CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76268

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 76-268 SPONSOR : Jerome Stevens Pharmaceuticals, Inc.
DRUG AND DOSAGE FORM: Digoxin Tablet, USP
STRENGTH(S): 0.250 mg & 0.125 mg
TYPES OF STUDIES: Single-dose fasting and postprandial

CLINICAL STUDY SITE:

ANALYTICAL SITE:

STUDY SUMMARY: Acceptable fasting and postprandial studies

DISSOLUTION: Acceptable.

DSI INSPECTION STATUS

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

PRIMARY REVIEWER: James Chaney BRANCH: I

INITIAL: JC DATE: 4/30/2002

TEAM LEADER: Yih-Chain Huang BRANCH: I

INITIAL: YHH DATE: 4/30/2002

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

INITIAL : DPC DATE : 4/30/02

Digoxin Tablet, USP
0.250 mg & 0.125 mg
ANDA 76-268
Reviewer: James Chaney

Jerome Stevens Pharmaceuticals, Inc.
Bohemia, NY
Submission Date:
March 11, 2002

Review of an Amendment
(Long Term Stability Data on Digoxin in Frozen Serum)

History of Bioequivalence Submissions

- **10/29/01 -** Original submission including fasting and non-fasting studies on the 0.25 mg tablet. Dissolution data on 0.125 mg and 0.25 mg tablets. Waiver requests on the 0.125 mg strength. No frozen serum stability data was included in the original submission
- **1/24/02** - DBE requested stability data via telephone .
- **1/28/02** - Firm faxed an amendment including limited long-term stability data on digoxin in frozen serum which was not reported in the original 10/29/01 submission.
- **2/14/02 Review (J. Chaney) of Two Bioequivalence Studies, Dissolution Data, A Waiver Request -** The long-term stability data on digoxin in frozen serum did not cover the fed study. Otherwise, the submission was acceptable.
- **2/21/02** – DBE issued a deficiency letter per above review.

Deficiency – Noted to Firm in DBE Letter of 2/21/02

The long term stability data on digoxin in frozen serum submitted in your January 28, 2002 submission in response to our January 24, 2002 telephone request showed that digoxin is stable in serum at . This stability data is inadequate in that the maximum time samples were stored frozen from the first day of collection to the last day of analysis was 47 days in the fed study. You need to document that digoxin is stable in your serum study samples at -20°C for 47 days.

Firm's Response to Deficiency Letter of 2/21/02

The frozen human serum samples were shown to be stable for 212 days.

Reviewer's Comment

The frozen human serum samples were shown to be stable for 212 days and the longest period of actual study sample storage was no more than 47 days. The firm's establishment of stability of the drug in frozen human serum over a period of time exceeding the length of time that the samples from the bioequivalence studies were actually stored is acceptable.

Recommendations

1. The single-dose, fasting bioequivalence study and the single-dose, post-prandial bioequivalence study conducted by Jerome Stevens Pharmaceuticals, Inc. on the test product, digoxin tablet 0.25 mg, lot 003501, comparing it with the reference product, Lanoxin® tablet 0.25 mg, lot 8ZP1806 manufactured by Glaxo Wellcome have been found acceptable by the Division of Bioequivalence. The studies demonstrate that the test product, Jerome Stevens Pharmaceuticals, Inc.'s digoxin tablet 0.25 mg, is bioequivalent to the reference product, Lanoxin® tablet 0.25 mg under fasting and nonfasting conditions.

2. The *in-vitro* dissolution testing conducted by Jerome Stevens Pharmaceuticals, Inc. on its digoxin tablet 0.25 mg has been found acceptable.

The dissolution testing should be conducted in 500 mL of 0.1N HCL at 37°C using USP apparatus I (basket) at 120 rpm. The test product should meet the following USP specifications:

Not less than % (Q) of the labeled amount of digoxin is dissolved in 60 minutes. Per USP25-NF20 Supplement 1 the requirement is met if the quantities dissolved from the tablets tested conform to the following USP acceptance table specific for digoxin tablets instead of the table shown under USP 24 *Dissolution* <711>.

Stage	Number Tested	Acceptance Criteria
S1	6	Each unit is not less than Q + 5%.
S2	6	Average of 12 units (S1 + S2) is equal to or greater than Q, and no unit is less than Q - 5%.

3. The formulation for the 0.125 mg tablet is proportionally identical to that of the 0.25 mg tablet, which underwent bioequivalency testing. The waiver of *in vivo* bioequivalence study requirements for the 0.125 mg tablet of the test product is granted. The 0.125 mg and 0.25 mg test tablets are therefore deemed bioequivalent to Lanoxin® 0.125 mg and 0.25 mg tablets manufactured by Glaxo Wellcome.

