24, 2003 with Mr. Gregory Davis, Branch Chief, Division of Labeling and Program Support, Office of Generic Drugs, regarding the proper filing mechanism for this ANDA. Mylan obtained approval of our generic Levothyroxine Sodium Tablet product, ANDA 76-187, on June 5, 2002, which provided for a Bioequivalence (AB) rating to the reference listed drug, Jerome Stevens' Unithroid® (Levothyroxine Sodium Tablets, USP). Mylan has a separate ANDA 76-647, currently under review, which seeks approval for a Bioequivalence (AB) rating of our generic Levothyroxine Sodium product to the reference listed drug, Jones Pharma's Levoxyl®.

As recommended by Mr. Davis, we are submitting a new ANDA to request a Bioequivalence (AB) rating of our generic Levothyroxine Sodium product to the reference listed drug, Abbott's Synthroid®. In support of this application, a single-dose fasting *in vivo* bioequivalency study (LEVO-02144) demonstrating the bioequivalence of our Levothyroxine Sodium Tablets, USP to the reference listed drug, Abbott's Synthroid® Tablets, was conducted using a commercial lot of our Levothyroxine Sodium Tablets, USP that was manufactured in accordance with our approved ANDA 76-187. Results of the study are included in Section VI of this application.

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Department—Fax Numbers

Accounting (304) 285-6403  
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Human Resources (304) 598-5406

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Purchasing

Quality Control  
Research & Development  
Sales & Marketing

(304) 598-5401  
(304) 598-5407  
(304) 285-6409  
(304) 598-3232

As recommended by Mr. Davis, this application has been organized according to the Agency's February 1999 Guidance for Industry - 'Organization of an ANDA'. In each Section it has been noted whether applicable information has been incorporated by reference to the appropriate sections of the approved ANDA 76-187, and if any additional information has been included. Per Mr. Davis' request, please note that the following additional chemistry, manufacturing and controls information has been provided herein:

- Lot numbers and Certificates of Analysis for representative lots of each strength of Mylan's Levothyroxine Sodium Tablets, USP
- Dissolution Profile data for the same representative lots of each strength of Mylan's Levothyroxine Sodium Tablets, USP
- Dissolution Profile data for each strength of Abbott's Synthroid® Tablets
- A commitment to provide a copy of executed manufacturing batch records upon request.

Mylan confirms that the test product, Mylan's Levothyroxine Sodium Tablets USP, 200mcg, Lot 1K3174, used to dose the bioequivalency study (LEVO-02144) included in Section VI of this application, was manufactured and controlled under the same conditions as those approved in ANDA 76-187. A copy of the executed batch records for Lot 1K3174 is provided in Section XII, and Certificates of Analysis for the inactive ingredients and packaging components are included in Sections VIII and XIII, respectively. As requested, Mylan commits to providing copies of the executed batch records for the representative lots of each strength of Mylan's Levothyroxine Sodium Tablets, USP upon request.

We certify that a true copy of the technical sections of this application, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office. The following Table of Contents details the documentation submitted in support of this application.

All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (304) 599-2595, extension 6551 and/or facsimile number (304) 285-6407.

Sincerely,



S. Wayne Talton  
Executive Director  
Regulatory Affairs

SWT/nk

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

**and/or confidential**

**commercial information**

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