Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-210	**Relevant IND**:	[ ]
Brand Name:	Unithroid®	**Generic Name**:	Levothyroxine Sodium
Strength(s):	25, 50, 75, 88, 100, 112, 125, 150, 175, 200, and 300 mcg tablets		
Sponsor:	Jerome Stevens Pharmaceuticals, Inc. 60 DaVinci Drive, Bohemia, NY 11716		
Submission Date:	19-OCT-99		
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, Jerome Stevens Pharmaceuticals, Inc., submitted NDA 21-210 on October 19, 1999 for Unithroid® Tablets (levothyroxine sodium tablets, USP), in eleven 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 In accordance with the "Draft Guidance for Industry," the sponsor has submitted two *in vivo* BA/BE studies and an *in vitro* dissolution study for their levothyroxine sodium product.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, 254-98-134-3, evaluated the relative bioavailability of the sponsor's 100 mcg tablets with an equivalent oral solution of levothyroxine sodium. The second *in vivo* study, 254-98-135-2, 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 Unithroid® Tablets, USP, are 99% bioavailable relative to an oral solution, and that 50 mcg, 100 mcg, and 300 mcg tablets are

dosage-form equivalent. Since these three strengths, representing low, middle, and high tablet strengths, are dosage-form equivalent, the individual tablet strength formulations are proportionally similar in active and inactive ingredients, and the dissolution data meet the Sponsor's designated specifications, sufficient evidence is provided to grant a biowaiver for the intermediate strengths.

An *in vitro* dissolution study included data and specifications for a single dissolution method conducted on three lots of each of the eleven to-be-marketed strengths. The dissolution data submitted in this application were found to be acceptable. However, a phase 4 commitment, in which USP 24 is used, will be asked of the sponsor.

In addition, DSI was asked by OCPB to conduct a site audit to verify the results of the BA/BE studies. Jerome Stevens Pharmaceuticals, Inc., was not singled out nor was there any reason to believe that they engaged in any scientifically unsound behavior. Results of the DSI audit reveal that the analytical data for total T_4 in studies 254-98-134-3 and 254-98-135-2 are acceptable for Agency review.

Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed NDA 21-210 submitted 19-OCT-99. The overall Human Pharmacokinetic Section is acceptable to OCPB. Please convey ***Comments to Firm***, ***Phase 4 Commitments***, and ***Labeling Comments*** to the sponsor as appropriate. (AP)

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	determine the dosage-form equivalence between the to-be-marketed tablet strengths.	
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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?

Each strength tablet is proportionally similar in its active and inactive ingredients, but quantitatively different in the amounts of levothyroxine and color additives. The levothyroxine [ ] is formulated with increasing amounts of levothyroxine sodium, USP, [ ], for each of the respective tablet strengths. Unithroid® tablets will be packaged in 100 and 1000 count containers for each of the eleven to-be-marketed strengths ranging from 25 mcg to 300 mcg per tablet.