4. From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing and the application is acceptable.

/S/

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang /S/ Date 4/30/2002

Concur: /S/ Date 4/30/02
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

JEC/043002

BIOEQUIVALENCY COMMENTS

ANDA: 76-268 APPLICANT: Jerome Stevens Pharmaceuticals, Inc.

DRUG PRODUCT: Digoxin Tablet USP, 0.250 mg and 0.125 mg

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

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP25-NF20 Supplement 1.

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

Sincerely yours,

/S/

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

CC: ANDA 76-268
ANDA DUPLICATE
DIVISION FILE
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DRUG FILE

HFD-652/ J. Chaney J. Chaney 4/30/2002
HFD-652/ Y. Huang 4/30/2002
HFD-617/ K. Scardina 4/30/02
HFD-650/ D. Conner 4/30/02

BIOEQUIVALENCY – ACCEPTABLE

Submission date: March 11, 2002

STUDY AMENDMENT (STA) o/c

Strength: 0.125 mg and 0.25 mg
Outcome: AC

NOTE:

AC - Acceptable
NC - No Action
UN - Unacceptable
IC - Incomplete

Outcome Decision: Incomplete

WINBIO COMMENTS:

The firm's data on long term digoxin stability in frozen serum is acceptable. The firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing and the application is acceptable.

Digoxin Tablet, USP
0.250 mg & 0.125 mg
ANDA 76-268
Reviewer: James Chaney

Jerome Stevens Pharmaceuticals, Inc.
Bohemia, NY
Submission Date:
October 29, 2001
~~January 28, 2002~~ (JS)

Review of Two Bioequivalence Studies, Dissolution Data, A Waiver Request and New Correspondence (Long Term Stability Data on Digoxin in Frozen Serum) (Electronic Submission)

I. Introduction

Indication:
Digoxin is indicated for the treatment of mild to moderate heart failure. Also, It is indicated for the control of ventricular response rate in patients with chronic atrial fibrillation.

Type of Submission: Original

Contents of Submissions:

- Fasting and non-fasting studies on the 0.25 mg tablet (October 29, 2001 submission)
- Dissolution data on 0.125 mg and 0.25 mg tablets (October 29, 2001 submission)
- Waiver requests on the 0.125 mg strength (October 29, 2001 submission)
- January 28, 2002 faxed amendment including long term stability data on digoxin in frozen serum which was not reported in the original 10/29/01 submission. This stability data was requested via telephone on 1/24/02.

RLD: Glaxo Wellcome's Lanoxin Tablets. Lanoxin® (digoxin) tablets are available in two strengths: 0.125 mg and 0.25 mg tablets.

Recommended Dose:
Therapy is generally initiated at a dose of 0.250 mg once daily and followed with maintenance oral doses of 0.125 to 0.500 mg/day as a single daily dose and adjusted according to desired serum concentrations.

First Generic: No

Financial Disclosure: Form FDA 3454 was submitted. The firm has no conflict of interest with the investigators.

Bioequivalence Requirements for Digoxin
The Division of Bioequivalence recommends the following for approval of Digoxin Tablets:

- Conduct of both fasting and non-fasting studies on the 0.25 mg tablet with measurement of serum levels of digoxin only for bioequivalence assessment.
- Dissolution testing on the 0.25-mg and 0.125 mg strengths

II. Background

Pharmacokinetics:
Following oral administration, peak serum concentrations of digoxin occur at 1 to 3 hours.
In subjects with normal renal function, digoxin has a half-life of 1.5 to 2 days.
Elimination of digoxin follows first-order kinetics.

Food Effect:
When digoxin tablets are taken after meals, the rate of absorption slows down, but the total amount of digoxin absorbed does not change. When taken with meals high in bran fiber, however, the amount absorbed from an oral dose may be reduced.

Metabolites:
Only a small percentage (16%) of a dose of digoxin is metabolized. The end metabolites are polar. The metabolism of digoxin is not dependent upon the cytochrome P-450 system, and digoxin is not known to induce or inhibit the cytochrome P-450 system. Therefore, the quantitation of metabolites of digoxin is not requested for the BE studies.

III. Single-dose Fasting Bioequivalence Study on the 0.25 mg Strength

Study Information

STUDY FACILITY INFORMATION

Clinical Facility:
Medical Director:
Scientific Director:
Clinical Study Dates: 07/16/01 to 08/08/01
Analytical Facility
Principal Investigator:
Analytical Study Dates: 08/08/01 to 08/17/01
Storage Period: The maximum time samples were stored frozen(-20°C) from the first day of collection (07/16/01) to the last day of analysis (08/17/01) was 32 days. The validated frozen serum stability is 35 days.

