CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74467

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA: #74-467 **SPONSOR:** Geneva Pharmaceuticals
Drug: Ranitidine HCl
DOSAGE FORM: Tablets
STRENGTH: 300 mg
TYPE OF STUDY: Single/Fasting
CLINICAL SITE:
ANALYTICAL SITE:

STUDY SUMMARY:

Twenty-six (26) healthy male volunteers participated and completed the study. Blood samples were collected from 0.0 - 24.0 hours. Serum levels of ranitidine were measured using assay method. The 90% confidence intervals calculated for the Ln-transformed parameters of AUC (0-T), AUC(0-Inf), and C(max) fall in the acceptable range of 80% - 125%. The bioequivalence study conducted under fasting conditions has been found acceptable by the Division of Bioequivalence.

DISSOLUTION:

The dissolution testing conducted on 12 units of the test and reference products are acceptable. Not Less Than 80% (Q) of the labeled amount was dissolved in 45 minutes

PRIMARY REVIEWER: F. Nouravarsani **BRANCH:** III

SIGNITURE: /S/ **DATE:** 12/19/95

BRANCH CHIEF: R. Mhatre **BRANCH:** III

SIGNITURE: /S/ **DATE:** 12/19/95

DIRECTOR: K. Chan
DIVISION OF BIOEQUIVALENCE:

SIGNITURE: /S/ **DATE:** 1/31/96

DIRECTOR:
OFFICE OF GENERIC DRUGS:

SIGNITURE: _____ **DATE:** _____

DEC 18 1995

Ranitidine HCl Tablets
USP, 300 & 150 mg
ANDA #74-467
Reviewer: F. Nouravarsani
74467ADW.295

Geneva Pharmaceuticals, Inc.
Broomfield, CO
Submission Date:
February 24, 1995
October 27, 1995

REVIEW OF BIOEQUIVALENCE STUDY AMENDMENTS, DISSOLUTION TESTING AND A WAIVER REQUEST

INTRODUCTION:

Geneva Pharmaceuticals, Inc. has responded to the Division of Bioequivalence deficiency letter dated January 09, 1995.

The firm had submitted a fasting bioequivalence study and dissolution testing conducted on its test product, Ranitidine Hydrochloride Tablets, 300 mg, and Zantac Tablets, Ranitidine Hydrochloride, 300 mg, manufactured by Glaxo Pharmaceuticals (NDA #18703-002) as the listed reference product.

Deficiency #1:

The samples from all 26 subjects were assayed by error, but the data from 24 subjects were analyzed statistically. The firm was requested to submit the data for all of the subjects, and conduct statistical data analyses using all 26 subjects.

Response to Deficiency #1:

The data were reanalyzed statistically to include subjects #25 and #26. The pharmacokinetic parameters are compared in Table 1.

The AUC(0-T) for the test product, 5176.6 hr*ng/mL, is comparable with the AUC(0-T) of 5166.8 hr*ng/mL for the reference product.

The AUC(0-Inf) for the test product, 5218.0 hr*ng/mL, is comparable with the one obtained for the reference product, 5203.8 hr*ng/mL.

The C(Max) for the test product, 1124.4 ng/mL, is comparable with the C(Max) of 1109.2 ng/mL for the reference product.

Results of the GLM statistical data analyses were not included in the submission dated February 24, 1995. This information was submitted on October 27, 1995 in response to phone call by Dr. Jason Gross. There are no product, period (p=0.05) and sequence (p=0.1) effects observed for the pharmacokinetic parametetrs using Ln-transformed or un-transformed parameters.

The 90% confidence intervals for ln-transformed parameters, AUC(0-T), AUC(0-Inf), and C(Max) fall in the required range by the Division of Bioequivalence (summarized in Table 1).

No errors were found by spot checking of the calculations and statistical data analysis.