Components and Composition			
Component	**Amount Per Tablet**	**Component**	**Amount Per Tablet**
25 mcg Tablet		***125 mcg Tablet***	
Levothyroxine [ ] Lactose, NF Microcrystalline Cellulose, NF Sodium Starch Glycoate, NF Magnesium Stearate, NF Colloidal Silicon Dioxide, NF FD&C Yellow #6 Aluminum Lake	0.0250 mg	Levothyroxine [ ] Lactose, NF Microcrystalline Cellulose, NF Sodium Starch Glycoate, NF Magnesium Stearate, NF Colloidal Silicon Dioxide, NF FD&C Yellow #6 Aluminum Lake FD&C Red #40 Aluminum Lake FD&C Blue #1 Aluminum Lake	0.1250 mg
50 mcg Tablet		***150 mcg Tablet***	
Levothyroxine [ ] Lactose, NF Microcrystalline Cellulose, NF Sodium Starch Glycoate, NF Magnesium Stearate, NF Colloidal Silicon Dioxide, NF	0.0500 mg	Levothyroxine [ ] Lactose, NF Microcrystalline Cellulose, NF Sodium Starch Glycoate, NF Magnesium Stearate, NF Colloidal Silicon Dioxide, NF FD&C Blue #2 Aluminum Lake	0.1500 mg
75 mcg Tablet		***175 mcg Tablet***	
Levothyroxine [ ] Lactose, NF Microcrystalline Cellulose, NF Sodium Starch Glycoate, NF Magnesium Stearate, NF Colloidal Silicon Dioxide, NF FD&C Blue #2 Aluminum Lake FD&C Red #40 Aluminum Lake	0.0750 mg	Levothyroxine [ ] Lactose, NF Microcrystalline Cellulose, NF Sodium Starch Glycoate, NF Magnesium Stearate, NF Colloidal Silicon Dioxide, NF FD&C Blue #1 Aluminum Lake D&C Red #27 Aluminum Lake	0.1750 mg
88 mcg Tablet		***200 mcg Tablet***	
Levothyroxine [ ] Lactose, NF Microcrystalline Cellulose, NF Sodium Starch Glycoate, NF Magnesium Stearate, NF Colloidal Silicon Dioxide, NF D&C Yellow #10 Aluminum Lake FD&C Yellow #6 Aluminum Lake FD&C Blue #1 Aluminum Lake	0.0880 mg	Levothyroxine [ ] Lactose, NF Microcrystalline Cellulose, NF Sodium Starch Glycoate, NF Magnesium Stearate, NF Colloidal Silicon Dioxide, NF FD&C Red #40 Aluminum Lake	0.2000 mg
100 mcg Tablet		***300 mcg Tablet***	
Levothyroxine [ ] Lactose, NF Microcrystalline Cellulose, NF Sodium Starch Glycoate, NF Magnesium Stearate, NF Colloidal Silicon Dioxide, NF D&C Yellow #10 Aluminum Lake FD&C Yellow #6 Aluminum Lake	0.1000 mg	Levothyroxine [ ] Lactose, NF Microcrystalline Cellulose, NF Sodium Starch Glycoate, NF Magnesium Stearate, NF Colloidal Silicon Dioxide, NF D&C Yellow #10 Aluminum Lake FD&C Blue #1 Aluminum Lake FD&C Yellow #6 Aluminum Lake	0.3000 mg
112 mcg Tablet			
Levothyroxine [ ] Lactose, NF Microcrystalline Cellulose, NF Sodium Starch Glycoate, NF Magnesium Stearate, NF Colloidal Silicon Dioxide, NF D&C Red #27 Aluminum Lake	0.1120 mg		

D&C Red #27 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 55% (Q) in 80 minutes, as per the USP 23 monograph for levothyroxine sodium tablets. Dissolution data from three lots of each of the to-be-marketed tablet strengths were submitted for review. Dissolution samples were analyzed by a validated [ ] method. The dissolution method and resultant data are presented in the following two tables:

Dissolution Method	
Apparatus:	2 (paddles)
Speed:	100 RPM
Medium:	pH 7.4 0.05 M Phosphate Buffer
Volume:	500 mL
Units Tested:	12
Time Points:	10, 20, 30, and 45 minutes
Specifications:	NLT 55% (Q) @ 80 minutes

Dissolution

Str (mcg)	Time (min)	Lot #s			Str (mcg)	Time (min)	Lot #s		
F_2 = N/A		**9498**	**12098**	**12198**	**F_2 = N/A**		**8898**	**11898**	**11998**
25	**10**	68.4	72.6	59.5	**125**	**10**	67.3	77.5	76.5
	20	91.3	100.6	88.5		**20**	94.8	104.9	102.5
	30	94.5	102.7	95.5		**30**	93.8	105.6	104.0
	40	96.7	107.0	97.6		**40**	95.7	105.0	105.2
F_2 = N/A		**2498**	**10698**	**10798**	**F_2 = N/A**		**7998**	**9398**	**10498**
50	**10**	64.2	70.6	71.2	**150**	**10**	71.2	74.6	75.9
	20	87.8	103.4	102.9		**20**	98.1	96.2	97.8
	30	92.2	103.6	104.4		**30**	97.9	97.0	98.4
	40	96.8	105.7	103.9		**40**	99.7	98.4	99.0
F_2 = N/A		**1/12/99**	**11098**	**399**	**F_2 = N/A**		**1999**	**2099**	**2199**
75	**10**	69.0	69.4	65.4	**175**	**10**	62.1	68.1	65.8
	20	102.2	99.8	91.1		**20**	90.1	99.0	99.0
	30	103.2	100.7	96.7		**30**	91.0	99.9	102.9
	40	104.3	103.0	100.1		**40**	91.4	104.3	100.8
F_2 = N/A		**1099**	**1199**	**1299**	**F_2 = N/A**		**8198**	**12798**	**12898**
88	**10**	69.6	64.0	67.8	**200**	**10**	64.8	77.5	71.1
	20	101.0	90.0	97.9		**20**	91.5	98.4	93.8
	30	101.0	91.3	101.1		**30**	92.9	99.7	96.6
	40	101.8	94.3	101.9		**40**	93.3	101.0	96.8
F_2 = N/A		**10598**	**11398**	**11598**	**F_2 = N/A**		**12598**	**13298**	**13798**
100	**10**	70.6	73.3	73.5	**300**	**10**	70.6	60.1	69.2
	20	96.7	99.1	98.0		**20**	93.5	79.1	87.6
	30	98.1	100.1	100.2		**30**	94.1	84.5	92.0
	40	98.5	99.9	99.9		**40**	94.4	89.0	94.0
F_2 = N/A		**1699**	**1799**	**8898**					
112	**10**	65.7	67.4	63.7					
	20	91.7	94.0	92.8					
	30	96.2	97.3	94.8					
	40	96.2	102.2	97.2					

