CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-116

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

NDA #:	21-116 / N-132		
BRAND NAME:	Thyro-Tabs®	**GENERIC NAME:**	Levothyroxine sodium
STRENGTH(S):	25 mcg – 300 mcg	**DOSAGE FORM:**	Tablets
APPLICANT:	Lloyd, Inc. PO Box 130 – 604 West Thomas Ave, Shenandoah, Iowa, 51601-0130		
LETTER DATE:	05-OCT-2001		
OCPB DIVISION:	DPE-2 – (HFD-870)	**ORM DIVISION:**	DMEDP – (HFD-510)
CPB REVIEWER:	Steven B. Johnson, Pharm.D.	**CPB TEAM LEADER:**	Hae-Young Ahn, Ph.D.

SYNOPSIS

In accordance to a request from the Agency, Lloyd, Inc., has submitted this amendment to NDA 21-116 for THYRO-TABS (levothyroxine sodium tablets). This submission consists of a multipoint dissolution comparison between 300 mcg tablets manufactured by two different methods, and a comparison of all to-be-marketed strengths using the dissolution method described in the USP 24 S1 monograph for levothyroxine sodium tablets (see TABLE 1) – both include f2 similarity evaluations. Tablets from — count lots were used for each of the dissolution tests.

TABLE 1: USP 24 Supplement 1	
Medium:	0.01 N HCl containing 0.2% sodium lauryl sulfate
Volume:	500 mL
Apparatus:	2 (paddles)
Speed:	50 RPM
Time:	10, 20, 30, & 45 minutes
Tolerances:	— (Q) of the labeled amount of levothyroxine sodium is dissolved in 45 minutes

In order to overcome the stability problems that the sponsor encountered with their original — method) formulation, the sponsor has proposed a — method of manufacture. During a teleconference held 05-JUN-2001 between the Agency and the sponsor, the Agency agreed with the sponsor that the — method appeared to be better than the original method. As such, the Agency asked the sponsor to establish a link between the two manufacturing methods by either conducting successful dissolution testing OR perform a bioequivalency study. The sponsor opted to conduct the multipoint dissolution testing. In addition, the Agency also requested that the sponsor conduct a multipoint dissolution comparison between the to-be-marketed tablets manufactured by the — method using an appropriate dissolution method.

PLOTS 1 and 2 are the results from the two multipoint dissolution comparisons.

To demonstrate adequate similarity between the original — and the proposed — methods, and that there was sufficient similarity between the eleven to-be-marketed strengths such that a biowaiver could be granted for the strengths not evaluated *in vivo*, (f_2) was calculated (see TABLE 2 & 3).

TABLE 2: Similarity Comparisons		
Strength	300 mcg (Original)	300 mcg (two premix)
Status	REF	TEST
f_2	NA	64

TABLE 3: Similarity Comparisons											
Strength	300 mcg	25 mcg	50 mcg	75 mcg	88 mcg	100 mcg	112 mcg	125 mcg	150 mcg	175 mcg	200 mcg
—	REF	97.4	83.3	58.5	77.5	90.5	90.8	71.4	85.8	84.9	97.8
f_2	83.3	86.1	REF	54.8	77.1	74.7	76.6	60.6	97.7	78.5	87.6
	90.5	87.1	74.7	63.5	71.0	REF	93.9	58.8	73.2	79.3	85.9

Both the qualitative (PLOTS 1 & 2) and quantitative (TABLES 2 & 3) results of these two dissolution studies show that the tablets manufactured using the proposed — method is similar to the original method. Additionally, a biowaiver can be granted for the strengths not studied *in vivo* given that the f_2 values were well above a score of 50. Also, and most importantly, the dissolution method appears to be appropriate for THYRO-TABS.

Based upon the data submitted, the dissolution tolerances should be set at — (Q) @ — minutes.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed amendment 17 to NDA 21-116 and finds that the results are acceptable such that a biowaiver can be granted for the intermediate strengths not studied *in vivo*. Please convey the **COMMENTS TO FIRM** as appropriate.

COMMENTS TO FIRM

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-116 and finds that the overall Human Pharmacokinetics section is acceptable. The dissolution specification for THYRO-TABS should be as follows:

TABLE 1: USP 24 Supplement 1	
Medium:	0.01 N HCl containing 0.2% sodium lauryl sulfate
Volume:	500 mL
Apparatus:	2 (paddles)
Speed:	50 RPM
Tolerances:	— (Q) of the labeled amount of levothyroxine sodium is dissolved in — minutes

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/s/

Steve Johnson
11/19/01 09:07:17 AM
BIOPHARMACEUTICS

Hae-Young Ahn
11/30/01 12:19:32 PM
BIOPHARMACEUTICS

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-116		
Brand Name:	Thyro-Tabs®	**Generic Name:**	Levothyroxine Sodium
Strength(s):	25, 50, 75, 100, 125, 150, 175, 200, and 300 mcg tablets		
Sponsor:	Lloyd, Incorporated PO Box 130, 604 West Thomas Ave, Shenandoah, Iowa 51601-0130		
Submission Date:	19-AUG-99 12-JAN-00		
Submission Type:	New Drug Application		
Reviewer:	Steven B. Johnson, B.S.Pharm, Pharm.D.		

Terms and Abbreviations

Agency	Food and Drug Administration
AUC	Area under the plasma-concentration-time curve
BA	Bioavailability
BE	Bioequivalence
C_{max}	Maximum drug concentration
DMEDP	Division of Metabolic and Endocrine Drug Products
DSI	Division of Scientific Investigation
Industry	Pharmaceutical Industry
OCPB	Office of Clinical Pharmacology and Biopharmaceutics
NDA	New Drug Application
NTR	Narrow therapeutic range
T_{max}	Time of maximum drug concentration
T_4	Levothyroxine
T_3	Triiodothyronine
rT_3	Reverse triiodothyronine
$t_{1/2}$	Drug elimination half-life

Synopsis

The sponsor, Lloyd, Incorporated, submitted NDA 21-116 on August 19, 1999 for Thyro-Tabs® (levothyroxine sodium tablets), in nine strengths ranging from 25 mcg to 300 mcg. In accordance with the "Draft Guidance for Industry," the sponsor has submitted two *in vivo* BA/BE studies and an *in vitro* dissolution study for their levothyroxine sodium product.

The first *in vivo* study, LLOY-9801, evaluated the relative bioavailability of the sponsor's 300 mcg tablets with an equivalent oral solution of levothyroxine sodium. The second *in vivo* study, LLOY-9802, evaluated the dosage-form equivalence between 50 mcg, 100 mcg, and 300 mcg tablets following a single oral dose equivalent to 600 mcg levothyroxine sodium. Results of these studies indicate that Lloyd's Levothyroxine Sodium Tablets are 94% bioavailable relative to an oral solution, and that 50 mcg, 100 mcg, and 300 mcg

tablets are dosage-form equivalent. These three strengths, representing low, middle, and high tablet strengths, are dosage-form equivalent, and the eleven individual tablet strength formulations are proportionally similar in active and inactive ingredients. However, it was found that the dissolution profiles were not similar between all of the to-be-marketed strengths. Therefore, a biowaiver cannot be granted for the 25 mcg, 125 mcg and 150 mcg strength tablets.

An *in vitro* dissolution study included data and specifications for a single dissolution method (current USP 24 monograph) conducted on one lot each of all of the nine to-be-marketed strengths. However, dissolution specifications do not meet the current USP 24 monograph tolerances. Therefore, a USP designation cannot be given to Thyro-Tabs®. In addition, the sponsor's proposed dissolution tolerances are not supported by the dissolution data provided in this application.

DSI was asked by OCPB to conduct a site audit to verify the results of the BA/BE studies. Lloyd, Incorporated, was not singled out nor was there any reason to believe that they engaged in any scientifically unsound behavior. Results of the DSI audit can be found in the appendix to this review.

Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed NDA 21-116 submitted 19-AUG-99. The overall Human Pharmacokinetic Section is acceptable to OCPB, pending additional dissolution data. At this time, sufficient information has been provided for only 6 of the 9 to-be-marketed strength tablets. The dissolution data for the 25 mcg, 125 mcg and 150 mcg strength tablets are insufficient for approval. Please convey ***Comments to Firm*** and ***Labeling Comments*** to the sponsor as appropriate.

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Background

The production of endogenous levothyroxine hormone is regulated by the hypothalamus-pituitary axis through a negative feedback system. When hormone levels are inadequate, the hypothalamus secretes thyroid stimulating hormone-releasing hormone (TSH-RH), which stimulates the anterior pituitary to produce thyroid stimulating-hormone (TSH). TSH then stimulates the thyroid gland to produce levothyroxine (T_4) and triiodothyronine (T_3). T_4 is subsequently converted to the highly active T_3 in the peripheral tissues. High levels of T_4 inhibit the production of TSH and to a lesser extent, TSH-RH. This effect in turn decreases the further production of T_4.

Because of the negative feedback controlled regulatory system for T_4, analysis of *in vivo* levothyroxine sodium pharmacokinetic sample data from healthy volunteers, regarding baseline-corrected vs. uncorrected approaches, is subject to several facts:

Fact A: Levothyroxine has a half-life of approximately 6 to 7 days in healthy individuals.

Fact B: Since levothyroxine enjoys such a long half-life, T_4 levels remain fairly static and are not greatly affected by circadian rhythm.

Fact C: When a hyperphysiologic dose of levothyroxine sodium is given to a healthy subject, as in the case of the BA/BE studies in this submission, and because of the exquisite sensitivity of the thyroid hormone regulatory system to subtle changes in T_4 levels, endogenous T_4 production and secretion approaches zero within 1 hour. Subsequently, as exogenous T_4 levels begin to approach normal physiologic values, endogenous production and secretion resumes.