Samples from subjects #25 and #26 were assayed with runs BWE 18 and BWE 19, respectively. The accuracy and precision for the Standard and Quality Control Samples including all runs are summarized as follows:

Accuracy:

(a) From the standard samples, interday-
concentration range of ng/mL: %

(b) From the quality control samples, interday-
concentration of ng/mL: 95.5% (N=35)
concentration of ng/mL: 103.6% (N=42)
concentration of ng/mL: 98.8% (N=41)

Precision:

(a) From the standard samples, interday-
concentration range of ng/mL: %

(b) From the quality control samples, interday-
concentration of ng/mL: 10.1% (N=35)
concentration of ng/mL: 11.0% (N=42)
concentration of ng/mL: 10.1% (N=41)

Reviewer Comment:

The firm's response is acceptable.

Deficiency #2:

Limit Of Quantification (LOQ) was set at ng/mL. The firm was advised to increase the LOQ to a higher value, since significant interferences were observed for the following subject samples:

Response to Deficiency #2:

has stated that a higher LOQ will be set for ranitidine studies in the future. However, Cmax values were higher than 400 times the LOQ. Therefore, the bioequivalence study should not be affected by this interference.

Reviewer Comment:

The response is acceptable for this study.

Deficiency #3:

The firm was requested to report all original values together with reassayed, values which were used in the study, reason for reassaying, and rationale for the used values summarized in a table.

Response to Deficiency #3:

The firm had not submitted the original or reassayed values for all of the reanalyzed samples in its amendment dated February 24, 1995. These information were requested by phone call of Dr. Jason Gross. The values for all of the reassayed samples were submitted in the current amendment (submition date: October 27, 1995).

Reviewer Comment:

The response is acceptable.

Deficiency #4:

The waiver request for bioequivalence study requirements for 150 mg Ranitidine HCl Tablets was not granted, since the bio-study conducted on 300 mg Tablets was found incomplete.

Response to Deficiency #4:

The firm has resubmitted its request for waiver of bioequivalence study requirements for Ranitidine Tablets, 150 mg based on:

a. the bioequivalence study conducted on the 300 mg strength,

b. the comparative dissolution testing conducted on 300 mg and 150 mg of the test and reference products (Table 2), and

c. the similar composition of the products (Table 3).

The results of the in vitro studies are summarized as follows:

Dissolution Testing:

A. Results of the dissolution testing conducted on 12 units of the test product, Ranitidine Tablets, 300 mg (lot #6493066) and the reference product, Zantac Tablets, 300 mg (lot #Z10203 BP) are shown in Table 2. Not less than % (mean of 12 units) of the labeled amount of ranitidine was dissolved in 45 minutes for the test or reference product using USP XXII method. The dissolution of no unit was less than Q % at 45 minutes.

B. Results of the dissolution testing conducted on 12 units of the test product, 150 mg tablets (lot #6493065) and reference product, 150 mg Zantac tablets (lot #Z10773 FP) are shown in Table 2. Not less than % (mean of 12 units) of the labeled amount of ranitidine was dissolved in 45 minutes for the test or reference product using USP XXII method. The dissolution of no unit was less than Q % at 45 minutes.

Potency:

The assayed potencies of the test products, Ranitidine HCl Tablets, 300 mg, and 150 mg were % (CV = 0.6, N=6) and % (CV = 0.4%, N=6) of the labeled amount claimed, respectively. These values fall in the USP required range of %. The assayed potencies of the reference products was reported as % (CV = 0.8%, N=3)) for the 300 mg tablets, and % (CV =2.1%, N = 6) for 150 mg tablets.

Content Uniformity:

Values of % (CV = 1.4%, N=10) and % (CV = 2.3%, N=10) were obtained as means of percentage of the labeled amount claimed for 10 Ranitidine HCl Tablets, 300 mg, and 150 mg, respectively. The content uniformities of the reference products were % (CV = 1.3%, N=10) for 300 mg Tablets, and % (CV = 1.5%, N=10) for 150 mg Tablets. These values fall in the USP range of % with a CV of NMT %.

Reviewer Comment:

The waiver of bioequivalence study requirements for Ranitidine Tablets, 150 mg may be granted.

Deficiency #5:

It was stated that study samples will be stored frozen until 5/25/94, then they will be discarded. The samples were stored less than one year, since the clinical study was started on October 8, 1993. The firm was informed that the storage period should be increased to at least one year for the future studies.