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Digoxin	Lanoxin
Manufacturer:	Jerome Stevens Pharmaceuticals	Glaxo Wellcome Inc.
Manufacture Date:	4/4/01	N/A
Expiration Date:	N/A	NOV 01
ANDA Batch Size:		--
Full Batch Size:		--
Batch/Lot Number:	3501	8ZP1806
Potency:	98.3%	102.1%
Content Uniformity:	99.7 (97.6 – 101.7) 1.3%CV	101.7 (94.9 – 104.9) 2.9%CV
Strength:	0.25 mg	0.25 mg
Dosage Form:	Round, biconvex tablet	Round, biconvex tablet
Dose Administered:	0.5 mg	0.5 mg
Study Condition:	Fasting	Fasting
Length of Fasting:	12 hours	12 hours

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	Crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	14 days

AB: 1, 2, 7, 8, 9, 11, 12, 13, 18, 19, 21, 24, 27, 28
BA: 3, 4, 5, 6, 10, 14, 15, 16, 17, 20, 22, 23, 25, 26

The randomization scheme was balanced with 14 subjects receiving each drug treatment in each study period. The dropout of Subject No. 01 did not affect the balance of the study because in accordance with protocol, only the first 24 subjects completing the study were analyzed and used for pharmacokinetic and statistical analysis.

Demographics of the 28 Enrolled Subjects

Age (yrs): 32±10 (18-51)			Race:	Asian	0
Age Groups:				Black	0
	< 18 yrs	0		Caucasian	27 (96%)
	18-40 yrs	21 (75%)		Hispanic	0
	41-64 yrs	7 (25%)		Other (Amer. Hisp.)	1 (4%)
	65-75 yrs	0	Weight (lbs): 153.0±4.8 (128.3-169.3)		
	> 75 yrs	0	Height (in): 68.1±6.4 (63.2-73.6)		
Sex	Females	0			
	Males	28			

DOSING		SUBJECTS	
Single or Multiple Dose:	Single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	28
Route of Administration:	Oral	**No. of Subjects Completing:**	27
Dosing Interval:	N/A	**No. of Subjects Serum Analyzed:**	24*
Number of Doses:	N/A	**No. of Dropouts:**	1
Loading Dose:	N/A	**Sex(es) Included:**	Male
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**No. of Adverse Events:**	32

*Per protocol

Dietary Restrictions: Supervised overnight fast of 12 hours. Subjects abstained from food and drink containing xanthine, alcohol, and grapefruit products.

Activity Restrictions: Subjects advised to remain seated for up to 4 hours after dosing, unless medically necessary or procedurally-required; complete rest was prohibited during this interval.

Drug Restrictions: No concomitant medications other than those to counter an adverse event were to be utilized.

Blood Sampling: Pre-dose and at the following times post-dose: 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 2.0, 24.0, 48.0, 72.0, 96.0, 120, and 144 hours post-dose (1 x 7 mL).

Study Results

1) Clinical

Adverse Events:

The adverse reactions included drowsiness, pain at left arm (catheter site), pain in legs, pain at catheter sites (arms), hot flushes, tooth ache, blisters on skin (generalized), dizziness during catheter insertion, burning esophagus, pain at venipuncture site, scratches on arms and legs, hot flushes, dizziness, weakness, numbness of arms and legs, dizziness, fatigue, and headache.

A total of 32 post-dose adverse events were reported: 23 following administration of treatment A and 9 following administration of treatment B. All of the adverse events reported were mild or moderate in severity and no serious, severe or significant adverse events were reported. The 32 adverse events were experienced by 15 subjects. Eighteen of the events were judged as unrelated to the study medications. Nine events were judged as remotely related to the study medications. Five events were judged as possibly related to the study medications and all five followed the test product (A). The

adverse events possibly related to the test product (A) included dizziness, headache, weakness & blisters.

Protocol Deviations:
Minor deviations were noted (Vol. 1.2, pp. 228-231). The Principal Investigator judged the deviations unlikely to have affected the bioavailability comparison.

Dropouts:

SUBJECT NO.:	1
REASON:	Missed 3 consecutive blood draws (96-144-hour post-dose)
PERIOD:	1
REPLACEMENT:	N

2) Analytical

Comments:

- The reviewer substituted the original analytical values into the data set, statistically reanalyzed the data and found that the log-transformed 90% confidence intervals for LAUCT, LAUCI and Cmax changed only slightly and remained within the range of 80-125%.
- The analytical validation is incomplete per lack of long term stability data on digoxin in frozen (-20°C) serum.

