NDA 76187

Levothyroxine Sodium Tablets USP

0.025mg, 0.05mg, 0.075mg, 0.088mg, 0.1mg, 0.122mg, 0.125mg, 0.15mg, 0.175mg, 0.2mg and 0.3mg

Mylan Pharmaceuticals
Approval Date: June 5, 2002

Bioequivalence

A.1.1 N Schwart.

OCT 10 2001

BIOEQUIVALENCY DEFICIENCIES

ANDA: 76-187 APPLICANT: Mylan Pharmaceuticals

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

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

In the assay methodology reports of all 3 studies:

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]

In the study clinical reports, the following information was not provided for all 3 bio studies and currently requested by the Division of Bioequivalence:

The demographic information concerning the race of all subjects who were enrolled in the studies.

Please provide the above listed items.

Sincerely yours,

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

BIOEQUIVALENCY AMENDMENT

ANDA 76-187

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

OCT 10 2001

TO: APPLICANT: Mylan Pharmaceuticals Inc. TEL: 304-599-2595

ATTN: Frank R. Sisto FAX: 304-285-6407

FROM: Krista M. Scardina, Pharm.D. PROJECT MANAGER: 301-827-5847

Dear Mr. Sisto:

This facsimile is in reference to the bioequivalency data submitted on June 5, 2001, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Levothyroxine Sodium Tablets USP, 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 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 of the submission(s) referenced above and has identified deficiencies which are presented on the attached __1___ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

MODE = MEMORY TRANSMISSION START=OCT-10 16:30 END=OCT-10 16:31

FILE NO.=330

STN NO.	COMM.	ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
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-CDER OGD DOC RM -

BIOEQUIVALENCY AMENDMENT

ANDA 76-187

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

OCT 10 2001

Center for Drug Evaluation and Research FDA

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The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __1___ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

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SPECIAL INSTRUCTIONS:

LEVOTHYROXINE SODIUM TABLETS
USP, 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.200 mg & 0.300 mg
ANDA 76-187
Reviewer: Hoainhon Nguyen
W #76187sdw.601

Mylan Pharmaceuticals
Morgantown, WV

Submission Date: 06/05/01

Review of Three Bioequivalence Studies, Dissolution Data and Waiver Requests (Electronic Submission)

I. Introduction

Indication: For the treatment of hypothyroidism --As replacement or supplemental therapy in congenital or acquired hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis. Specific indications include: primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) hypothyroidism and subclinical hypothyroidism. Also, for the treatment or prevention of various types of euthyroid goiters including thyroid nodules, subacute or chronic lymphocytic thyroiditis (Hashimoto's thyroiditis), multinodular goiter and, as an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent well-differentiated thyroid cancer.

Contents of Submission: Three single-dose fasting bioequivalence studies of the 0.300 mg, 0.125 mg and 0.075 mg strengths of the test and reference products, dissolution data for all strengths of the test and reference products, and waiver requests for the 0.200 mg, 0.175 mg, 0.150 mg, 0.112 mg, 0.100 mg, 0.088 mg, 0.050 mg and 0.025 mg strengths of the test product.

RLD: Unithroid tablets, 0.300 mg, manufactured by Jerome Stevens Pharmaceuticals; other available strengths are 0.200 mg, 0.175 mg, 0.150 mg, 0.125 mg, 0.112 mg, 0.100 mg, 0.088 mg, 0.075 mg, 0.050 mg and 0.025 mg.

NOTE: ***It should be noted that the reference products used in the in vivo bioequivalence studies and in vitro dissolution studies contained in this application are Thyrox Tablets and Levotab Tablets manufactured by Jerome Stevens. These products were used since the product sold under the brand name Unithroid was not available in the marketplace at the time the bioequivalence studies were conducted. The OGD informed Mylan that the formulations of Jerome Stevens' levothyroxine tablet products used in Mylan's bioequivalence studies are the same as the formulations approved in the NDA for Unithroid. (p. xxv, Vol. A 1.1, and the email from Don Hare to Gary Buehler, January 4, 2001, attached in the Vol. A1.1)***

Recommended Dose: The average full replacement dose of levothyroxine is approximately 1.7 mcg/kg/day (e.g., **100-125 mcg/day** for a 70 kg adult) for hypothroidism in adults and in children in whom growth and puberty are complete. For younger children with hypothyroidism, the recommended doses are as follows:

Levothyroxine Dosing Guidelines for Pediatric Hypothyroidism	
AGE	Daily Dose Per Kg Body Weight
0-3 months	10-15 mcg/kg/day
3-6 months	8-10 mcg/kg/day
6-12 months	6-8 mcg/kg/day
1-5 years	5-6 mcg/kg/day
6-12 years	4-5 mcg/kg/day
>12 years	2-3 mcg/kg/day
Growth and puberty complete	1.7 mcg/kg/day

For TSH suppression in well-differentiated thyroid cancer and thyroid nodule, a levothyroxine dose of **greater than 2 mcg/kg/day** is usually required .

II. Background

Absorption --Absorption of orally administered levothyroxine (T_4) from the gastrointestinal (GI) tract ranges from 40% to 80%. The majority of the levothyroxine dose is absorbed from the jejunum and upper ileum. The relative bioavailability of levothyroxine tablets, compared to an equal nominal dose of oral levothyroxine sodium solution, is approximately 99%.
T_4 absorption is increased by fasting, and decreased in malabsorption syndromes and by certain foods such as soybean infant formula. Dietary fiber decreases bioavailability of T_4. Absorption may also decrease with age. In addition, many drugs and foods affect T_4 absorption.

Distribution --Circulating thyroid hormones are greater than 99% bound to plasma proteins, including thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), and albumin (TBA), whose capacities and affinities vary for each hormone. The higher affinity of both TBG and TBPA for T_4 partially explains the higher serum levels, slower metabolic clearance, and longer half-life of T_4 compared to triiodothyroxine (T_3). Protein-bound thyroid hormones exist in reverse equilibrium with small amounts of free hormone. Only unbound hormone is metabolically active. Many drugs and physiologic conditions affect the binding of thyroid hormones to serum proteins. Thyroid hormones do not readily cross the placental barrier.

Metabolism --T_4 is slowly eliminated . The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately eighty-percent of circulating T_3 is derived from peripheral T_4 by monodeiodination. The liver is the major site of degradation for both T_4 and T_3; with T_4 deiodination also occurring at a number of additional sites, including the kidney and other tissues. Approximately 80% of the daily dose of T_4 is deiodinated to yield equal amounts of T_3 and reverse T_3 (rT_3). T_3 and rT_3 are further deiodinated to diiodothyronine. Thyroid hormones are also metabolized via conjugation with glucuronides and sulfates and excreted directly into the bile and gut where they undergo enterohepatic recirculation.

Elimination --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_4 is eliminated in the stool. Urinary excretion of T_4 decreases with age.

The most frequent adverse events associated with levothyroxine are fatigue, increased appetite, weight loss, heat intolerance, fever, excessive sweating. (Reference: Physicians' Desk Reference, pp.1374-1377, 1998)

Conditions for Bioequivalence Approval: The current bioequivalence conditions are as communicated in the [redacted] The DBE requests only a single-dose fasting *in vivo* bioequivalence study be conducted comparing the 300 mcg strength of the test product to the RLD product. Only levothyroxine (T4) is recommended for quantitation. Biowaiver requests for all of the lower strengths may be accepted based on (1) acceptable bioequivalence study of the 300 mcg strength, (2) acceptable *in vitro* dissolution testing for all strengths, and (3) proportional similarity in the formulations of all strengths.

Financial Disclosure: p. 471, Vol. A1.1.

III. Protocol No. LEVO-0057: Single-Dose Fasting In Vivo Bioequivalence Study of Levothyroxine Sodium Tablets (75 µg; Mylan) to Levothyroxine Sodium Tablets, USP (75 µg; Jerome Stevens) in Healthy Volunteers

1) Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	[redacted]
Principal Investigators:	[redacted]
Clinical Study Dates:	10/06/00 to 11/20/00
Analytical Facility	[redacted]
Principal Investigator:	[redacted]
Analytical Study Dates:	11/28/00 to 12/07/00 (T4 Analysis)
Maximum Storage Period:	62 days

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Levothyroxine Sodium	Levothyroxine Sodium
Manufacturer:	Mylan	Jerome Stevens
Manufacture Date:	03/15/00	N/A
Expiration Date:	N/A	04/02
ANDA Batch Size:	[redacted]	
Batch/Lot Number:	R1H0747	004100
Potency:	99.5%	95.0%
Strength:	0.075 mg	0.075 mg
Dosage Form:	tablet	Tablet
Dose Administered:	0.600 mg (8x0.075 mg)	0.600 mg (8x0.075 mg)
Study Condition:	fasting	Fasting
Length of Fasting:	overnight	Overnight

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	42 days

DOSING		SUBJECTS	
Single or Multiple Dose:	single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	34
Route of Administration:	oral	**No. of Subjects Completing:**	33
		No. of Subjects Serum Analyzed:	33
		No. of Dropouts:	1
		Sex(es) Included:	Male (16) Female (18)
		Healthy Volunteers Only:	Y
		Mean Age (yrs)(Range):	Male: 22 (18-29); Female: 27 (18-45)
		Mean Height (cm)(Range):	Male: 181 (165-190) Female: 166 (150-178)
		Mean Weight (kg) (Range):	Male: 80 (62-98) Female: 64 (54-75)

Dietary Restrictions:	No alcohol- or xanthine-containing beverages/foods for the 48 hours before dosing and throughout the period of sample collection.
Activity Restrictions:	Strenuous activity or complete rest was not permitted at any time during the housing period.
Drug Restrictions:	No medication (including over-the-counter products) for the 14 days preceding the study and throughout the entire study.
Confinement:	From the evening before dosing until after the 24-hour blood draw.
Inclusion/Exclusion Criteria:	pp. 542-544, Vol. A1.2.
Blood Sampling:	-0.5, -0.25, 0(predose), 0.5, 1, 1.50, 2, 2.5, 3, 4, 6, 8, 12, 18, 24 and 48 hours

2) Study Results

Clinical Adverse Events: There was no serious adverse event reported. Three and four mild drug-related adverse reactions were reported during the Test and Reference treatment, respectively. The reactions were abdominal pain and headache.

Protocol Deviations: None was likely to affect the study outcome as judged by the study investigator.

Dropouts: Subject #12 withdrew prior to dosing due to fainting during the pre-dose blood sampling of Period I. Subject #22 was dropped prior to dosing in Period I due to impetigo. Subject #27 withdrew after the 0.5 hour blood sampling of Period I for personal reasons.

3) **Analytical (Not to be Released Under FOI)** Both L-Thyroxine (T4) and L-Triiodothyronine (T3) were measured. However, only T4 data are requested and reviewed.