Response to Deficiency #5:

The firm responded that: "The samples continue to remain in storage at . The statement in the analytical report was incorrect and should indicate that the samples will remain in storage until 25May94 at which time the client will be contacted regarding further retention of stored samples."

Reviewer Comment:

The firm's response is acceptable.

RECOMMENDATIONS:

1. The bioequivalence study conducted by Geneva Pharmaceuticals, Inc. on its Ranitidine HCl Tablets, 300 mg, lot #6493066, comparing it to Zantac Tablets, 300 mg, lot #Z10203BP manufactured by Glaxo Pharmaceuticals has been found acceptable by the Division of Bioequivalence.

2. The dissolution testings conducted by the Geneva Pharmaceuticals, Inc. on its Ranitidine HCl Tablets, 300 mg, lot #6493066, and Ranitidine HCl Tablets, 150 mg, lot #6493065 are acceptable.

3. From the bioequivalence point of view, the firm has met the requirements of in-vivo bioequivalence and in-vitro dissolution testing.

4. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37° C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than ¾ of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

5. Waiver of bioequivalence study requirements may be granted for the firm's Ranitidine HCl Tablets, 150 mg.

/S/

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE /S/
FT INITIALED RMHATRE 12/18/95

Concur: /S/ Date: 12/18/95
for Keith Chan, Ph.D.
Director
Division of Bioequivalence

FNouravarsani/12-08-95/74467ADW.295

Table 1:

Comparison of Mean (CV%) Ranitidine Pharmacokinetic Parameters, and 90% CI (ln-transformed) Obtained for 300 mg Tablets of the Test and Reference Products, N=26:

Parameter	Test	Reference	90% CI (ln-trans.)
AUC(0-T) hr*ng/mL	5176.6(25)	5166.8(22)	92.1% - 107.0%
AUC(0-Inf) hr*ng/mL	5218.0(25)	5203.8(22)	92.3% - 107.1%
C(Max) ng/mL	1124.4(44)	1109.2(38)	87.5% - 110.2%
T(Max) hr	2.602 (33)	2.500 (35)	
K(Elm) 1/hr	0.2205(16)	0.2201(11)	
T(1/2) hr	3.219 (16)	3.192 (12)	

Table 2:

Drug (Generic Name):Ranitidine HCl Tablets, USP
Dose Strength: 300 mg, 150 mg
ANDA: #74-467: Geneva Pharmaceuticals, Inc
Submission Date: February 24, 1995

In Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXII Basket ___ Paddle X RPM 50 No. Units Tested 12

Medium: Water at 37° C Volume: 900 mL

Reference Drug, (Manuf.) Zantac, (Glaxo)

Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times	Test Product Lot # 6493066			Reference Product Lot # Z10203BP		
Minutes	Strength (mg) 300			Strength (mg) 300		
	Mean%	Range%	(CV%)	Mean %	Range%	(CV%)
15	88.0	-	(08.8)	70.0	-	(11.7)
30	100.0	-	(01.8)	93.0	-	(04.4)
45	100.0	-	(01.9)	97.0	-	(02.5)
60	101.0	-	(01.7)	99.0	-	(01.9)

Sampling Times	Test Product Lot # 6493065			Reference Product Lot # Z10773FP		
Minutes	Strength (mg) 150			Strength (mg) 150		
	Mean%	Range%	(CV%)	Mean %	Range%	(CV%)
15	84.0	-	(13.1)	41.0		(12.4)
30	98.0	-	(01.6)	72.0		(06.0)
45	99.0		(01.6)	89.0		(07.5)
60	99.0		(01.7)	94.0		(04.1)

Table 3:

Formulation Comparison:

Ingredients	150 mg Tablet	300 mg Tablet
Ranitidine HCl, USP	mg(a)	mg(b)
Microcrystalline Cellulose, NF	mg	mg
Hydroxypropyl Methylcellulose 2910 USP	mg	ng
Sodium Starch Glycolate, NF	mg	ng
Magnesium Stearate, NF	mg	mg
Opadry Pink YS-5-1296	mg	
Opadry Orange Y-5-2394		mg
Opadry Clear YS-1-7006	mg	mg
Purified Water		

(a) Equivalent to 150 mg ranitidine base.

(b) Equivalent to 300 mg ranitidine base.

