CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-301

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ADDENDUM

NDA # 21-301	**SUBMISSION DATE: 28-July-2000, 30-January-2001, 15-March-2001, 06-April-2001**
BRAND NAME:	**Levoxyl®**
GENERIC NAME:	**Levothyroxine Sodium, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg oral tablets**
REVIEWER:	**Wei Qiu, Ph.D**
CONSULTANT:	**Steven Johnson, B.S.Pharm, Pharm.D**
SPONSOR:	**Jones Pharma, Inc.,1945 Craig Road, P.O.Box 46903, St. Louis, Missouri 63146**
TYPE OF SUBMISSION:	**New Drug Application**

The Agency has the following recommendation on dissolution specification:

Apparatus	2 (paddle)
Speed	50 rpm
Media	0.01 N hydrochloric acid containing 0.2% sodium lauryl sulfate
Volume	500 ml

The appropriate dissolution specification should be not less than — in 15 minutes.

Hae-Young Ahn, Team Leader

Wei Qiu, Biopharm Reviewer

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/s/

Wei Qiu
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PHARMACOLOGIST

Hae-Young Ahn
5/18/01 06:08:52 PM
BIOPHARMACEUTICS

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CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA # 21-301	**SUBMISSION DATE: 28-July-2000, 30-January-2001, 15-March-2001, 06-April-2001**
BRAND NAME:	**Levoxyl®**
GENERIC NAME:	**Levothyroxine Sodium, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg oral tablets**
REVIEWER:	**Wei Qiu, Ph.D**
CONSULTANT:	**Steven Johnson, B.S.Pharm, Pharm.D**
SPONSOR:	**Jones Pharma, Inc.,1945 Craig Road, P.O.Box 46903, St. Louis, Missouri 63146**
TYPE OF SUBMISSION:	**New Drug Application**

TERMS AND ABBREVIATIONS:

AUC .... area under the plasma-concentration-time curve
BA..... ..... Bioavailability
BE..... ..... Bioequivalence
Cmax .. .. Maximum drug concentration
DMEDP..... Division of Metabolic and Endocrine Drug Products
DSI..... ..... Division of Scientific Investigation
NDA.... ..... New Drug Application
OCPB.. ..... Office of Clinical Pharmacology and Biopharmaceutics
SLS..... ..... Sodium Lauryl Sulfate
T1/2..... ..... Drug elimination half-life
T3..... ..... L-triiodothyronine
T4..... ..... L-thyroxine
Tmax... ..... Time to reach maximum drug concentration

SYNOPSIS:

Jones Pharma Inc. has submitted NDA 21-301 for Levoxyl® (Levothyroxine sodium) 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, and 300 mcg tablets on July 28, 2000. The Human Pharmacokinetics and Bioavailability section of this application contained two clinical pharmacokinetics studies and relevant in vitro dissolution testing information for review.

A single oral dose bioavailability study (338-03) compared 300 mcg Levoxyl® tablets manufactured by Jones Pharma Incorporated and 200 mcg Synthroid® injection given as an oral solution manufactured by Knoll Pharmaceutical Company following a single 600 mcg dose. It was found that the relative bioavailability of Levoxyl® tablets based on AUC values was 98%.

A single dose bioequivalence study (338-04) evaluated the dosage-form proportionality between three different strengths of Levoxyl® tablets 50 mcg, 100 mcg and 300 mcg following a single 600 mcg dose. The dosage-form proportionality between the examined three strengths was established.

An in vitro dissolution study examined the multi-point dissolution profiles for all strengths to be marketed. The sponsor used USP 24 monograph with the specification of not less than 70% in 45 minutes. There were some issues raised concerning the rapid dissolution and downward curvature of dissolution profiles using USP 24 dissolution method. Stability tests in USP 24 dissolution medium showed that this product

was stable for at least 10 hours. The Agency conducted dissolution tests with 100 mcg strength of Levoxyl® using USP 24 method. The results confirmed the stability of the drug under proper analytical conditions as well as the rapid dissolution for this product under USP 24 conditions. The USP 24 dissolution method is acceptable to the Agency if the sponsor agreed the specification tolerance of not less than —— in 15 minutes.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 21-301 submitted on 28-July-00, 31-January-01, 15-March-01, and 06-April-01. The overall Human Pharmacokinetic Section is acceptable providing reserve sample retention and software problems are solved. There are no further comments to be sent to the sponsor.

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(Appendices and/or Attachments available from DMEDP filing room or DFS, if not included)

BACKGROUND:

Levothyroxine sodium is indicated as replacement or substitution therapy for diminished or absent thyroid function such as cretinism, myxedema, non-toxic goiter or hypothyroidism. The diminished or absent thyroid function may result from functional deficiency, primary atrophy, from partial or complete absence of the gland or from the effects of surgery, radiation or antithyroid agents.

Levothyroxine sodium is the sodium salt of the levo isomer of the thyroid hormone, thyroxine. The production of levothyroxine hormone is regulated by the hypothalamus-pituitary axis through a negative feedback system. When hormone levels are inadequate, the hypothalamus secrets 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 (T4) and triiodothyronine (T3). T4 acts as a substrate for physiologic deiodination to T3 in the peripheral tissues. The physiologic effects of thyroid hormones are mediated at the cellular level primarily by T3. High levels of T4 inhibit the production of TSH and TSH-RH to a lesser degree. This effect decreases the further production of T4.

Circulating T4 is gradually eliminated from the body with a plasma half-life of about 7 days. An oral dose given once daily, once the dose is stabilized, results in a fairly stable level of serum T4 over the course of the next 24 hours. The circulating T3 formed from circulating T4, on the other hand, is cleared from the blood much more rapidly with a plasma half-life of about 1 to 1.5 days. Thus, the oral dosing of T4 results in a steady, stable serum level of T4 that in turn provides an equally stable level of serum T3.

Since levothyroxine is a narrow therapeutic index agent, it is important that the drug products available to patients are consistent in potency and bioavailability.

STUDY SUMMARY INDEX

DRUG FORMULATION:

Q. Is the composition of each strength tablet similar?

The differences in composition among all strength tablets are displayed in Table 1. The total weight of the dosage form remains nearly the same for all strengths ——— The same inactive ingredients were used for all strengths except the color additives, and the change in any strength was obtained by altering the amount of the active ingredient, microcrystalline cellulose and color additives. The Levoxyl® tablet compositions are proportionally similar across strengths.

Table 1. Composition of all strength tablets of Levoxyl®

Strength	Levothyroxine Sodium, USP (mg/tablet)	Microcrystalline Cellulose, NF (mg/tablet)	Croscarmellose Sodium, NF (mg/tablet)	Magnesium Stearate, NF (mg/tablet)	Color Additive(s)	Amt. of Color Additive(s) (mg/tablet)
25 mcg	0.025				FD&C Yellow #6	
50 mcg	0.050				N/A	
75 mcg	0.075				Lake Blend # (blend of D&C Red #30 and FD&C Blue #1)	
88 mcg	0.088				Lake Blend # (Blend of FD&C Yellow #6, and FD&C Blue #1)	
100 mcg	0.100				Lake Blend # (Blend of FD&C Yellow #6 and D&C Yellow#10)	
112 mcg	0.112				Lake Blend (Blend of FD&C Yellow #6, D&C Rd #30 and FD&C Red #40)	
125 mcg	0.125				Lake Blend (Blend of D&C Yellow # 10 and FD&C Red#40)	
137 mcg	0.137				FD&C Blue #1	
150 mcg	0.150				Lake Blend # (Blend of D&C Red #30 and FD&C Blue #1)	
175 mcg	0.175				Lake Blend	

			(Blend of D&C Yellow #10 and FD&C Blue #1)	
200 mcg	0.200		Lake Blend (Blend of D&C Yellow #10 and D&C Red #30)	
300 mcg	0.300		Lake Blend (Blend of FD&C Yellow #6, D&C Yellow #10 and FD&C Blue #1)	

DISSOLUTION:

Q. Is the dissolution method and specification appropriate?

The sponsor used USP 24 monograph under supplement 1 as the dissolution method (Table 2). The results of this study demonstrated that the multi-point dissolution profiles for Levoxyl tablets were similar across tablet strengths (Table 3 and Figure 1). However, it appeared that all the strengths of tablets dissolved more than — in 2.5 minutes and then the dissolution rates declined after 2.5 minutes. The sponsor was asked to submit 45-minute dissolution data to support the complete dissolution in 45 minutes (Table 4). Although the 45-minute dissolution data showed that for all the strengths tested more than of labeled claim dissolved in 45 minutes, the downward curvature of dissolution profiles could not be explained reasonably. In addition, because the product dissolved very fast (more than — of labeled claim dissolved within 2.5 minutes), the sponsor was asked to perform dissolution testing without surfactant SLS in the media at paddle speed 50 and 75 rpm to determine if SLS was a necessary component. The results are displayed in Table 5. It was found that using either paddle speed 50 rpm or 75 rpm the Levoxyl did not dissolve more than — and the dissolution profiles without SLS still exhibited a declined dissolution. The sponsor was requested to perform assay validation test including stability over 10 hour period of time with and without 0.2% SLS. The stability results (Table 6) showed that this product was stable for at least 10 hours in USP 24 dissolution medium. In addition, the Agency conducted dissolution tests with 100 mg tablet using USP 24 method to characterize the products (Attachment-FDA DPA Test). The results confirmed the stability of this product in USP 24 dissolution medium and rapid dissolution behavior. However, the downward curvature of the sponsor's dissolution profile can not be explained. It was agreed by the Agency that USP 24 dissolution method with specification of not less than — in 15 minutes will be appropriate for this product.

Table 2. Dissolution Method

Apparatus	2 (paddle)
Speed	50 rpm
Media	0.01 N hydrochloric acid containing 0.2% sodium lauryl sulfate
Volume	500 ml
Tolerance	— (Q) of the labeled amount is dissolved in 45 minutes
Strengths tested	25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, 300 mcg
No. of batches/strength	3
No. of tablets/dissolution	12
Time points	1, 2.5, 5, 7.5, and 10 minutes

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Table 4. 45-Minute Multi-Strength Dissolution Profile using USP 24

Lot Number	TT57	TT24*	TT31	TT33	TT25*	TT36	TT39	TT43	TT45	TT48	TT51	TT26*
Packed in	100ct	100ct	100ct	100ct	100ct	100ct	100ct	100ct	100ct	100ct	100ct	100ct
Strength (mcg)	25	50	75	88	100	112	125	137	150	175	200	300
Vessel 1												
Vessel 2												
Vessel 3												
Vessel 4												
Vessel 5												
Vessel 6												
Average	91.6	97.6	100.6	99.5	93.1	94.5	100.2	97.2	97.8	99.9	101.9	94.6
RSD(%)	2.50	7.33	4.21	3.57	2.21	1.84	3.23	1.57	1.85	3.34	1.62	4.15

* Pivotal Batches

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Table 5. Levoxyl 100 mcg dissolution profile using USP 24 without SLS at paddle speed of 50 rpm and 75 rpm.

Time (minutes)	50 rpm			75 rpm		
	Mean	Range (n=3)	RSD (%)	Mean	Range (n=3)	RSD (%)
1.0	16.7		40.95	36.1		14.50
2.5	42.6		7.39	42.7		9.86
5	53.2		10.41	55.1		3.77
7.5	51.2		15.33	55.9		5.50
10.0	57.1		5.06	51.0		11.57
15.0	58.1		4.21	54.9		9.99
20.0	54.9		6.67	50.9		4.49
30.0	52.3		6.98	49.7		11.90
40.0	47.6		16.46	43.3		12.09
45.0	48.5		3.52	44.5		8.34
50.0	42.2		15.60	42.1		5.35
60.0	40.8		17.89	39.2		6.89

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N21-301 Levoxyl Dissolution Profiles: USP 24

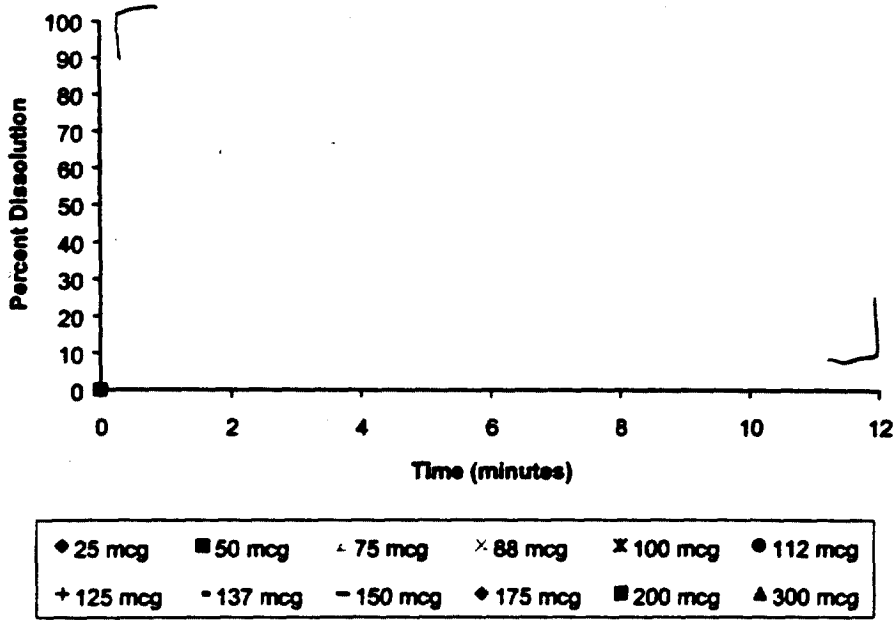

Figure 1. Levoxyl dissolution profile using USP 24.

Table 3. Dissolution profile of each strength of Levoxyl® using USP 24.

strength	1 min	2.5 min	5 min	7.5 min	10 min	Batch No.
25 mcg						TT55, TT56, TT57
50 mcg						TT18, TT21, TT24(clinical study batch)
75 mcg						TT30, TT31, TT32
88 mcg						TT33, TT34, TT35
100 mcg						TT19, TT22, TT25(clinical study batch)
112 mcg						TT36, TT37, TT38
125 mcg						TT39, TT40, TT41
137 mcg						TT42, TT43, TT44
150 mcg						TT45, TT46, TT47
175 mcg						TT48, TT49, TT50
200 mcg						TT51, TT52, TT53
300 mcg						TT20, TT23, TT26(clinical study batch)

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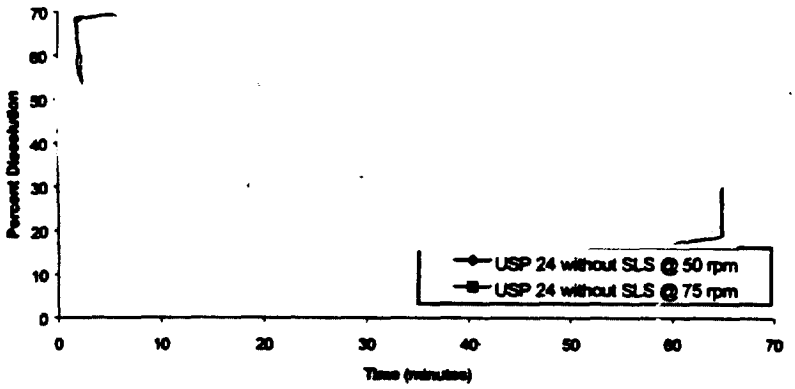


Figure 2. Levoxyl dissolution profiles using USP 24 without SLS at paddle speed 50 rpm and 75 rpm.