These facts suggest that only baseline-uncorrected data be used for analysis.

Levothyroxine sodium is the synthetic sodium salt of the levo-isomer of the endogenous thyroid hormone, thyroxine (T_4). The two, levothyroxine sodium and T_4, are identical in form and function and cannot be distinguished from one another. Levothyroxine sodium is considered a narrow therapeutic range (NTR) drug and dosing must be individualized based on T_4 and thyroid stimulating hormone (TSH) levels for each patient. Therefore, levothyroxine is supplied in numerous strengths ranging from 25 mcg to 300 mcg. The average daily dose rarely exceeds 180 mcg/day. Levothyroxine sodium products have been used extensively in the clinical setting for the treatment of conditions related to thyroid hormone deficiency, thyroid nodules, and goiters.

Drug Formulation

Is the composition of each strength tablet similar?

Thyro-Tabs® will be packaged in 100 and 1000 count containers for each of the nine to-be-marketed strengths ranging from 25 mcg to 300 mcg per tablet. Each strength tablet is proportionally similar in its active and inactive ingredients, but quantitatively different in the amounts of levothyroxine sodium. (Microcrystalline Cellulose, NF), and color additives.

Components and Composition			
Component	**Amount Per Tablet**	**Component**	**Amount Per Tablet**
25 mcg Tablet		***150 mcg Tablet***	
Levothyroxine		Levothyroxine	
Microcrystalline Cellulose		Microcrystalline Cellulose	
Calcium Phosphate Dibasic		Calcium Phosphate Dibasic	
Povidone		Povidone	
Magnesium Stearate		Magnesium Stearate	
FD&C Yellow #6 Aluminum Lake		FD&C Blue #2 Aluminum Lake	
50 mcg Tablet		***175 mcg Tablet***	
Levothyroxine		Levothyroxine	
Microcrystalline Cellulose		Microcrystalline Cellulose	
Calcium Phosphate Dibasic		Calcium Phosphate Dibasic	
Povidone		Povidone	
Magnesium Stearate		Magnesium Stearate	
		FD&C Blue #1 Aluminum Lake	
		D&C Red #30 Aluminum Lake	
		D&C Red #27 Aluminum Lake	
75 mcg Tablet		***200 mcg Tablet***	
Levothyroxine		Levothyroxine	
Microcrystalline Cellulose		Microcrystalline Cellulose	
Calcium Phosphate Dibasic		Calcium Phosphate Dibasic	
Povidone		Povidone	
Magnesium Stearate		Magnesium Stearate	
FD&C Red #40 Aluminum Lake		FD&C Red #40 Aluminum Lake	
FD&C Blue #2 Aluminum Lake			
100 mcg Tablet		***300 mcg Tablet***	
Levothyroxine		Levothyroxine	
Microcrystalline Cellulose		Microcrystalline Cellulose	
Calcium Phosphate Dibasic		Calcium Phosphate Dibasic	
Povidone		Povidone	
Magnesium Stearate		Magnesium Stearate	
FD&C Yellow #6 Aluminum Lake		FD&C Blue #1 Aluminum Lake	
D&C Yellow #10 Aluminum Lake		D&C Yellow #10 Aluminum Lake	
		FD&C Yellow #6 Aluminum Lake	
125 mcg Tablet			
Levothyroxine			
Microcrystalline Cellulose			
Calcium Phosphate Dibasic			
Povidone			
Magnesium Stearate			
FD&C Blue #1 Aluminum Lake			
FD&C Red #40 Aluminum Lake			
FD&C Yellow #6 Aluminum Lake			

Dissolution

1. **Has the sponsor proposed an appropriate dissolution method and specification?**
2. **Was sufficient data submitted for evaluation of the dissolution method and specification?**

The sponsor has proposed a single quality control dissolution method with release specification of Q — in — minutes. Dissolution data on one lot of each of the to-be-marketed tablet strengths were submitted for review. Dissolution samples were analyzed by a validated HPLC method. The dissolution method and resultant data are presented in the following two tables:

Dissolution Method	
Apparatus:	2 (paddles)
Speed:	50 RPM
Medium:	0.01 N HCl containing 0.2% sodium lauryl sulfate
Volume:	500 mL
Units Tested:	12
Time Points:	10, 20, 30, 45, 60, 80, 100. and 120 minutes
Specifications:	NLT — (Q) @ —

Dissolution Results					
25 mcg tablets (lot # KA34198)			*125 mcg tablets (lot # KB00499)*		
Time:	10 minutes		Time:	10 minutes	
	20 minutes			20 minutes	
F_2 = 56.4	30 minutes		F_2 = 45.9	30 minutes	
	45 minutes			45 minutes	
	60 minutes			60 minutes	
	80 minutes			80 minutes	
	100 minutes			100 minutes	
	120 minutes			120 minutes	
50 mcg tablets (lot # KA28998)			*150 mcg tablets (lot # KC00499)*		
Time:	10 minutes		Time:	10 minutes	
	20 minutes			20 minutes	
F_2 = 46.7	30 minutes		F_2 = 44.1	30 minutes	
	45 minutes			45 minutes	
	60 minutes			60 minutes	
	80 minutes			80 minutes	
	100 minutes			100 minutes	
	120 minutes			120 minutes	
75 mcg tablets (lot # KA00499)			*175 mcg tablets (lot # KD00499)*		
Time:	10 minutes		Time:	10 minutes	
	20 minutes			20 minutes	
F_2 = 70.5	30 minutes		F_2 = 58.1	30 minutes	
	45 minutes			45 minutes	
	60 minutes			60 minutes	
	80 minutes			80 minutes	
	100 minutes			100 minutes	
	120 minutes			120 minutes	
100 mcg tablets (lot # KA31098)			*200 mcg tablets (lot # KA32498)*		
Time:	10 minutes		Time:	10 minutes	
	20 minutes			20 minutes	
F_2 = ref.	30 minutes		F_2 = 61.0	30 minutes	
	45 minutes			45 minutes	
	60 minutes			60 minutes	
	80 minutes			80 minutes	
	100 minutes			100 minutes	
	120 minutes			120 minutes	
300 mcg tablets (lot # KA30298)					
Time:	10 minutes		Time:	60 minutes	
	20 minutes			80 minutes	
F_2 = 67.8	30 minutes			100 minutes	
	45 minutes			120 minutes	
Mean dissolved / %CV [100 * (SD / Mean)]					

The dissolution method that the sponsor has proposed is acceptable, as it follows USP 24. However, it is clear that Lloyd's levothyroxine tablets do not meet the current USP tolerances (i.e., NLT 70% (Q) @ 45 minutes). In fact, only — to-be-marketed strengths has passed these tolerances. Because of this failure to meet USP 24 specifications, the sponsor has proposed the following tolerances for their product: NLT — (Q) @ — minutes. The sponsor's proposed specification seems to be too relaxed and will not serve as a viable quality control measure. The Agency recommends the following specification: Q = — at — based on the data from one lot each of the to-be-marketed strengths In addition, the product will not be given a USP designation. This information (i.e., USP designation issue) was conveyed to the sponsor in a follow-up telephone conference to a 03-FEB-00 telephone conference.

Calculations to determine the degree of curve similarity between dissolution data (F_2) showed a high degree of variability. As a bracketing approach was used in the dosage-form equivalence studies, representing the high, middle, and low tablet strengths, a similar approach was used to compare the dissolution curves. The 300 mcg strength tablet dissolution curve was used as the reference for strengths between 300 mcg and 100 mcg, the 100 mcg tablet dissolution curve was the reference for the strengths between 100 mcg and 50 mcg, and the 50 mcg tablet was the reference for the 25 mcg tablets. Results of these calculations showed that the 125 mcg, and 150 mcg strength tablets were dissimilar to the 300 mcg reference and the 25 mcg tablets were dissimilar to the 50 mcg reference (dissimilar defined as an F_2 value of less than 50.0). Intra-strength similarity calculations were not made because only one full size production batch for each proposed market strength was submitted. This does not follow the procedure laid out in the levothyroxine draft guidance, however, the submission of a single lot at each to-be-marketed strength was agreed to by the Agency in a 14-DEC-98 pre-IND/NDA meeting.

USP 24 Monograph for Levothyroxine Sodium Tablets – Effective 01-JAN-00

Medium:	0.01 N HCl containing 0.2% sodium lauryl sulfate
Volume:	500 mL
Apparatus:	2 (paddles)
Speed:	50 RPM
Time:	45 minutes
Tolerances:	NLT — (Q) of the labeled amount of levothyroxine sodium is dissolved in 45 minutes

Analytical Methodology

Have the analytical methods been sufficiently validated?

Human plasma samples were analyzed for total thyroxine (T_4) and triiodothyronine (T_3) to determine the bioavailability of levothyroxine sodium by — Thyroxine and triiodothyronine samples were analyzed using a commercial radioimmunoassay kit —

Analytical methods were found to be acceptable by the Agency. However, upon inspection of — — DSI revealed several inconsistancies (refer to DSI audit reports) in the companies standard of practice. As a result of DSI's report, the objectionable data from the biostudies was removed and results were recalculated. Results of the quality control analysis are presented in the following table:

	T_3		T_4	
			9801	9802
LOQ (ng/mL):		LOQ (mcg/dL):		
Calibration (ng/mL):		Calibration (mcg/dL):		
Precision (%RSD):		Precision (%RSD):		
Accuracy (%):		Accuracy (%):		

Human Pharmacokinetics and Bioavailability Studies

1. Single-Dose Bioavailability Study

What is the bioavailability of the to-be-marketed formulation of levothyroxine relative to a reference oral solution under fasting conditions?