DEC 9 1994

Ranitidine HCl Tablets
300 & 150 mg
ANDA #74-467
Reviewer: F. Nouravarsani
74467SDW.294

Geneva Pharmaceuticals, Inc.
Broomfield, CO
Submission Date:
February 16, 1994

REVIEW OF A BIOEQUIVALENCE STUDY, DISSOLUTION TESTING AND A WAIVER REQUEST

INTRODUCTION:

Geneva Pharmaceuticals, Inc. has submitted a bioequivalence study and dissolution testing conducted on its test product, Ranitidine Hydrochloride Tablets, 300 mg, and Zantac Tablets, Ranitidine Hydrochloride, 300 mg, manufactured by Glaxo Pharmaceuticals (NDA #18703-002) as the listed reference product.

Ranitidine Hydrochloride, a histamine H_2-receptor antagonist inhibits daytime and nocturnal basal gastric acid secretions. It also inhibits the gastric acid secretion stimulated by meal, pentagastrin, and betazole. The oral absolute bioavailability of Zantac is 50%. Mean peak levels of ranitidine are 440 to 545 ng/mL observed at 2 to 3 hours following a 150 mg dose. The administration of food or antacids does not show a significant effect on the absorption of the Zantac. It has been reported in one study that simultaneous administration of Zantac with a high potency antacid (150 m mol) reduced the absorption of Zantac in fasting subjects. The elimination half-life is reported to be 2.5 to 3 hours (PDR 47, 1994).

BIOEQUIVALENCE STUDY:

Objectives:

1. Determine the bioequivalency of the test product, Ranitidine Hydrochloride Tablets, 300 mg and the reference product, Zantac Tablets, 300 mg, under fasting conditions.

2. Compare the in vitro dissolution testing conducted on the test and reference products.

3. Request a waiver of bioequivalence study requirements for Ranitidine Hydrochloride Tablets, 150 mg.

Sponsor: Geneva Pharmaceuticals, Inc., Broomfield, CO
Manufactured by: Geneva Pharmaceuticals, Inc.
Contract Facility:

Study Design:

A single dose of treatment A (test product, lot #6493066, expiration date of September 1995) and treatment B (reference product, lot #Z10203BP, expiration date of February 1995) was administered randomly to healthy volunteers in a two - way crossover study design (protocol/report No. 930825).

Clinical Study Dates:

Phase I: October 8, 1993
Phase II: October 15, 1993
Washout period: 7 days

Subjects:

Twenty six (26) healthy male volunteers were enrolled and completed the study. Subjects number 2, 3, 5, 8, 10, 11, 13, 16, 17, 19, 21, 23, and 25 received treatment A for phase I study. The rest of the volunteers (1, 4, 6, 7, 9, 12, 14, 15, 18, 20, 22, 24, and 26) were dosed treatment A for phase II. The subject age, weight, and height are summarized as following:

Age : 19 - 45 years
Weight: 61.4 - 89.8 kg
Height: 158 - 192 cm

The samples from all 26 subjects were assayed, however statistical data analyses was conducted using subjects 1-24.

Housing, Food and Fluid Intake:

All volunteers were housed in the
from 12 hours prior to the dose administration until after last blood sample collection at 24 hours. The subjects fasted overnight prior to the dosing until 5 hours after the dosing. The standard meals were served 5 hours and 10 hours after the dose. Water was not allowed from 2 hours before the dose until 5 hours after the dose.

Blood Samples:

Blood samples were collected at predose and after the dose at 0.33, 0.50, 0.67, 1.0, 1.33, 1.5, 1.67, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, and 24.0 hours.

Analytical Procedures:

Limit of Quantitation:

The lower limit of quantitation was set at ng/mL (the lowest non-zero concentration of a standard sample).

Assay Range: ng/mL, using Ln polynomial regression.

Statistical Analysis:

The data were analyzed using SAS - GLM procedure. The two one sided t-test procedure (90% confidence intervals) was used to compare the least square means of the parameters of AUC(0-t), AUC(0-Inf), and C(Max) obtained from the test and reference products.