3) Pharmacokinetics:

Mean Serum Concentrations:	Table 1, Figure 1	
Pharmacokinetic Parameters:	Tables 2 and 3	
90% Confidence Intervals:	LAUC0-t	88.6-117.1%
	LAUC0-inf	89.1-112.0%
	LCmax	85.2-106.2%
Arith. Mean AUCT/AUCI Ratios:	Test	0.77±0.06 (0.65-0.86)
	Ref	0.76±0.08 (0.57-0.85)
Arith. Mean T/R Ratios:	AUC0-t	1.10±0.49 (0.48-2.46)
	AUC0-inf	1.05±0.36 (0.55-2.04)
	Cmax	0.99±0.27 (0.38-1.55)
Root MSE:	LAUC0-t	0.279880
	LAUC0-inf	0.230020
	LCmax	0.220444

Comments On Fasting Study:

- The reviewer recalculated pharmacokinetic parameters and 90% confidence intervals. The reported values are in satisfactory agreement with those obtained by the reviewer.
- There were no measurable drug concentrations at 0 hr. There was no observation of first measurable drug concentration as Cmax.
- The fasting study is acceptable.

IV. Single-dose Post-Prandial Bioequivalence Study on the 0.25 mg Strength

A. Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	
Medical Director:	
Scientific Director:	
Clinical Study Dates:	07/19/01 to 08/08/01
Analytical Facility	
Principal Investigator:	
Analytical Study Dates:	08/15/01 to 09/04/01
Storage Period:	The maximum time samples were stored frozen (-20°C) from the first day of collection (07/19/01) to the last day of analysis (09/04/01) was 47 days. The validated frozen serum stability is 35 days.

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Digoxin	Lanoxin
Manufacturer:	Jerome Stevens Pharmaceuticals	Glaxo Wellcome Inc.
Manufacture Date:	4/4/01	N/A
Expiration Date:	N/A	NOV 01
ANDA Batch Size:		--
Full Batch Size:		--
Batch/Lot Number:	3501	8ZP1806
Potency:	98.3%	102.1%
Content Uniformity:	99.7 (97.6-101.7) 1.3%CV	101.7 (94.9-104.9) 2.9%)
Strength:	0.25 mg	0.25 mg
Dosage Form:	Round, biconvex tablet	Round, biconvex tablet
Dose Administered:	0.5 mg	0.5 mg
Study Condition:	Fed	Fed
Length of Fasting:	Overnight	Overnight

Standardized Breakfast:	Y	Y
Breakfast Specifics:	1 English muffin, 1 fried egg, 2 strips bacon, 1 slice American cheese, 1 serving hash brown potatoes, 240 mL whole milk, 180 mL orange juice	1 English muffin, 1 fried egg, 2 strips bacon, 1 slice American cheese, 1 serving hash brown potatoes, 240 mL whole milk, 180 mL orange juice

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	Crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	14 days

AB: 2, 4, 6, 7, 9, 10, 14, 15, 18, 21, 22, 23, 26, 27
BA: 1, 3, 5, 8, 11, 12, 13, 16, 17, 17, 19, 20, 25, 28

The randomization scheme was balanced with 14 subjects to receive each drug treatment in each study period. The dropout of Subject No. 24 did not affect the balance of the study because in accordance with protocol, only the first 24 subjects completing the study were analyzed and used for pharmacokinetic and statistical analysis.

Demographics of the 28 Enrolled Subjects

Age (yrs): 34±11 (18-54)
Age Groups:

	< 18 yrs	0
	18-40 yrs	21 (75%)
	41-64 yrs	7 (25%)
	65-75 yrs	0
	> 75 yrs	0
Sex	Females	0
	Males	28

Race:	Asian	0
	Black	1 (4%)
	Caucasian	26 (92%)
	Hispanic	0
	Other (Amer. Hisp.)	1 (4%)

Weight (lbs): 152.3±4.4 (136.2-169.1)
Height (in): 68.1±6.4 (62.8-72.4)

DOSING		SUBJECTS	
Single or Multiple Dose:	Single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	180 mL	**No. of Subjects Enrolled:**	28
Route of Administration:	Oral	**No. of Subjects Completing:**	27
Dosing Interval:	NA	**No. of Subjects Serum Analyzed:**	24
Number of Doses:	N/A	**No. of Dropouts:**	1
Loading Dose:	N/A	**Sex(es) Included:**	male
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**No. of Adverse Events:**	30

Dietary Restrictions:	Supervised overnight fast of 12 hours. Subjects abstained from food and drink containing xanthine, alcohol, and grapefruit products.
Activity Restrictions:	Subjects advised to remain seated for up to 4 hours after dosing, unless medically necessary or procedurally-

required; complete rest was prohibited during this interval.

Drug Restrictions: No concomitant medications other than those to counter an adverse event were to be utilized.