Total T4 serum levels were determined by a radioimmunoassay (RIA).

Pre-Study Stability in Serum:
a) **Short-term Storage:**
b) **Freeze-Thaw Cycles:**
c) **Long-term Storage**

Specificity: The specificity data for T4 anti-serum was provided by % Cross-reactivity for L-Thyroxine, D-Thyroxine, L-Triiodothyronine and D-Triodothyronine are 104, 92, 2.1 and 2.1, respectively. % Cross-reactivity for other substances was <0.1.

DURING STUDY ASSAY VALIDATION FOR T4 - STUDY #LEVO-0057

Parameter	Quality Control Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)		
Intra day Precision (%CV) (Pre-Study)		
Intra day Accuracy (%Actual) (Pre-Study)		
Inter day Precision (%CV)		
Inter day Accuracy (%Actual)		
Linear Range (ng/mL)		
Sensitivity/LOQ (ng/mL)		

Repeat samples: The list of repeat samples was not provided.

4) **Pharmacokinetic:**

PARAMETER	CALCULATION METHOD
AUC 0-t	Linear trapezoidal rule
Cmax	Observed Data
Tmax	Observed Data

Results:

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TABLE 1

MEAN (%CV) BASELINE UNCORRECTED TOTAL L-THYROXINE PHARMACOKINETIC PARAMETERS IN THIRTY-THREE HEALTHY SUBJECTS FOLLOWING A SINGLE ORAL 600 μg (8 x 75 μg) DOSE OF LEVOTHYROXINE SODIUM TABLETS UNDER FASTING CONDITIONS

(PROTOCOL LEVO-0057)

Parameter	Arithmetic Mean A = Mylan	Arithmetic Mean B = Levothyroxine Sodium Tablets, USP***	LSMEANS Ratio (A/B)	90% Confidence Interval**
AUC_{0-48} (ng x hr/mL)	5734 (12.77)	5824 (13.88)	0.99	96% - 101%
CPEAK (ng/mL)	155.4 (15.56)	160.8 (15.21)	0.97	94% - 100%
TPEAK (hr)	3.394 (48.27)	2.485 (52.40)	-----	-----

Ratio (A/B) $= e^{[\text{LSMEAN of LNA - LSMEAN of LNB}]}$

**Used Natural Log Transformed Parameter

***Manufactured by Jerome Stevens

TABLE 2

FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #LEVO-0057 ARITHMETIC MEAN L-THYROXINE SERUM CONCENTRATIONS [ng/mL] VERSUS TIME (CV%) IN THIRTY-THREE (33) SUBJECTS

	Treatment				
	A (Levothyroxine Na Mylan #R1H0747)		B (Levothyroxine Na, USP Jerome Stevens #004100)		A VS B
	Mean (ng/mL)	%CV	Mean (ng/mL)	%CV	P(|T|>t)
Dnaw Time					
-0.50 hours	84.54	14.60	83.56	16.90	0.5776
-0.25 hours	82.85	17.95	83.94	14.45	0.5165
0.00 hours	85.09	15.57	82.42	14.06	0.0622
0.50 hours	91.62	17.68	93.99	18.11	0.4373
1.00 hours	115.83	17.21	133.25	20.75	0.0001
1.50 hours	129.89	18.95	147.82	20.09	0.0001
2.00 hours	139.88	16.58	149.48	16.14	0.0016
2.50 hours	142.52	18.13	149.31	12.79	0.0808
3.00 hours	143.64	14.57	148.24	13.25	0.1978
4.00 hours	142.89	16.04	144.25	13.35	0.7247
6.00 hours	135.45	14.47	137.58	12.62	0.3909
8.00 hours	128.28	12.92	128.77	14.02	0.8136
12.00 hours	124.42	14.11	127.76	14.05	0.2055
18.00 hours	115.00	13.31	116.96	15.94	0.3977
24.00 hours	117.86	14.51	119.86	16.36	0.3203
48.00 hours	112.15	13.61	111.56	14.46	0.7245

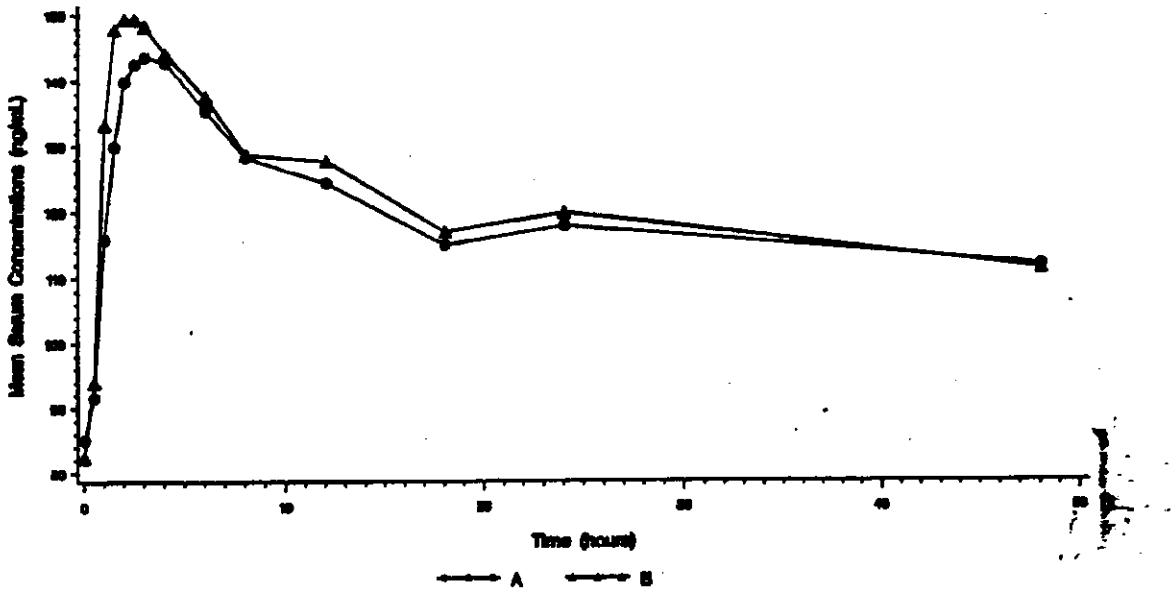
FIGURE 1

LEVOTHYROXINE Na (LEVO – 0057)

Total Dose: 600 ug (8x75ug Tablets), Study Type: Fasting

Mean L-thyroxine Serum Concentrations

N=33



Treatment A is A (Levothyroxine Na – – Mylan #R1H0747)
Treatment B is B (Levothyroxine Na, USP – – Jerome Stevens #004100)

5) **Statistical Analysis:** Thirty-three of 34 enrolled subjects completed the study (See Dropouts, p. 5 above). Thirty-three data sets were used in the statistical analysis for the study.

There was no statistically significant difference (alpha=0.05) between treatments for LAUC(0-T) or LCMAX.

Comments: The study is incomplete, see Deficiency Comments, page 30.

IV. Protocol No. LEVO-0054: Single-Dose Fasting In Vivo Bioequivalence Study of Levothyroxine Sodium Tablets (125 µg; Mylan) and Levothyroxine Sodium Tablets, USP (125 µg; Jerome Stevens) in Healthy Volunteers

1) Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	[redacted]
Principal Investigators:	[redacted]
Clinical Study Dates:	09/23/00 to 11/07/00
Analytical Facility	[redacted]
Principal Investigator:	[redacted]
Analytical Study Dates:	11/16/00 to 11/28/00
Storage Period:	66 days

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Levothyroxine Sodium	Levothyroxine Sodium
Manufacturer:	Mylan	Jerome Stevens
Manufacture Date:	03/16/00	N/A
Expiration Date:	N/A	05/02
ANDA Batch Size:	[redacted]	
Batch/Lot Number:	R1H0750	003799
Potency:	97.2%	94.6%
Strength:	0.125 mg	0.125 mg
Dosage Form:	tablet	Tablet
Dose Administered:	0.500 mg (4x0.125 mg)	0.500 mg (4x0.125 mg)
Study Condition:	fasting	Fasting
Length of Fasting:	overnight	Overnight

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	42 days

DOSING		SUBJECTS	
Single or Multiple Dose:	single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	30
Route of Administration:	oral	**No. of Subjects Completing:**	27
		No. of Subjects Analyzed:	30*
		No. of Dropouts:	3
		Sex(es) Included:	Male (15) Female (15)
		Healthy Volunteers Only:	Y
		Mean Age (yrs)(Range):	Male: 26 (18-44); Female: 33 (20-48)
		Mean Height (cm)(Range):	Male: 181 (168-193) Female: 167 (152-188)
		Mean Weight (kg) (Range):	Male: 78 (67-100) Female: 68 (58-95)

***NOTE:** Although Subjects #2, 3 and 6 were dropped from the study (See page 17 of this review), these subjects completed Period I and their Period I samples were analyzed and included in the study results.

Dietary/Drug/Activity Restrictions: See the Fasting Study of the 75 µg strength above.

Blood Sampling: -0.5, -0.25, 0(predose), 0.5, 1, 1.50, 2, 2.5, 3, 4, 6, 8, 12, 18, 24 and 48 hours

2) Study Results

Clinical Adverse Events: There was no serious adverse event reported. Two and one mild drug-related adverse reactions were reported during the Test and Reference treatments, respectively. The reactions were dyspepsia and headache.

Protocol Deviations: None was likely to affect the study outcome as judged by the study investigator.

Dropouts:

Subjects #2 and 6 failed to report for Period II check-in. Subject #3 was dropped prior to dosing in Period II due to a scheduled eye surgery.

3) **Analytical (Not to be Released Under FOI)** Both L-Thyroxine (T4) and L-Triiodothyronine (T3) were measured. However, only T4 data are requested and reviewed.

T4 serum levels were determined by a radioimmunoassay (RIA).

DURING STUDY ASSAY VALIDATION FOR T4 - STUDY #LEVO-0054

Parameter	Quality Control Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)		
Intra day Precision (%CV) (Pre-Study)		
Intra day Accuracy (%Actual) (Pre-Study)		
Inter day Precision (%CV)		
Inter day Accuracy (%Actual)		
Linear Range (ng/mL)		
Sensitivity/LOQ (ng/mL)		

Repeat samples: The list of repeat samples was not provided, see Deficiency Comments, page 30.