Table 6. The stability of the dissolution test solution hourly for up to 10 hours in USP 24 dissolution medium

Interval-injection time	TT 25 100 µg/tab				
	Vessel 1 % Dissolved	Vessel 2 % Dissolved	Vessel 3 % Dissolved	Mean	RSD
45 min				95.6	1.39
1 hour				95.8	0.57
2 hour				95.7	0.95
3 hour				95.7	1.00
4 hour				95.3	0.99
5 hour				96.2	1.36
6 hour				95.9	1.30
7 hour				95.1	1.61
8 hour				95.7	1.49
9 hour				95.6	1.52
10 hour				96.1	1.27

ANALYTICAL METHODOLOGY:

Q. Have the analytical methods been validated?

Total T4 and T3 in human serum were analyzed to assess the relative bioavailability of Levothyl® relative to solution and dosage-form proportionality. A method was validated for the determination of total (free and protein-bound) thyroxine (T4) and a method was used for the determination of total (free and protein bound) triiodo-l-thyronine (T3) using (Table 7). The validation is acceptable.

Table 7: Analytical Method Validation for T4 and T3

Analyte	T4		Analyte	T3	
Protocol #	338-03	338-04	Protocol #	338-03	338-04
ULQ(µg/dL)	—	—	ULQ (ng/ml)	—	—
LLQ(µg/dL)	—	—	LLQ (ng/ml)	—	—
Calibration (µg/dL)	3-24	3-24	Calibration (ng/ml)	0.5 – 8.00	0.5 – 8.0
Precision (C.V.%)			Precision (C.V.%)		
6.49 µg/dL	3.81	5.25	0.949 ng/ml	8.46	15.40
10.5 µg/dL	3.56	4.98	1.50 ng/ml	N/A	8.05
20.4 µg/dL	2.88	4.16	2.95 ng/ml	9.46	7.34
			5.94 ng/ml	7.64	not used
Accuracy (R.E.%)			Accuracy (R.E.%)		
6.49 µg/dL	+1.08	-0.15	0.949 ng/ml	-4.11	-5.58
10.5 µg/dL	+7.14	+1.43	1.50 ng/ml	N/A	+0.20
20.4 µg/dL	+9.02	+7.11	2.95 ng/ml	+0.37	-0.68
			5.94 ng/ml	+10.57	not used

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES:

I. Relative Bioavailability

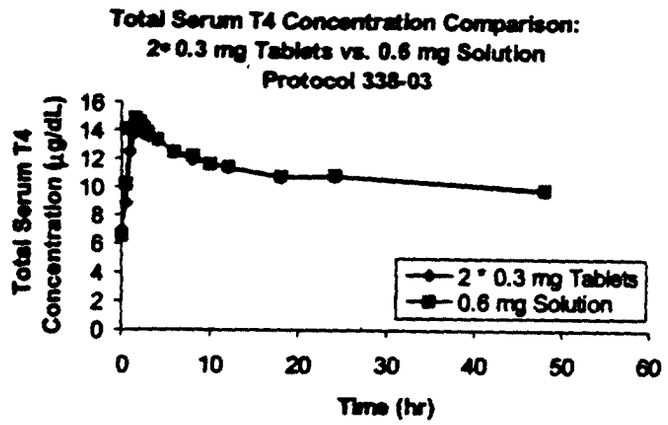
Q. What is the relative bioavailability of Levoxyl® tablets relative to Synthroid® solution?

The study, 338-03, submitted in this application was a two-way crossover single dose design in normal healthy subjects under fasting condition. The bioavailability of Levoxyl® 0.3 mg tablets manufactured by Jones Pharma Inc., relative to Knoll Pharmaceutical Company's levothyroxine sodium 200 µg (Synthroid®) injection given as an oral solution following a single 0.6 mg dose was determined. A total of 30 subjects were enrolled in the study, and 27 subjects completed the study. The relative bioavailability of a single dose of two 0.3 mg tablets of Levoxyl® was found to be 98% based on log-transformed AUC(0-t) values of T4. Results of this BA study are presented in Table 8 and Figure 3.

Table 8. Summary of the Pharmacokinetic Parameters of Serum T4 and T3 for Treatment A and B

	T4			T3			
	Treatment A	Treatment B			Treatment A	Treatment B	
PK Parameters	Arithmetic Mean ± SD	Arithmetic Mean ± SD	%Mean Ratio* (90% CI)	PK parameter	Arithmetic Mean ± SD	Arithmetic Mean ± SD	% Mean Ratio* (90% CI)
Cmax (µg/dL)	14.48 ± 1.93	15.09 ± 2.10	—	Cmax (ng/mL)	1.165±0.156	1.140 ± 0.119	—
Tmax (hr)	2.17 ± 0.810	1.62 ± 0.502	—	Tmax (hr)	14.6 ± 15.2	16.3 ± 17.0	—
AUC(0-t) (µg·hr/dL)	524.3 ± 59.07	529.3 ± 62.83	—	AUC(0-t) (ng·hr/mL)	51.25±6.163	50.07 ± 5.311	—
ln(Cmax)	2.663 ± 0.1434	2.705 ± 0.1339	94.5 (91.1–98.1)	ln(Cmax)	0.1444± 0.1289	0.1255±0.103 4	100.0 (96.8-103.4)
ln[AUC(0-t)]	6.256 ± 0.1167	6.265 ± 0.1169	98.0 (95.6-100.5)	ln[AUC(0-t)]	3.930± 0.1209	3.908± 0.1059	100.7 (97.7-103.8)

Treatment A = 2 x 0.3 mg Levoxyl Tablets: test
Treatment B = 0.6 mg Synthroid Reconstitute Oral Solution: reference
* = based on LS Means



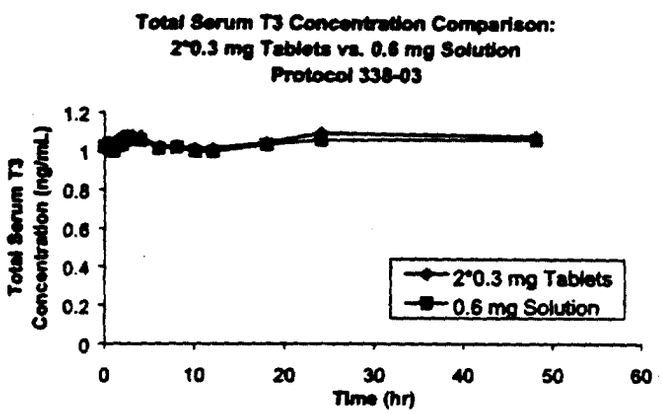


Figure 3. Total serum T4 (upper panel) and T3 (lower panel) comparison between 2*0.3 mg tablets and 0.6 mg solution.

II. Dosage-Form Proportionality

Q. Was dosage form proportionality established between the to-be-marketed formulations?

The study, 338-04, was a three-way crossover single dose design in normal healthy subjects. The dosage form proportionality between 50 mcg, 100 mcg, and 300 mcg of Levoxyl® tablets following a single 600 mcg dose was evaluated under fasting condition. A total of 28 subjects were enrolled in the study, and 24 subjects completed the study. Results of this study are presented in Table 9 and Table 10. Comparison of total T4 and T3 pharmacokinetics following administration of 12x50 mcg, 6x100 mcg, and 2x300 mcg Levoxyl® tablets indicated that these three formulations met the requirement for bioequivalence. The 90% confidence intervals for the comparisons of ln(Cmax) and ln[AUC(0-t)] for T4 and T3 among the three treatments were within the 80% to 125% ranges required for bioequivalence. Therefore, the dosage form proportionality is established.

Table 9. Summary of the Pharmacokinetic Parameters of Serum T4 for Treatment A, B and C

	Arithmetic Mean ± SD			% Mean Ratio* (90% CI)		
Pharmacokinetic Parameters	Treatment A	Treatment B	Treatment C	A vs. B	B vs. C	A vs. C
Cmax(µg/dL)	13.70 ± 1.82	14.13 ± 1.48	14.15 ± 1.50	—	—	—
Tmax (hr)	2.37 ± 1.04	1.98 ± 0.827	2.40 ± 1.09	—	—	—
AUC(0-t)(µg·hr/dL)	509.0 ± 58.36	528.3 ± 72.41	528.7 ± 57.13	—	—	—
ln(Cmax)	2.609 ± 0.1378	2.643 ± 0.1095	2.644 ± 0.1065	96.6 (93.6 – 100.1)	100.0 (96.7 – 103.4)	96.6 (93.6 – 100.1)
ln(AUC(0-t)]	6.226 ± 0.1200	6.261 ± 0.1379	6.265 ± 0.1089	96.7 (93.4 – 100.0)	99.7 (96.4 – 103.1)	96.4 (93.1 – 99.7)

*Treatment A = 12 x 50 mcg Levoxyl Tablets
** Treatment B = 6 x 100 mcg Levoxyl Tablets
*** Treatment C = 2 x 300 mcg Levoxyl Tablets

Table 10. Summary of the Pharmacokinetic Parameters of Serum T3 for Treatment A, B and C

	Arithmetic Mean ± SD			% Mean Ratio* (90% CI)		
Pharmacokinetic Parameters	Treatment A	Treatment B	Treatment C	A vs. B	B vs. C	A vs. C
Cmax(ng/mL)	1.173 ± 0.138	1.142 ± 0.133	1.167 ± 0.169	—	—	—
Tmax (hr)	12.9 ± 19.0	12.1 ± 16.1	11.5 ± 16.4	—	—	—
AUC(0-t)(ng·hr/mL)	49.43 ± 6.872	50.35 ± 8.994	49.36 ± 7.680	—	—	—
ln(Cmax)	0.1523± 0.1226	0.1264±0.1194	0.1437± 0.1491	102.6 (98.1 – 107.3)	98.2 (93.9 – 102.7)	100.7 (96.3 – 105.4)
ln[AUC(0-t)]	3.890 ± 0.1538	3.905 ± 0.1731	3.886 ± 0.1705	98.5 (93.1 – 104.3)	101.6 (96.2 – 107.8)	100.3 (94.7 – 106.2)

*Treatment A = 12 x 50 mcg Levoxyl Tablets
** Treatment B = 6 x 100 mcg Levoxyl Tablets
*** Treatment C = 2 x 300 mcg Levoxyl Tablets

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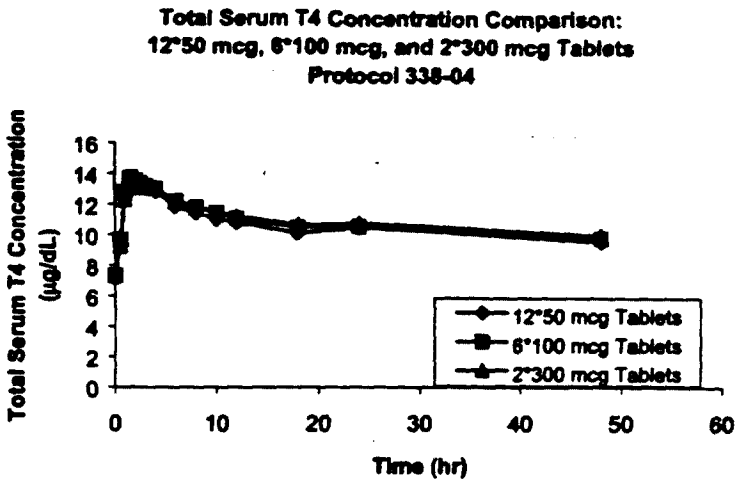

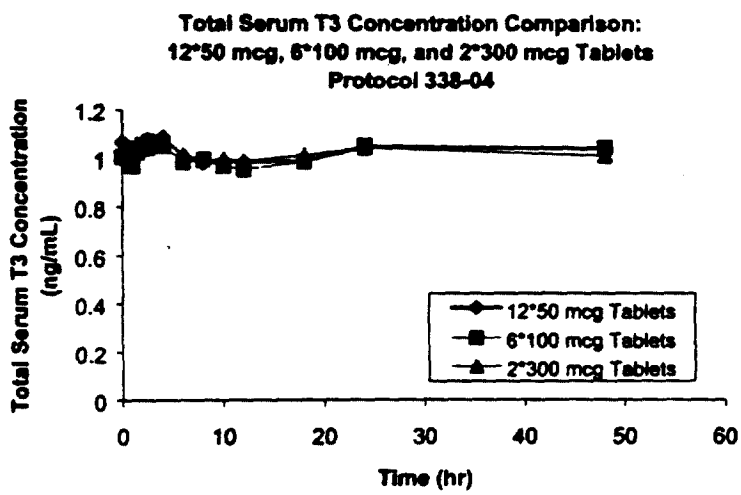

Figure 4. Total serum T4 concentration comparison among 12 × 50 mcg, 6 × 100 mcg, and 2 × 300 mcg tablets.

III Biowaivers

Q. Can the biowaiver request be granted for the tablet strengths that have not been tested in vivo?

1. The dosage-form proportionality among three strengths of tablets, 50 mcg, 100 mcg, and 300 mcg, representing low, middle, and high strengths of the formulation, were found to be acceptable.
2. Each tablet strength differs only in the amount of levothyroxine sodium and filler needs to maintain the tablet weights.
3. Multi-point dissolution profiles are similar across tablet strengths using USP 24 dissolution method.

Therefore, the biowaiver request can be granted.

LABELING COMMENTS:

(~~Strikeout text~~ should be removed from labeling; Double underlined text should be added to labeling; ☞ indicates an explanation only and is not intended to be included in the labeling)

☞ DMEDP is using similar labeling for all levothyroxine sodium submissions.

PHARMACOKINETICS

Absorption – Absorption of orally administered 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 Levoxyl® tablets, compared to an equal nominal dose of oral levothyroxine sodium solution, is approximately 98%. 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 (see **PRECAUTIONS, Drug Interactions** and **Drug-Food Interactions**).

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 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 (see **PRECAUTIONS, Drug Interactions** and **Drug-Laboratory Test Interactions**). Thyroid hormones do not readily cross the placental barrier (see **PRECAUTIONS, Pregnancy**).

Metabolism – T_4 is slowly eliminated (see **TABLE 1**). 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.