The relative bioavailability (F_{rel}) of levothyroxine sodium was studied in 28 healthy volunteers (27 completed study) given either a single dose of two 300 mcg tablets (Lloyd, Inc., lot # KA30298) or a single 600 mcg dose (Synthroid Injection; Knoll Pharmaceutical, lot # 80120028) of an oral solution in a two-way crossover study (9801), under fasting conditions. The relative bioavailability of a single dose of two 300 mcg tablets of levothyroxine sodium, compared to an equivalent oral solution dose, was found to be approximately 94%. Results and 90% confidence intervals are presented in the following two tables:

Summary of Bioavailability Data – T_4 Baseline Uncorrected – Study Number 9801		
Parameters	Treatment A* 2 x 300 mcg tablets	Treatment B** 600 mcg oral solution
AUC_{0-48}	459 ± 83.4	490 ± 89.0
C_{max}	12.3 ± 2.48	13.6 ± 3.04
T_{max}	4.11	3.76
Mean ± SD		

Least Squares Mean – 90% Confidence Interval – Study Number 9801				
Treatment Comparison	Parameter	Point Estimate	CI (low)	CI (high)
A vs. B	ln C_{max}	90.90	86.45	95.59
	ln AUC_{0-48}	93.90	90.51	97.42
Treatment A = 2 x 300 mcg levothyroxine tablets – Test – (%CV: C_{max} = 20.17; AUC_{0-48} = 18.17) Treatment B = 600 mcg levothyroxine oral solution – Reference – (%CV: C_{max} = 22.32; AUC_{0-48} = 18.14) %CV calculated from untransformed data = total variability				

2. Dosage Form Equivalence Studies

Has the dosage form equivalence been established between the to-be-marketed strengths?

The sponsor submitted study 9802 to establish dosage form equivalence between the 50 mcg, 100 mcg, and 300 mcg tablet strengths. The study design was a three-way crossover in 30 (27 completed all three study periods) healthy subjects, following a 10 hour fast. Results show that 12 x 50 mcg, 6 x 100 mcg, and 2 x 300 mcg tablets are dosage-form equivalent. Percent coefficients of variation were consistent and 90% confidence intervals for C_{max} and AUC_{0-48} parameters were within acceptable limits.

Summary of Bioavailability Data – T_4 Baseline Uncorrected – Study Number 9802			
Parameters	Treatment A 12 x 50 mcg tablets	Treatment B 6 x 100 mcg tablets	Treatment C 2 x 300 mcg tablets
AUC_{0-48}	488 ± 84.0	487 ± 100.1	509 ± 104.8
C_{max}	13.08 ± 2.37	13.14 ± 2.54	13.96 ± 2.74
T_{max}	3.52	3.56	2.98
Mean ± SD			

Least Squares Mean – 90% Confidence Interval – Study Number 9802				
Treatment Comparison	Parameter	Point Estimate	CI (low)	CI (high)
A vs. B	ln C_{max}	101.01	96.59	105.63
	ln AUC_{0-48}	99.54	94.53	104.83
C vs. B	ln C_{max}	106.64	101.94	111.56
	ln AUC_{0-48}	104.14	98.86	109.71
Treatment A = 12 x 50 mcg levothyroxine tablets – Test – (%CV: C_{max} = 13.08; AUC_{0-48} = 17.21) Treatment B = 6 x 100 mcg levothyroxine tablets – Reference – (%CV: C_{max} = 19.35; AUC_{0-48} = 20.56) Treatment C = 2 x 300 mcg levothyroxine tablets – Test – (%CV: C_{max} = 19.60; AUC_{0-48} = 20.59) %CV calculated from untransformed data = total variability				

It should be noted, that AUC_{0-inf} is an unreliable measure of bioequivalence because it uses the values of K_e that cannot be estimated reliably using baseline-uncorrected data because the T_4 approached baseline asymptotically which overestimates the $t_{½}$. Therefore, AUC_{0-48} and C_{max} are the most reliable parameters for determining extent and rate of absorption and the most reliable measures of bioequivalence. For the purposes of this review, only AUC_{0-48} and C_{max} will be used for comparison.

3. Biowaivers

Can the biowaiver request be granted for the nine tablet strengths that have not been clinically tested?

- Three strengths of tablets, 50 mcg, 100 mcg, and 300 mcg, representing low, middle, and high strengths of the formulation, were found to be dosage-form equivalent.
- Each strength tablet is proportionally similar in its active and inactive ingredients.
- Sufficient information was provided to determine dissolution specifications for all strengths except the 25 mcg, 125 mcg, and 150 mcg strength tablets.

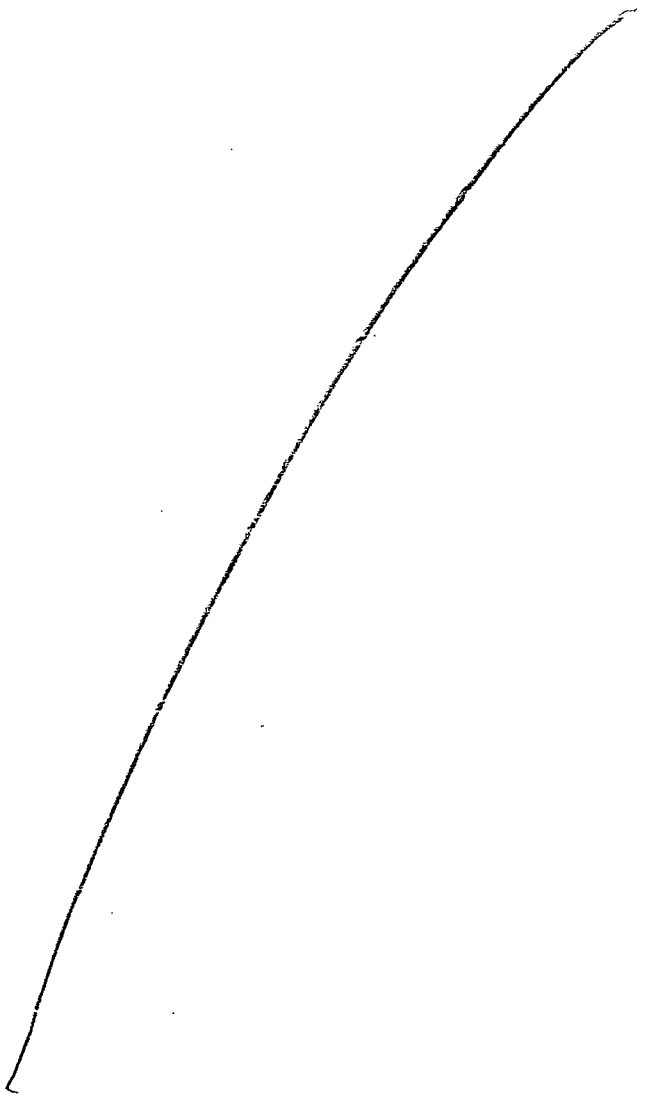
Therefore, a biowaiver, for the 75 mcg, 175 mcg, and 200 mcg strengths not used in the *in vivo* studies, can be granted for NDA 21-116. Additional information is necessary before biowaivers can be granted for the 25 mcg, 125 mcg, and 150 mcg strength tablets.

Labeling Comments

(Where applicable, ~~strikeout~~ text should be removed from labeling. Double <u>underlined</u> text should be added to labeling. ✍ Indicates an explanation only and is not intended to be included in the labeling).

✍ Because of the number of NDAs submitted for levothyroxine sodium products, DMEDP is using class labeling for all levothyroxine sodium submissions. In the following "class labeling" for pharmacokinetics, content must remain intact with the exception of agent specific information.

PHARMACOKINETICS – (class content and agent specific – absorption)



Comments to Firm

1. In your NDA 21-116 for Thyro-Tabs®, the dissolution tolerances did not meet the current USP 24 monograph criteria. Therefore, a USP designation cannot be given to this product.

2. Since the dissolution method for Thyro-Tabs® does not meet the current USP 24 monograph, and the dissolution curves are so highly variable, it may be prudent to alter your current dissolution method such that it better reflects your product. Currently, the dissolution curves of the 25 mcg, 125 mcg, and 150 mcg strength tablets using the USP 24 dissolution method do not show adequate similarity to grant a biowaiver.

3. In addition, the Agency feels that the Sponsor's proposed dissolution tolerance, — Q) at — — , is too relaxed based on a single lot of each of the to-be-marketed strength tablets and will not serve as a viable quality control measure. Our recommendation is — Q) at — for Thyro-Tabs®.