4) Pharmacokinetic:

PARAMETER	CALCULATION METHOD
AUC 0-t	Linear Trapezoidal Rule
Cmax	Observed Data
tmax	Observed Data

Results:

TABLE 3

MEAN (%CV) BASELINE UNCORRECTED TOTAL L-THYROXINE PHARMACOKINETIC PARAMETERS IN HEALTHY SUBJECTS FOLLOWING A SINGLE ORAL 500 µg (4 x 125 µg) DOSE OF LEVOTHYROXINE SODIUM TABLETS UNDER FASTING CONDITIONS

(PROTOCOL LEVO-0054)

Parameter	Arithmetic Mean A = Mylan N=28	Arithmetic Mean B = Jerome Stevens N=29	LSMEANS Ratio (A/B)*	90% Confidence Interval**
$AUC_{0\text{-}48hr}$ (ng x hr/mL)	5539 (12.47)	5537 (11.66)	0.99	97% - 101%
CPEAK (ng/mL)	142.5 (13.18)	147.1 (12.98)	0.96	93% - 99%
TPEAK (hr)	3.089 (42.03)	2.724 (57.33)	-----	-----

*Ratio (A/B) $= e^{[LSMEAN\ of\ LNA\ -\ LSMEAN\ of\ LNB]}$

**Used Natural Log Transformed Parameter

TABLE 4

FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #LEVO-0054 ARITHMETIC MEAN L-THYROXINE SERUM CONCENTRATIONS [ng/mL] VERSUS TIME (CV%) IN THIRTY (30) SUBJECTS

	Treatment				
	A (Levothyroxine Na-Mylan #R1H0750)		B (Levothyroxine Na--Jerome Stevens #003799)		A VS B
	Mean (ng/mL)	%CV	Mean (ng/mL)	%CV	P(|T|>t)
Draw Time					
-0.50 hours	84.43	15.35	82.18	13.64	0.3726
-0.25 hours	83.77	13.17	82.71	13.23	0.8036
0.00 hours	83.57	13.90	82.52	13.52	0.7733
0.50 hours	92.79	17.02	92.00	16.66	0.9615
1.00 hours	113.44	17.43	124.30	16.89	0.0015
1.50 hours	126.67	17.95	138.86	16.29	0.0007
2.00 hours	132.57	16.85	141.95	13.40	0.0085
2.50 hours	133.22	13.32	139.08	10.26	0.0144
3.00 hours	132.98	12.91	137.78	12.29	0.0243
4.00 hours	133.12	13.57	135.47	12.08	0.1410
6.00 hours	130.20	13.55	129.89	11.39	0.7767
8.00 hours	123.43	12.75	122.40	12.18	0.9999
12.00 hours	122.07	14.62	119.63	11.82	0.5194
18.00 hours	110.42	16.97	112.63	10.51	0.2434
24.00 hours	113.57	12.49	114.47	13.33	0.2981
48.00 hours	109.38	12.81	106.13	12.42	0.1192

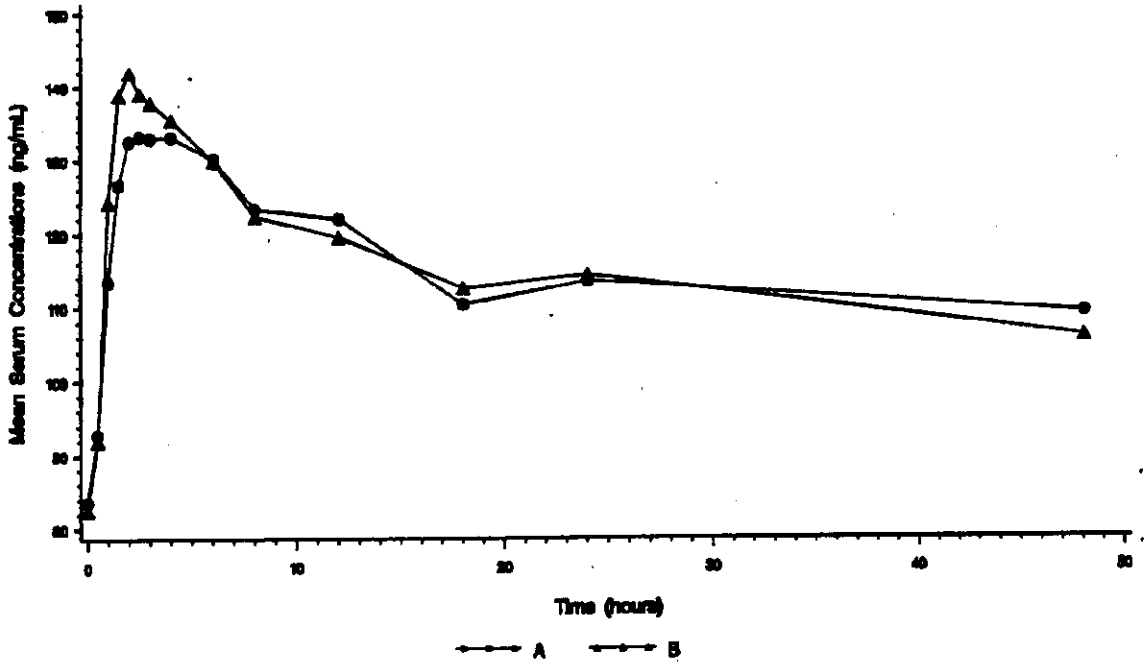
FIGURE 2

LEVOTHYROXINE Na (LEVO-0054)

Total Dose: 500 ug (4x125ug Tablets), Study Type: Fasting

Mean L-thyroxine Serum Concentrations

N=30



Treatment A is A (Levothyroxine Na--Mylan #RIH0750)

Treatment B is B (Levothyroxine Na--Jerome Stevens #0003799)

5) Statistical Analysis: Twenty-seven of 30 enrolled subjects completed the study (See Dropouts, p. 11 above). Subjects #2, 3, and 6 completed only Period I. However, the Period I data from these subjects were also included in the statistical analysis for the study and the analysis was based on 30 subjects.

There was statistically significant difference (alpha=0.05) between treatments for LCMAX (p=0.0304).

Comments: The study is incomplete, see Deficiency Comments, page 30.

V. Protocol No. LEVO-0062: Single-Dose Fasting In Vivo Bioequivalence Study of Levothyroxine Sodium Tablets (300 µg; Mylan) and Levothyroxine Sodium Tablets, USP (300 µg; Jerome Stevens) in Healthy Volunteers

1) Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	[redacted]
Principal Investigators:	[redacted]
Clinical Study Dates:	12/08/00 to 01/15/01
Analytical Facility	[redacted]
Principal Investigator:	[redacted]
Analytical Study Dates:	01/23/01 to 02/08/01
Storage Period:	62 days

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Levothyroxine Sodium	Levothyroxine Sodium
Manufacturer:	Mylan	Jerome Stevens
Manufacture Date:	03/17/00	N/A
Expiration Date:	N/A	06/02
ANDA Batch Size:	[redacted]	
Batch/Lot Number:	R1H0708	008500
Potency:	102.2%	97.1%
Strength:	0.300 mg	0.300 mg
Dosage Form:	tablet	Tablet
Dose Administered:	0.600 mg (2x0.300 mg)	0.600 mg (2x0.300 mg)
Study Condition:	fasting	Fasting
Length of Fasting:	overnight	Overnight

RANDOMIZATION		**DESIGN**	
Randomized:	Y	**Design Type:**	Crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	35 days

DOSING		SUBJECTS	
Single or Multiple Dose:	single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	36
Route of Administration:	oral	**No. of Subjects Completing:**	34
		No. of Subjects Analyzed:	36*
		No. of Dropouts:	2
		Sex(es) Included:	Male (25) Female (11)
		Healthy Volunteers Only:	Y
		Mean Age (yrs)(Range):	Male: 25 (18-50); Female: 29 (18-46)
		Mean Height (cm)(Range):	Male: 182 (173-196) Female: 168 (152-180)
		Mean Weight (kg) (Range):	Male: 78 (60-93) Female: 67 (58-90)

***NOTE:** Although Subjects #13 and 31 withdrew from the study, they completed Period I. Their Period I samples were analyzed and included in the study results.

Dietary/Drug/Activity Restrictions: See the Fasting Study of the 75 μg strength above.

Blood Sampling: -0.5, -0.25, 0(predose), 0.5, 1, 1.50, 2, 2.5, 3, 4, 6, 8, 12, 18, 24 and 48 hours

2) Study Results

Clinical Adverse Events: There was no serious adverse event reported. Two and three mild drug-related adverse reactions were reported during the Test and Reference treatments, respectively. The reactions were headache, body aching and rhinitis.

Protocol Deviations: None was likely to affect the study outcome as judged by the study investigator.

Dropouts:

Subjects #13 and 31 elected to withdraw prior to Period II dosing.

3) **Analytical (Not to be Released Under FOI)** Both L-Thyroxine (T4) and L-Triiodothyronine (T3) were measured. However, only T4 data are requested and reviewed.

T4 serum levels were determined by a radioimmunoassay (RIA).

DURING STUDY ASSAY VALIDATION FOR T4 - STUDY #LEVO-0062

Parameter	Quality Control Samples	Standard Curve Samples
QC or Std. Curve Conc. (ng/mL)		
Intra day Precision (%CV) (Pre-Study)		
Intra day Accuracy (%Actual) (Pre-Study)		
Inter day Precision (%CV)		
Inter day Accuracy (%Actual)		
Linear Range (ng/mL)		
Sensitivity/LOQ (ng/mL)		

Repeat samples: The list of repeat samples was not provided.