Table 1: Pharmacokinetic Parameters of Thyroid Hormones in Euthyroid Patients

Hormone	Ratio in Thyroid Gland	Biologic Potency	$t_{1/2}$ (days)	Protein Binding (%)[2]

Levothyroxine (T_4)	10 - 20	1	6-7[1]	99.96
Liothyronine (T_3)	1	4	≤ 2	99.5
[1] 3 to 4 days in hyperthyroidism, 9 to 10 days in hypothyroidism; [2] Includes TBG, TBPA, and TBA				

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Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader_____

OCPB Briefing April 3, 2001
attendees: Larry Lesko, Mei-Ling Chen, Hank Malinowski, John Hunt, John Lazor, Mehul Mehta, Hae-Young Ahn, Steven Johnson, Lawrance Yu, Yih Chain Huang, Larry Ouderkirk.

FT initialed by Hae-Young Ahn, Ph.D., Team Leader_____

CC: NDA # (orig.,1 copy), HFD-510(McCortS), HFD-870(Qiu, Ahn, Malinowski,), HFD-850(Lesko, Huang).

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Appendix 1. Study summaries

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2. SYNOPSIS

NAME OF COMPANY Jones Pharma Incorporated	INDIVIDUAL STUDY TABLE SYNOPSIS REFERRING TO PART 1 OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT Levoxyl®		
NAME OF ACTIVE INGREDIENT Levothyroxine sodium	Report No.: 20646 Volume: I	

Title of Study:	A Pharmacokinetic Study to Assess the Single Oral Dose Bioavailability of Two Formulations of Levothyroxine
Investigator:	[redacted]
Study Center:	[redacted]
Publication (Reference):	Not applicable
Studied period: **(date of first enrollment)** 07 Dec 1999 **(date of last completed)** 14 Jan 2000	**Phase of development:** I

Objectives: To determine the bioavailability of levothyroxine sodium (Levoxyl®) 0.3 mg tablets manufactured by Jones Pharma Incorporated, relative to Knoll Pharmaceutical Company's levothyroxine sodium 500 µg (Synthroid®) injection given as an oral solution following a single 0.6 mg dose.

Methodology: Single-dose, randomized, open-label, two-way crossover design.

Number of Subjects (planned and analyzed): A total of 30 subjects were enrolled in the study, and 27 subjects completed the study. All 30 subjects were included in the safety analyses and 27 subjects who completed the study were included in the pharmacokinetic analyses.

Diagnosis and Main Criteria for Inclusion: All subjects enrolled in this study were judged by the investigator to be healthy volunteers who met all inclusion and exclusion criteria.

Test Product, Dose, Duration, Mode of Administration, and Batch Number: The test product was levothyroxine sodium (Levoxyl®) 2 x 0.3 mg tablets (Jones Pharma Incorporated) administered as a single oral dose. Batch number TT26.

Reference Product, Dose, Duration, Mode of Administration, and Batch Number: The reference product was levothyroxine sodium (Synthroid®) 500 µg injection vials (Knoll Pharmaceutical Company) reconstituted resulting in a 600 µg/15 mL solution administered orally. Batch number 80130028.

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NAME OF COMPANY Jones Pharma Incorporated	INDIVIDUAL STUDY TABLE SYNOPSIS REFERRING TO PART 1 OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT Levoxyl®		
NAME OF ACTIVE INGREDIENT Levothyroxine sodium	Report No.: 20646 Volume: I	

Criteria for Evaluation:

Pharmacokinetics: Pharmacokinetic assessment consisted of the determination of total (bound + free) T4 and T3 concentrations in serum at specified time points following drug administration. From the serum data, the parameters AUC(0-t), *Cmax*, and *Tmax* were calculated.

Safety: Safety assessment included vital signs, clinical laboratory evaluation (including TSH), physical examination, and adverse events (AEs) assessment.

Statistical Methods:

Pharmacokinetics: Descriptive statistics (arithmetic mean, standard deviation (SD), coefficient of variation (CV), standard error of the mean (SE), sample size (N), minimum, and maximum) were provided for all pharmacokinetic parameters. The effects of baseline and baseline-by-treatment interaction were evaluated using a parametric (normal-theory) general linear model (ANCOVA) with treatment, period, sequence, subject within sequence, ln(baseline), and interaction between ln(baseline) and treatment as factors, applied to the ln-transformed pharmacokinetic parameters and Cmax. In the absence of significant ln(baseline) and interaction between ln(baseline) and treatment, these parameters were removed from the model. The two one-sided hypotheses were tested at the 5% level of significance for ln[AUC(0-t)] and ln(Cmax) by constructing 90% confidence intervals for the ratio of Treatment A to Treatment B.

Safety: Frequency counts of all subjects enrolled in the study, completing the study, and discontinuing early were tabulated. Descriptive statistics were calculated for continuous demographic variables, and frequency counts were tabulated for categorical demographic variables for each gender and overall.

AEs were coded using the 5th Edition of the COSTART dictionary. AEs were summarized by the number and percentage of subjects experiencing each coded event. A summary of the total number of each coded event and as a percentage of total AEs was also provided.

Laboratory summary tables included descriptive statistics for continuous serum chemistry and hematology results at each time point. Out-of-range values were listed by subject for each laboratory parameter.

Descriptive statistics for vital sign measurements at each time point and change from baseline to each time point were calculated by treatment group.

Shifts from screening to poststudy results for physical examinations were tabulated.

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NAME OF COMPANY Jones Pharma Incorporated	INDIVIDUAL STUDY TABLE SYNOPSIS REFERRING TO PART 1 OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT Levoxyl®		
NAME OF ACTIVE INGREDIENT Levothyroxine sodium	Report No.: 20646 Volume: I	

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS:

Serum T4: ANCOVA analyses indicated that the effects of ln(baseline) and interaction between ln(baseline) and treatment were not significant. Thus, these factors were removed from the general linear model and an ANOVA with treatment, period, sequence, and subject within sequence was applied to the ln-transformed Cmax and AUC(0-t) parameters. The arithmetic means of serum T4 pharmacokinetic parameters for Treatments A and B and the statistical comparison for ln-transformed parameters are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Serum T4 for Treatments A and B

	Serum T4					
	Treatment A		Treatment B			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI*	% Mean Ratio*
Cmax(ug/dL)	14.49	1.93	15.09	2.10	. - .	.
Tmax(hr)	2.17	0.810	1.82	0.802	. - .	.
AUC(0-t)(ug*hr/dL)	624.3	59.07	629.3	62.83	. - .	.
ln(Cmax)	2.663	0.1434	2.706	0.1339	91.1 - 98.1	94.6
ln(AUC(0-t))	6.256	0.1167	6.266	0.1169	96.6 - 100.6	98.0

Treatment A = 2 x 0.3 mg Levoxyl(R) Tablets: test
Treatment B = 0.6 mg Synthroid(R) Reconstitute Oral Solution: reference
* = Based on LS Means from Table 14.2.2.4.

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NAME OF COMPANY Jones Pharma Incorporated	INDIVIDUAL STUDY TABLE SYNOPSIS REFERRING TO PART 1 OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT Levoxyl®		
NAME OF ACTIVE INGREDIENT Levothyroxine sodium	Report No.: 20646 Volume: I	

Serum T3: ANCOVA analyses indicated that the effects of ln(baseline) and interaction between ln(baseline) and treatment were not significant and were removed from the ANOVA model, except for ln(baseline) on ln(Cmax) which was significant and was kept in the model. An ANOVA with treatment, period, sequence, subject within sequence, and ln(baseline), when significant, was applied to the ln-transformed Cmax and AUC(0-t) parameters. The arithmetic means of serum T3 pharmacokinetic parameters for Treatments A and B and the statistical comparison for ln-transformed parameters are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Serum T3 for Treatments A and B

	Serum T3					
	Treatment A		Treatment B			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI*	% Mean Ratio*
Cmax(ng/mL)	1.166	0.156	1.140	0.119	. - .	.
Tmax(hr)	14.6	15.2	16.3	17.0	. - .	.
AUC(0-t)(ng*hr/mL)	51.25	5.163	50.07	6.311	. - .	.
ln(Cmax)	0.1444	0.1298	0.1255	0.1034	95.8-103.4	100.9
ln(AUC(0-t)]	3.930	0.1209	3.908	0.1068	97.7-103.8	100.7

Treatment A = 2 x 0.3 mg Levoxyl(R) Tablets: test
Treatment B = 0.6 mg Synthroid(R) Reconstitute Oral Solution: reference
* = Based on LS Means from Table 14.2.3.4.

SAFETY RESULTS: A total of 18 treatment-emergent AEs were experienced by 11 (37%) of the 30 subjects dosed. Headache was the most common event, reported following both treatments. The majority of the AEs were mild or moderate in severity, and no serious adverse events occurred during the trial.

No clinically significant changes were observed regarding vital signs, physical examination, or clinical laboratory evaluations for either treatment.

CONCLUSION: Comparison of total T4 and T3 pharmacokinetics following administration of Levoxyl® (Treatment A, test formulation) and Synthroid® (Treatment B, reference formulation) indicated that the test formulation met the requirements for bioequivalence with the reference formulation.

The 90% confidence intervals for the comparisons of ln(Cmax) and ln[AUC(0-t)] for T4 and T3 were within the 80% to 125% range required for bioequivalence.

In regard to subject safety, both treatments appeared to be equally safe and well tolerated.

Date of the Report: May 2000

1. SYNOPSIS

NAME OF COMPANY Jones Pharma Incorporated	INDIVIDUAL STUDY TABLE SYNOPSIS REFERRING TO PART 1 OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT Levoxyl®		
NAME OF ACTIVE INGREDIENT Levothyroxine sodium	Report No.: 20655 Volume: 1	

Title of Study:	A Pharmacokinetic Study to Assess the Single Dose Bioequivalence of Three Strengths of Levothyroxine (Levoxyl®) Tablets
Investigator:	[redacted]
Study Center:	[redacted]
Publication (Reference):	Not applicable
Studied period: **(date of first enrollment)** 03 Dec 1999 **(date of last completed)** 20 Mar 2000	**Phase of development:** 1
Objectives: The objective of this study was to determine the dosage-form bioequivalence between three different strengths of levothyroxine sodium (Levoxyl®) tablets following a single 600 mcg dose.	
Methodology: This was a single dose, randomized, open-label, three-way crossover study conducted in healthy male and female subjects. Subjects were randomly assigned to receive a single 600 mcg dose of one of the levothyroxine sodium treatments (given as multiples of the 50 mcg, 100 mcg, or 300 mcg tablet) after an overnight fast. The alternate products were administered during subsequent study periods. A minimum 35-day washout interval separated each dosing period.	
Number of Subjects (planned and analyzed): A total of 28 subjects, 15 males and 13 females, were enrolled in the study and 24 subjects, 14 males and 10 females, completed the study. There were 24 subjects included in pharmacokinetic analyses and 28 subjects included in the safety analyses.	
Diagnosis and Main Criteria for Inclusion: All subjects enrolled in this study were judged by the investigator to be healthy volunteers who met inclusion and exclusion criteria.	
Test Product, Dose, Duration, Mode of Administration, and Batch Number: Subjects randomized to Treatment A received a single oral dose of 12 x 50 mcg levothyroxine sodium tablets (Levoxyl®), Lot No. TT24. Subjects randomized to Treatment B received 6 x 100 mcg levothyroxine sodium tablets (Levoxyl®), Lot No. TT25. Subjects randomized to Treatment C received 2 x 300 mcg levothyroxine sodium tablets (Levoxyl®), Lot No. TT26. All treatments were taken with 240 mL of water. Test products were manufactured by JMI-Daniels Pharmaceuticals, a subsidiary of Jones Pharma Incorporated.	
Reference Product, Dose, Duration, Mode of Administration, and Batch Number: Not applicable.	

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NAME OF COMPANY Jones Pharma Incorporated	INDIVIDUAL STUDY TABLE SYNOPSIS REFERRING TO PART 1 OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT Levoxyl®		
NAME OF ACTIVE INGREDIENT Levothyroxine sodium	Report No.: 20655 Volume: 1	

Criteria for Evaluation:

Pharmacokinetics: Pharmacokinetic assessment consisted of the determination of total (bound + free) T4 and T3 concentration in serum at specified time points following drug administration. From the serum data, the parameters AUC(0-t), Cmax, and Tmax were calculated.

Safety: The safety evaluation included monitoring of sitting vital signs, clinical laboratory measurements, thyroid-stimulating hormone (TSH), physical examination, electrocardiogram (ECG), and adverse events (AEs).

Statistical Methods:

Pharmacokinetics: Descriptive statistics (arithmetic mean, standard deviation [SD], coefficient of variation [CV], standard error of the mean [SEM], sample size [N], minimum, and maximum) were provided for all pharmacokinetic parameters. A parametric (normal-theory) general linear model with treatment, period, sequence, and subject within sequence as factors was applied to the ln-transformed Cmax and AUC(0-t). The two one-sided hypotheses were tested at the 5% level of significance for ln[AUC(0-t)] and ln(Cmax) by constructing 90% confidence intervals for the ratios of Treatment A to Treatment B, Treatment A to Treatment C, and Treatment B to Treatment C.

Safety: Frequency counts of all subjects enrolled in the study, completing the study, and discontinuing early were tabulated. Descriptive statistics were calculated for continuous demographic variables and frequency counts were tabulated for categorical demographic variables for each gender and overall. AEs were coded using the 5th Edition of the COSTART dictionary. AEs were summarized by the number and percentage of subjects experiencing each coded event. A summary of the total number of each coded event and as a percentage of total AEs was also provided. Laboratory summary tables included descriptive statistics for continuous serum chemistry and hematology results at each timepoint. Out-of-range values were listed by subject for each laboratory parameter. Descriptive statistics for results at each time point and change from baseline to each time point were calculated by treatment group. Shifts from screening to poststudy results for physical examinations were tabulated.

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NAME OF COMPANY Jones Pharma Incorporated	INDIVIDUAL STUDY TABLE SYNOPSIS REFERRING TO PART 1 OF THE DOSSIER Report No.: 20655 Volume: 1	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT Levoxyl®		
NAME OF ACTIVE INGREDIENT Levothyroxine sodium		

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS:

Serum T4: The arithmetic means of serum T4 pharmacokinetic parameters for Treatments A and B and the statistical comparison for the ln-transformed parameters are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Serum T4 for Treatments A and B

	Serum T4					
	Treatment A		Treatment B			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI*	% Mean Ratio*
Cmax(ug/dL)	13.79	1.82	14.13	1.48	: - :	:
Tmax(hr)	2.37	1.04	1.98	0.827	: - :	:
AUC(0-t)(ug*hr/dL)	509.0	80.36	520.3	72.41	: - :	:
ln(Cmax)	2.609	0.1378	2.643	0.1095	93.6-100.1	96.8
ln(AUC(0-t))	6.226	0.1200	6.251	0.1379	93.4-100.0	96.7

Treatment A = 12 x 50 mcg Levothyroxine Sodium Tablets
Treatment B = 6 X 100 mcg Levothyroxine Sodium Tablets
* = Based on LS Means from Table 14.2.2.4.1.