Steven B. Johnson, B.S.Pharm, Pharm.D
Division of Pharmaceutical Evaluation-II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader: 16-MAY-00

OCPB Briefing on: 22-MAY-00

Briefing Attendees: Steven B. Johnson, Hae-Young Ahn, Shiew-Mei Huang, John Hunt, Robbie Patnaik, and Yie-Chain Huang

FT initialed by Hae-Young Ahn, Ph.D., Team Leader: 01-JUN-00

CC: NDA 21-116 (orig., 1 copy), HFD-510 (OrloffD, TemeckJ, McCortS), HFD-870 (AhnH, HuangS, JohnsonST), HFD-850 (Lesko, ChenME), CDR

Code: AE

BIOAVAILABILITY STUDY REPORT

A SINGLE-DOSE, RANDOMIZED, CROSSOVER STUDY ESTIMATING THE BIOAVAILABILITY OF LLOYD, INCORPORATED LEVOTHYROXINE TABLETS RELATIVE TO AN ORAL SOLUTION IN HEALTHY, MALE AND FEMALE SUBJECTS FOLLOWING A 600 MCG DOSE UNDER FASTED CONDITIONS

PROTOCOL NUMBER: LLOY-9801

Name of Drug:	Levothyroxine
Study Design:	Single-dose, randomized, open-label, two-period, two-way crossover
Sponsor:	Lloyd, Incorporated
Sponsor Contact:	Joseph W. Denhart, DVM, MS Vice President, Regulatory Affairs and Quality Assurance Lloyd, Incorporated 604 West Thomas Avenue Shenandoah, IA 51601-0130
Drug Development Phase:	Phase I
Dosing Dates:	30 January 1999 6 March 1999
Sample Analysis Dates:	Total T3: 12 March 1999 to 22 March 1999 Total T4: 12 March 1999 to 23 March 1999
Clinical Study Site:	
Analytical Study Site:	
Principal Investigator:	Krishna Talluri, M.D.
Report Date:	20 April 1999

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1. ETHICS

Institutional Review Board

The investigator obtained institutional review board (IRB) approval for the protocol and written informed consent form prior to study initiation in conformance with 21 CFR 50 and 21 CFR 56.

Ethical Conduct of the Study

This study was conducted under the principles of the World Medical Assembly Declaration of Helsinki and its most recent amendments.

Subject Information and Consent

Written informed consent was obtained from each subject at the first screening visit. Subjects reviewed the subject instructions and the informed consent form, and were allowed to ask and have answered questions concerning all portions of the conduct of the study.

Subjects were provided with a copy of the signed written informed consent form and subject instructions. The originals are on file at the clinical research facility. A copy of the protocol, written informed consent form, IRB approval, Form FDA 1572 and the investigator's curriculum vitae are presented in Appendix 1.

2. BACKGROUND[1]

The major thyroid hormones are L-thyroxine (T4) and L-triiodothyronine (T3). The amounts of T4 and T3 released into the circulation from the normally functioning thyroid gland are regulated by the amount of thyrotropin (TSH) secreted from the anterior pituitary gland. TSH secretion is in turn regulated by the levels of circulating T4 and T3 and by secretion of thyrotropin releasing factor (TRH) from the hypothalamus. Recognition of this complex feedback system is important in the diagnosis and treatment of thyroid dysfunction. The principal effect of exogenous thyroid hormone is to increase the metabolic rate of body tissues.

The thyroid hormones are also concerned with growth and differentiation of tissues. In deficiency states in the young there is retardation of growth and failure of maturation of the skeletal and other body systems, especially in failure of ossification in the epiphyses and in the growth and development of the brain. The precise mechanism of action by which thyroid hormones affect thermogenesis and cellular growth and differentiation is not known. It is recognized that these physiologic effects are mediated at the cellular level primarily by T3, a large part of which is derived from T4 by deiodination in the peripheral tissues. Thyroxine (T4) is the major component of normal secretions of the thyroid gland and is thus the primary determinant of normal thyroid function.

Depending on other factors, absorption has varied from 48 to 79 percent of the administered dose. Fasting increases absorption. Malabsorption syndromes, as well as dietary factors, (children's soybean formula, concomitant use of anionic exchange resins such as cholestyramine) cause excessive fecal loss.

[1] Physicians' Desk Reference. 52nd ed. Montvale, NJ: Medical Economics Company, 1998: 950-951.

More than 99 percent of circulating hormones are bound to serum proteins, including thyroid-binding globulin (TBg), thyroid-binding prealbumin (TBPA), and albumin (TBa), whose capacities and affinities vary for the hormones. L-thyroxine displays greater binding affinity than L-triiodothyronine, both in the circulation and at the cellular level, which explains its longer duration of action. The half-life of T4 in normal plasma is 6-7 days while that of T3 is about 1 day. The plasma half-lives of T4 and T3 are decreased in hyperthyroidism and increased in hypothyroidism.

3. STUDY OBJECTIVE

The study objective was to determine the bioavailability of the to-be-marketed levothyroxine tablets relative to an oral solution after administration of an equal dose of 600 mcg to healthy male and female subjects under fasting conditions.

4. STUDY DESIGN

This was a single-dose, randomized, open-label, two-period, two-way crossover study of the test formulation (Levothyroxine 2 x 300 mcg Tablets, Lloyd, Incorporated) and the reference formulation (Levothyroxine oral solution, Knoll Pharmaceutical) in fasted subjects. Each subject received a single oral 600 mcg dose of the test formulation in the fasted state and the reference formulation in the fasted state.

5. STUDY INVESTIGATORS AND CONTRACT LABORATORY

The study was conducted at [redacted]. The study principal investigator was Krishna Talluri, M.D.

6. INFORMED CONSENT AND IRB APPROVAL

Subjects gave written informed consent before their acceptance into the study. The study protocol was reviewed and approved by an IRB before its initiation.

7. SUBJECT SELECTION CRITERIA

Twenty-eight (28) subjects were enrolled in the study.

Subjects selected for the study met the following acceptance criteria:

1. Age between 18 and 50 years, inclusive.
2. Weight within -15% to +15% of the desired weight for their height and body frame, according to the 1983 Metropolitan Life Insurance Table.
3. Good health as determined by the Principal Investigator evaluation of medical history, physical examination and clinical laboratory results.
4. Willing and able to give written informed consent.
5. Women were either 12 months post-menopausal, surgically sterile or using an effective form of birth control (e.g. intrauterine device, diaphram with spermicide, cervical cap, consort use of condom or male sterilization, or abstinence) during study participation.

6. No clinical laboratory values more than ±10% outside the laboratory's stated normal range, unless the investigator decides they are not clinically significant and records this on the case report form.
7. Negative hepatitis B surface antigen (HBsAg) and human immunodeficiency virus (HIV) test results.
8. All thyroid function tests (free and total thyroxine and TSH) should be within normal limits.
9. Negative serum pregnancy test (administered to women of child bearing age before each dosing period).
10. Normal ECG.

Subjects that met the following criteria were excluded from the study:

1. Relevant deviations from normal in physical examination or clinical laboratory tests as evaluated by the investigator.
2. Any clinically significant illness within 30 days preceding entry into this study.
3. If female, pregnancy or positive pregnancy test.
4. History of significant neurological, hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary, psychiatric or metabolic disease as determined by the investigator.
5. Use of any prescription medication or OTC medication within 1 month of dosing or used any prescription or OTC medication during the study that may have interfered with the evaluation of the study medication.
6. History of chronic alcohol consumption and/or drug addiction in the past year or a current positive drug screen.
7. History of allergy or hypersensitivity to levothyroxine.
8. Consumption of alcohol and/or caffeine or xanthine containing products within 72 hours prior to dosing.
9. Participation in another drug study within 4 weeks prior to initiation of this study.
10. Donation or loss of a significant volume of blood (>450 mL) within 4 weeks of the study.
11. Unwilling to reside in the study unit for the duration of the inpatient portions of the study or to cooperate fully with the investigator or site personnel.
12. Ingestion of any vitamins within the 48 hours prior to the initial dose of the study medication.
13. Use of any tobacco products within 90 days of dosing.
14. Lactating women.
15. Use of any medication known to affect thyroid hormone metabolism.
16. Subjects with a concurrent medical condition known to interfere with the absorption or metabolism of thyroid hormones.
17. Subjects with a sufficiently sensitive TSH assay identifying subtle abnormalities of thyroid function.

All examinations were performed at the [redacted]. Clinical laboratory assessments were performed by [redacted]

Subjects underwent the following evaluations:

1. Medical history.
2. Vital sign assessment.
3. Physical examination and ECG.
4. Body height and weight measurements.
5. Clinical laboratory tests:
   a. Hematology: white blood cell count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, differential, platelet count and absolute segmented neutrophils.

b. Serum Chemistry: albumin, alkaline phosphatase, alanine transaminase, aspartate transaminase, total bilirubin, blood urea nitrogen, cholesterol, creatinine, glucose, lactate dehydrogenase, phosphorus, calcium, total protein, triglycerides, uric acid, potassium, sodium, carbon dioxide, chloride, gamma glutamyl transferase and globulin.
c. Urinalysis: appearance, color, pH, specific gravity, protein, glucose, ketone, bilirubin, blood, nitrite, leukocytes and microscopic examination of sediment (if dipstick test is positive).
d. Urine screen for drugs of abuse: amphetamines, barbiturates, cocaine metabolites, opiates, benzodiazepines and cannabinoids.
e. HIV and HBsAg tests.
f. One set of thyroid function tests (free and total thyroxine and TSH)
g. Pregnancy tests (females).

Special precautions taken and restrictions applied to subjects during the study included:
1. No prescription or OTC medication that may interfere with the study medication.
2. Subjects were confined to the facility from the evening prior to dosing (at least 12 hours) until 48 hours after dosing.
3. Subjects fasted for 10 hours prior to dosing.
4. Dosing was followed by a 4 hour fast.
5. Fluid intake was prohibited from 1 hour prior to and after drug administration.
6. Standard meals were provided at 4 hours after dosing.

8. DRUG TREATMENTS

8.1. Levothyroxine Tablets (Test)

Levothyroxine, 300 mcg tablets, Lloyd, Incorporated, Lot # KA30298, Expiration Date: NA.

Dose: 2 x 300 mcg tablets with 240 mL water.

8.2. Levothyroxine oral solution (Reference)

Levothyroxine oral solution – SYNTHROID Injection, levothyroxine sodium powder for reconstitution, 200 mcg, Knoll Pharmaceutical, Lot # 80120028, Expiration Date: 04/2000.