Blood Sampling: Pre-dose and at the following times post-dose: 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 2.0, 24.0, 48.0, 72.0, 96.0, 120, and 144 hours post-dose (1 x 7 mL).

Study Results

1) Clinical

Adverse Events:

	Treatment A	Treatment B
Total # of events	9	10
Possibly drug related	2[a]	7[b]

[a]Nature of events possibly related to A: Nausea & confusion

[b]Nature of events possibly related to B: Dizziness, tiredness, palpitations, headache & small face pimples

Eleven of the 30 adverse events were associated with clinically significant post-study laboratory results (exact onset time and date unknown). All of the adverse events reported were mild or moderate in severity and no serious, severe or significant adverse events were reported.

Protocol Deviations:

Minor deviations were noted (Vol. 1.6, pp 2369-2372). The Principal Investigator judged the deviations unlikely to have affected the bioavailability comparison.

Dropouts:

SUBJECT NO.: 24
REASON: Not dosed – withdrew (personal reasons)
PERIOD: 1
REPLACEMENT: N

The randomization scheme was balanced with 14 subjects to receive each drug treatment in each study period. The dropout of Subject No. 24 did not affect the balance of the study because in accordance with protocol, only the first 24 subjects completing the study were analyzed and used for pharmacokinetic and statistical analysis.

2) Analytical

Comments:
The analytical method is incomplete

3) Pharmacokinetics:

Mean Serum Concentrations:	Table 4, Figure 2	
Pharmacokinetic Parameters:	Tables 5 and 6	
Arith. Mean AUCT/AUCI Ratios:	Test	0.74±0.08 (0.54-0.86), N=23
	Reference	0.74±0.07 (0.57-0.87), N=24
Arith. Mean T/R Ratios:	AUC0-t	1.04±0.37 (0.53-2.48)
	AUC0-inf	1.03±0.28 (0.62-2.02)
	Cmax	1.06±0.23 (0.69-1.57)

Comments on Nonfasting Study:

- There were no measurable drug concentrations at 0 hr. There was no observation of first measurable drug concentration as Cmax.
- The point estimates for AUCt, AUCi, Cmax are within the acceptable limits of 80-125%.
- The firm reported that 90% confidence intervals for log transformed AUC0-t, AUC0-inf, and Cmax are within acceptable limits of 80-125%, but they are not currently required by DBE for food studies.
- Pharmacokinetic parameters calculated by the reviewer are in satisfactory agreement with firm's calculations.
- The nonfasting bioequivalence study is acceptable pending submission of documentation that digoxin is stable in serum at

IV. Formulation

- Formulation information is provided in Table 7.
- All inactive ingredients in the formulation were present at or below the levels cited in the FDA Inactive Ingredient Guide (1996) for approved drug products.

- The formulation for the 0.125-mg digoxin tablets is exactly proportional to that of the 0.25-mg strength per definition 1 in BA/BE Guidance for Industry for Orally Administered Drug Products issued on October 27, 2000.

V. Dissolution

A. Dissolution Method Used by Firm

The firm used the USP method.
No. Units Tested: 12 tablets
USP XXIV apparatus: 1 (Basket)
Medium: 0.1N HCl
Temperature: 37ºC
Volume: 500 mL
Rpm: 120
Sampling Times: 15, 30, 45, and 60 minutes
Tolerance: NLT % (Q) in 60 min

B. Results

Dissolution data are presented in Table 8.

C. Comments:

- Dissolution testing was conducted by Jerome Stevens Pharmaceuticals, Inc.
- The Similarity Factors (f_2) calculated by the reviewer are as follows:
  70 for 0.125 mg test vs 0.25 mg test
  77 for 0.25 mg test vs 0.25 mg reference
  53 for 0.125 mg test vs 0.125 mg reference.
- The dissolution testing is acceptable.

VI. Deficiency

The long term stability data on digoxin in frozen serum submitted in the January 28, 2002 amendment in response to the telephone request of 1/24/02 showed that digoxin is stable in serum at This stability data is inadequate in that the maximum time samples were stored frozen , from the first day of collection to the last day of analysis was days in the fed study. The firm should document that digoxin is stable in serum at

VII. Recommendations

1. The single-dose, fasting bioequivalence study conducted by Jerome Stevens Pharmaceuticals, Inc. on the test product, digoxin tablet 0.25 mg, lot 003501, comparing it with the reference product, Lanoxin® tablet 0.25 mg, lot 8ZP1806 manufactured by Glaxo Wellcome has been found acceptable by the Division of Bioequivalence. The study demonstrates that the test product, Jerome Stevens Pharmaceuticals, Inc.'s digoxin tablet 0.25 mg, is bioequivalent to the reference product, Lanoxin® tablet 0.25 mg under fasting conditions.