The arithmetic means of serum T4 pharmacokinetic parameters for Treatments A and C and the statistical comparison for the ln-transformed parameters are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Serum T4 for Treatments A and C

	Serum T4					
	Treatment A		Treatment C			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI*	% Mean Ratio*
Cmax(ug/dL)	13.79	1.82	14.15	1.80	: - :	:
Tmax(hr)	2.37	1.04	2.40	1.08	: - :	:
AUC(0-t)(ug*hr/dL)	509.0	80.36	530.7	87.13	: - :	:
ln(Cmax)	2.609	0.1378	2.644	0.1085	93.6-100.1	96.8
ln(AUC(0-t))	6.226	0.1200	6.265	0.1680	93.1- 99.7	96.4

Treatment A = 12 x 50 mcg Levothyroxine Sodium Tablets
Treatment C = 2 X 300 mcg Levothyroxine Sodium Tablets

The arithmetic means of serum T4 pharmacokinetic parameters for Treatments B and C and the statistical comparison for the ln-transformed parameters are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Serum T4 for Treatments B and C

	Serum T4					
	Treatment B		Treatment C			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI*	% Mean Ratio*
Cmax(ug/dL)	14.13	1.48	14.15	1.80	: - :	:
Tmax(hr)	1.98	0.827	2.40	1.08	: - :	:
AUC(0-t)(ug*hr/dL)	520.3	72.41	530.7	87.13	: - :	:
ln(Cmax)	2.643	0.1095	2.644	0.1085	99.7-103.4	100.9
ln(AUC(0-t))	6.251	0.1379	6.265	0.1680	98.4-103.1	99.7

Treatment B = 6 X 100 mcg Levothyroxine Sodium Tablets
Treatment C = 2 X 300 mcg Levothyroxine Sodium Tablets
* = Based on LS Means from Table 14.2.2.4.3.

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NAME OF COMPANY Jones Pharma Incorporated	INDIVIDUAL STUDY TABLE SYNOPSIS REFERRING TO PART 1 OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT Levoxyl®		
NAME OF ACTIVE INGREDIENT Levothyroxine sodium	Report No.: 20655 Volume: 1	

Serum T3: The arithmetic means of serum T3 pharmacokinetic parameters for Treatments A and B and the statistical comparison for the ln-transformed parameters are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Serum T3 for Treatments A and B

Pharmacokinetic Parameters	Serum T3 Treatment A Arithmetic Mean	SD	Serum T3 Treatment B Arithmetic Mean	SD	90% CI*	% Mean Ratio*
Cmax(ng/mL)	1.173	0.138	1.142	0.133	. .	.
Tmax(hr)	12.9	10.0	12.1	10.1	. .	.
AUC(0-t)(ng*hr/mL)	40.43	6.872	80.36	8.994	. .	.
ln(Cmax)	0.1523	0.1226	0.1264	0.1194	98.1-107.3	102.6
ln(AUC(0-t))	3.880	0.1538	3.905	0.1731	93.1-104.3	98.5

Treatment A = 12 x 50 mcg Levothyroxine Sodium Tablets
Treatment B = 6 X 100 mcg Levothyroxine Sodium Tablets

* = Based on LS Means from Table 14.2.3.4.1.

The arithmetic means of serum T3 pharmacokinetic parameters for Treatments A and C and the statistical comparison for the ln-transformed parameters are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Serum T3 for Treatments A and C

Pharmacokinetic Parameters	Serum T3 Treatment A Arithmetic Mean	SD	Serum T3 Treatment C Arithmetic Mean	SD	90% CI*	% Mean Ratio*
Cmax(ng/mL)	1.173	0.138	1.167	0.168	. .	.
Tmax(hr)	12.9	10.0	11.5	10.4	. .	.
AUC(0-t)(ng*hr/mL)	40.43	6.872	40.36	7.880	. .	.
ln(Cmax)	0.1523	0.1226	0.1437	0.1491	96.3-105.4	100.7
ln(AUC(0-t))	3.880	0.1538	3.886	0.1706	94.7-106.2	100.3

Treatment A = 12 x 50 mcg Levothyroxine Sodium Tablets
Treatment C = 2 X 300 mcg Levothyroxine Sodium Tablets
* = Based on LS Means from Table 14.2.3.4.2.

The arithmetic means of serum T3 pharmacokinetic parameters for Treatments B and C and the statistical comparison for the ln-transformed parameters are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Serum T3 for Treatments B and C

Pharmacokinetic Parameters	Serum T3 Treatment B Arithmetic Mean	SD	Serum T3 Treatment C Arithmetic Mean	SD	90% CI*	% Mean Ratio*
Cmax(ng/mL)	1.142	0.133	1.167	0.168	. .	.
Tmax(hr)	12.1	10.1	11.5	10.4	. .	.
AUC(0-t)(ng*hr/mL)	80.36	8.994	40.36	7.880	. .	.
ln(Cmax)	0.1264	0.1194	0.1437	0.1491	93.9-102.7	98.2
ln(AUC(0-t))	3.905	0.1731	3.886	0.1706	98.2-107.8	101.8

Treatment B = 6 X 100 mcg Levothyroxine Sodium Tablets
Treatment C = 2 X 300 mcg Levothyroxine Sodium Tablets
* = Based on LS Means from Table 14.2.3.4.3.

NAME OF COMPANY Jones Pharma Incorporated	INDIVIDUAL STUDY TABLE SYNOPSIS REFERRING TO PART 1 OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT Levoxyl®		
NAME OF ACTIVE INGREDIENT Levothyroxine sodium	Report No.: 20655 Volume: 1	

SAFETY RESULTS: There was a total of 59 treatment-emergent AEs reported by 15 (54%) of the 28 subjects dosed with study treatment. Incidence of AEs was similar across treatments. Headache was the most frequently reported event. The majority of reported AEs were mild in intensity. There was one subject who experienced a serious adverse event of chest pain, considered by the investigator to be unrelated to treatment.

No trends were noted in vital signs, clinical laboratory results, or ECGs to suggest treatment-related differences.

CONCLUSION: Comparison of total T4 and T3 pharmacokinetics following administration of 12 x 50 mcg Levoxyl® tablets (Treatment A) and 6 x 100 mcg Levoxyl® tablets (Treatment B) indicated that the two formulations met the requirements for bioequivalence. The 90% confidence intervals for the comparisons of ln(Cmax) and ln[AUC(0-t)] for T4 and T3 were within the 80% to 125% range required for bioequivalence.

Comparison of total T4 and T3 pharmacokinetics following administration of 12 x 50 mcg Levoxyl® tablets(Treatment A) and 2 x 300 mcg Levoxyl® tablets (Treatment C) indicated that the two formulations met the requirements for bioequivalence. The 90% confidence intervals for the comparisons of ln(Cmax) and ln[AUC(0-t)] for T4 and T3 were within the 80% to 125% range required for bioequivalence.

Comparison of total T4 and T3 pharmacokinetics following administration of 6 x 100 Levoxyl® tablets (Treatment B) and 2 x 300 mcg Levoxyl® tablets (Treatment C) indicated that the two formulations met the requirements for bioequivalence. The 90% confidence intervals for the comparisons of ln(Cmax) and ln[AUC(0-t)] for T4 and T3 were within the 80% to 125% range required for bioequivalence.

The test formulations appeared to be safe and generally well tolerated when given to healthy adult volunteers.

Date of the Report: June 2000

SECTION 6

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY

6.3 Results of the In-Vitro Bioavailability Study Levoxyl® Tablets

Study Objective:
To determine the multi-point dissolution profiles for all levothyroxine sodium tablet strengths to be marketed.

Study Scope:
The intent is to demonstrate that the multi-point dissolution profiles are similar across tablet strengths.

Protocol Reference:
Guidance for Industry: In Vivo Pharmacokinetics and Bioavailability Studies and In Vitro Dissolution Testing for Levothyroxine Sodium Tablets (June 1999). This protocol was submitted in IND ———

Analytical Method and Method Reference:
——— (Refer to **Attachment 1**)
USP 24 Supplement 1 page 2638

Protocol:
Perform multi-point dissolution testing using the following criteria and method

- Include all to be marketed levothyroxine sodium tablet strengths: 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200 and 300 mcg tablets.
- The batches used in the Clinical Trials (TT24, TT25, TT26) will be included.
- The batch size will be 1/10th scale or ——— tablets per batch.
- The number of batches tested per strength will be 3.
- The number of tablets tested for each dissolution will be 12.
- The time points tested will be 1, 2.5, 5, 7.5 and 10 minutes.

Results:
The following data presents the mean result for each of the tablet strengths of Levoxyl tested. Each point is the mean of three dissolutions, testing 12 tablets per dissolution or n=36. The mean data is presented in table form followed by a graph. The data is presented as percent of label claim dissoluted vs dissolution time. The individual values for each strength and each batch of Levoxyl tested is presented in **Attachment 2**.

Conclusions:
The results of this study demonstrate that the multi-point dissolution profiles for Levoxyl tablets are similar across tablet strengths.

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SECTION 6

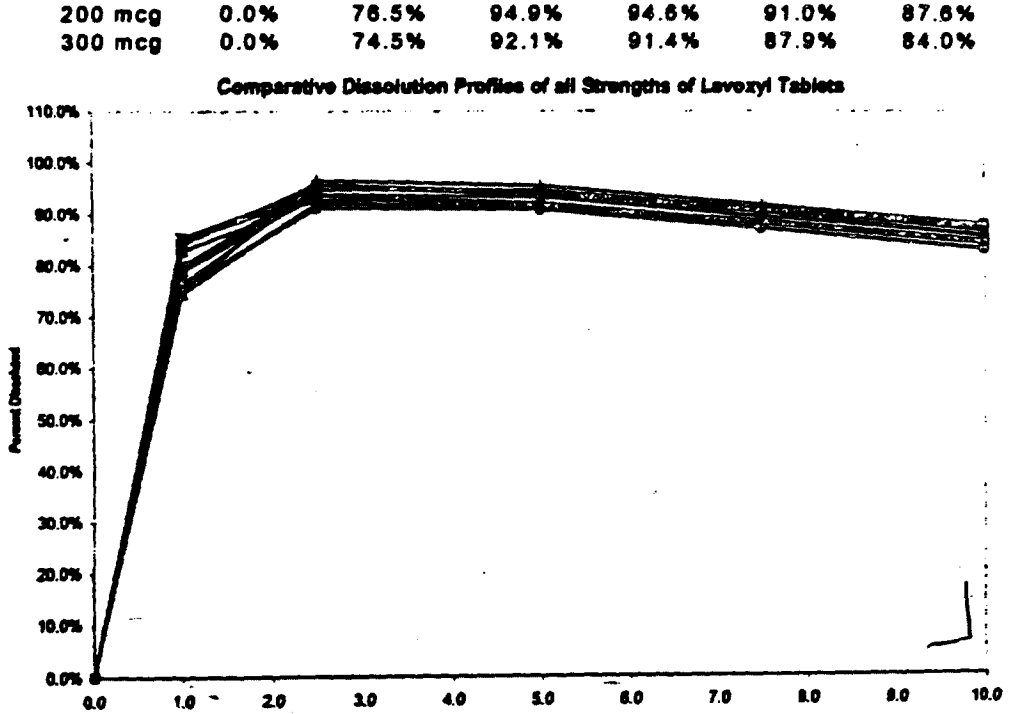
HUMAN PHARMACOKINETICS AND BIOAVAILABILITY

6.3 Results of the In-Vitro Bioavailability Study Levoxyl® Tablets

Comparative Dissolution Data of all Strengths of Levoxyl Tablets

	0 minutes	1 minute	2.5 minute	5 minutes	7.5 minutes	10 minutes
25 mcg	0.0%	84.9%	93.7%	90.9%	88.6%	84.7%
50 mcg	0.0%	82.8%	92.7%	91.8%	87.8%	84.4%
75 mcg	0.0%	78.9%	93.6%	92.2%	88.3%	84.7%
88 mcg	0.0%	79.8%	95.6%	94.1%	90.5%	86.9%
100 mcg	0.0%	85.4%	94.8%	94.5%	90.7%	86.5%
112 mcg	0.0%	75.5%	91.1%	90.7%	87.0%	82.9%
125 mcg	0.0%	75.0%	96.5%	95.5%	91.7%	87.8%
137 mcg	0.0%	79.9%	93.9%	93.2%	89.4%	85.7%
150 mcg	0.0%	75.6%	91.9%	91.4%	88.7%	84.6%
175 mcg	0.0%	84.2%	95.7%	93.5%	90.3%	85.5%
200 mcg	0.0%	76.5%	94.9%	94.6%	91.0%	87.6%
300 mcg	0.0%	74.5%	92.1%	91.4%	87.9%	84.0%

Comparative Dissolution Profiles of all Strengths of Levoxyl Tablets



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45 minute Multi-Strength Dissolution Profile

Lot Number	TT57	TT24*	TT31	TT33	TT25*	TT36	TT39	TT43	TT45	TT48	TT51	TT26*
Packaged in	100ct	100ct	100ct	100ct	100ct	100ct	100ct	100ct	100ct	100ct	100ct	100ct
Tablet Strength	25mcg	50mcg	75mcg	88mcg	100mcg	112mcg	125mcg	137mcg	150mcg	175mcg	200mcg	300mcg
Vessel 1												
Vessel 2												
Vessel 3												
Vessel 4												
Vessel 5												
Vessel 6												
Average % Dissoluted	91.6	97.6	100.6	99.5	93.1	94.5	100.2	97.2	97.6	99.9	101.9	94.6
RSD	2.50%	7.33%	4.21%	3.57%	2.21%	1.64%	3.23%	1.57%	1.85%	3.34%	1.62%	4.15%

* Pivotal Batches

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The Effects of Omitting Sodium Lauryl Sulfate (SLS) from the Dissolution Medium on the Dissolution Rate of Levoxyl (levothyroxine sodium tablets, USP)

Purpose of the Current Study:

The NDA for Levoxyl (levothyroxine sodium tablets, USP) (NDA 21-301) includes dissolution data on three lots of all the to-be-marketed strengths (Original Submission – Section 6.3 submitted 7/28/00 and Amendment 3.1 submitted 1/29/01). These dissolutions were conducted according to the USP 24 procedure which requires the addition of 0.2% SLS to the dissolution medium.

In reviewing NDA 21-301, the FDA Biopharmaceutics reviewers requested further analysis to determine what effect, if any, omitting the SLS from the dissolution medium would have on the dissolution rate of Levoxyl tablets.