Dose: Oral administration of 600 mcg levothyroxine sodium powder for reconstitution with 240 mL water.

The certificates of analyses for the test and reference formulations are provided in Appendix 6.

9. STUDY SCHEDULES

Subjects entered the test facility at least 12 hours prior to dosing.

Subject numbers were assigned to a sequence as subjects enrolled in the study. Subjects were randomly assigned to treatment groups according to a schedule generated by

After a 10 hour overnight fast, subjects were administered a single 600 mcg dose of either the test or reference formulation with 240 mL of room-temperature tap water. The dosing was followed by a 4 hour fast.

Other than the water used when taking the study drug, no fluids were allowed from 1 hour before until 1 hour after dosing. Standardized lunches were served 4 hours after dosing. Meals were identical for both study periods.

Venous blood samples were collected at the following times: 30 and 15 minutes prior to dosing, immediately before dosing (0 hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24 and 48 hours post-dose. Samples were processed in a refrigerated centrifuge and stored frozen at -20°C until analysis. There was a 35 day washout between doses.

Vital signs were measured at screening, prior to each dose and at 1, 2, 4, 8, 12, 24 and 48 hours post-dose.

10. ANALYTICAL METHODOLOGY

Analysis of samples for L-triiodothyronine (T3) and L-thyroxine (T4) was performed at [redacted]. Serum concentrations of L-triiodothyronine (T3) and L-thyroxine (T4) were measured by a validated radioimmunoassay method developed at [redacted]. The assay calibration range was [redacted] to [redacted] for L-thyroxine (T4), and the calibration range for L-triiodothyronine (T3) was [redacted] to [redacted]. Samples were stored in [redacted] at -20° C until analysis.

The analytical method and validation can be found in Appendix 3.

10.1. Chromatograms

Representative chromatograms of the standard curves, quality control samples and unknown sample assays can be found in Appendix 3.

11. STATISTICAL ANALYSIS

The statistical analysis was based on the (27) subjects enrolled that completed all treatment periods. Subject #007 dropped from the study prior to Period 2 dosing, the last PK sample was obtained at the 48 hour point in Period 1. All sampling deviations were utilized for the computations.

11.1. Methods

An analysis of variance (ANOVA) was utilized (PROC GLM, SAS Inst., Cary, NC) to compare treatment effects between the test and reference formulations for the pharmacokinetic (PK) parameters and for each concentration draw time. The full model had terms for sequence, subject within sequence, treatment and phase. The SAS model for this analysis was:

y = sequence + subject(sequence) + treatment + phase

The subject within sequence interaction effect was used as the error term to evaluate the sequence effect at the $\alpha = 0.10$ level of significance. The mean square error (MSE) of the model was used to evaluate the treatment and phase effects at the $\alpha = 0.05$ level of significance.

Two sets of confidence intervals are presented in this report, potency uncorrected and corrected. The potency uncorrected 90% confidence intervals were calculated (PROC MIXED, SAS Inst., Cary, NC) to examine the difference between estimate (test least squares mean {LSM} minus reference LSM) and standard error of the estimate provided by the ANOVA model. Logarithmic transformations (natural log) were performed on AUC(0-t) and C_{max}. ANOVA models and 90% confidence intervals were also performed on the ln-transformed parameters.

The relative bioavailability, corrected for the potencies of the test and reference formulations, were calculated as follows:

AUC(0-t) Ratio = $100\%*(e^{(Diff + CF)})$
90% CI Lower Limit = $100\%*(e^{(Diff + CF - T*SED)})$
90% CI Upper Limit = $100\%*(e^{(Diff + CF + T*SED)})$, where

Diff = estimated difference between the test and reference ln-transformed PK parameters.
CF = correction factor (natural logarithm of the ratio of potencies of the test and reference formulations).
$T = t_{0.05, 25}$
SED = Standard error of the estimated difference = $(2*MS\ Residual/N)^{0.5}$
N = 27.

11.2. Pharmacokinetic Parameters

The following non-compartmental pharmacokinetic (PK) parameters were estimated from the serum concentration profiles for each subject. Sampling deviations were utilized for computation.

AUC(0-t)	area under the serum concentration-time curve (time 0 to time of last quantifiable concentration) calculated by the linear trapezoidal rule
C_{max}	maximum serum concentration over the entire sampling phase, directly obtained from the experimental data of serum concentration versus time curves, without interpolation
T_{max}	time to attain C_{max}

Baseline serum concentrations of T3 and T4 were calculated by averaging the three pre-dose concentration values. These averages were subtracted from the post-dose serum concentrations of T3 and T4 to obtain the corresponding baseline-corrected values.

11.3. Results

The following results are based on the baseline-uncorrected total T3 and T4 serum concentrations.

11.3.1. L-triiodothyronine (T3)

No statistically significant treatment, phase or sequence effects were observed for the untransformed or ln-transformed AUC(0-t) or C_{max}.

Mean AUC(0-t) and C_{max} values were similar for the reference solution and tablet formulations (Table 7). Point estimates (90% CI) of AUC(0-t) and C_{max} for the comparison of the tablet formulation (Treatment A) relative to the oral solution (Treatment B) were 0.97(94.11% - 99.74%) and 0.97(93.36% - 100.73%), respectively (Table 6).

11.3.2. L-thyroxine (T4)

No statistically significant phase or sequence effects were observed for the untransformed or ln-transformed AUC(0-t) or C_{max}. Significant treatment effects ($p<0.05$) were observed for both untransformed and ln-transformed AUC(0-t) and C_{max}.

Mean AUC(0-t) and C_{max} values were similar for the reference solution and tablet formulations (Table 9) inspite of significant treatment effects. Point estimates (90% CI) of AUC(0-t) and C_{max} for the comparison of the tablet formulation (treatment A) relative to the oral solution (treatment B) are 0.94(90.51% – 97.42%) and 0.91(86.45% – 95.59%), respectively (Table 8).

Baseline-corrected T3 and T4 serum concentration data and statistics are presented in Attachments 1 and 2 of Appendix 5, respectively.

11.4. Data Displays

Table 1 presents the randomization for each subject. Table 2 presents subject demographics. Adverse events are presented in Table 3. Tables 4 and 5 present the mean (CV%) for L-triiodothyronine (T3) and L-thyroxine (T4) concentration values at each time for each treatment, respectively. The least square mean values for each pharmacokinetic parameter (for each treatment), 90% confidence intervals and ratios of treatment means are presented in Tables 6 and 8. Tables 7 and 9 provide the arithmetic mean values for each pharmacokinetic parameter (for each treatment) and ratios of treatment means. Table 10 provides the potency corrected relative bioavailability ratios for the test formulation based on T3 and T4 AUC(0-t).

Mean serum L-triiodothyronine (T3) and L-thyroxine (T4) concentrations (for all subjects and treatments) are plotted as a function of time on both linear and semi-log scales in Figures 1 through 4, respectively.

Total T3 and T4 graphs and statistical listings are provided in Attachments 1 and 2 of Appendix 2 of this report. Individual serum concentrations versus time plots of L-triiodothyronine (T3) for all subjects are presented in Section 1.1. Individual serum L-triiodothyronine (T3) concentration data are presented in Section 1.2. Summary statistics and ANOVA results for serum L-triiodothyronine (T3) concentrations at each sampling time are presented in Sections 1.3 and 1.4, respectively.

Listings of pharmacokinetic parameters and summary statistics for L-triiodothyronine (T3) are presented in Sections 1.5 and 1.6. ANOVA results for untransformed and ln-transformed pharmacokinetic parameters for L-triiodothyronine (T3) are presented in Section 1.7.

Individual serum concentrations versus time plots of L-thyroxine (T4) for all subjects are presented in Section 2.1. Individual serum L-thyroxine (T4) concentration data are presented in Section 2.2. Summary statistics and ANOVA results for serum L-thyroxine (T4) concentrations at each sampling time are presented in Sections 2.3 and 2.4, respectively.

Listings of pharmacokinetic parameters and summary statistics for L-thyroxine (T4) are presented in Sections 2.5 and 2.6. ANOVA results for untransformed and ln-transformed pharmacokinetic parameters for L-thyroxine (T4) are presented in Section 2.7.

Baseline-corrected T3 and T4 graphs and statistical listings are provided in Attachments 1 and 2 of Appendix 5 of this report. Baseline-corrected T3 mean serum concentration profiles are presented in Section 1.1. Individual serum concentrations versus time plots of L-triiodothyronine (T3) (baseline corrected) for all subjects are presented in Section 1.2. Individual serum L-triiodothyronine (T3) (baseline corrected) concentration data are presented in Section 1.3. Summary statistics and ANOVA results for serum L-triiodothyronine (T3) (baseline corrected) concentrations at each sampling time are presented in Sections 1.4 and 1.5, respectively.

Listings of pharmacokinetic parameters and summary statistics for L-triiodothyronine (T3) (baseline corrected) are presented in Sections 1.6 and 1.7. ANOVA results for untransformed and ln-transformed pharmacokinetic parameters for L-triiodothyronine (T3) (baseline corrected) are presented in Section 1.8.

Baseline-corrected T4 mean serum concentration profiles are presented in Section 2.1. Individual serum concentrations versus time plots of L-thyroxine (T4) (baseline corrected) for all subjects are presented in Section 2.2. Individual serum L-thyroxine (T4) (baseline corrected) concentration data are presented in Section 2.3. Summary statistics and ANOVA results for serum L-thyroxine (T4) (baseline corrected) concentrations at each sampling time are presented in Sections 2.4 and 2.5, respectively.