2. The single-dose, post-prandial bioequivalence study conducted by Jerome Stevens Pharmaceuticals, Inc. on the test product, digoxin tablet 0.25 mg, lot 003501, comparing it with the reference product, Lanoxin® tablet 0.25 mg, lot 8ZP1806 manufactured by

Glaxo Wellcome has been found incomplete by the Division of Bioequivalence per the deficiency on the long term stability of digoxin in frozen serum.

3. The in-vitro dissolution testing conducted by Jerome Stevens Pharmaceuticals, Inc. on its digoxin tablet 0.25 mg is acceptable.

   The dissolution testing should be conducted in 500 mL of 0.1N HCL at 37°C using USP apparatus I (basket) at 120 rpm. The test product should meet the following USP specifications:

   Not less than % (Q) of the labeled amount of digoxin is dissolved in 60 minutes. Per USP24-NF19 Supplement 4 the requirement is met if the quantities dissolved from the tablets tested conform to the following USP acceptance table specific for digoxin tablets instead of the table shown under USP 24 *Dissolution* <711>.

Stage	Number Tested	Acceptance Criteria
S1	6	Each unit is not less than Q + 5%.
S2	6	Average of 12 units (S1 + S2) is equal to or greater than Q, and no unit is less than Q - 5%.

4. The formulation for the 0.125 mg tablet is proportionally identical to that of the 0.25 mg tablets, which underwent bioequivalency testing. The waiver of *in vivo* bioequivalence study requirements for the 0.125 mg tablets of the test product is pending the submission of acceptable long term stability data on digoxin in frozen serum.

5. From the bioequivalence point of view, the application is incomplete due to inadequate documentation of digoxin stability in serum at

/S/

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang /S/
FT INITIALED YCHuang _____ Date 2/14/02

Concur: /S/ Date 2/14/2002
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

JEC/021402

Table 1. Fasting Single-Dose In Vivo Bioequivalence Study
Arithmetic Mean Serum Concentrations (pg/mL) vs. Time in 24 Subjects

TIME HR	TEST	SD	REFERENCE	SD	T/R
0	0.00	0.00	0.00	0.00	.
0.25	168.45	218.30	196.03	232.63	0.86
0.5	1116.60	540.30	1079.22	611.75	1.03
0.75	1752.94	480.51	1746.54	750.53	1.00
1	1968.93	574.12	1914.73	710.44	1.03
1.25	1921.20	636.99	1911.07	628.16	1.01
1.5	1791.57	622.41	1782.67	528.85	1.00
2	1533.93	384.96	1596.46	515.33	0.96
2.5	1341.30	292.64	1395.02	397.48	0.96
3	1183.03	261.01	1205.99	321.08	0.98
4	924.57	198.96	940.38	218.28	0.98
6	616.13	155.11	612.10	166.07	1.01
8	443.59	107.76	452.29	113.20	0.98
12	340.34	85.31	350.21	89.81	0.97
24	336.86	94.18	341.19	86.05	0.99
48	196.12	67.87	179.48	82.51	1.09
72	115.92	74.43	115.34	80.83	1.01
96	48.19	64.72	65.14	61.80	0.74
120	9.17	31.07	10.04	34.27	0.91
144	4.46	21.40	0.00	0.00	.

Units: Serum Level = pg/mL, Time=Hrs

Figure 1. Serum Concentrations (pg/mL) vs. Time
Single-Dose Fasting Study #01185

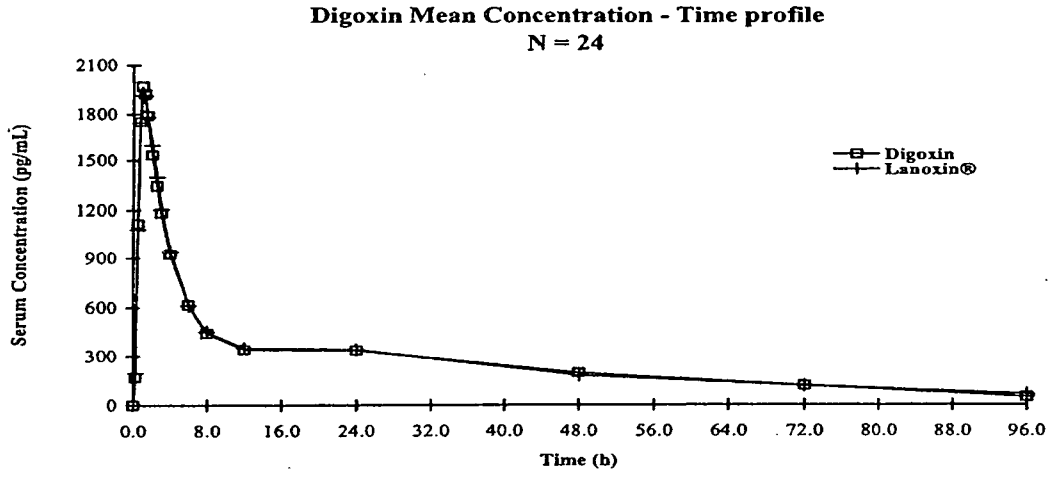

Table 2. Fasting Single-Dose In Vivo Bioequivalence Study
Arithmetic Means of Pharmacokinetic Parameters For Treatments in 24 Subjects