For the purpose of this study, the 100 mcg strength Levoxyl tablets (Batch # TT25) was selected. This strength was selected because the 100 mcg strength is the middle strength of the to-be-marketed strengths and represents the major market volume of Levoxyl tablets. This batch was selected because it is one of the clinical pivotal batches submitted in NDA 21-301.

Study Objectives:

1. To determine the effects of omitting the SLS from the dissolution medium on the dissolution rate of Levoxyl tablets.

2. To determine the effects of two paddle speeds using media without SLS on the dissolution rate of Levoxyl tablets.

3. To determine the dissolution rate for an extended period of time.

Materials and Methods:

Experiment 1

1. Product Tested:
   a) Levoxyl 100 mcg tablets – Batch # TT25
   b) Number of Tablets Tested: 3
2. Procedure: The dissolution procedure stated in USP 24 for levothyroxine sodium tablets with a paddle speed of 50 rpm was used with the following variations:
   a) Dissolution Medium: 0.01*N* HCl (SLS was omitted)
   b) Sample Intervals Tested: 1.0, 2.5, 5.0, 7.5, 10.0, 15.0, 20.0, 30.0, 40.0, 45.0, 50.0 and 60.0 minutes

The Effects of Omitting Sodium Lauryl Sulfate (SLS) from the Dissolution Medium on the Dissolution Rate of Levoxyl (levothyroxine sodium tablets, USP) – Page 2

Materials and Methods (Continued):

Experiment 2:

1. Product Tested:
   a) Levoxyl 100 mcg tablets – Batch # TT25
   b) Number of Tablets Tested: 3
2. Procedure: The dissolution procedure stated in USP 24 for levothyroxine sodium tablets with the following variations:
   a) Dissolution Medium: 0.01*N* HCl (SLS was omitted)
   b) Paddle Speed: 75 rpm
   b) Sample Intervals Tested: 1.0, 2.5, 5.0, 7.5, 10.0, 15.0, 20.0, 30.0, 40.0, 45.0, 50.0 and 60.0 minutes

Results:

Historical Data:

For the purposes of comparison, the data presented in **FIGURE 1** are the dissolution results for Levoxyl 100 mcg – TT25. The data are presented in table and graphic forms. These data have been previously submitted in NDA 21-301 (Original Submission). The specification for the dissolution of levothyroxine sodium tablets stated in USP is not less than 70% *(Q)* within 45 minutes. The results presented in FIGURE 1 show that at 2.5 minutes, the dissolution rate was well above the *Q* of 70%. In addition, the 45.0 minute results of —— (data submitted in Amendment 3.1) show that Levoxyl has satisfied the USP specification of not less than *(Q)* 70% within 45 minutes

Experiment 1:

The data presented in **FIGURE 2** are the dissolution results for Experiment 1. The mean of the values obtained from the tablets tested was calculated. The mean, the RSD and the range (low and high value) for each data set are reported. The results presented in FIGURE 2 show that without the presence of 0.2% SLS, none of the individual vessels reached a dissolution rate of 70% within the required 45.0 minutes. The mean dissolution rate at 45.0 minutes was found to be —— which is lower than the USP specification of 70.0%. Even after 60.0 minutes the mean dissolution rate was only ——

Experiment 2:

The data presented in **FIGURE 3** are the dissolution results for Experiment 2. The paddle speed for this dissolution was increased from 50 rpm to 75 rpm. The mean, the RSD and the range (low and high value) for each data set are reported. The results presented in FIGURE 3 show that without the presence of 0.2% SLS, even if the paddle speed is increased to 75 rpm, the results do not conform to the USP specification. At 45.0 and 60.0 minutes the mean values were found to be ———— respectively.

The Effects of Omitting Sodium Lauryl Sulfate (SLS) from the Dissolution Medium on the Dissolution Rate of Levoxyl (levothyroxine sodium tablets, USP) – Page 3

Results (Continued):

Comparative Review:
The data presented in **FIGURE 4** compares the dissolution values obtained with and without the addition of SLS in the dissolution medium for the time points up to 10.0 minutes. **FIGURE 5** compares the dissolution values obtained with and without the addition of SLS and includes the extended time points of 45.0 minutes for the historical data and 45.0 and 60.0 minutes for the experiments without SLS. The data reveals a significant effect on dissolution release rates in the absence of the surfactant. At the initial 1.0 minute interval, without SLS, there is about a ———— decrease in dissolution rate for the 50 rpm and 75 rpm dissolutions respectively. Subsequent time points show similar results.

Discussion:

According to the Pharmacopeial Forum (Volume 24, No. 6, Nov.-Dec. 1998, "Proposed Revision to the Dissolution Test for Levothyroxine Sodium Tablets), the SLS was "found to reduce or completely eliminate the observed adsorptive loss of Levothyroxine in contact with glass surfaces". The dissolution profile for Levoxyl tablets using the current USP monograph procedure shows that Levoxyl tablets are fast releasing. Over —— of the labeled amount of the drug dissolved within 2.5 minutes.

As requested by the FDA Biopharmaceutics Reviewers, this study was conducted to determine if the SLS was needed in the dissolution medium. The results of this study show that in the absence of SLS, the dissolution of Levoxyl tablets is significantly reduced. This dissolution rate is reduced to such an extent that the values obtained without SLS do not conform to the USP specifications for levothyroxine sodium tablets, regardless of the paddle speed used in the test. The absence of the SLS in the dissolution medium would not be a viable option for Levoxyl.

Conclusion:

The results of this study clearly demonstrate that SLS is a necessary component of the dissolution medium for Levoxyl tablets and that the analytical method listed in USP 24 is the method of choice when performing such testing. Therefore, all the dissolution data submitted in NDA 21-301 using hydrochloric acid dissolution medium containing 0.2% sodium lauryl sulfate present a dissolution profile for Levoxyl tablets that is consistent with USP monograph criteria. No further testing is warranted unless requested by FDA.

FIGURE 1

HISTORICAL DATA

Dissolution Profile – Levoxyl 100 mcg – TT25 (with SLS @ 50 rpm)

Time	Mean Value	Range (n= 12)	RSD
1.0 minute	81.4%		19.50%
2.5 minutes	92.0%		3.36%
5.0 minutes	92.5%		4.54%
7.5 minutes	88.0%		1.08%
10.0 minutes	83.1%		1.14%

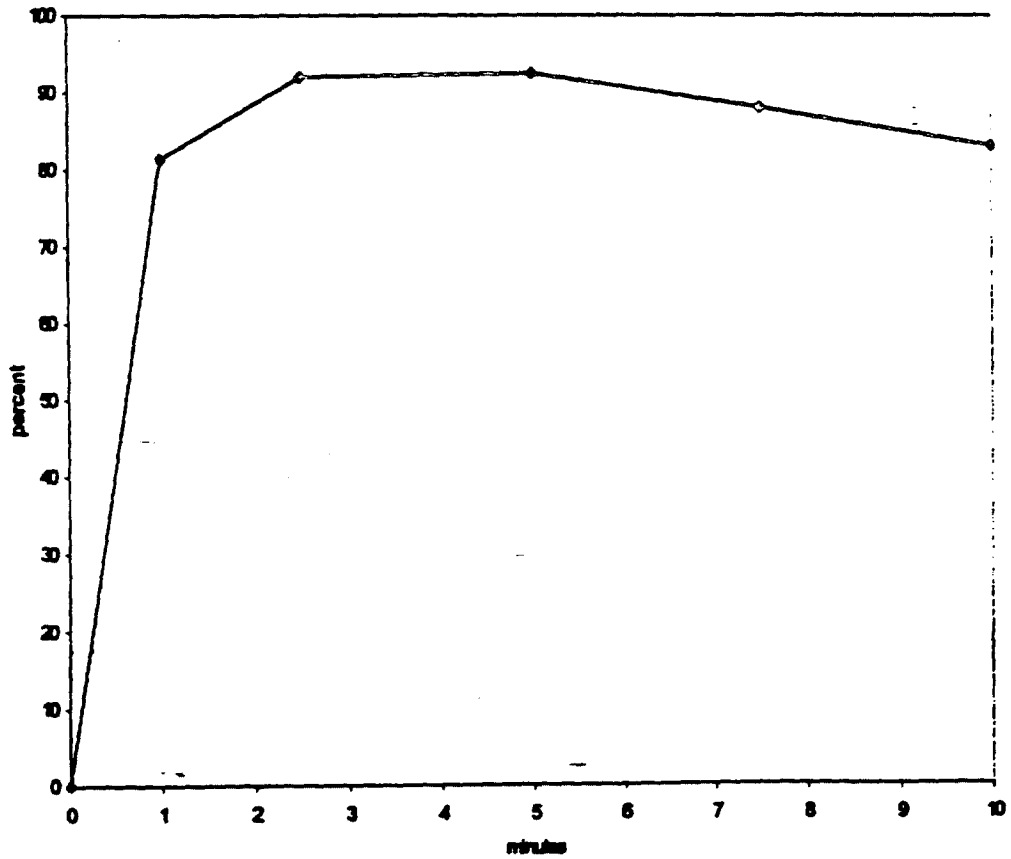


FIGURE 2

EXPERIMENT 1

Dissolution Profile – Levoxyl 100 mcg – TT25 (without SLS @ 50 rpm)

Time	Mean Value	Range (n= 3)	RSD
1.0 minute	16.7%		40.95%
2.5 minutes	42.6%		7.39%
5.0 minutes	53.2%		10.41%
7.5 minutes	51.2%		15.33%
10.0 minutes	57.1%		5.06%
15.0 minutes	58.1%		4.21%
20.0 minutes	54.9%		6.67%
30.0 minutes	52.3%		6.98%
40.0 minutes	47.6%		16.46%
45.0 minutes	48.5%		3.52%
50.0 minutes	42.2%		15.60%
60.0 minutes	40.8%		17.89%

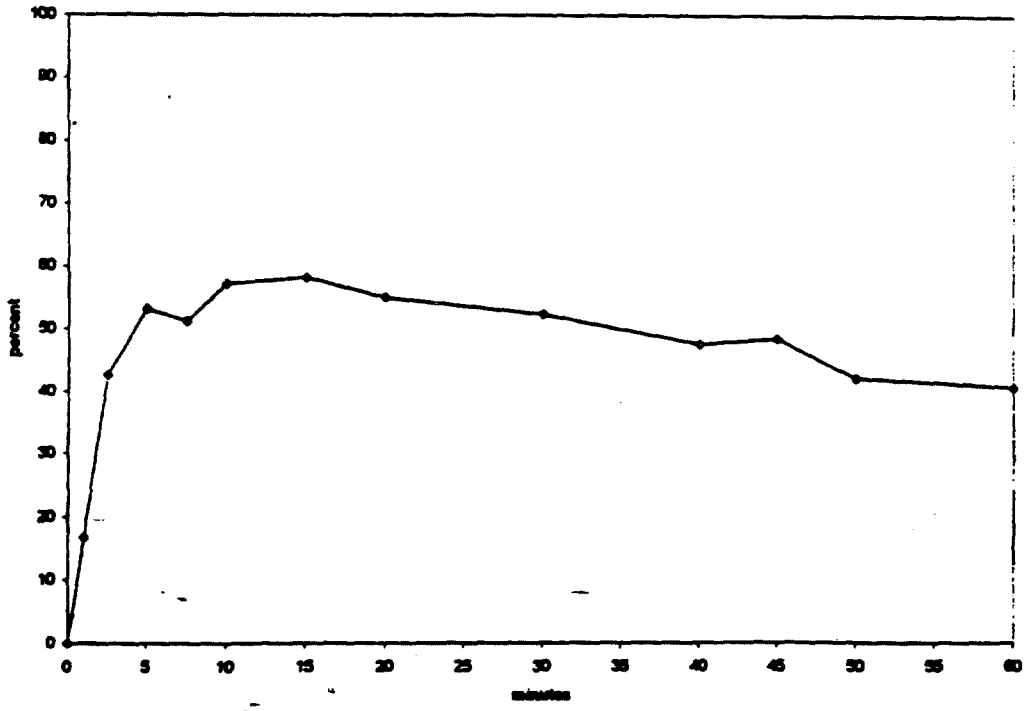


FIGURE 3

EXPERIMENT 2

Dissolution Profile – Levoxyl 100 mcg – TT25 (without SLS @ 75 rpm)

Time	Mean Value	Range (n= 3)	RSD
1.0 minute	36.1%		14.50%
2.5 minutes	42.7%		9.86%
5.0 minutes	55.1%		3.77%
7.5 minutes	55.9%		5.50%
10.0 minutes	51.0%		11.57%
15.0 minutes	54.9%		9.99%
20.0 minutes	50.9%		4.49%
30.0 minutes	49.7%		11.90%
40.0 minutes	43.3%		12.09%
45.0 minutes	44.5%		8.34%
50.0 minutes	42.1%		5.35%
60.0 minutes	39.2%		6.89%

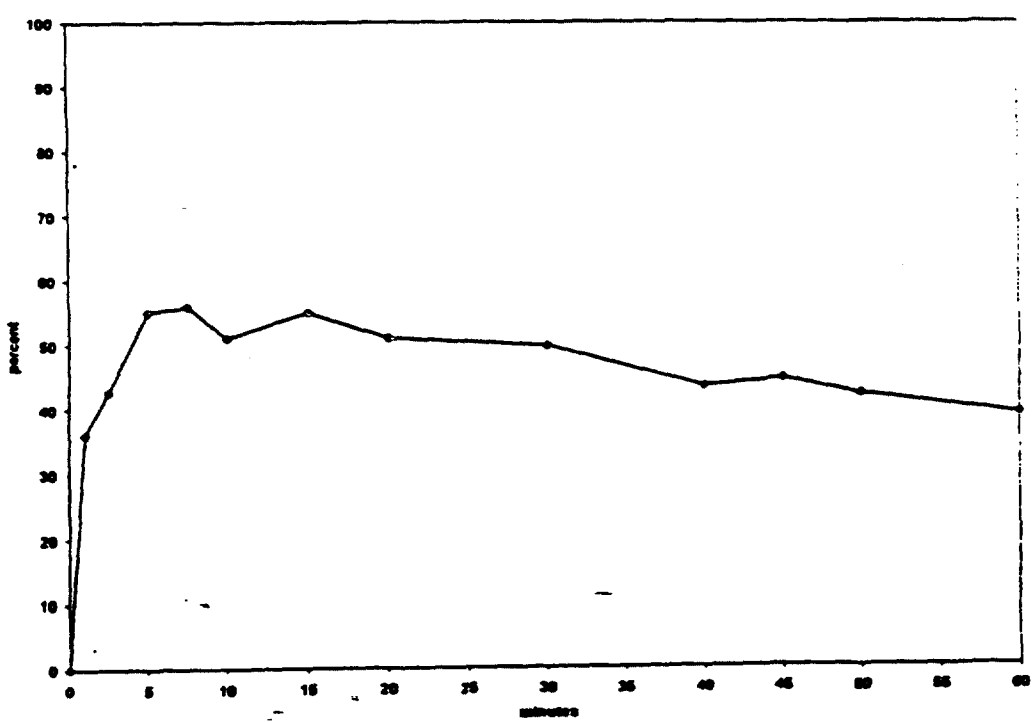


FIGURE 4

COMPARATIVE REVIEW

Levoxyl 100 mcg – TT25
(with SLS @ 50 rpm and without SLS @ 50 and 75 rpm)