Listings of pharmacokinetic parameters and summary statistics for L-thyroxine (T4) (baseline corrected) are presented in Sections 2.6 and 2.7. ANOVA results for untransformed and ln-transformed pharmacokinetic parameters for L-thyroxine (T4) (baseline corrected) are presented in Section 2.8.

Sampling deviations are provided in Attachment 3 of Appendix 2.

12. CLINICAL NOTES

Study Phase 1 dosing was conducted on 30 January 1999 and Phase 2 dosing was conducted on 6 March 1999. The study subjects were Asian/Black/Caucasian males and females between the ages of 18 and 50, inclusive. Subject demographics are presented in Table 2. Twenty-seven (27) subjects completed both phases of the study. Subject #007 dropped from the study prior to Period 2 dosing, the last PK sample was obtained at the 48 hour point in Period 1.

A total of 17 adverse events reported were considered to be related to administration of the study medication, 10 were considered probably related, 1 was considered possibly related and 6 were considered remotely related. Sixteen (16) of these adverse events resolved spontaneously, and 1 resolved with treatment. All of the adverse events that occurred during the study are summarized in Table 3. All adverse events were mild or moderate and were equally distributed between both treatments. No serious adverse events occurred during the study. Thyroid function tests (TSH, free and total thyroxine) were performed at screening and at study exit. These results are presented with the case report forms in Appendix 4. All the TSH values appeared to be normal both at screening and study exit.

13. STUDY RESULTS

Both the AUC and Cmax values for T3 and T4 were similar following administration of the tablet and reference solution formulations. The relative bioavailability of the tablet formulation based on AUC(0-t) of T3 and T4 were 96.51% (93.02% - 100.00%) and 93.72% (90.28% – 97.16%), respectively.

The relative bioavailability(potency corrected) of the test formulation based on T3 and T4 AUC(0-t) were 107.35% (104.27% - 110.51%) and 104.05% (100.29% – 107.95%), respectively

BIOEQUIVALENCE STUDY REPORT

A SINGLE-DOSE, RANDOMIZED, CROSSOVER STUDY COMPARING THE DOSAGE-FORM EQUIVALENCE BETWEEN THREE DIFFERENT STRENGTHS OF LLOYD, INCORPORATED LEVOTHYROXINE TABLETS IN HEALTHY, MALE AND FEMALE SUBJECTS FOLLOWING A 600 MCG DOSE UNDER FASTED CONDITIONS

PROTOCOL NUMBER: LLOY-9802

Name of Drug:	Levothyroxine
Study Design:	Single-dose, randomized, open-label, three-treatment, three-period, six-sequence crossover
Sponsor:	Lloyd, Incorporated
Sponsor Contact:	Joseph W. Denhart, DVM, MS Vice President, Regulatory Affairs and Quality Assurance Lloyd, Incorporated 604 West Thomas Avenue Shenandoah, IA 51601-0130
Drug Development Phase:	Phase I
Dosing Dates:	30 January 1999 6 March 1999 10 April 1999
Sample Analysis Dates:	Total T3: 21 April 1999 to 12 May 1999 Total T4: 21 April 1999 to 12 May 1999
Clinical Study Site:	
Analytical Study Site:	
Principal Investigator:	Aziz Laurent, M.D.
Report Date:	28 May 1999

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1. ETHICS

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Ethical Conduct of the Study

This study was conducted under the principles of the World Medical Assembly Declaration of Helsinki and its most recent amendments.

Subject Information and Consent

Written informed consent was obtained from each subject at the first screening visit. Subjects reviewed the subject instructions and the informed consent form, and were allowed to ask and have answered questions concerning all portions of the conduct of the study.

Subjects were provided with a copy of the signed written informed consent form and subject instructions. The originals are on file at the clinical research facility. A copy of the protocol, written informed consent form, IRB approval, Form FDA 1572 and the investigator's curriculum vitae are presented in Appendix 1.

2. BACKGROUND

The major thyroid hormones are L-thyroxine (T4) and L-triiodothyronine (T3). The amounts of T4 and T3 released into the circulation from the normally functioning thyroid gland are regulated by the amount of thyrotropin (TSH) secreted from the anterior pituitary gland. TSH secretion is in turn regulated by the levels of circulating T4 and T3 and by secretion of thyrotropin releasing factor (TRH) from the hypothalamus. Recognition of this complex feedback system is important in the diagnosis and treatment of thyroid dysfunction. The principal effect of exogenous thyroid hormone is to increase the metabolic rate of body tissues.

The thyroid hormones are also concerned with growth and differentiation of tissues. In deficiency states in the young there is retardation of growth and failure of maturation of the skeletal and other body systems, especially in failure of ossification in the epiphyses and in the growth and development of the brain. The precise mechanism of action by which thyroid hormones affect thermogenesis and cellular growth and differentiation is not known. It is recognized that these physiologic effects are mediated at the cellular level primarily by T3, a large part of which is derived from T4 by deiodination in the peripheral tissues. Thyroxine (T4) is the major component of normal secretions of the thyroid gland and is thus the primary determinant of normal thyroid function.

Depending on other factors, absorption has varied from 48 to 79 percent of the administered dose. Fasting increases absorption. Malabsorption syndromes, as well as dietary factors, (children's soybean formula, concomitant use of anionic exchange resins such as cholestyramine) cause excessive fecal loss.

More than 99 percent of circulating hormones are bound to serum proteins, including thyroid-binding globulin (TBg), thyroid-binding prealbumin (TBPA), and albumin (TBa), whose capacities and affinities vary for the hormones. L-thyroxine displays greater binding affinity than L-triiodothyronine, both in the circulation and at the cellular level, which explains its longer duration of action. The half-life of T4 in normal plasma is 6-7 days while that of T3 is about 1 day. The plasma half-lives of T4 and T3 are decreased in hyperthyroidism and increased in hypothyroidism.

3. STUDY OBJECTIVE

The study objective was to determine the dosage-form equivalence between the to-be-marketed tablet strengths of levothyroxine sodium (50, 100 and 300mcg) after administration of an equal dose of 600 mcg to healthy male and female subjects under fasting conditions.

4. STUDY DESIGN

This was a single-dose, randomized, open-label, three-treatment, three-period, six-sequence crossover study of the three dosage strengths (50, 100 and 300 mcg) of levothyroxine sodium tablets (Lloyd, Incorporated) in fasted subjects. Each subject received a single oral 600 mcg dose of all three strengths of levothyroxine sodium tablets in the fasted state.

5. STUDY INVESTIGATORS AND CONTRACT LABORATORY

The study was conducted at [redacted]. The study principal investigator was Aziz Laurent M.D.

6. INFORMED CONSENT AND IRB APPROVAL

Subjects gave written informed consent before their acceptance into the study. The study protocol was reviewed and approved by an IRB before its initiation.

7. SUBJECT SELECTION CRITERIA

Thirty (30) subjects were enrolled in the study.

Subjects selected for the study met the following acceptance criteria:

1. Age between 18 and 50 years, inclusive.
2. Weight within -15% to +15% of the desired weight for their height and body frame, according to the 1983 Metropolitan Life Insurance Table.
3. Good health as determined by the Principal Investigator evaluation of medical history, physical examination and clinical laboratory results.
4. Willing and able to give written informed consent.
5. Women were either 12 months post-menopausal, surgically sterile or using an effective form of birth control (e.g. intrauterine device, diaphragm with spermicide, cervical cap, consort use of condom or male sterilization, or abstinence) during study participation.

6. No clinical laboratory values more than ±10% outside the laboratory's stated normal range, unless the investigator decides they are not clinically significant and records this on the case report form.
7. Negative for hepatitis B surface antigen (HBsAg) and human immunodeficiency virus (HIV).
8. Thyroid function tests (free and total thyroxine, and TSH) within normal limits.
9. In women of child- bearing potential, negative serum pregnancy tests within 24 hours before each drug treatment period.
10. Normal ECG.

Subjects that met the following criteria were excluded from the study:

1. Relevant deviations from normal in physical examination or clinical laboratory tests as evaluated by the investigator.
2. Any clinically significant illness within 30 days preceding entry into this study.
3. If female, pregnancy or positive pregnancy test.
4. History of significant neurological, hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary, psychiatric or metabolic disease as determined by the investigator.
5. Use of any prescription medication or OTC medication within 1 month of dosing or will use any prescription or OTC medication during the study that may have interfered with the evaluation of the study medication.
6. History of chronic alcohol consumption and/or drug addiction in the past year or a current positive drug screen.
7. History of allergy or hypersensitivity to levothyroxine.
8. Consumption of alcohol and/or caffeine or xanthine containing products within 72 hours prior to dosing.
9. Participation in another drug study within 4 weeks prior to initiation of this study.
10. Donation or loss of a significant volume of blood (>450 mL) within 4 weeks of the study.
11. Unwilling to reside in the study unit for the duration of the inpatient portions of the study or to cooperate fully with the investigator or site personnel.
12. Ingestion of any vitamins within the 48 hours prior to the initial dose of the study medication.
13. Use of tobacco products within 90 days prior to study start.
14. Lactating women.
15. Subjects taking medications known to affect thyroid hormone metabolism, e.g. oral contraceptives, androgens, anabolic steroids, etc.
16. Subtle abnormalities of thyroid function as determined by a sufficiently sensitive TSH assay.
17. Subjects with a concurrent medical condition known to interfere with the absorption or metabolism of thyroid hormones.