PARAMETER	TEST	SD	REFERENCE	SD	T/R
AUCI	31964.25	9702.09	32449.84	10177.14	0.99
AUCT	24940.24	8294.86	24983.54	8735.66	1.00
CMAX	2173.07	571.68	2276.51	592.78	0.95
KE	0.02	0.01	0.02	0.01	0.95
THALF	38.92	10.91	39.58	13.71	0.98
TMAX	1.21	0.52	1.29	0.57	0.94

Units: AUC = pg*hr/mL; Cmax=pg/mL, Tmax=hr, T1/2=hr

Table 3. Fasting In Vivo Bioequivalence Study. Geometric Least-Squares Means and 90% Confidence Intervals for Pharmacokinetic Parameters

PARAMETER	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
LAUCI	30606.44	30630.41	1.00	89.12	112.03
LAUCT	23590.67	23161.00	1.02	88.62	117.07
LCMAX	2111.74	2220.65	0.95	85.22	106.12

Units: AUC = pg*hr/mL, Cmax=pg/mL

Table 4. Fed In Vivo Bioequivalence Study. Arithmetic Mean Serum Concentrations (pg/mL) vs. Time in 24 Subjects

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.25	45.75	75.17	79.73	119.29	0.57
0.5	517.14	481.03	559.69	489.50	0.92
0.75	1015.60	729.57	1096.98	710.15	0.93
1	1380.98	794.73	1461.64	778.40	0.94
1.25	1549.70	659.23	1589.26	677.07	0.98
1.5	1688.43	558.58	1647.21	516.99	1.03
2	1624.27	411.44	1576.61	320.22	1.03
2.5	1298.95	218.64	1336.75	202.12	0.97
3	1125.52	244.64	1123.24	192.84	1.00
4	850.37	159.68	852.82	151.02	1.00
6	498.30	59.56	518.79	68.44	0.96
8	408.06	52.72	423.32	73.26	0.96
12	322.59	55.23	331.64	59.06	0.97
24	337.74	73.32	348.32	73.19	0.97
48	216.92	65.62	214.18	47.54	1.01
72	143.05	57.56	133.18	58.72	1.07
96	64.51	67.88	65.13	65.19	0.99
120	28.11	49.93	19.56	44.88	1.44
144	0.00	0.00	0.00	0.00	.

Units: Serum Level = pg/mL, Time=Hrs

Figure 2. Serum Concentrations (pg/mL) vs. Time Single-Dose Fed Study #01186

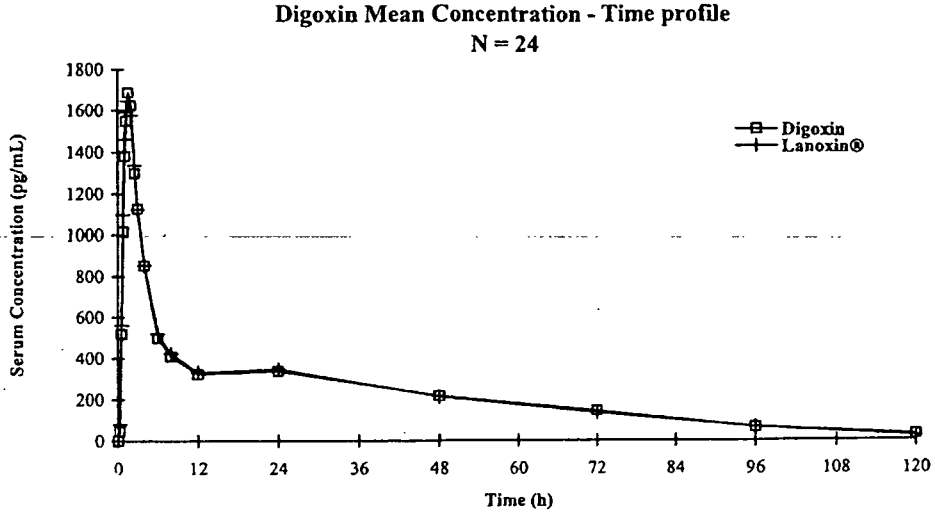

Table 5. Fed Single-Dose In Vivo Bioequivalence Study . Arithmetic Means of Pharmacokinetic Parameters For Treatments in 24 Subjects