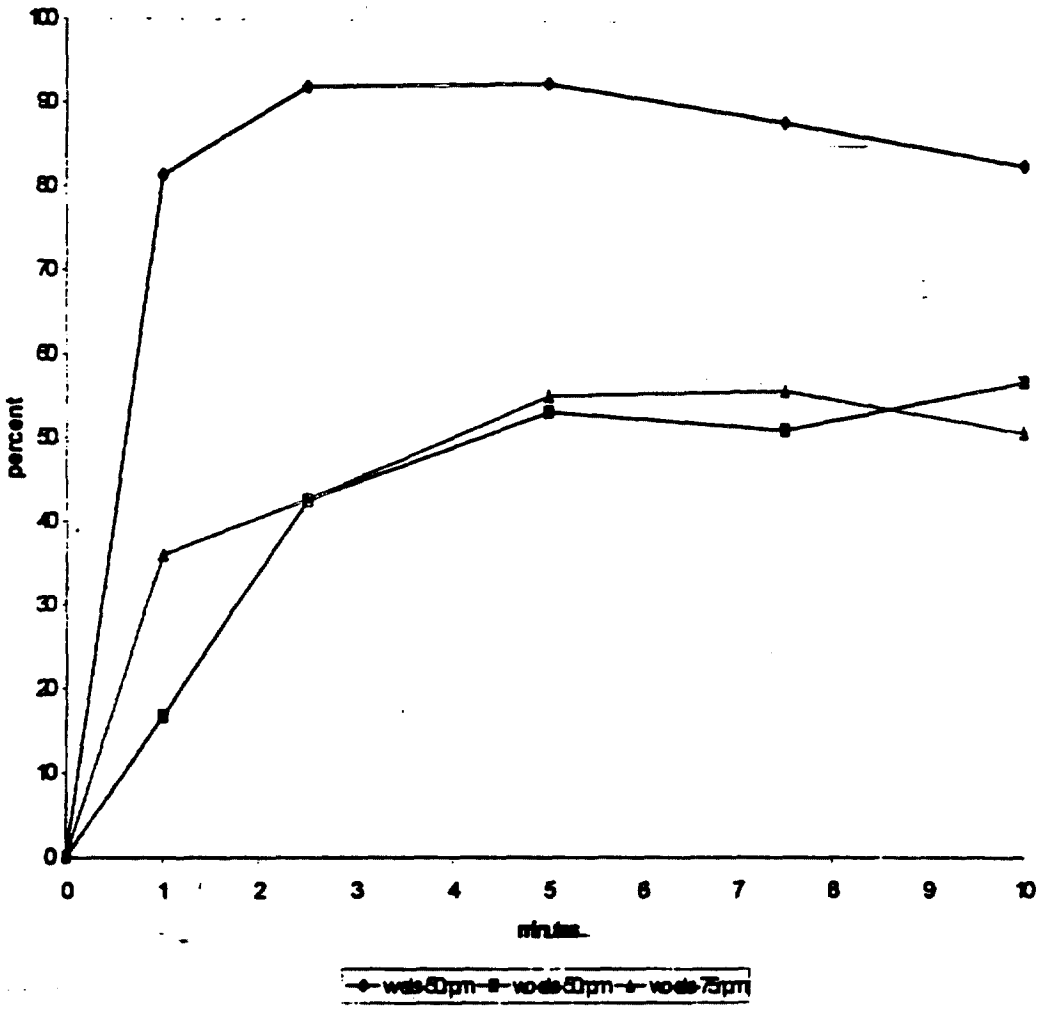
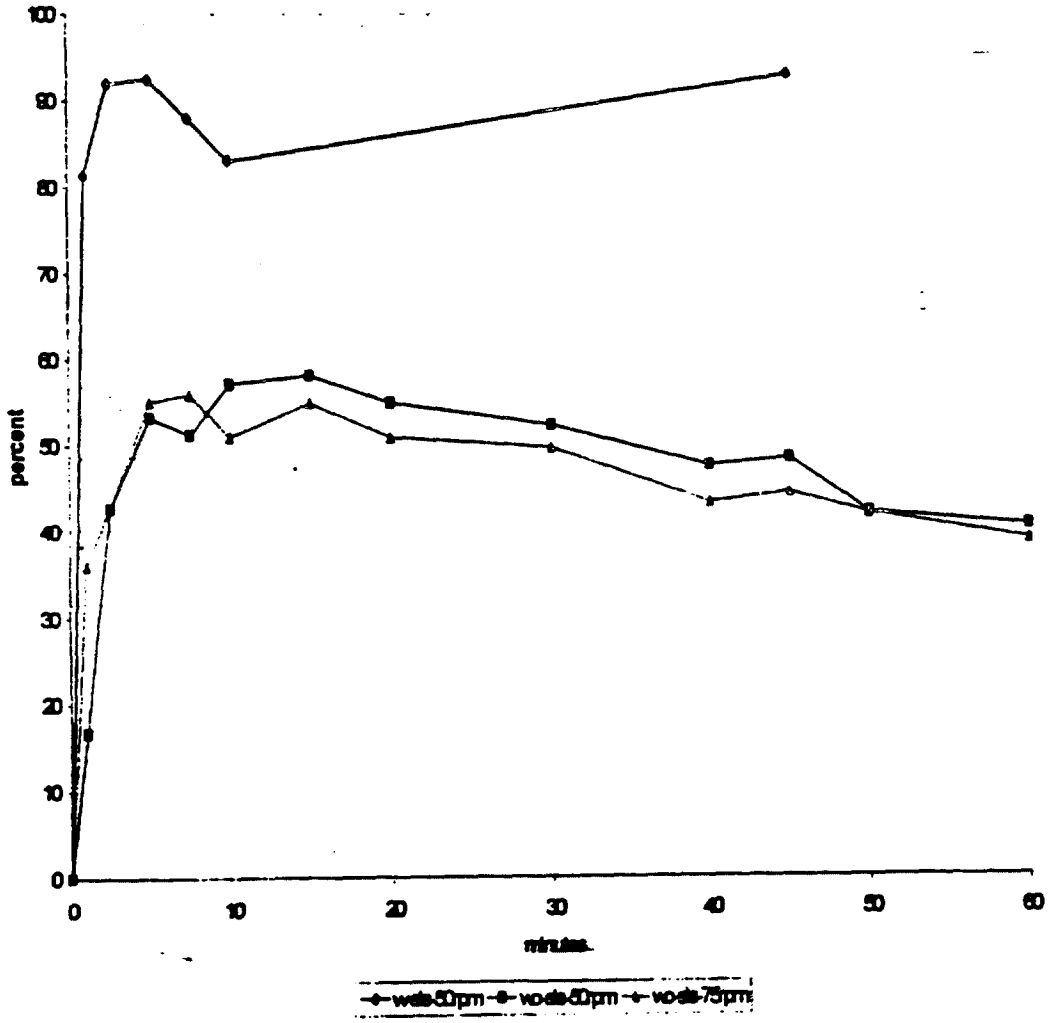


FIGURE 5

COMPARATIVE REVIEW

Levoxyl 100 mcg – TT25
(with SLS @ 50 rpm and without SLS @ 50 and 75 rpm)



JMI-Daniels Pharmaceuticals, Inc.	Report: QCSP-121
Title: Potency and Dissolution – Stability of the Levothyroxine Sodium in the HPLC vial over time.	Department: Quality Control

Purpose: TT 25, 100 µg/tab, 100 ct bottle was analyzed over a period of time to determine if the Pharmaceutical Active Ingredient (Levothyroxine Sodium) degrades over time. Dissolution 45 min interval was injected at t=0 and every hour after t=0 up to t=10 hours.

Procedure and Summary:

I. The following sample was used in this study:
TT 25: 100 µg per tablet (100 ct bottle)

II. Dissolution per _____ was used where the sampling time is at 45 minutes (t=0). A single volume of approximately 45 cc was drawn from each vessel. This single sample was utilized to fill all individual HPLC injection vials simultaneously. Each vial would represent the injection times as depicted in the tables below.

A. Data for the 100 µg/ml TT25 dissolution with the SLS is found in Table A.

Table A

Interval – inj time	TT 25 100 µg/tab with SLS				
	Ves 1 % Diss	Ves 2 % Diss	Ves 3 % Diss	Mean	RSD
45 min, t = 0				95.6	1.39
t = 1				95.8	0.57
t = 2				95.7	0.95
t = 3				95.7	1.00
t = 4				95.3	0.99
t = 5				96.2	1.36
t = 6				95.9	1.30
t = 7				95.1	1.61
t = 8				95.7	1.49
t = 9				95.6	1.52
t = 10				96.1	1.27

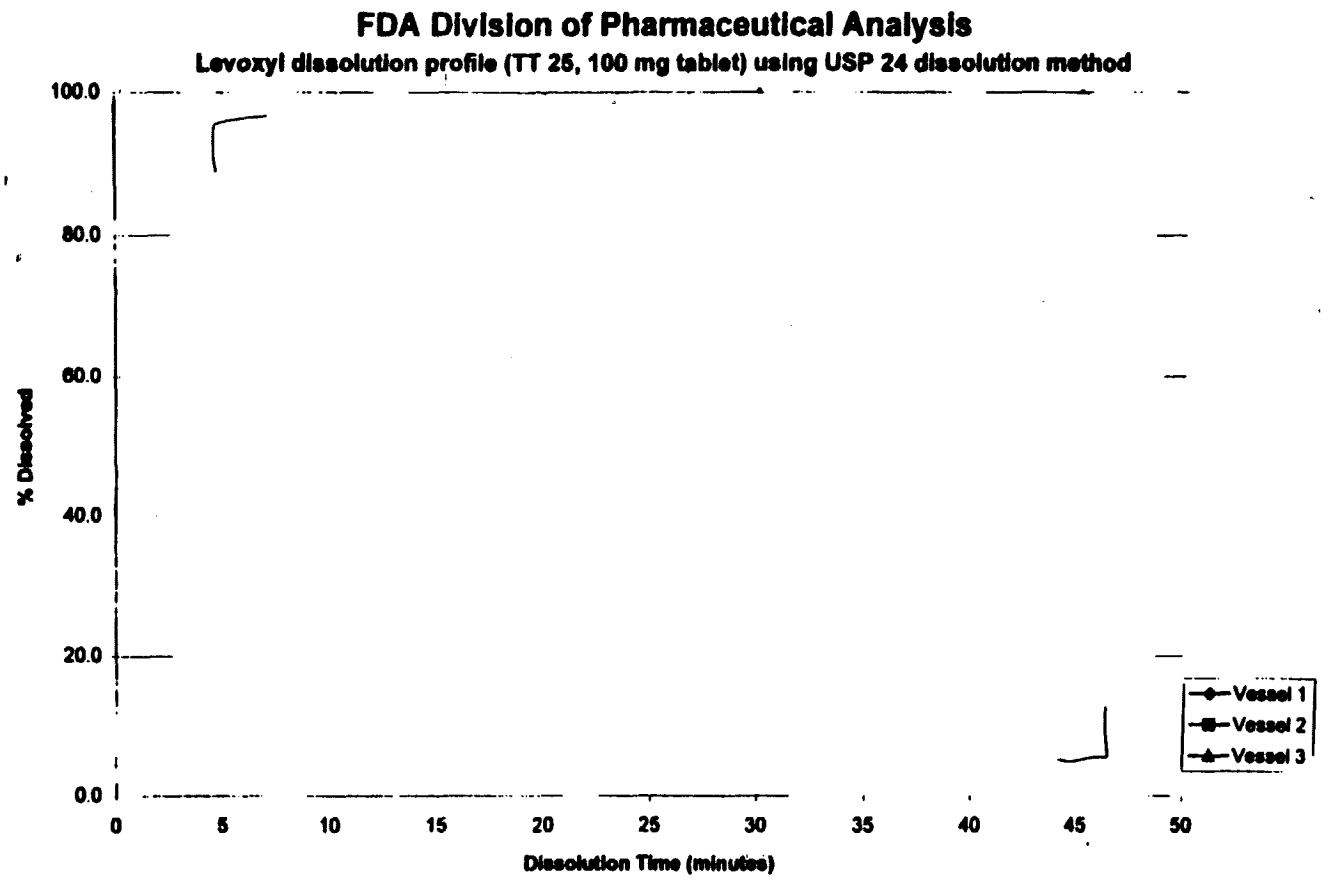
System Suitability RSD 0.17%; Standard over the run RSD 0.47%

B. Data for the 100 µg/ml TT25 dissolution without the SLS is found in Table B.

Table B

Interval – inj time	TT 25 100 µg/tab without SLS				
	Ves 1 % Diss	Ves 2 % Diss	Ves 3 % Diss	Mean	RSD
45 min, t = 0				94.7	3.62
t = 1				91.6	6.14
t = 2				90.5	4.56
t = 3				89.5	2.56
t = 4				85.0	9.89
t = 5				88.1	5.51
t = 6				88.3	4.12
t = 7				84.8	5.76
t = 8				82.9	7.63
t = 9				76.3	2.37
t = 10				81.1	6.13

System Suitability RSD 1.44%; Standard over the run RSD 2.78%



APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

DATE: March 26, 2001

FROM: Michael F. Skelly, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: FAX
C. T. Viswanathan, Ph.D. /S/ 3/26/01
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 21-301, Levoxil® (levothyroxine sodium), sponsored by Jones Pharmaceuticals

TO: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products (HFD-510)

As requested by HFD-510, the Division of Scientific Investigations initiated an audit of the analytical portions of the following bioequivalence studies.

Study 338-03: (Project 20646) "A Pharmacokinetic Study to Assess the Single Oral Dose Bioavailability of Two Formulations of Levothyroxine"

Study 338-04: (Project 20655) "A Pharmacokinetic Study to Assess the Single Oral Dose Bioavailability of Three Strengths of Levothyroxine (Levoxyl®)"

The site of the analytical portions of the studies was [redacted] (now [redacted] The clinical portion of study #338-03 was conducted at [redacted] and the clinical portion of study #338-04 was conducted at [redacted] The inspection was limited to the analytical portion, as requested by HFD-510.