All examinations were performed at the [redacted] Clinical laboratory assessments were performed by [redacted]

Subjects underwent the following evaluations:

1. Medical history.
2. Vital sign assessment and ECG.
3. Physical examination.
4. Pregnancy test (females).
5. Clinical laboratory tests:
   a. Hematology: white blood cell count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin concentration, differential, platelet count, absolute segmented neutrophils and mean corpuscular hemoglobin.
   b. Serum Chemistry: albumin, alkaline phosphatase, alanine transaminase, aspartate transaminase, total bilirubin, blood urea nitrogen, cholesterol, creatinine, glucose, lactate

dehydrogenase, phosphorus, calcium, total protein, triglycerides, uric acid, potassium, sodium, carbon dioxide, chloride, gamma glutamyl transferase and globulin..

c. Urinalysis: appearance, color, pH, specific gravity, protein, glucose, ketone, bilirubin, blood, nitrite, leukocytes and microscopic examination of sediment (if dipstick test is positive).
d. Urine screen for drugs of abuse: amphetamines, barbiturates, cocaine metabolites, opiates, benzodiazepines and cannabinoids.
e. Thyroid Function Tests: free and total thyroxine and TSH.
f. HIV and HBsAg tests.

Special precautions taken and restrictions applied to subjects during the study included:

1. No prescription or OTC medication.
2. The consumption of alcohol and/or caffeine or xanthine-containing beverages and foods was prohibited.
3. Subjects were confined to the facility from the evening prior to dosing (at least 12 hours) until 48 hours after dosing.
4. Subjects fasted for 10 hours prior to dosing.
5. Dosing was followed by a 4 hour fast.
6. Fluid intake was prohibited from 1 hour prior to and after drug administration.
7. Standard meals were provided at 4 hours after dosing.

8. DRUG TREATMENTS

Treatment A: Levothyroxine Tablets
Levothyroxine Tablets, 12 x 50 mcg, Lloyd, Incorporated.
Lot # KA28998, Expiration Date: NA

Treatment B: Levothyroxine Tablets
Levothyroxine Tablets, 6 x 100 mcg tablets, Lloyd, Incorporated.
Lot # KA31098, Expiration Date: NA

Treatment C: Levothyroxine Tablets
Levothyroxine Tablets, 2 x 300 mcg, Lloyd, Incorporated.
Lot # KA30298, Expiration Date: NA

9. STUDY SCHEDULES

Subjects entered the test facility at least 12 hours prior to dosing.

Subject numbers were assigned in sequence as subjects enrolled in the study. Subjects were randomly assigned to treatment groups according to a schedule generated by

Following a 10 hour overnight fast, subjects were administered a single 600 mcg dose of one of the three dosage strengths of levothyroxine sodium tablets with 240 mL of room-temperature tap water. The dosing was followed by a 4 hour fast.

Other than the water used when taking the study drug, no fluids were allowed from 1 hour before until 1 hour after dosing. Standardized lunches were served 4 hours after dosing. Meals were identical for all study periods.

Venous blood samples were collected at the following times: 30 and 15 minutes prior to dosing, immediately before dosing (0 hour) and post-dose at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24 and 48 hours. Samples were processed on ice and in a refrigerated centrifuge and stored frozen at -20°C until analysis. There was a 35 day washout between doses.

Vital signs were measured at screening, immediately before dosing (0 hour) and post-dose at 1, 2, 4, 8, 12, 24 and 48 hours.

10. ANALYTICAL METHODOLOGY

Analysis of samples for L-triiodothyronine (T3) and L-thyroxine (T4) was performed at . Serum concentrations of L-triiodothyronine (T3) and L-thyroxine (T4) were measured by a validated radioimmunoassay method developed at The assay calibration range was for L-thyroxine (T4), and the calibration range for L-triiodothyronine (T3) was . Samples were stored in , at -20° C until analysis.

The analytical method and validation can be found in Appendix 3.

10.1. Chromatograms

Representative chromatograms of the standard curves, quality control samples and unknown sample assays can be found in Appendix 3.

11. STATISTICAL ANALYSIS

The statistical analysis was based on the (27) subjects enrolled that completed all treatment periods. All sampling deviations were utilized for the computations.

11.1. Methods

An analysis of variance (ANOVA) appropriate for a three-way crossover design was utilized (PROC GLM, SAS Inst., Cary, NC) to compare treatment effects between the test and reference formulations for the PK parameters and for each concentration draw time. The 100 mcg dosage strength (Treatment B) was used as the reference formulation. The full model had terms for sequence, subject within sequence, treatment, phase and residual (carry-over). The SAS model for this analysis was:

y = sequence + subject(sequence) + treatment + phase + resid1 +resid2

The subject within sequence interaction effect was used as the error term to evaluate the sequence effect at the $\alpha = 0.10$ level of significance. The mean square error (MSE) of the model was used to evaluate the treatment and phase effects at the $\alpha = 0.05$ level of significance.

The 90% confidence intervals were calculated (PROC MIXED, SAS Inst., Cary, NC) to examine the difference between estimate (test least squares mean {LSM} minus

reference LSM) and standard error of the estimate provided by the ANOVA model. Logarithmic transformations (natural log) were performed on AUC(0-t) and C_{max}. ANOVA models and 90% confidence intervals were also performed on the ln-transformed parameters.

The pair-wise ratio of the test least squares mean (LSM) to the reference LSM was examined for inclusion within the boundary conditions of 0.80 to 1.20 for the PK parameters of interest (AUC(0-t) and C_{max}).

11.2. Pharmacokinetic Parameters

The following non-compartmental pharmacokinetic (PK) parameters were estimated from the serum concentration profiles for each subject. Sampling deviations were utilized for computation.

AUCT	area under the serum concentration-time curve (time 0 to time of last quantifiable concentration) calculated by the linear trapezoidal rule
C_{max}	maximum serum concentration over the entire sampling phase, directly obtained from the experimental data of serum concentration versus time curves, without interpolation
T_{max}	time to attain C_{max}

Baseline serum concentrations of T3 and T4 were calculated by averaging the three pre-dose concentration values. These averages were subtracted from the post-dose serum concentrations of T3 and T4 to obtain the corresponding baseline-corrected values.

11.3. Results

The following results are based on the baseline-uncorrected total T3 and T4 serum concentrations.

11.3.1. L-triiodothyronine (T3)

No statistically significant phase, sequence or carryover effects were observed for the untransformed or ln-transformed AUC(0-t). A significant treatment effect was observed for the untransformed AUC(0-t) (Treatment C vs Treatment B). Significant phase effects were observed for the untransformed and ln-transformed C_{max}. A significant sequence effect was also observed for the ln-transformed C_{max}.

Mean AUC(0-t) and C_{max} values were similar for all the three treatments (Table 8). Point estimates (90% CI) of ln AUC(0-t) for the comparison of the 50 and 300 mcg tablets (Treatment A and C, respectively) relative to the 100 mcg tablet (Treatment B) were 1.04(98.83% - 110.09%) and 1.07(101.57% - 113.24%), respectively (Tables 6 and 10). Point estimates (90% CI) of ln C_{max} for the comparison of the 50 and 300 mcg tablets (Treatment A and C, respectively) relative to the 100 mcg tablet (Treatment B) were 1.04(100.02% - 107.49%) and 1.03(99.81% - 107.31%), respectively (Tables 6 and 10).

Mean T_{max} values were highly variable among the three treatments (Table 8). The % CVs for the T_{max} values ranged from 91.72% to 129%. However, ANOVA

results for T_{max} showed no statistically significant differences between the three treatments at at a significance level of $\alpha = 0.05$ (Appendix 2). Moreover, T_{max} is not considered to be a primary PK endpoint for the purposes of establishing dosage-form equivalence. Therefore the differences in T_{max} values between the treatments can be considered inconsequential.

11.3.2. L-thyroxine (T4)

No statistically significant treatment, phase, sequence or carryover effects were observed for the untransformed or ln-transformed AUC(0-t). Significant treatment (Treatment C vs Treatment B) and sequence effects were observed for the untransformed and ln-transformed C_{max}.

Mean AUC(0-t) and C_{max} values were similar for all the three treatments (Table 9). Point estimates (90% CI) of ln AUC(0-t) for the comparison of the 50 and 300 mcg tablets (Treatment A and C, respectively) relative to the 100 mcg tablet (Treatment B) were 1.00(94.53% - 104.83%) and 1.04(98.86% - 109.71%), respectively (Tables 7 and 11). Point estimates (90% CI) of ln C_{max} for the comparison of the 50 and 300 mcg tablets (Treatment A and C, respectively) relative to the 100 mcg tablet (Treatment B) were 1.01(96.59% - 105.63%) and 1.07(101.94% - 111.56%), respectively (Tables 7 and 11).

Baseline-corrected T3 and T4 serum concentration data and statistics are presented in Attachments 1 and 2 of Appendix 5, respectively.

11.4. Data Displays

Table 1 presents the randomization for each subject. Table 2 presents subject demographics. Adverse events are presented in Table 3. Tables 4 and 5 present the mean (CV%) for L-triiodothyronine (T3) and L-thyroxine (T4) concentration values at each time for each treatment, respectively. The least square mean values for each pharmacokinetic parameter (for each treatment) and ratios of treatment means are presented in Tables 6 and 7. The arithmetic mean values for each PK parameter and the ratios of treatment means are presented in Tables 8 and 9. The 90% confidence intervals for the ratios of means for the untransformed and ln-transformed PK parameters (for each comparison) are presented in Tables 10 and 11.

Mean serum L-triiodothyronine (T3) and L-thyroxine (T4) concentrations (for all subjects and treatments) are plotted as a function of time on both linear and semi-log scales in Figures 1 through 4, respectively.