4) Pharmacokinetic:

PARAMETER	CALCULATION METHOD
AUC 0-t	Linear Trapezoidal Rule
Cmax	Observed Data
tmax	Observed Data

Results:

TABLE 5

MEAN (%CV) BASELINE UNCORRECTED TOTAL L-THYROXINE PHARMACOKINETIC PARAMETERS IN HEALTHY SUBJECTS FOLLOWING A SINGLE ORAL 600 µg (2 x 300 µg) DOSE OF LEVOTHYROXINE SODIUM TABLETS UNDER FASTING CONDITIONS

(PROTOCOL LEVO-0062)

Parameter	Arithmetic Mean A = Mylan N=35	Arithmetic Mean B = Jerome Stevens N=35	LSMEANS Ratio (A/B)*	90% Confidence Interval**
$AUC_{0\text{-}48hr}$ (ng x hr/mL)	5952 (9.920)	6050 (10.31)	0.99	97% - 100%
CPEAK (ng/mL)	159.4 (10.55)	165.1 (10.26)	0.96	94% - 98%
TPEAK (hr)	3.129 (73.48)	2.400 (40.99)	-----	-----

*Ratio (A/B) $= e^{[\text{LSMEAN of LNA - LSMEAN of LNB}]}$

**Used Natural Log Transformed Parameter

TABLE 6
FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #LEVO-0062 ARITHMETIC MEAN L-THYROXINE SERUM CONCENTRATIONS [ng/mL] VERSUS TIME (CV%) IN THIRTY-SIX (36) SUBJECTS

	Treatment				
	A (Levothyroxine Na--Mylan #R1H0708)		B (Levothyroxine Na, USP-Jerome Stevens #008500)		A VS B
	Mean (ng/mL)	%CV	Mean (ng/mL)	%CV	P(|T|>t)
Draw Time					
-0.50 hours	82.99	16.13	83.62	14.71	0.8958
-0.25 hours	82.18	14.41	84.05	14.66	0.2531
0.00 hours	84.35	14.73	84.85	13.50	0.9192
0.50 hours	92.98	15.73	92.76	16.17	0.7408
1.00 hours	123.33	19.22	132.94	18.37	0.0199
1.50 hours	144.16	17.89	151.36	16.06	0.0813
2.00 hours	148.87	14.50	154.89	12.85	0.0963
2.50 hours	147.07	10.55	156.42	10.85	0.0060
3.00 hours	150.42	11.65	151.01	10.42	0.8120
4.00 hours	145.44	10.65	149.53	11.54	0.0562
6.00 hours	141.71	10.37	147.39	11.95	0.0065
8.00 hours	137.73	10.92	140.01	10.00	0.1951
12.00 hours	132.89	10.41	131.26	11.13	0.4719
18.00 hours	119.09	11.82	120.15	11.54	0.6739
24.00 hours	121.53	11.32	124.31	11.68	0.1863
48.00 hours	114.45	11.97	115.91	11.39	0.7205

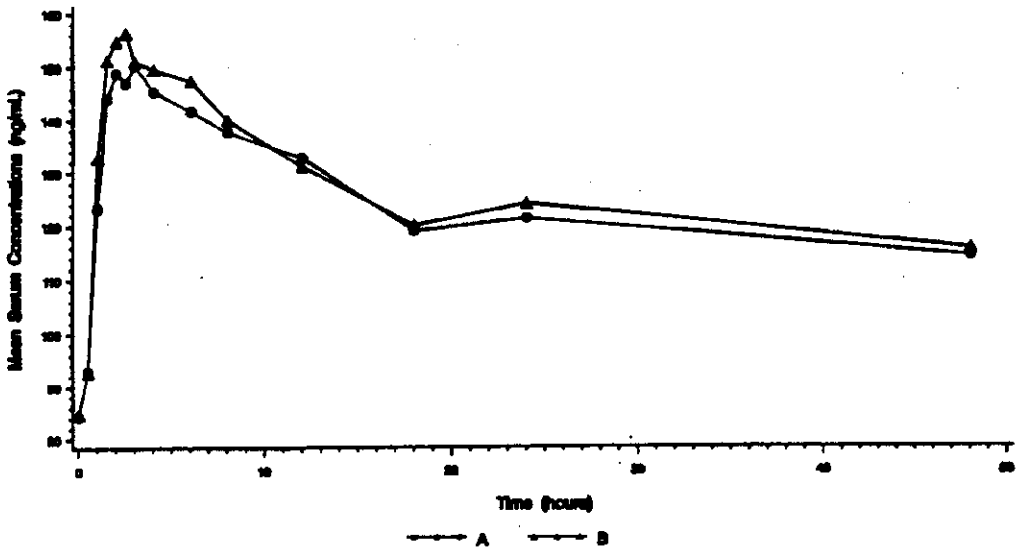
FIGURE 3

LEVOTHYROXINE Na (LEVO – 0062)

Total Dose: 600 ug (2x300ug Tablets), Study Type: Fasting

Mean L-thyroxine Serum Concentrations

N=36



Treatment A is A (Levothyroxine Na – – Mylan #RW0708)
Treatment B is B (Levothyroxine Na, USP – – Jerome Stevens #006800)

5) Statistical Analysis: Thirty-four of 36 enrolled subjects completed the study (See Dropouts, p. 17 above). Subjects #13 and 31 completed only Period I. However, the Period I data from these subjects were also included in the statistical analysis for the study and the analysis was based on 36 subjects.

There was no statistically-significant difference (alpha=0.05) between treatments for LCMAX or LAUC (0-48).

Comments: The study is incomplete, see Deficiency Comments, page 30.

VI. Waiver Request: The waiver requests for the 0.025 mg, 0.050 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.150 mg and 0.200 mg strengths of the test product are granted based on the acceptable bio studies of the 0.075 mg, 0.125 mg and 0.300 mg strengths above, the dissolution testing of all strengths (See below) and proportionality between the formulations of all strengths (See below).

1) Formulations:

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COMPARATIVE QUANTITATIVE COMPOSITIONS

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

	25MCG		50MCG		75MCG		88MCG		100MCG		112MCG	
	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%
ACTIVE COMPONENT												
Levothyroxine Sodium, USP	0.025	0.02	0.050	0.04	0.075	0.06	0.088	0.07	0.100	0.08	0.112	0.09
INACTIVE COMPONENTS												
Mannitol USP,												
Sucrose, NF												
Butylated Hydroxyanisole, NF												
Povidone, NF												
Purified Water, USP[1]												
Alcohol USP												
Microcrystalline Cellulose, NF												
Crospovidone, NF												
Magnesium Stearate/Sodium Lauryl Sulfate												
Colloidal Silicon Dioxide, NF												
FD&C Yellow #6 Lake HT												
FD&C Blue #2 Lake HT												
FD&C Red #40 Lake HT												
FD&C Blue #1 Lake HT												
D&C Yellow #10 Lake HT												
D&C Red #27 Lake HT												
D&C Red #30 Lake HT												
FD&C Red #40 Lake HT												
TOTAL THEORETICAL WEIGHT	130.0	100.0	130.0	100.0	130.0	100.0	130.0	100.0	130.0	100.0	130.0	100.0

(1) Purified Water USP and Alcohol USP, do not contribute to the total theoretical weight; therefore, their quantities are expressed parenthetically.

COMPARATIVE QUANTITATIVE COMPOSITIONS (continued)

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

	125MCG		150MCG		175MCG		200MCG		300MCG	
	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%
ACTIVE COMPONENT										
Levothyroxine Sodium, USP	0.125	0.10	0.150	0.11	0.175	0.14	0.200	0.16	0.300	0.24
INACTIVE COMPONENTS										
Mannitol USP,										
Sucrose, NF										
Butylated Hydroxyanisole, NF										
Povidone, NF										
Purified Water, USP[1]										
Alcohol, USP										
Microcrystalline Cellulose, NF										
Crospovidone, NF										
Magnesium Stearate/Sodium Lauryl Sulfate										
Colloidal Silicon Dioxide, NF										
FD&C Yellow #6 Lake HT										
FD&C Blue #2 Lake HT										
FD&C Red #40 Lake HT										
FD&C Blue #1 Lake HT										
D&C Yellow #10 Lake HT										
D&C Red #27 Lake HT										
D&C Red #30 Lake HT										
FD&C Red #40 Lake HT										
TOTAL THEORETICAL WEIGHT	130.0	100.0	130.0	100.0	130.0	100.0	130.0	100.0	130.0	100.0

(1) Purified Water USP and Alcohol USP, do not contribute to the total theoretical weight; therefore, their quantities are expressed parenthetically.

Formulation Comments: All inactive ingredients in the formulations of all strengths were reviewed and found to be present at or below levels cited in the FDA Inactive Ingredient Guide (1996) for approved drug products. The formulations are proportionally similar by Definition 2 of the current general BA/BE guidance.

2) **Dissolution**(Not to be released under FOI)

NOTE: All dissolution testing in support of this application was conducted in the Chemistry Research and Development Laboratories of Mylan Pharmaceuticals Inc. located at 3711 Collins Ferry Road, Morgantown, WV, 26505. The name of the person responsible for oversight of the dissolution testing is Dan Snider, Ph.D., Director, Chemistry Research and Development. The **Date of Assay** indicated on each Dissolution Profile is the date that the dissolution testing was performed.

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

DISSOLUTION PROFILE SUMMARY AND F_2 ANALYSIS

DISSOLUTION PROFILE SUMMARY

	10 MINUTES	20 MINUTES	30 MINUTES	45 MINUTES
Mylan Lot R1H0854 (25mcg) Mean	57%	77%	83%	87%
Range				
RSD	15.5%	4.8%	4.1%	6.3%
Thyrox® Lot 001600 (25mcg) Mean	60%	85%	91%	94%
Range				
RSD	14.5%	6.3%	4.7%	4.6%
Mylan Lot R1H0715 (50mcg) Mean	62%	76%	79%	83%
Range				
RSD	8.7%	6.2%	5.4%	4.7%
Thyrox® Lot 003800 (50mcg) Mean	53%	84%	91%	94%
Range				
RSD	7.9%	6.2%	4.2%	3.7%
Mylan Lot R1H0747 (75mcg) Mean	70%	78%	82%	85%
Range				
RSD	6.7%	5.8%	5.2%	4.9%
Thyrox® Lot 004100 (75mcg) Mean	55%	89%	96%	99%
Range				
RSD	15.7%	5.7%	2.9%	2.7%
Mylan Lot R1H0748 (88mcg)* Mean	72%	80%	83%	86%
Range				
RSD	10.4%	7.2%	6.1%	5.7%
Unithroid® Lot 013800 (88mcg) Mean	55%	84%	93%	94%
Range				
RSD	18.5%	8.1%	3.2%	2.8%

CONDITIONS (USP METHOD):

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

Apparatus: 2 (Paddles)

Speed: 50 rpm

Sample Times: 10, 20, 30 and 45 minutes

Limits: NLT 70% (Q) in 45 minutes

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

DISSOLUTION PROFILE SUMMARY AND F_2 ANALYSIS (continued)

DISSOLUTION PROFILE SUMMARY (continued)

	10 MINUTES	20 MINUTES	30 MINUTES	45 MINUTES
Mylan Lot R1H0707 (100mcg) Mean	73%	79%	82%	85%
Range				
RSD	3.8%	4.1%	4.3%	4.3%
Thyrox® Lot 001200 (100mcg) Mean	56%	83%	92%	93%
Range				
RSD	15.5%	9.2%	4.2%	3.1%
Mylan Lot R1H0749 (112mcg) Mean	51%	75%	80%	84%
Range				
RSD	14.6%	5.8%	5.0%	4.6%
Unithroid® Lot 014000 (112mcg) Mean	59%	84%	87%	88%
Range				
RSD	17.8%	7.6%	4.3%	3.7%
Mylan Lot R1H0750 (125mcg) Mean	63%	76%	80%	83%
Range				
RSD	13.0%	5.1%	4.4%	3.9%
Levotab® Lot 003799 (125mcg) Mean	57%	84%	91%	94%
Range				
RSD	13.9%	6.7%	4.5%	3.9%
Mylan Lot R1H0751 (150mcg) Mean	61%	79%	84%	86%
Range				
RSD	8.9%	3.5%	3.8%	5.9%
Thyrox® Lot 010399 (150mcg) Mean	59%	85%	90%	93%
Range				
RSD	18.2%	7.6%	5.6%	3.8%