The dissolution method that the sponsor has proposed is acceptable, as it follows USP 23. However, the sponsor will be asked to submit dissolution data using the USP 24 monograph in a Phase 4 commitment, as USP 23 is non-discriminatory for Unithroid® Tablets. (See ***Phase 4 Commitments***).

Similarity calculations using F_2 cannot be made for these dissolution data, because of the need for at least two measurement points that are less than or equal to 85 percent, and no more than one data point greater than 85 percent. Using more than one data point above 85-percent will skew the data such that false similarities may be concluded. The sponsor did submit an amendment to this application on 22-MAR-00 updating the dissolution method to the current USP 24. However, they did not include any dissolution data using the new method.

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 70% (Q) of the labeled amount of levothyroxine sodium is dissolved in 45 minutes

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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 (AxSYM Total T_4 and AxSYM Total T_3, Abbott Laboratories).

Analytical methods were found to be acceptable by the Agency. Results of the quality control analysis are presented in the following table:

	T_3			T_4	
	254-98-134-3	**254-98-135-2**		**254-98-134-3**	**254-98-135-2**
LOQ (ng/mL):	0.500	0.500	**LOQ (mcg/dL):**	3.00	3.00
Calibration (ng/mL):	0.500 – 8.00	0.500 – 8.00	**Calibration (mcg/dL):**	3 – 24	3 – 24
Precision (%RSD):			**Precision (%RSD):**		
0.70 ng/mL	8.96	9.52	**4.50 mcg/dL**	5.33	6.29
1.50 ng/mL	6.38	5.71	**8.00 mcg/dL**	2.78	3.67
3.70 ng/mL	3.28	5.01	**15.0 mcg/dL**	3.33	3.38
Accuracy (%):			**Accuracy (%):**		
0.70 ng/mL	95.71	90.00	**4.50 mcg/dL**	104.22	98.89
1.50 ng/mL	94.00	93.33	**8.00 mcg/dL**	103.50	105.50
3.70 ng/mL	90.54	91.62	**15.0 mcg/dL**	102.20	98.60

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 26 healthy volunteers (23 completed study) given either a single dose of six 100 mcg tablets (lot # 10598) or a single 600 mcg dose (Synthroid Injection; Knoll Pharmaceutical, lot # 80120028) of an oral solution in a two-way crossover study (254-98-

134-3), 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 99%. Results and 90% confidence intervals are presented in the following two tables:

Summary of Bioavailability Data – T_4 Baseline Uncorrected – Study Number 254-98-134-3		
Parameters	**Treatment A* 6 x 100 mcg tablets**	**Treatment B** 600 mcg oral solution**
AUC_{0-48} (mcg*hr/dL)	523.09 ± 75.01	532.77 ± 73.69
C_{max} (mcg/dL)	14.25 ± 2.31	14.79 ± 1.87
T_{max} (hours)	2.22 ± 0.74	2.24 ± 1.96
Mean ± SD		

Least Squares Mean – 90% Confidence Interval – Study Number 254-98-134-3				
Treatment Comparison	**Parameter**	**Point Estimate**	**CI (low)**	**CI (high)**
A vs. B	ln C_{max} ln AUC_{0-48}	97 99	92.89 95.33	100.66 101.87
Treatment A = 6 x 100 mcg levothyroxine tablets – Test – (%CV: C_{max} = 16.22; AUC_{0-48} = 14.34) Treatment B = 600 mcg levothyroxine oral solution – Reference – (%CV: C_{max} = 12.62; AUC_{0-48} = 13.83)				