Total T3 and T4 graphs and statistical listings are provided in Attachments 1 and 2 of Appendix 2 of this report. Individual serum concentrations versus time plots of L-triiodothyronine (T3) for all subjects are presented in Section 1.1. Individual serum L-triiodothyronine (T3) concentration data are presented in Section 1.2. Summary statistics and ANOVA results for serum L-triiodothyronine (T3) concentrations at each sampling time are presented in Sections 1.3 and 1.4, respectively.

Listings of pharmacokinetic parameters and summary statistics for L-triiodothyronine (T3) are presented in Sections 1.5 and 1.6. ANOVA results for untransformed and ln-transformed pharmacokinetic parameters for L-triiodothyronine (T3) are presented in Section 1.7.

Individual serum concentrations versus time plots of L-thyroxine (T4) for all subjects are presented in Section 2.1. Individual serum L-thyroxine (T4) concentration data are presented in Section 2.2. Summary statistics and ANOVA results for serum L-thyroxine (T4) concentrations at each sampling time are presented in Sections 2.3 and 2.4, respectively.

Listings of pharmacokinetic parameters and summary statistics for L-thyroxine (T4) are presented in Sections 2.5 and 2.6. ANOVA results for untransformed and ln-transformed pharmacokinetic parameters for L-thyroxine (T4) are presented in Section 2.7.

Baseline-corrected T3 and T4 graphs and statistical listings are provided in Attachments 1 and 2 of Appendix 5 of this report. Individual serum concentrations versus time plots of L-triiodothyronine (T3) (baseline corrected) for all subjects are presented in Section 1.1. Individual serum L-triiodothyronine (T3) (baseline corrected) concentration data are presented in Section 1.2. Summary statistics and ANOVA results for serum L-triiodothyronine (T3) (baseline corrected) concentrations at each sampling time are presented in Sections 1.3 and 1.4, respectively.

Listings of pharmacokinetic parameters and summary statistics for L-triiodothyronine (T3) (baseline corrected) are presented in Sections 1.5 and 1.6. ANOVA results for untransformed and ln-transformed pharmacokinetic parameters for L-triiodothyronine (T3) (baseline corrected) are presented in Section 1.7.

Individual serum concentrations versus time plots of L-thyroxine (T4) (baseline corrected) for all subjects are presented in Section 2.1. Individual serum L-thyroxine (T4) (baseline corrected) concentration data are presented in Section 2.2. Summary statistics and ANOVA results for serum L-thyroxine (T4) (baseline corrected) concentrations at each sampling time are presented in Sections 2.3 and 2.4, respectively.

Listings of pharmacokinetic parameters and summary statistics for L-thyroxine (T4) (baseline corrected) are presented in Sections 2.5 and 2.6. ANOVA results for untransformed and ln-transformed pharmacokinetic parameters for L-thyroxine (T4) (baseline corrected) are presented in Section 2.7.

Sampling deviations are provided in Attachment 3 of Appendix 2. The certificates of analyses for the three different dosage strengths of Levothyroxine sodium are provided in Appendix 6.

12. CLINICAL NOTES

Study Phase 1 dosing was conducted on 30 January 1999, Phase 2 dosing was conducted on 6 March 1999 and Phase 3 dosing was conducted on 10 April 1999. The study subjects were Black/Caucasian/Hispanic males and females between the ages of 18 and 50, inclusive. Subject demographics are presented in Table 2. Twenty-seven subjects completed all phases of the study. Subject #024 dropped from the study prior to Period 2 dosing, the last PK sample was obtained at the 48 hour point of Period 1. Subject #012 dropped from the study prior to Period 3 dosing, the last PK sample was obtained at the 48 hour point of Period 2. Subject #027 dropped from the study prior to Period 3 dosing, the last PK sample was obtained at the 48 hour point of Period 2.

A total of 12 adverse events reported were considered to be related to administration of the study medication, 6 were considered probably related, 3 were considered possibly related and 3 were considered remotely related. The 12 adverse events, considered related to the study medication, resolved spontaneously. All of the adverse events, which occurred during the study, are summarized in Table 3. All adverse events were mild or moderate. No serious adverse events occurred during the study.

13. STUDY RESULTS

Both the AUC(0-t) and C_{max} values for baseline-uncorrected T3 and T4 were similar following administration of the three treatments (12 x 50, 6 x 100 and 2 x 300 mcg levothyroxine tablets). The to-be-marketed tablet strengths of levothyroxine sodium (50, 100 and 300mcg) were found to be dosage-form equivalent after administration of an equal dose of 600 mcg to healthy male and female subjects under fasting conditions.

The 90% CI for the point estimates of AUC(0-t) and C_{max} (T3 and T4) for the treatment comparisons (A vs. B and C vs. B) were found to be within 80-125% of the reference (Treatment B).

5 Page(s) Withheld

FEB 23 1999

Clinical Pharmacology and Biopharmaceutics Review

IND:	57,315 serial002
Levothyroxine Sodium Tablets	
Submission Date:	1/22/99
Sponsor:	Lloyd, Inc
Type of Submission:	Protocol Amendment
Reviewer:	Michael J. Fossler

Submission

The submission to IND 57,315 dated 1/22/99 contains two bioavailability protocols for levothyroxine sodium tablets. These protocols were previously reviewed by OCPB under the original submission dated 11/20/98. The revised protocols in this submission reflect some minor changes in exclusion criteria, as well as the deletion of the trade-name —. The study designs remain the same as before. Therefore, no further action is necessary at this time.

/S/ 12/23/98

Michael J. Fossler, Pharm.D., Ph.D.

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

FT initialed by Hae-Young Ahn, Ph.D., Team Leader /S/ 2/23/99

CC: IND 57,315(orig., 1 copy), HFD-510(McCort), HFD-850(Huang, Lesko), HFD-870(M.Chen, Fossler, Ahn), Central Document Room(Barbara Murphy)
2/24/98

Recommendation Code: ND

DEC 22 1998

Clinical Pharmacology and Biopharmaceutics Review

IND:	57,315 serial 000
Levothyroxine Sodium Tablets	
Submission Date:	20 November 1998
Sponsor:	Lloyd, Inc.
Type of Submission:	Investigational New Drug Application
Reviewer:	Michael J. Fossler

Submission

The submission dated 11/20/98 is in response to the Federal Register Notice of 8/14/97 declaring levothyroxine sodium to be a new drug. Lloyd, Inc. has been manufacturing levothyroxine tablets for veterinary use under GMP conditions for more than 15 years. In response to the FR notice, the firm has modified its formulation for human use and plans to submit an NDA for the usual strengths (25-300 µg). The proposed formulation is detailed in Table 1.

Table 1: Tablet Formulation

Ingredient	50 µg Formulation (mg/tablet)	100 µg Formulation (mg/tablet)	300 µg Formulation (mg/tablet)
Microcrystalline cellulose			
Mg Stearate			
‡Levothyroxine Na •2 H_2O			
Ca Phosphate, Dibasic			
Povidone, USP			
Dyes			
Total Tablet Weight			

§ Yellow FDC#6 and Yellow FDC #10
§§Yellow FDC #6 and #10, Blue FDC # 1
‡formulated to include a

Study Design

Title:	LLOY-9801: A single-dose, Randomized, crossover study estimating the bioavailability of Lloyd levothyroxine sodium tablets relative to an oral solution in healthy male and female subjects following a 600 µg dose under fasted conditions
Study Site:	
Objective:	To determine the bioavailability of Lloyd levothyroxine tablets
Study Design:	Single-dose, randomized, open-label, two-period crossover study in healthy male and female volunteers. Each subject (non-smoking male or female age 18-50) will be randomized to each of the following treatments: • 600 µg levothyroxine as 2 x 300 µg Thyrocap tablets • 600 µg levothyroxine given orally as a solution, using the intravenous formulation

Subjects will be fasted 10 hours before and 4 hours after drug administration. Sampling times are as per OCPB recommendations.

Analytical Method: — analyzer for both total T4 and total T3.

Statistical Plan: Non-compartmental methods using both baseline-corrected and uncorrected data.

Title: LLOY-9802: A single-dose, Randomized, crossover study comparing the dosage-form equivalence between three different strengths of Lloyd levothyroxine sodium tablets in healthy male and female volunteers following a 600 μg dose under fasting conditions.

Study Site: —

Objective: To determine the dosage-form equivalence of Lloyd levothyroxine tablets

Study Design: Single-dose, randomized, open-label, three-period, six sequence crossover study in healthy male and female volunteers. Each subject (non-smoking male or female age 18-50) will be randomized to each of the following treatments:

- 600 μg levothyroxine as 2 x 300 μg — ablets
- 600 μg levothyroxine as 6 x 100 μg — ablets
- 600 μg levothyroxine as 12 x 50 μg — tablets

Subjects will be fasted 10 hours before and 4 hours after drug administration. Sampling times are as per OCPB recommendations.

Analytical Method: — analyzer for both total T4 and total T3.

Statistical Plan: Non-compartmental methods using both baseline-corrected and uncorrected data. The two one-sided test procedure will be used to compare the dosage forms, using 100 μg as the reference formulation

Recommendations

The proposed studies are acceptable. The studies should be allowed to proceed if HFD-510 agrees. There are no comments to the firm at this time.

/S/ 12/22/98

Michael J. Fossler, Pharm.D., Ph.D.

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD/FD initialed by Hae-Young Ahn, Ph.D., Team Leader /S/ 12/22/98

CC: NDA 57,315(orig., 1 copy), HFD-510(Temeck, McCort), HFD-850(Huang, Lesko), HFD-870(M.Chen, Ahn), Central Document Room(Barbara Murphy)

Recommendation Code: ND