CONDITIONS (USP METHOD):

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

Apparatus: 2 (Paddles)

Speed: 50 rpm

Sample Times: 10, 20, 30 and 45 minutes

Limits: NLT 70% (Q) in 45 minutes

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

DISSOLUTION PROFILE SUMMARY AND F_2 ANALYSIS (continued)

DISSOLUTION PROFILE SUMMARY (continued)

	10 MINUTES	20 MINUTES	30 MINUTES	45 MINUTES
Mylan Lot R1H0752 (175mcg) Mean Range RSD	66% 10.9%	77% 7.0%	81% 6.3%	85% 5.9%
Unithroid® Lot 014200 (175mcg) Mean Range RSD	55% 13.5%	84% 6.1%	88% 5.3%	88% 4.6%
Mylan Lot R1H0753 (200mcg) Mean Range RSD	60% 13.9%	78% 5.5%	82% 4.6%	87% 5.0%
Levotab® Lot 012798 (200mcg) Mean Range RSD	49% 13.0%	78% 9.3%	84% 7.0%	86% 4.6%
Mylan Lot R1H0708 (300mcg) Mean Range RSD	56% 10.4%	83% 5.0%	88% 4.6%	90% 3.7%
Thyrox® Lot 008500 (300mcg) Mean Range RSD	44% 13.0%	81% 7.5%	95% 5.7%	99% 5.3%

CONDITIONS (USP METHOD):

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

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

DISSOLUTION PROFILE SUMMARY AND F_2 ANALYSIS (continued)

F_2 Analysis

1. Analysis of Profiles Generated at Initial Release

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

LOT NUMBER	STRENGTH	TIME (minutes)				f_2
		10	20	30	45	
R1H0854	25mcg	58	78	83	87	69.40
R1H0746	50mcg	59	74	79	83	56.30
R1H0747	75mcg(bio lot)	70	78	82	85	53.64
R1H0748	88mcg	67	78	82	85	56.94
R1H0707	100mcg	59	78	82	86	66.20
R1H0749	112mcg	59	79	83	88	70.97
R1H0750	125mcg(bio lot)	63	76	80	83	56.7[illegible]
R1H0751	150mcg	53	75	80	84	58.8[illegible]
R1H0752	175mcg	56	78	82	86	67.3[illegible]
R1H0753	200mcg	58	79	83	86	69.73
R1H0708	300mcg	56	83	88	90	

Acceptance Criteria: $50 < f_2 < 100$

2. Analysis of Profiles Generated to Coincide with Testing of Innovator Non-Bio Strengths

Samples of the non-bio strengths of the referenced listed drug were not available at the time the initial dissolution profiles for Mylan's Levothyroxine Sodium Tablets, USP were performed. Additional dissolution profiles for Mylan's non-bio strengths were performed to coincide with the subsequent testing of the referenced listed drug.

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

LOT NUMBER	STRENGTH	TIME (minutes)				f_2
		10	20	30	45	
R1H0854	25mcg	57	77	83	87	68.17
R1H0746	50mcg	62	76	79	83	56.54
R1H0748	88mcg	72	80	83	86	52.77
R1H0707	100mcg	73	79	82	85	50.85
R1H0749	112mcg	51	75	80	84	57.91
R1H0751	150mcg	61	79	84	86	67.89
R1H0752	175mcg	66	77	81	85	56.79
R1H0753	200mcg	60	78	82	87	66.20
R1H0708	300mcg	56	83	88	90	

Acceptance Criteria: $50 < f_2 < 100$

Dissolution Comments: The test and reference products meet the USP specification of NLT 70% of the labeled amount of levothyroxine dissolved in 45 minutes. Similarity Factor F2 calculated between the highest strength and other strengths was acceptable (greater than 50). The dissolution data are acceptable.

VII. Deficiencies: The following deficiencies have been found in the assay methodology reports of all 3 studies:

1. [redacted]
2. [redacted]
3. [redacted]
4. [redacted]

The following information was not provided for the 3 bio studies and currently requested by the DBE:

The information on the race of all subjects who participated in the studies.

VIII. Recommendations:

1. The single-dose, fasting bioequivalence study conducted by Mylan on the test product, Levothyroxine Sodium Tablets, 300 µg, lot # R1H0708, comparing it with the reference product, Jerome Stevens' Levothyroxine Sodium Tablets, 300 µg, lot # 008500, has been found **incomplete** by the Division of Bioequivalence due to the reasons cited in the Deficiencies above.

2. The single-dose, fasting bioequivalence study conducted by Mylan on the test product, Levothyroxine Sodium Tablets, 125 µg, lot # R1H0750, comparing it with the reference product, Jerome Stevens' Levothyroxine Sodium Tablets, 125 µg, lot # 003799, has been found **incomplete** by the Division of Bioequivalence due to the reasons cited in the Deficiencies above.

3. The single-dose, fasting bioequivalence study conducted by Mylan on the test product, Levothyroxine Sodium Tablets, 75 µg, lot # R1H0747, comparing it with the reference product, Jerome Stevens' Levothyroxine Sodium Tablets, 75 µg, lot # 004100, has been found **incomplete** by the Division of Bioequivalence due to the reasons cited in the Deficiencies above.

4. The *in vitro* dissolution testing conducted by Mylan on its Levothyroxine Sodium Tablets, 300 µg, 200 µg, 175 µg, 150 µg, 125 µg, 112 µg, 100 µg, 88 µg, 75 µg, 50 µg and 25 µg, has been found **acceptable** by the Division of Bioequivalence.

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

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

3. The firm has demonstrated that the formulations of its Levothyroxine Sodium Tablets, 200 µg, 175 µg, 150 µg, 112 µg, 100 µg, 88 µg, 50 µg and 25 µg, are proportionally similar to the formulations of the 300 µg, 125 µg and 75 µg strengths that underwent in vivo bioavailability testing. However, the biowaivers of these strengths are not considered at the present time pending acceptable biostudy results of the 300 µg, 125 µg and 75 µg strengths.

/S/

Hoaihon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG /S/ 8/28/2001
FT INITIALED YHUANG

/S/

Concur: _____ Date: 9/27/2001
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

cc: ANDA # 76-187 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File
HNguyen/07-30-01/W #76187sdw.601
Also as V:\firmsam\mylan\ltrs&rev\76187sdw.601
Attachment: None

BIOEQUIVALENCY DEFICIENCIES

ANDA: 76-187 APPLICANT: Mylan Pharmaceuticals

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

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

In the assay methodology reports of all 3 studies:

1. [redacted]
2. [redacted]
3 [redacted]
c [redacted]
1 [redacted]

In the study clinical reports, the following information was not provided for all 3 bio studies and currently requested by the Division of Bioequivalence:

The demographic information concerning the race of all subjects who were enrolled in the studies.

Please provide the above listed items.

Sincerely yours.

/S/

for

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

CC:ANDA 76-187
ANDA DUPLICATE
DIVISION FILE -
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen 8/28/2001
HFD-652/ YHuang
HFD-617/ K. Scardin
HFD-650/ D. Conner 8/27/2001

V:\FIRMSAM\MYLAN\LTRS&REV\76187SDW.601
Printed in final on / /

BIOEQUIVALENCY - INCOMPLETE

Submission date: 06-05-01

1. FASTING STUDY (STF) o/c
   Clinical: ———
   Analyti ———
   Strength: 0.075 mg
   Outcome: IC

2. FASTING STUDY (STF) o/c
   Clinical: ———
   Analytic ———
   Strength: 0.125 mg
   Outcome: IC

3. FASTING STUDY (STF) o/c
   Clinical: ———
   Analyti ———
   Strength: 0.300 mg
   Outcome: IC

4. DISSOLUTION WAIVER (DIW) o/c
   (each strength is DIW and Outcome is IC)
   Strength: 0.200 mg, 0.175 mg, 0.150 mg, 0.112 mg, 0.100 mg, 0.088 mg, 0.050 mg & 0.025 mg
   Outcome: IC

OUTCOME DECISIONS: IC - Incomplete UN - Unacceptable
AC - Acceptable -

WINBIO COMMENTS:

MYLAN PHARMACEUTICALS INC.

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

	25MCG		50MCG		75MCG		88MCG		100MCG		112MCG	
ACTIVE COMPONENT	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%
Levothyroxine Sodium, USP	0.025	0.02	0.050	0.04	0.075	0.06	0.088	0.07	0.100	0.08	0.112	0.09
INACTIVE COMPONENTS												
Mannitol USP,												
Sucrose, NF												
Butylated Hydroxyanisole, NF												
Povidone, NF												
Purified Water, USP[1]												
Alcohol, USP												
Microcrystalline Cellulose, NF												
Crospovidone, NF												
Magnesium Stearate/Sodium Lauryl Sulfate												
Colloidal Silicon Dioxide, NF												
FD&C Yellow #6 Lake HT												
FD&C Blue #2 Lake HT												
FD&C Red #40 Lake HT												
FD&C Blue #1 Lake HT												
D&C Yellow #10 Lake HT												
D&C Red #27 Lake HT												
D&C Red #30 Lake HT												
FD&C Red #40 Lake HT												
TOTAL THEORETICAL WEIGHT	130.0	100.0	130.0	100.0	130.0	100.0	130.0	100.0	130.0	100.0	130.0	100.0

Purified Water USP and Alcohol USP , do not contribute to the total theoretical weight; therefore, their quantities are expressed parenthetically.

7/2/01
pg. #

MYLAN PHARMACEUTICALS INC.