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCI	34299.29	7686.01	33965.94	6849.27	1.01
AUCT	25524.43	6908.00	25415.41	6441.09	1.00
CMAX	2038.99	449.98	1951.40	465.25	1.04
THALF	47.79	12.21	46.36	9.79	1.03
TMAX	1.72	0.67	1.69	0.60	1.02

Units: AUC = pg*hr/mL, Cmax=pg/mL, Tmax=hr, T1/2=hr

Table 6. Fed Single-Dose In Vivo Bioequivalence Study. Geometric Least-Squares Means for Pharmacokinetic Parameters

PARAMETER	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
LAUCI	33339.99	33301.42	1.00	92.81	107.99
LAUCT	24471.11	24627.79	0.99	90.74	108.80
LCMAX	1985.65	1896.60	1.05	97.26	112.70

Units: AUC = pg*hr/mL, Cmax=pg/mL

Table 7. Digoxin Tablet (Test Product) Formulations
(NOT TO BE RELEASED UNDER FOI)

Ingredient	Amount (mg) per Dosage Unit Strength	
	0.125 mg Tablet	0.250 mg Tablet
Digoxin, USP	0.1275	0.255
Lactose Anhydrous		
Microcrystalline Cellulose		
Stearic Acid		
Croscarmellose Sodium		
Magnesium Stearate		
Colloidal Silicon Dioxide		
D&C Yellow Aluminum Lake #10		
Total Tablet Weight	65.31	130.75

Table 8. In Vitro Dissolution Testing Results

Sampling Times (minutes)	Test Product: Digoxin Lot #: 004001 Strength: 0.125 mg			Reference Product: Lanoxin® Lot #: 8ZP1043 Strength: 0.125 mg		
	Mean %	Range (min)	RSD	Mean %	Range (min)	RSD
15	60.0		2.1	72.8		1.9
30	75.7		2.0	82.7		1.6
45	83.7		1.4	87.8		1.4
60	88.9		1.9	90.0		1.1
Sampling Times (minutes)	Test Product: Digoxin Lot #: 003501 Strength: 0.250 mg			Reference Product: Lanoxin® Lot #: 8ZP1806 Strength: 0.250 mg		
	Mean %	Range (min)	RSD	Mean %	Range (min)	RSD
15	64.9		2.0	63.9		1.8
30	79.4		1.0	76.8		1.6
45	86.7		1.1	83.0		1.1
60	90.3		1.7	84.9		1.1

FEB 21 2002

BIOEQUIVALENCY DEFICIENCY

ANDA: 76-268 APPLICANT: Jerome Stevens Pharmaceuticals, Inc.

DRUG PRODUCT: Digoxin Tablet USP, 0.250 mg & 0.125 mg

The Division of Bioequivalence has completed its review. The following deficiency have been identified:

The long term stability data on digoxin in frozen serum submitted in your January 28, 2002 submission in response to our January 24, 2002 telephone request showed that digoxin is stable in serum at . This stability data is inadequate in that the maximum time samples were stored frozen , from the first day of collection to the last day of analysis was 47 days in the fed study. You need to document that digoxin is stable in your serum study samples at days.

Sincerely yours,

/S/

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

CC: ANDA 76-268
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

HFD-652/ J. Chaney J. Chaney 1/31/2002
HFD-652/ Y. Huang 1/31/2002 on file for Y. C. Huang 2/14/02
HFD-617/ K. Scardina 2/15/02
HFD-650/ D. Conner for 2/14/2002

BIOEQUIVALENCY – INCOMPLETE — Submission date: 10/29/01

FASTING STUDY (STF) olc — Strength: 0.25 mg
Outcome: AC
Submission date: 10/29/01

Clinical Study Site:

Analytical Sites:

FOOD STUDY (STP) olc — Strength: 0.25 mg
Outcome: UN
Submission date: 10/29/01

Clinical Study Site:

Analytical Sites:

DISSOLUTION WAIVER (DIW) olc — Strength: 0.125 mg
Outcome: AC
Submission date: 10/29/01

NEW CORRESPONDENCE (NC) — Strengths: All (Frozen Stability)
Outcome: UN
Submission date: 1/28/02

NOTE:

AC - Acceptable
NC - No Action
UN - Unacceptable
IC - Incomplete

Outcome Decision: Incomplete

WINBIO COMMENTS:
The biostudy under fasting conditions and the dissolution testing were found acceptable. The biostudy under fed conditions was found incomplete due to lack of documentation of satisfactory long term digoxin stability in frozen serum. Therefore, the application was found incomplete.