2. Dosage Form Equivalence Studies

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

The sponsor submitted study 254-98-135-2 to establish dosage form equivalence between the 50 mcg (lot # 10698), 100 mcg (lot # 10598), and 300 mcg (lot # 12598) tablet strengths. The study design was a three-way crossover study 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 – All Subjects – Study Number 254-98-135-2			
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} (mcg*hr/dL)	555.82 ± 78.53	548.33 ± 81.85	547.17 ± 86.50
C_{max} (mcg/dL)	14.87 ± 2.03	14.77 ± 2.47	14.80 ± 2.67
T_{max} (hours)	2.74 ± 1.87	2.63 ± 1.07	2.31 ± 0.97
Mean ± SD			

Least Squares Mean – 90% Confidence Interval – All Subjects – Study Number 254-98-135-2				
Treatment Comparison	**Parameter**	**Point Estimate**	**CI (low)**	**CI (high)**
A vs. B	ln C_{max} ln AUC_{0-48}	101 102	97.56 99.26	104.79 104.03
C vs. B	ln C_{max} ln AUC_{0-48}	100 100	96.60 97.46	103.73 102.12
Treatment A = 12 x 50 mcg levothyroxine tablets – Test – (%CV: C_{max} = 13.66; AUC_{0-48} = 14.13) Treatment B = 6 x 100 mcg levothyroxine tablets – Reference – (%CV: C_{max} = 16.74; AUC_{0-48} = 14.93) Treatment C = 2 x 300 mcg levothyroxine tablets – Test – (%CV: C_{max} = 18.04; AUC_{0-48} = 15.81) %CV calculated from untransformed data = total variability				

In addition to analyzing the study data for all subjects, gender specific analysis was also conducted. Results of these analysis concluded that there existed a significant gender effect on PK. However, this effect has no impact on the dosage-form equivalence of this product (see ***Appendix*** for complete study

report). The clinical result of this gender effect is not a critical issue, in that all patients must be titrated to therapeutic effect. The higher AUC values seen in females are likely due to the increased TBG levels associated with estrogen.

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.

Therefore, a biowaiver, for the 8 intermediate strengths not used in the *in vivo* studies can be granted for NDA 21-210.

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).

💣 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)

Absorption – Absorption of orally administered T_4 from the GI tract ranges from 40% to 80%. <u>The relative bioavailability of Unithroid® tablets, compared to an equivalent dose of oral levothyroxine sodium solution, is approximately 99%</u>. The majority of the dose is absorbed from the jejunum and upper ileum. T_4 absorption is increased by fasting, and decreased in malabsorption syndromes and by certain foods such as soybean formula. Absorption may also decrease with age. In addition, many drugs affect T_4 absorption (see **DRUG-DRUG INTERACTIONS** and **DRUG-LABORATORY TEST INTERACTIONS**).

Distribution – Greater than 99% of circulating thyroid hormones are 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. Both protein-bound 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 **DRUG-DRUG INTERACTIONS** and **DRUG-LABORATORY TEST INTERACTIONS**). Thyroid hormones do not readily cross the placental barrier.

Metabolism – T_4 is slowly eliminated (see **TABLE 1**). Eighty-percent of circulating T_3 comes from peripheral T_4 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. The major pathway of thyroid hormone metabolism is through sequential deiodination. Approximately 80% of the daily dose of T_4 is deiodinated to yield equal amounts of T_3 and 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.

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

Hormone	Ratio Released from Thyroid Gland	Biologic Potency	$t_{1/2}$ (days)	Protein Binding (%)[2]
Levothyroxine (T_4)	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

Comments to Firm

In your NDA 21-210 for Unityroid® Tablets, the dissolution specifications were sufficient for approval. However, as of January 1, 2000, a new USP dissolution method became official for levothyroxine sodium tablets – USP 24 (see ***Phase 4 Commitments***). Your amendment to this application, dated 22-MAR-00, addresses the change from using the USP 23 to USP 24 dissolution method, however no dissolution data was included (see ***Phase 4 Commitments***).

Phase 4 Commitments

Within one year of approval, dissolution testing must be conducted, using either USP 24 or other discriminating method specific to your product, for one lot each of all marketed strengths, and the data submitted to the Agency for review.

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: 10-JUL-00

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

Code: AP