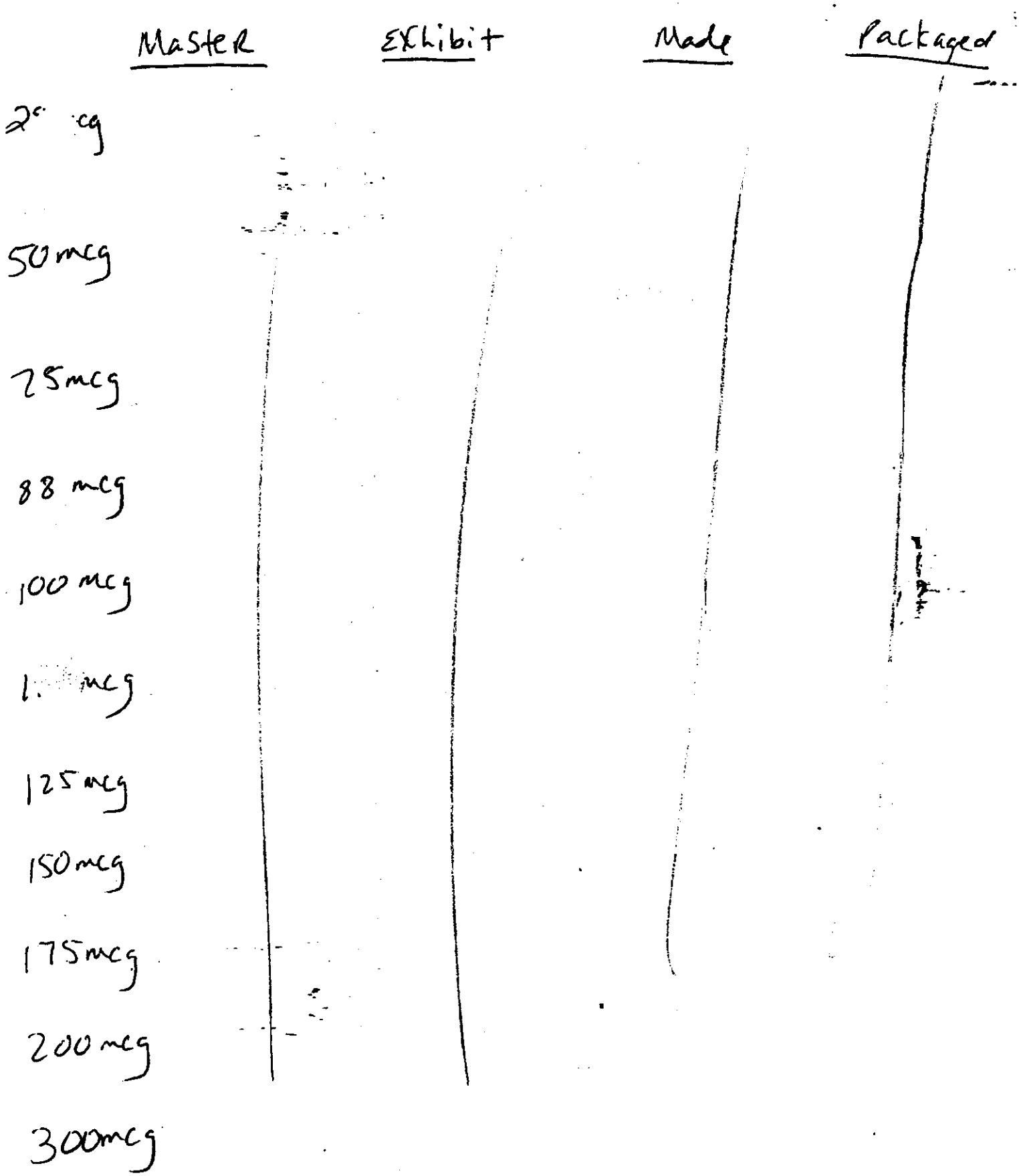
COMPARATIVE QUANTITATIVE COMPOSITIONS (continued)

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

	125MCG		150MCG		175MCG		200MCG		300MCG	
	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%	MG PER TABLET	%
ACTIVE COMPONENT										
Levothyroxine Sodium, USP	0.125	0.10	0.150	0.12	0.175	0.14	0.200	0.16	0.300	0.24
INACTIVE COMPONENTS										
Mannitol USP,										
Sucrose, NF										
Butylated Hydroxyanisole, NF										
Povidone, NF										
Purified Water, USP[1]										
Alcohol, USP										
Microcrystalline Cellulose, NF										
Crospovidone, NF										
Magnesium Stearate/Sodium Lauryl Sulfate										
Colloidal Silicon Dioxide, NF										
FD&C Yellow #6 Lake HT										
FD&C Blue #2 Lake HT										
FD&C Red #40 Lake HT										
FD&C Blue #1 Lake HT										
D&C Yellow #10 Lake HT										
D&C Red #27 Lake HT										
D&C Red #30 Lake HT										
FD&C Red #40 Lake HT										
TOTAL THEORETICAL WEIGHT	130.0	100.0	130.0	100.0	130.0	100.0	130.0	100.0	130.0	100.0

(1) Purified Water USP and Alcohol USP, do not contribute to the total theoretical weight; therefore, their quantities are expressed parenthetically.

4469


Master
Exhibit
Made
Packaged
2[illegible] cg
50 mcg
75 mcg
88 mcg
100 mcg
1[illegible] mcg
125 mcg
150 mcg
175 mcg
200 mcg
300 mcg

M E M O R A N D U M

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

DATE : June 20, 2001

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence studies and request for waiver submitted with an ANDA for 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, and 0.3 mg to determine if the application is substantially complete for filing.

Mylan Pharmaceuticals Inc. has submitted ANDA 76-187 for Levothyroxine Sodium Tablets USP. The ANDA contains a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence studies and request for waiver are complete, and could establish that the product is bioequivalent.

Please evaluate whether the studies and request for waiver submitted by Mylan on June 5, 2001 for its Levothyroxine Sodium product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   (c) Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

✓ Study meets statutory requirements

_____ Study does **NOT** meet statutory requirements

Reason:

CONCUR:

6/21/01

✓ Waiver meets statutory requirements

_____ Waiver does **NOT** meet statutory requirements

Reason:

Director, Division of Bioequivalence

6/25/01
Date

6/14/01

Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Rd.
P.O. Box 4310
Morgantown, WV 26504-4310

Reference Number: OGD# 00-472

Dear Mr. Sisto:

This letter is in response to your correspondence dated November 2, 2000. You request that the Office of Generic Drugs (OGD) provide bioequivalence recommendations regarding Levothyroxine Tablets, 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 175 mcg, 200 mcg, and 300 mcg. OGD provides the following comments:

1. The labeling for the reference listed drug (RLD), Unithroid™ Tablet (Levothyroxine Sodium), states that it should be taken on an empty stomach. Therefore, the Division of Bioequivalence (DBE) requests that you conduct only a single-dose fasting *in-vivo* bioequivalence study comparing your Levothyroxine Tablets, 300 mcg, to the RLD. This recommendation is consistent with the Guidance for Industry, "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations," issued on October 27, 2000. The DBE recommends that you use a 35-day washout period for a two-way crossover design. Alternatively, you may use a parallel design with equal numbers of male and female subjects in each treatment group.

2. The DBE recommends that you measure only levothyroxine (T4). A 600 mcg dose is recommended to detect T4 above baseline levels. Blood samples should be collected up to 48 hours.

3. The lower strengths of the Levothyroxine Sodium Tablets are eligible for a waiver of in-vivo bioequivalence study requirements based on (1) acceptable bioequivalence study on the 300 mcg strength, (2) acceptable dissolution testing for all strengths, and (3) proportional similarity in the formulations of all strengths.

If you have any questions, please call Steven Mazzella, R.Ph., Project Manager, Division of Bioequivalence at (301) 827-5847. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

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

Bartle, Margo L

Warzala, Ruth A; Sponaugle Jr, Richard G
Scardina, Krista; Mazzella, Steven; Nwaba, Nina
Subject: 30 DAY EVA 76-187 REC 6-6-2001

76-187 LEVOTHYROXINE SODIUM TABLETS USP, 11 STRENGTHS MYLAN RECEIVED 6-6-2001

DISKETTES PROVIDING THE BIO ELECTRONIC SUBMISSION ESD BA/BE EVA WILL BE FORWARDED WITHIN 30 DAYS

THANKS,

MARGO

Bartle, Margo L

Patel, Rashmikant M; Fang, Florence S
Beers Block, Patricia M; Holcombe Jr, Frank O; Sayeed, Vilayat A; Smela Jr, Michael
Subject: FIRST GENERIC 76-187

FIRST GENERIC 76-187 LEVOTHYROXINE SODIUM TABLETS USP, 11 STRENGTHS
MYLAN RECEIVED 6-6-2001

TEAM LEADER IS MIKE SMELA

THANKS,

MARGO

AB

ORIG AMENDMENT
N/AB

November 7, 2001

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: ANDA 76-187; LEVOTHYROXINE SODIUM TABLETS, USP
25mcg, 50mcg, 75mcg, 88mcg, 100mcg, 112mcg, 125mcg, 150mcg, 175mcg, 200mcg and 300mcg

Dear Mr. Buehler,

Reference is made to Mylan Pharmaceuticals' Abbreviated New Drug Application identified above for Levothyroxine Sodium Tablets, USP. Reference is also made to the Agency's October 10, 2001 correspondence to Mylan providing comments regarding the bioequivalence studies submitted in the referenced application. The Agency requested a copy of the SOP's for the analytical method used in the conduct of the bioequivalence studies. It is our pleasure to provide to you the SOP's for the analytical method of the above study that were requested. The analytical method is ——— therefore

If you have any questions please do not hesitate to contact me at ———

CENTER FOR DRUG EVALUATION AND RESEARCH
NOV 0 9 2001
OGD

c.c. Scott W. Chervenick, Ph.D., Mylan Pharmaceuticals Inc.

************* -COMM. JOURNAL- ******************* DATE MAR-28-2002 ***** TIME 08:20 ******** Last Bio Rev Lri

MODE = MEMORY TRANSMISSION START=MAR-28 08:18 END=MAR-28 08:20

FILE NO.=149

STN NO.	COMM.	ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	*	913042856407	002/002	00:00:38

-FDA CDER OGD CHEMI -

ANDA 76-187

OFFICE OF GENERIC DRUGS

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

FAX TRANSMISSION COVER SHEET

TO: APPLICANT: Mylan Pharmaceuticals Inc. TEL: 304-599-2595

ATTN: Frank R. Sisto FAX: 304-285-6407

FROM: Sarah Ho PROJECT MANAGER: 301-827-5754

DATE: March 28, 2002 PAGES: 1 (excluding cover page)

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated June 5, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Levothyroxine Sodium Tablets USP, 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg.

Reference is also made to your amendments dated November 7, and November 12, 2001.

SPECIAL INSTRUCTIONS:
Bioequivalency comments provided.

ANDA 76-187

OFFICE OF GENERIC DRUGS

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

FAX TRANSMISSION COVER SHEET

TO: APPLICANT: Mylan Pharmaceuticals Inc. TEL: 304-599-2595

ATTN: Frank R. Sisto FAX: 304-285-6407

FROM: Sarah Ho PROJECT MANAGER: 301-827-5754

DATE: March 28, 2002 PAGES: 1 (excluding cover page)

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated June 5, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Levothyroxine Sodium Tablets USP, 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg, and 300 mcg.

Reference is also made to your amendments dated November 7, and November 12, 2001.

SPECIAL INSTRUCTIONS:
Bioequivalency comments provided.