Following the analytical site inspection (2/26-3/2/2001), Form FDA-483 was issued. Our evaluation of the inspectional findings is provided below.

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1a. Reserve samples for Jones Pharma levothyroxine study #338-04/20655 were returned to the manufacturer and therefore were not available to FDA for sampling at this clinical site ——

1b. Reserve samples for Jones Pharma levothyroxine study #338-03/20646 were not selected and retained at the clinical site

Although the inspection was intended to cover only the analytical portions of the studies, the discussion of reserve sample retention was noticed during a review of correspondence files. The failure to retain reserve samples at the clinical sites is a violation of 21 CFR 320.38(b)(3). Thus, the identity of the test and reference drug products used in the studies cannot be verified. However, please note that DSI has not examined comparable records of clinical portions of bioequivalence studies for other levothyroxine NDAs.

2. Software Problem Report #15192 was written in response to a user-reported error in regression calculation in study 338-04/20655-2 dated 3/2/2000. To date, there has been no final conclusion, resolution, correction, or evaluation of this error report. The extent and impact on data generated by the affected program, ——— has not been determined.
3. The information systems standard operating procedures for software problem reporting are inadequate in that:

a) Software problems are not resolved in a timely manner.
b) Software problem report summaries are not reviewed on a periodic basic.

——————— calibration curves were fitted with a computer program ——— written for ——————— by a consultant. Calibration data from one run caused the program to abort. The failure could be reproduced on ——— at ——————— but not at the consultant's site. Thus, the software failure is unique to the ——————— installation. As of this writing, ——————————— has not determined the cause of the failure. Therefore, the extent of its impact on other data in these studies is unknown.

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Conclusion:

We recommend that the data from Studies #338-03 and 338-04 be not accepted unless and until it is shown that software failure did not affect other data.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

/S/

Michael F. Skelly, Ph.D.

DSI Final Classification:

VAI - (These studies only.)

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

/s/

Wei Qiu
5/1/01 11:06:51 AM
PHARMACOLOGIST

Steve Johnson
5/9/01 11:51:30 AM
BIOPHARMACEUTICS
Dr. Steven B. Johnson [acting team leader] signing off for Dr. Hae-Young Ahn. The final draft was reviewed by Dr. Ahn.

APPEARS THIS WAY
ON ORIGINAL

3.6 Human Pharmacokinetics and Bioavailability Summary:

3.6.1 Summary of the Pharmacokinetic Study to Assess the Single Oral Dose Bioavailability of Two Formulations of Levothyroxine (Refer to Section 6)

Study Objective:
To determine the bioavailability of levothyroxine sodium (Levoxyl®) 0.3mg tablets manufactured by JONES PHARMA INCORPORATED, relative to Knoll Pharmaceutical Company's levothyroxine sodium 200ug (Synthroid®) injection given as an oral solution following a single 0.6mg dose.

Study Methodology::
Single-dose, randomized, open-label, two-way crossover design

Protocol Reference:
Guidance for Industry: In Vivo Pharmacokinetics and Bioavailability Studies and In Vitro Dissolution Testing for Levothyroxine Sodium Tablets (June 1999). This protocol was submitted in IND ———

Study Center and Investigator:

[ ]

Study Period:
Date of first enrollment: December 7, 1999
Date of last completion: January 14, 2000

Number of Subjects:
A total of 30 subjects were enrolled in the study, and 27 subjects completed the study. All 30 subjects were included in the safety analysis and 27 subjects who completed the study were included in the pharmacokinetic analyses.

Diagnosis and Main Criteria for Inclusion:
All subjects enrolled in this study were judged by the investigator to be healthy volunteers who met all inclusion and exclusion criteria.

Test Product, Dose, Duration, Mode of Administration, and Batch Number:
The test product was levothyroxine sodium (Levoxyl®) 2 X 0.3mg tablets (JONES PHARMA INCORPORATED) administered as a single oral dose. The batch number utilized in this study was TT26.

Reference Product, Dose, Duration, Mode of Administration, and Batch Number:
The reference product was levothyroxine sodium (Synthroid®) 2 X 500ug injection vials (Knoll Pharmaceutical Company) reconstituted and 600ug administered orally. The reference product used was the 500ug injection instead of 200ug due to the unavailability of sufficient quantities of 200ug injection to conduct the study. The batch number utilized in this study was 80130028.

3.6 Human Pharmacokinetics and Bioavailability Summary (Continued):

3.6.1 Summary of the Pharmacokinetic Study to Assess the Single Oral Dose Bioavailability of Two Formulations of Levothyroxine (Continued)

Criteria for Evaluation:

Pharmacokinetics:

Pharmacokinetic assessment consisted of the determination of total (bound + free) T4 and T3 concentrations in serum at specified time points following drug administration. From the serum data, the parameters AUC(0-t), Cmax, and Tmax were calculated.

Safety:

Safety assessment included vital signs, clinical laboratory evaluation (including TSH), physical examination, and adverse events (AEs) assessment.

Statistical Methods:

Pharmacokinetics:

Descriptive statistics (arithmetic mean, standard deviation (SD), coefficient of variation (CV), standard error of the mean (SE), sample size (N), minimum, and maximum) were provided for all pharmacokinetic parameters. The effects of baseline and baseline-by treatment interaction were evaluated using a parametric (normal-theory) general linear model (ANCOVA) with treatment, period, sequence, subject within sequence, ln(baseline), and interaction between ln(baseline) and treatment as factors, applied to the ln-transformed pharmacokinetic parameters and Cmax. In the absence of significant ln(baseline) and interaction between ln(baseline) and treatment, these parameters were removed from the model. The two one-sided hypotheses were tested at the 5% level of significance for ln[AUC(0-t)] and ln(Cmax) by constructing 90% confidence intervals for the ratio of Treatment A to Treatment B.

Safety:

Frequency counts of all subjects enrolled in the study, completing the study, and discontinuing early were tabulated. Descriptive statistics were calculated for continuous demographic variables, and frequency counts were tabulated for categorical demographic variables for each gender and overall.

AEs were coded using the 5th Edition of the COSTART dictionary. AEs were summarized by the number and percentage of subjects experiencing each coded event. A summary of the total number of each coded event and as a percentage of total AEs was also provided.

Laboratory summary tables included descriptive statistics for continuous serum chemistry and hematology results at each time point. Out-of-range values were listed by subject for each laboratory parameter.

3.6 Human Pharmacokinetics and Bioavailability Summary (Continued):

3.6.1 Summary of the Pharmacokinetic Study to Assess the Single Oral Dose Bioavailability of Two Formulations of Levothyroxine (Continued)

Statistical Methods (Continued):

Safety (Continued):

Descriptive statistics for vital sign measurements at each time point and change from baseline to each time point were calculated by treatment group.

Shifts from screening to poststudy results for physical examinations were tabulated.

PHARMACOKINETIC RESULTS – T4:

ANCOVA analyses indicated that the effects of ln(baseline) and interaction between ln(baseline) and treatment were not significant. Thus, these factors were removed from the general linear model and an ANOVA with treatment, period, sequence, and subject within sequence was applied to the ln-transformed Cmax and AUC(0-t) parameters. The arithmetic means of serum T4 pharmacokinetic parameters for Treatments A and B and the statistical comparison for ln-transformed parameters are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Serum T4 for Treatments A and B

	Treatment A*		Treatment B**			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	% Mean Ratio
Cmax (ug/dL)	14.48	1.93	15.09	2.10	—	—
Tmax (hr)	2.17	0.810	1.62	0.502	—	—
AUC(0-t) (ug*hr/dL)	524.3	59.07	529.3	62.83	—	—
ln (Cmax)	2.663	0.1434	2.705	0.1339	91.1-98.1	94.5
ln [AUC(0-t)]	6.256	0.1167	6.265	0.1169	95.6-100.5	98.0

* Treatment A = 2 X 0.3mg Levoxyl Tablets: test

**Treatment B = 0.6mg Synthroid Reconstitute Oral Solution: reference

PHARMACOKINETIC RESULTS – T3:

ANCOVA analyses indicated that the effects of ln(baseline) and interaction between ln(baseline) and treatment were not significant and were removed from the ANOVA model, except for ln(baseline) on ln(Cmax) which was significant and was kept in te model. An ANOVA with treatment, period, sequence, and subject within sequence, and ln(baseline), when significant, was applied to the ln-transformed Cmax and AUC(0-t) parameters. The arithmetic means of serum T3 pharmacokinetic parameters for Treatments A and B and the statistical comparison for ln-transformed parameters are summarized in the following table.

3.6 Human Pharmacokinetics and Bioavailability Summary (Continued):

3.6.1 Summary of the Pharmacokinetic Study to Assess the Single Oral Dose Bioavailability of Two Formulations of Levothyroxine (Continued)

PHARMACOKINETIC RESULTS – T3 (CONTINUED):

Summary of the Pharmacokinetic Parameters of Serum T3 for Treatments A and B

	Treatment A*		Treatment B**			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	% Mean Ratio
Cmax (ng/mL)	1.165	0.156	1.140	0.119	—	—
Tmax (hr)	14.6	15.2	16.3	17.0	—	—
AUC(0-t) (ng*hr/mL)	51.25	6.163	50.07	5.311	—	—
ln (Cmax)	0.1444	0.1289	0.1255	0.1034	96.8-103.4	100.0
ln [AUC(0-t)]	3.930	0.1209	3.908	0.1059	97.7-103.8	100.7

* Treatment A = 2 X 0.3mg Levoxyl Tablets: test
**Treatment B = 0.6mg Synthroid Reconstitute Oral Solution: reference

SAFETY RESULTS:

A total of 18 treatment-emergent AEs were experienced by 11 (37%) of the 30 subjects dosed. Headache was the most common event, reported following both treatments. The majority of the AEs were mild or moderate in severity, and no serious adverse events occurred during the trial.

No clinically significant changes were observed regarding vital signs, physical examination, or clinical laboratory evaluations for either treatment.

Conclusion:

Comparison of total T4 and T3 pharmacokinetics following administration of Levoxyl (Treatment A, test formulation) and Synthroid (Treatment B, reference formulation) indicated that the test formulation met the requirements for bioequivalence with the reference formulation.

The 90% confidence intervals for the comparisons of ln(Cmax) and ln[AUC(0-t)] for T4 and T3 were within the 80% to 125% range required for bioequivalence.

In regard to subject safety, both treatments appeared to be equally safe and well tolerated.

3.6 Human Pharmacokinetics and Bioavailability Summary:

3.6.2 Summary of the Pharmacokinetic Study to Assess the Single Dose Bioequivalence of Three Strengths of Levothyroxine (Levoxyl®) Tablets (Refer to Section 6)

Study Objective:
The objective of this study was to determine the dosage-form bioequivalence between three different strengths of levothyroxine sodium (Levoxyl®) tablets following a single 600 mcg dose.

Study Methodology::
Single-dose, randomized, open-label, three-way crossover design

Protocol Reference:
Guidance for Industry: In Vivo Pharmacokinetics and Bioavailability Studies and In Vitro Dissolution Testing for Levothyroxine Sodium Tablets (June 1999). This protocol was submitted in IND ——

Study Center and Investigator:

[redacted]

Study Period:
Date of first enrollment: December 3, 1999
Date of last completion: March 20, 2000

Number of Subjects:
A total of 28 subjects were enrolled in the study, and 24 subjects completed the study. All 28 subjects were included in the safety analysis and 24 subjects who completed the study were included in the pharmacokinetic analyses.

Diagnosis and Main Criteria for Inclusion:
All subjects enrolled in this study were judged by the investigator to be healthy volunteers who met all inclusion and exclusion criteria.

Test Product, Dose, Duration, Mode of Administration, and Batch Number:
Subjects randomized to Treatment A received a single oral dose of 12 X 50 mcg levothyroxine sodium (Levoxyl®) tablets, Lot No. TT24. Subjects randomized to Treatment B received 6 X 100 mcg levothyroxine sodium (Levoxyl®) tablets, Lot No. TT25. Subjects randomized to Treatment C received 2 X 300 mcg levothyroxine sodium (Levoxyl®) tablets, Lot No. TT26. Test products were manufactured by JMI-Daniels, a subsidiary of Jones Pharma Incorporated.

Reference Product, Dose, Duration, Mode of Administration, and Batch Number:
Not applicable

3.6 Human Pharmacokinetics and Bioavailability Summary (Continued):

3.6.2 Summary of the Pharmacokinetic Study to Assess the Single Dose Bioequivalence of Three Strengths of Levothyroxine (Levoxyl®) Tablets

Criteria for Evaluation:

Pharmacokinetics:

Pharmacokinetic assessment consisted of the determination of total (bound + free) T4 and T3 concentrations in serum at specified time points following drug administration. From the serum data, the parameters AUC(0-t), Cmax, and Tmax were calculated.

Safety:

Safety assessment included monitoring of sitting vital signs, clinical laboratory measurements, thyroid-stimulating hormone (TSH), physical examination, electrocardiogram (ECG), and adverse events (AEs).

Statistical Methods:

Pharmacokinetics:

Descriptive statistics (arithmetic mean, standard deviation (SD), coefficient of variation (CV), standard error of the mean (SEM), sample size (N), minimum, and maximum) were provided for all pharmacokinetic parameters. A parametric (normal-theory) general linear model with treatment, period, sequence, and subject within sequence as factors was applied to the ln-transformed Cmax and AUC(0-t). The two one-sided hypotheses were tested at the 5% level of significance for ln[AUC(0-t)] and ln(Cmax) by constructing 90% confidence intervals for the ratios of Treatment A to Treatment B, Treatment A to Treatment C, and Treatment B to Treatment C.

Safety:

Frequency counts of all subjects enrolled in the study, completing the study, and discontinuing early were tabulated. Descriptive statistics were calculated for continuous demographic variables, and frequency counts were tabulated for categorical demographic variables for each gender and overall.

AEs were coded using the 5th Edition of the COSTART dictionary. AEs were summarized by the number and percentage of subjects experiencing each coded event. A summary of the total number of each coded event and as a percentage of total AEs was also provided.

Laboratory summary tables included descriptive statistics for continuous serum chemistry and hematology results at each time point. Out-of-range values were listed by subject for each laboratory parameter.

Descriptive statistics for vital sign measurements at each time point and change from baseline to each time point were calculated by treatment group.

Shifts from screening to poststudy results for physical examinations were tabulated.