BIOEQUIVALENCY COMMENTS

ANDA: 76-187 APPLICANT: Mylan Pharmaceuticals

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

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

We acknowledge that the dissolution testing has been incorporated into your stability and quality control programs as specified in USP 24.

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

Sincerely yours,

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

#3

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-187 SPONSOR : Mylan Pharmaceuticals
DRUG AND DOSAGE FORM : Levothyroxine Sodium Tablets USP
STRENGTH(S) : 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.200 mg & 0.300 mg
TYPES OF STUDIES : Fasting SD Studies (for 0.075mg, 0.125 mg & 0.300 mg)
CINICAL STUDY SITE(S) : ———
ANALYTICAL SITE(S) : ———

STUDY SUMMARY : Acceptable
DISSOLUTION: Acceptable
WAIVER REQUEST: Acceptable

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic YES New facility ____ For cause ____ Other ____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Hoainhon Nguyen BRANCH : I
INITIAL : ——— DATE : 11-29-01

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : ——— DATE : 11/30/2001

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

for INITIAL : ——— DATE : 12/31/2001

James Fan

LEVOTHYROXINE SODIUM TABLETS USP, 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.200 mg & 0.300 mg
ANDA 76-187
Reviewer: Hoainhon Nguyen
W #76187an01.doc

Mylan Pharmaceuticals
Morgantown, WV

Submission Date: 11/07/01 & 11/12/01

Review of a Study Amendment

The firm has submitted the current amendment in response to the DBE deficiency letter dated October 10, 2001. The deficiency comments were as follows:

[redacted]

The demographic information concerning the race of all subjects who were enrolled in the studies."

The firm's responses are summarized below.

I. Firm's Responses:

[redacted]

5. The demographic information including the race of all subjects was provided. The information is summarized below.

For Study LEVO-0057 (Fasting Study for the 75 µg Strength):

Gender (n)	Mean Age (Range)	Mean Height, cm (Range)	Mean Weight, kg (Range)
Female (18)	27 (18-45)	166 (150-178)	64 (54-75)
Male (16)	22 (18-29)	181 (165-190)	80 (62-98)

Race: Black (0), Caucasian (34), Hispanic (0), Asian (0)

For Study LEVO-0054 (Fasting Study for the 125 µg Strength):

Gender (n)	Mean Age (Range)	Mean Height, cm (Range)	Mean Weight, kg (Range)
Female (15)	33 (20-48)	167 (152-188)	68 (58-95)
Male (15)	26 (18-44)	181 (168-193)	78 (67-100)

Race: Black (0), Caucasian (29), Hispanic (0), Asian (0), Native American (1)

For Study LEVO-0062 (Fasting Study for the 300 µg Strength):

Gender (n)	Mean Age (Range)	Mean Height, cm (Range)	Mean Weight, kg (Range)
Female (11)	29 (18-46)	182 (173-196)	67 (58-90)
Male (25)	25 (18-50)	182 (173-196)	78 (60-93)

Race: Black (0), Caucasian (35), Hispanic (0), Asian (0), Native American (1)

II. Comments: All of the firm's responses are adequate and acceptable. The bioequivalence studies, Nos. LEVO-0057, LEVO-0054 and LEVO-0062, as reviewed in the current amendment and the original submission (06/05/01), are found acceptable. The studies demonstrate that the test and reference products are equivalent in the rate and extent of absorption as measured by log-transformed CMAX and AUC of T4.

From the review of the original submission, the following was also addressed:

1. Formulation Comments: All inactive ingredients in the formulations of all strengths were reviewed and found to be present at or below levels cited in the FDA Inactive Ingredient Guide (1996) for approved drug products. The formulations are proportionally similar by Definition 2 of the current general BA/BE guidance.

2. Dissolution Comments: The test and reference products meet the USP specification of NLT 70% of the labeled amount of levothyroxine dissolved in 45 minutes. Similarity Factor F2 calculated between the highest strength and other strengths was acceptable (greater than 50). The dissolution data are acceptable.

III. Recommendations:

1. The single-dose, fasting bioequivalence study conducted by Mylan on the test product, Levothyroxine Sodium Tablets, 300 µg, lot # R1H0708, comparing it with the reference product, Jerome Stevens' Levothyroxine Sodium Tablets, 300 µg, lot # 008500, has been found **acceptable** by the Division of Bioequivalence. The study demonstrates that the test product, Mylan's Levothyroxine Sodium Tablets, 300 µg, is bioequivalent to the reference product, Jerome Stevens' Levothyroxine Sodium Tablets, 300 µg, under fasting conditions.

2. The single-dose, fasting bioequivalence study conducted by Mylan on the test product, Levothyroxine Sodium Tablets, 125 µg, lot # R1H0750, comparing it with the reference product, Jerome Stevens' Levothyroxine Sodium Tablets, 125 µg, lot # 003799, has been found **acceptable** by the Division of Bioequivalence. The study demonstrates that the test product, Mylan's Levothyroxine Sodium Tablets, 125 µg, is bioequivalent to the reference product, Jerome Stevens' Levothyroxine Sodium Tablets, 125 µg, under fasting conditions.

3. The single-dose, fasting bioequivalence study conducted by Mylan on the test product, Levothyroxine Sodium Tablets, 75 µg, lot # R1H0747, comparing it with the reference product, Jerome Stevens' Levothyroxine Sodium Tablets, 75 µg, lot # 004100, has been found **acceptable** by the Division of Bioequivalence. The study demonstrates that the test product, Mylan's Levothyroxine Sodium Tablets, 75 µg, is bioequivalent to the reference product, Jerome Stevens' Levothyroxine Sodium Tablets, 75 µg, under fasting conditions.

4. The *in vitro* dissolution testing conducted by Mylan on its Levothyroxine Sodium Tablets, 300 µg, 200 µg, 175 µg, 150 µg, 125 µg, 112 µg, 100 µg, 88 µg, 75 µg, 50 µg and 25 µg, has been found **acceptable** by the Division of Bioequivalence.

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

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

5. The firm has demonstrated that the formulations of its Levothyroxine Sodium Tablets, 200 µg, 175 µg, 150 µg, 112 µg, 100 µg, 88 µg, 50 µg and 25 µg, are proportionally similar to the formulations of the 300 µg, 125 µg and 75 µg strengths that underwent in vivo bioavailability testing. The biowaiver request of these strengths is granted. The test product, Mylan's Levothyroxine Sodium Tablets, 200 µg, 175 µg, 150 µg, 112 µg, 100 µg, 88 µg, 50 µg and 25 µg, is deemed bioequivalent to the reference product, Jerome Stevens' Levothyroxine Sodium Tablets, 200 µg, 175 µg, 150 µg, 112 µg, 100 µg, 88 µg, 50 µg and 25 µg, respectively.

Hoaihon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG

11/30/2001

Concur. Date: 12/31/2001

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

cc: ANDA # 76-187 (original, duplicate), HFD-652(Huang, Nguyen), Drug File, Division File
HNguyen/07-30-01/W #76187an01.doc
Also as V:\firmsam\mylan\ltrs&rev\76187an01.doc
Attachment: None

BIOEQUIVALENCY COMMENTS

ANDA: 76-187 APPLICANT: Mylan Pharmaceuticals

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

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

We acknowledge that the dissolution testing has been incorporated into your stability and quality control programs as specified in USP 24.

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

Sincerely yours,

/S/

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

CC:ANDA 76-187
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ YHuang

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ YHuang 11/30/2001
HFD-617/ K. Scardina 3/4/02
HFD-650/ D. Conner 12/31/2001

V:\FIRMSAM\MYLAN\LTRS&REV\76187AN01.DOC

Printed in final on / /

BIOEQUIVALENCY - ACCEPTABLE

Submission date: 11-07-01
11-12-01

1. STUDY AMENDMENT (STA)

Strength: 0.075 mg, 0.125 mg & 0.300 mg
Outcome: AC

2. STUDY AMENDMENT (STA)

Strength: 0.075 mg, 0.125 mg & 0.300 mg
Outcome: AC

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable
AC - Acceptable

WINBIO COMMENTS:

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-187 SPONSOR : Mylan Pharmaceuticals
DRUG AND DOSAGE FORM : Levothyroxine Sodium Tablets USP
STRENGTH(S) : 0.025 mg, 0.050 mg, 0.075 mg, 0.088 mg, 0.100 mg, 0.112 mg, 0.125 mg, 0.150 mg, 0.175 mg, 0.200 mg & 0.300 mg
TYPES OF STUDIES : Fasting SD Studies (for 0.075mg, 0.125 mg & 0.300 mg)
CINICAL STUDY SITE(S)
ANALYTICAL SITE(S)

STUDY SUMMARY : Acceptable
DISSOLUTION: Acceptable
WAIVER REQUEST: Acceptable

DSI INSPECTION STATUS

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

PRIMARY REVIEWER : Hoainhon Nguyen BRANCH : I
INITIAL : /S/ _____ DATE : 11-29-01

TEAM LEADER : Yih-Chain Huang BRANCH : I
INITIAL : /S/ DATE : 11/30/2001

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.
for INITIAL : /S/ DATE : 12/31/2001

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

November 12, 2001

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

BIOEQUIVALENCE AMENDMENT

RE: ANDA 76-187; LEVOTHYROXINE SODIUM TABLETS, USP
0.025MG, 0.050MG, 0.075MG, 0.088MG, 0.100MG, 0.112MG, 0.125MG
0.150MG, 0.175MG, 0.200MG AND 0.300MG
RESPONSE TO AGENCY CORRESPONDENCE DATED OCTOBER 10, 2001

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the bioequivalency comments pertaining to this application which were provided to Mylan by facsimile on October 10, 2001 (refer to Attachment 1). In response to the October 10, 2001 comments, Mylan would like to amend this application as follows:

Regarding Assay Methodology Reports (all 3 studies):

FDA COMMENT 1:

MYLAN RESPONSE:

FDA COMMENT 2:

MYLAN RESPONSE:

NOV 13 2001
OGD
EVALUATION AND RESEARCH

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 599-7284
Human Resources (304) 598-5406
Information Systems
Label Control
Legal Services
Maintenance & Engineering
Medical Unit
(304) 285-
(800) 848-
(304) 598-5
(304) 598-5411
(304) 598-5445
Purchasing
Quality Control
Research & Development
Sales & Marketing
(304) 598-5401
(304) 598-5407
(304) 285-6409
(304) 598-3232

FDA COMMENT 3:

MYLAN RESPONSE:

FDA COMMENT 4.

MYLAN RESPONSE:

REGARDING CLINICAL STUDY REPORTS

FDA COMMENT: In the study clinical reports, the following information was not provided for all 3 biostudies and currently requested by the Division of Bioequivalence:

The demographic information concerning the race of all subjects who were enrolled in the studies.

MYLAN RESPONSE: The demographic summary tables that were previously submitted in the original application have been updated to provide race information. The revised demographic tables are provided in Attachments 11, 12, and 13 for LEVO-0057, LEVO-0054 and LEVO-0062, respectively.

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. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/tlr

G:\PROJECT\ANDA\LEVOTHYROXINE\AGENCY-BIO-LETTER-DATED-101001.doc

NDA 76187

Levothyroxine Sodium
Tablets USP

0.025mg, 0.05mg, 0.075mg,
0.088mg, 0.1mg, 0.122mg,
0.125mg, 0.15mg, 0.175mg,
0.2mg and 0.3mg

Mylan Pharmaceuticals
Approval Date: June 5, 2002

Correspondence

'16-101

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

July 12, 2001

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

NEW CORRESPONDENCE

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

BIOEQUIVALENCE ELECTRONIC SUBMISSION ESD

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) for the referenced product that was submitted to the Agency on June 5, 2001. Please find enclosed a diskette providing the electronic submission, ESD, for the bioequivalence studies [fasting studies LEVO-0057 (75mg), LEVO-0054 (125mg) and LEVO-0062 (300mg)] that were submitted in the ANDA. A copy of Mylan's declaration that the data contained on the electronic bioequivalence diskette is identical to the paper submission except as noted in the companion document is presented in Attachment 1.

Should you have any questions or require additional information, please contact the undersigned at telephone number (304) 599-2595, extension 6600 and/or facsimile number (304) 285-6407.

Sincerely,

Marlane Juran for

Frank R. Sisto
Vice President
Regulatory Affairs

CENTER FOR DRUG
JUL 16 2001
OGD
EVALUATION AND

Enclosures

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MYLAN PHARMACEUTICALS INC
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June 5, 2001

Concur.
11-JUL-2001

ELECTRONIC DATA ENCLOSED
BIOEQUIVALENCE DATA ENCLOSED

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Acting 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, 200MCG AND 300MCG

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, 200mcg and 300mcg

This application consists of a total of 37 volumes.

- Archival Copy - 16 volumes.
- Review Copy - 17 volumes.
  - Technical Section For Chemistry - 8 volumes.
  - Technical Section For Pharmacokinetics - 9 volumes.
- Analytical Methods - 2 extra copies; 2 volume each.

NOTE: The Technical Section for Pharmacokinetics of the review copy and the archival copy each contain a set of data diskettes for the bioequivalence studies conducted in support of this application. In addition, the diskettes providing the Bioequivalence Electronic Submission ESD (BA/BE) EVA will be forwarded to the Agency within the 30 day grace period.

This application provides for the manufacture of Levothyroxine Sodium Tablets USP, 25mcg, 50mcg, 75mcg, 88mcg, 100mcg, 112mcg, 125mcg, 150mcg, 175mcg, 200mcg and 300mcg. Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road, Morgantown, WV 26505-2730, performs all operations in the manufacture, packaging, and labeling of the drug product.

It should be noted that this Abbreviated New Drug Application has been organized according to the Agency's February 1999 Guidance for Industry - 'Organization of an ANDA'. Pursuant to this guidance, Mylan commits to resolve any issues identified in the methods validation process after approval.

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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 and Reader's Guide detail 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 6600 and/or facsimile number (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/dn

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Rockville, MD 20857

DATE: June 5, 2002

FROM: Lawrence X. Yu, Ph. D.
Deputy Director for Science (Actg.)
Office of Generic Drugs
Center for Drug Evaluation and Research

Lawrence Yu
June 5, 2002

SUBJECT: Approval of ANDA 76-187
Mylan Pharmaceuticals Inc
Levothyroxine Sodium Tablets

TO: The ANDA file for ANDA 76-187

Background

The Division of Bioequivalence, Office of Generic Drugs (OGD) has concluded that the Mylan ANDA 76-187, levothyroxine sodium tablets, meets the FDA's current bioequivalence criteria for AUC and Cmax (90% confidence interval with the limits of 80-125 based on log transformed data). The bioequivalence criteria are calculated using data that is not baseline corrected based upon current agency policy regarding this specific drug product. This policy is outlined in the Guidance to Industry *Guidance for Industry, Levothyroxine Sodium Tablets - In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing* issued December 2000. The bioequivalence study submitted in Mylan's ANDA was found to be acceptable on December 31, 2001.

On May 08, 2002, Abbott Laboratories (Abbott) wrote to the FDA to request a meeting, and contended that bioavailability parameters calculated from baseline uncorrected data is much less sensitive to changes in bioavailability than is the case for bioequivalence assessment of nonendogenous compounds for which baseline data are essentially zero. Abbott contends that baseline correction should be considered for levothyroxine sodium drug products. Abbott proposed two alternative baseline correction methods on calculation of pharmacokinetic parameters[1]. The FDA's current policy for levothyroxine sodium drug products is to not correct baseline in the bioequivalence determination.

[1] A third method was also mentioned in this letter, but Abbott has not completed the necessary studies for this method at this time. FDA has indicated a willingness to meet with Abbott to discuss this subject once the final study report for the ongoing study is available.

Although these two alternative methods set forth by Abbott are not validated or accepted regulatory methods, OGD applied them to Mylan ANDA 76-187 to address the issues raised by Abbott

Methods

Pharmacokinetic/Statistical Analysis of Abbott's Proposed Methods

STATISTICAL ANALYSIS:

AUC(0-48hrs), Cmax and log transformed AUC(0-48hrs), and Cmax were analyzed by Analysis of Variance (ANOVA) with effects for treatments, sequence of dosing, subjects within sequence, and study period in the statistical model.

The two one-sided hypotheses at the α=0.05 level of significance were tested for AUC(0-48hrs) and Cmax in original scale and after log transformation, by constructing the 90% confidence intervals for the differences between the test and the reference least squares means, and were reported relative to the reference means.

These AUC(0-48hrs) and Cmax values were subjected to two baseline correction methods proposed by Abbott.

Method 1- This method assumes that the contribution of endogenous levothyroxine to the observed levothyroxine concentration is constant. The average of the –0.5, -0.25 and 0 time concentration values prior to dosing ($C_{baseline}$) are taken as representative endogenous levothyroxine concentrations over the next 48 hrs. Baseline corrected Cmax and AUC (0-48hrs) were calculated by:

Corrected Cmax = Observed Cmax-$C_{baseline}$

Endogenous AUC (0-48 hrs) = $C_{baseline} \times 48$ hrs

Corrected AUC (0-48 hrs) = Observed AUC (0-48 hrs) – Endogenous AUC (0-48 hrs)

Method 2- This method assumes that large doses of levothyroxine completely suppress levothyroxine production at the time of dosing. Consequently, the concentration of endogenous material declines exponentially from the baseline level, with a half-life of 7 days (168 hrs) that corresponds to a value for β of log2/168. Baseline corrected Cmax and AUC (0-48hrs) were calculated by:

Corrected Cmax = Observed Cmax- $C_{baseline} \exp(-\beta \times$ Observed Tmax)

Endogenous AUC (0-48hrs) = $C_{baseline}/\beta\ (1-\exp(-48 \times \beta))$

Corrected AUC (0-48hrs) = Observed AUC (0-48hrs) - Endogenous AUC (0-48hrs)

All calculations were done using SAS (The code is available upon request).

Results

Table 1. Mean pharmacokinetic parameters (+ sd) for the 600 mcg dose of levothyroxine ANDA# 76187.

Parameter	**Test**	**Reference**	**Ratio(T/R)[1]**	**90% CI**
Ln AUC(0-48hrs), No baseline correction	8.64(0.12)	8.66(0.13)	0.98	96-100
Ln AUC(0-48hrs), Baseline correction, Method 1	7.40(0.24)	7.48(0.22)	0.92	85-99
Ln AUC(0-48hrs), Baseline correction, Method 2	7.61(0.19)	7.67(0.19)	0.94	88-99
Ln Cmax, No baseline correction	5.03(0.14)	5.06(0.14)	0.96	94-100
Ln Cmax, Baseline correction, Method 1	4.23(0.25)	4.32(0.21)	0.91	86-97
Ln Cmax, Baseline correction, Method 2	4.25(0.24)	4.33(0.21)	0.91	87-97

1.Ratio of Least Squares Geometric Means

Table 2. Mean pharmacokinetic parameters (+ sd) for the 500 mcg dose of Levothyroxine ANDA# 76187.

Parameter	**Test**	**Reference**	**Ratio(T/R)[1]**	**90% CI**
Ln AUC(0-48hrs), No baseline correction	8.61(0.12)	8.61(0.11)	0.99	97-101
Ln AUC(0-48hrs), Baseline correction, Method 1	7.29(0.25)	7.33(0.26)	0.94	90-99
Ln AUC(0-48hrs), Baseline correction, Method 2	7.52(0.20)	7.55(0.21)	0.96	92-99
Ln Cmax, No baseline correction	4.95(0.13)	4.98(0.12)	0.95	93-99
Ln Cmax, Baseline correction, Method 1	4.04(0.25)	4.14(0.21)	0.88	83-94
Ln Cmax, Baseline correction, Method 2	4.06(0.24)	4.16(0.20)	0.88	84-94

1.Ratio of Least Squares Geometric Means

Table 3 Mean pharmacokinetic parameters (± sd) for the 300 mcg dose of Levothyroxine ANDA# 76187.

Parameter	**Test**	**Reference**	**Ratio(T/R)[1]**	**90% CI**
Ln AUC(0-48hrs), No baseline correction	8.68(0.10)	8.70(0.10)	0.99	97-100
Ln AUC(0-48hrs), Baseline correction, Method 1	7.55(0.22)	7.58(0.18)	0.96	90-102
Ln AUC(0-48hrs), Baseline correction, Method 2	7.73(0.17)	7.76(0.15)	0.97	92-102
Ln Cmax, No baseline correction	5.06(0.10)	5.10(0.09)	0.96	94-98
Ln Cmax, Baseline correction, Method 1	4.31(0.18)	4.37(0.18)	0.94	90-97
Ln Cmax, Baseline correction, Method 2	4.33(0.17)	4.38(0.18)	0.94	90-97

1.Ratio of Least Squares Geometric Means

Conclusion:

FDA has determined that although these two alternative methods are not validated or accepted regulatory methods, the Mylan levothyroxine sodium tablets meet the 90% confidence interval limit of 80-125, for AUC and Cmax when the baseline is adjusted according to the methods proposed by Abbott. This does not mean that the FDA has in any manner endorsed these two methods proposed by Abbott.

In fact, the current bioequivalence criteria for an ANDA for levothyroxine sodium tablets does not utilize baseline corrected data. Mylan's application meets FDA's current bioequivalence criteria.