3.6 Human Pharmacokinetics and Bioavailability Summary (Continued):

3.6.2 Summary of the Pharmacokinetic Study to Assess the Single Dose Bioequivalence of Three Strengths of Levothyroxine (Levoxyl®) Tablets

PHARMACOKINETIC RESULTS – T4:

The arithmetic means of serum T4 pharmacokinetic parameters for Treatments A and B and the statistical comparison for the ln-transformed parameters are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Serum T4 for Treatments A and B

	Treatment A*		Treatment B**			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	% Mean Ratio
Cmax (ug/dL)	13.70	1.82	14.13	1.48	—	—
Tmax (hr)	2.37	1.04	1.98	0.827	—	—
AUC(0-t) (ug*hr/dL)	509.0	58.36	528.3	72.41	—	—
ln (Cmax)	2.609	0.1378	2.643	0.1095	93.6-100.1	96.8
ln [AUC(0-t)]	6.226	0.1200	6.261	0.1379	93.4-100.0	96.7

* Treatment A = 12 X 50 mcg Levoxyl Tablets
**Treatment B = 6 X 100 mcg Levoxyl Tablets

The arithmetic means of serum T4 pharmacokinetic parameters for Treatments A and C and the statistical comparison for the ln-transformed parameters are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Serum T4 for Treatments A and C

	Treatment A*		Treatment C**			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	% Mean Ratio
Cmax (ug/dL)	13.70	1.82	14.15	1.50	—	—
Tmax (hr)	2.37	1.04	2.40	1.09	—	—
AUC(0-t) (ug*hr/dL)	509.0	58.36	528.7	57.13	—	—
ln (Cmax)	2.609	0.1378	2.644	0.1085	93.6-100.1	96.8
ln [AUC(0-t)]	6.226	0.1200	6.265	0.1089	93.1-99.7	96.4

* Treatment A = 12 X 50 mcg Levoxyl Tablets
**Treatment C = 2 X 300 mcg Levoxyl Tablets

The arithmetic means of serum T4 pharmacokinetic parameters for Treatments B and C and the statistical comparison for the ln-transformed parameters are summarized in the following table.

3.6 Human Pharmacokinetics and Bioavailability Summary (Continued):

3.6.2 Summary of the Pharmacokinetic Study to Assess the Single Dose Bioequivalence of Three Strengths of Levothyroxine (Levoxyl®) Tablets

PHARMACOKINETIC RESULTS – T4 (Continued):

Summary of the Pharmacokinetic Parameters of Serum T4 for Treatments B and C

	Treatment B*		Treatment C**			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	% Mean Ratio
Cmax (ug/dL)	14.13	1.48	14.15	1.50	—	—
Tmax (hr)	1.98	0.827	2.40	1.09	—	—
AUC(0-t) (ug*hr/dL)	528.3	72.41	528.7	57.13	—	—
ln (Cmax)	2.643	0.1095	2.644	0.1085	96.7-103.4	100.0
ln [AUC(0-t)]	6.261	0.1379	6.265	0.1089	96.4-103.1	99.7

* Treatment B = 6 X 100 mcg Levoxyl Tablets
**Treatment C = 2 X 300 mcg Levoxyl Tablets

PHARMACOKINETIC RESULTS – T3:

The arithmetic means of serum T3 pharmacokinetic parameters for Treatments A and B and the statistical comparison for the ln-transformed parameters are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Serum T3 for Treatments A and B

	Treatment A*		Treatment B**			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	% Mean Ratio
Cmax (ng/mL)	1.173	0.138	1.142	0.133	—	—
Tmax (hr)	12.9	19.0	12.1	16.1	—	—
AUC(0-t) (ng*hr/mL)	49.43	6.872	50.35	8.994	—	—
ln (Cmax)	0.1523	0.1226	0.1264	0.1194	98.1-107.3	102.6
ln [AUC(0-t)]	3.890	0.1538	3.905	0.1731	93.1-104.3	98.5

* Treatment A = 12 X 50 mcg Levoxyl Tablets
**Treatment B = 6 X 100 mcg Levoxyl Tablets

The arithmetic means of serum T3 pharmacokinetic parameters for Treatments A and C and the statistical comparison for the ln-transformed parameters are summarized in the following table.

3.6 Human Pharmacokinetics and Bioavailability Summary (Continued):

3.6.2 Summary of the Pharmacokinetic Study to Assess the Single Dose Bioequivalence of Three Strengths of Levothyroxine (Levoxyl®) Tablets

PHARMACOKINETIC RESULTS – T3 (Continued):

Summary of the Pharmacokinetic Parameters of Serum T3 for Treatments A and C

	Treatment A*		Treatment C**			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	% Mean Ratio
Cmax (ng/mL)	1.173	0.138	1.167	0.169	—	—
Tmax (hr)	12.9	19.0	11.5	16.4	—	—
AUC(0-t) (ng*hr/mL)	49.43	6.872	49.36	7.680	—	—
ln (Cmax)	0.1523	0.1226	0.1437	0.1491	96.3-105.4	100.7
ln [AUC(0-t)]	3.890	0.1538	3.886	0.1705	94.7-106.2	100.3

* Treatment A = 12 X 50 mcg Levoxyl Tablets
**Treatment C = 2 X 300 mcg Levoxyl Tablets

The arithmetic means of serum T3 pharmacokinetic parameters for Treatments B and C and the statistical comparison for the ln-transformed parameters are summarized in the following table.

Summary of the Pharmacokinetic Parameters of Serum T3 for Treatments B and C

	Treatment B*		Treatment C**			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI	% Mean Ratio
Cmax (ng/mL)	1.142	0.133	1.167	0.169	—	—
Tmax (hr)	12.1	16.1	11.5	16.4	—	—
AUC(0-t) (ng*hr/mL)	50.35	8.994	49.36	7.680	—	—
ln (Cmax)	0.1264	0.1194	0.1437	0.1491	93.9-102.7	98.2
ln [AUC(0-t)]	3.905	0.1731	3.886	0.1705	96.2-107.8	101.8

* Treatment B = 6 X 100 mcg Levoxyl Tablets
**Treatment C = 2 X 300 mcg Levoxyl Tablets

SAFETY RESULTS:

There was a total of 59 treatment-emergent AEs reported by 15 (54%) of the 28 subjects dosed with study treatment. Incidence of AEs was similar across treatments. Headache was the most frequently reported event. The majority of the AEs were mild in intensity. There was one subject who experienced a serious adverse event of chest pain, considered by the Investigator to be unrelated to treatment.

No trends were noted in vital signs, clinical laboratory results, or ECGs to suggest treatment-related differences.

3.6 Human Pharmacokinetics and Bioavailability Summary (Continued):

3.6.2 Summary of the Pharmacokinetic Study to Assess the Single Dose Bioequivalence of Three Strengths of Levothyroxine (Levoxyl®) Tablets

Conclusion:

Comparison of total T4 and T3 pharmacokinetics following administration of 12 X 50 mcg Levoxyl® tablets (Treatment A) and 6 X 100 mcg Levoxyl® tablets (Treatment B) indicated that the two formulations met the requirements for bioequivalence. The 90% confidence intervals for the comparisons of ln(Cmax) and ln[AUC(0-t)] for T4 and T3 were within the 80% to 125% range required for bioequivalence.

Comparison of total T4 and T3 pharmacokinetics following administration of 12 X 50 mcg Levoxyl® tablets (Treatment A) and 2 X 300 mcg Levoxyl® tablets (Treatment C) indicated that the two formulations met the requirements for bioequivalence. The 90% confidence intervals for the comparisons of ln(Cmax) and ln[AUC(0-t)] for T4 and T3 were within the 80% to 125% range required for bioequivalence.

Comparison of total T4 and T3 pharmacokinetics following administration of 6 X 100 mcg Levoxyl® tablets (Treatment B) and 2 X 300 mcg Levoxyl® tablets (Treatment C) indicated that the two formulations met the requirements for bioequivalence. The 90% confidence intervals for the comparisons of ln(Cmax) and ln[AUC(0-t)] for T4 and T3 were within the 80% to 125% range required for bioequivalence.

The test formulations appear to be safe and generally well tolerated when given to healthy adult volunteers.

3.6 Human Pharmacokinetics and Bioavailability Summary (Continued):

3.6.3 Summary of the In-Vitro Bioavailability Study (Refer to Sections 4.2.11 and 6)

Study Objective:
To determine the multi-point dissolution profiles for all levothyroxine sodium tablet strengths to be marketed.

Study Scope:
The intent is to demonstrate that the multi-point dissolution profiles are similar across tablet strengths.

Protocol Reference:
Guidance for Industry: In Vivo Pharmacokinetics and Bioavailability Studies and In Vitro Dissolution Testing for Levothyroxine Sodium Tablets (June 1999). This protocol was submitted in IND ———

Analytical Method and Method Reference:
——— (Refer to Sections 4.2.11 and 6 – Attachment 1)
USP 24 Supplement 1 page 2638

Protocol:
Perform multi-point dissolution testing using the following criteria and method

- Include all to be marketed levothyroxine sodium tablet strengths: 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200 and 300 mcg tablets.
- The batches used in the Clinical Trials (TT24, TT25, TT26) will be included.
- The batch size will be 1/10th scale or ——— tablets per batch.
- The number of batches tested per strength will be 3.
- The number of tablets tested for each dissolution will be 12.
- The time points tested will be 1, 2.5, 5, 7.5 and 10 minutes.

Results:
The following data presents the mean result for each of the tablet strengths of Levoxyl tested. Each point is the mean of three dissolutions, testing 12 tablets per dissolution or n=36. The mean data is presented in table form followed by a graph. The data is presented as percent of label claim dissoluted vs dissolution time. The individual values for each strength and each batch of Levoxyl tested are presented in Sections 4.2.11 and 6 – Attachment 2.

Conclusions:

The results of this study demonstrate that the multi-point dissolution profiles for Levoxyl tablets are similar across tablet strengths.

3.6 Human Pharmacokinetics and Bioavailability Summary (Continued):

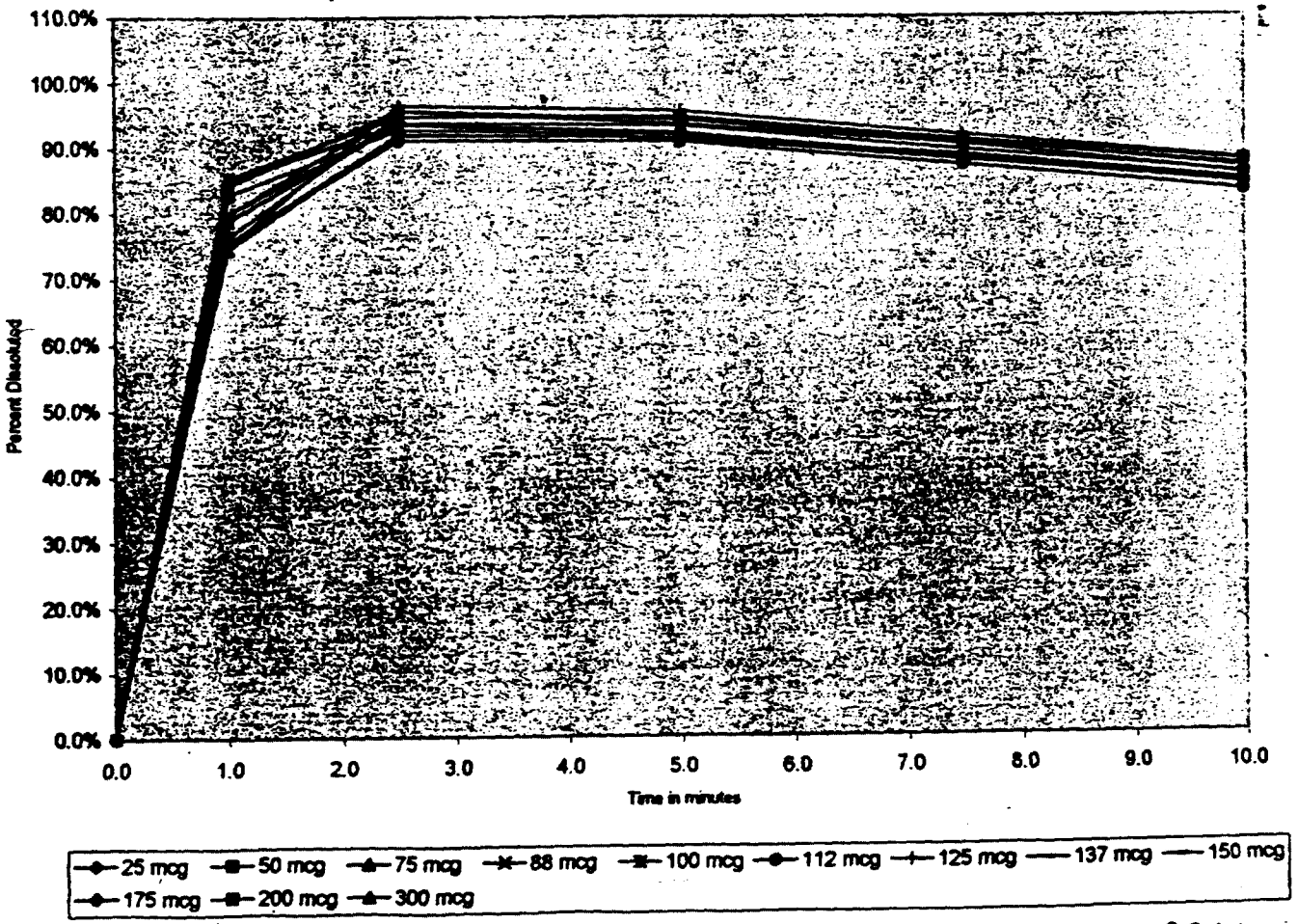
3.6.3 Summary of the In-Vitro Bioavailability Study (Continued)

Results of the In-Vitro Bioavailability Study

Comparative Dissolution Data of all Strengths of Levoxyl Tablets

	0 minutes	1 minute	2.5 minute	5 minutes	7.5 minutes	10 minutes
25 mcg	0.0%	84.9%	93.7%	90.9%	88.6%	84.7%
50 mcg	0.0%	82.8%	92.7%	91.8%	87.8%	84.4%
75 mcg	0.0%	78.9%	93.6%	92.2%	88.3%	84.7%
88 mcg	0.0%	79.8%	95.6%	94.1%	90.5%	86.9%
100 mcg	0.0%	85.4%	94.8%	94.5%	90.7%	86.5%
112 mcg	0.0%	75.5%	91.1%	90.7%	87.0%	82.9%
125 mcg	0.0%	75.0%	96.5%	95.5%	91.7%	87.8%
137 mcg	0.0%	79.9%	93.9%	93.2%	89.4%	85.7%
150 mcg	0.0%	75.6%	91.9%	91.4%	88.7%	84.6%
175 mcg	0.0%	84.2%	95.7%	93.5%	90.3%	85.5%
200 mcg	0.0%	76.5%	94.9%	94.6%	91.0%	87.6%
300 mcg	0.0%	74.5%	92.1%	91.4%	87.9%	84.0%

Comparative Dissolution Profiles of all Strengths of Levoxyl Tablets



Dissolution Profile (USP24) - NDA 21-301 - Jones Pharma, Inc.