Medical Events:

The reported non-serious, mild, expected drug related medical events are summarized as follows:

Medical Event	Subject #	Product
Headache	16	Test
Dizziness	4	Ref.
Dizziness on standing up	17	Ref.

Results:

The mean serum concentrations of ranitidine are summarized in Table 1. Linear and semi-ln Plots of the mean plasma concentrations of ranitidine versus time for both test and reference products are shown in Figures I and II. The pharmacokinetic parameters are compared in Table 2.

The AUC(0-T) for the test product, 5284.1 hr*ng/mL, is comparable with the AUC(0-T) of 5182.1 hr*ng/mL for the reference product.

The AUC(0-Inf) for the test product, 5323.7 hr*ng/mL, is comparable with the one obtained for the reference product, 5217.7 hr*ng/mL.

The C(Max) for the test product, 1171.0 ng/mL, is comparable with the C(Max) of 1124.9 ng/mL for the reference product.

Mean AUC(0-T)/AUC(0-Inf) ratios for the test and reference products were 99.2% and 99.3%, respectively (Table 3).

Mean test/reference ratios for AUC(0-T), AUC(0-Inf), and C(Max), were 103.7%, 103.7%, and 107.1%, respectively (Table 4).

The 90% confidence intervals for AUC(0-T), AUC(0-Inf), and C(Max) are summarized as follows:

Parameters	Ln-transformed	Un-transformed
AUC(0-T)	94.0 - 109.4	94.3 - 109.6
AUC(0-Inf)	94.1 - 109.5	94.4 - 109.6
C(Max)	91.1 - 114.4	92.1 - 116.1

There are no product, period (p=0.05) and sequence (p=0.1) effects observed for the above pharmacokinetic parametetrs using Ln-transformed or un-transformed parameters.

IN VITRO STUDIES:

Dissolution Testing:

A. Results of the dissolution testing conducted on 12 units of the test product, Ranitidine Tablets, 300 mg (lot #6493066) and the reference product, Zantac Tablets, 300 mg (lot #Z10203 BP) are shown in Table 5. Not less than % (mean of 12 units) of the labeled amount of ranitidine was dissolved in 45 minutes for the test or reference product using USP XXII method. The dissolution of no unit was less than Q % at 45 minutes.

B. Results of the dissolution testing conducted on 12 units of the test product, 150 mg tablets (lot #6493065) and reference product, 150 mg Zantac tablets (lot #Z10773 FP) are shown in Table 5. Not less than % (mean of 12 units) of the labeled amount of ranitidine was dissolved in 45 minutes for the test or reference product using USP XXII method. The dissolution of no unit was less than Q % at 45 minutes.

Potency:

The assayed potencies of the test products, Ranitidine HCl Tablets, 300 mg, and 150 mg were 98.3% (CV = 0.6, N=6) and % (CV = 0.4%, N=6) of the labeled amount claimed, respectively. These values fall in the USP required range of %. The assayed potencies of the reference products was reported as % (CV = 0.8%, N=3)) for the 300 mg tablets, and % (CV =2.1%, N = 6) for 150 mg tablets.

Content Uniformity:

Values of % (CV = 1.4%, N=10) and 100.8% (CV = 2.3%, N=10) were obtained as means of percentage of the labeled amount

claimed for 10 Ranitidine HCl Tablets, 300 mg, and 150 mg, respectively. The content uniformities of the reference products were % (CV = 1.3%, N=10) for 300 mg Tablets, and % (CV = 1.5%, N=10) for 150 mg Tablets. These values fall in the USP range of with a CV of NMT .

Waiver Request for Ranitidine HCl Tablets, 150 mg:

The firm requested a waiver of bioequivalence study requirements for its Ranitidine HCl Tablets, 150 mg based on "the similar composition of the products, the satisfactory dissolution profiles for the 150 mg strength, and the fact that an in vivo bioavailability study has been conducted on the 300 mg strength".

COMMENTS:

1. Lots #6493066 (test product) and #Z10203BP (reference product) were used for both the bioequivalence study and the dissolution testing. Theoretical batch size was tablets.

2. The dissolution testings conducted on 300 mg and 150 mg Ranitidine HCl Tablets are acceptable.

3. Application Form FDA 356h was not included in the jacket.

DEFICIENCIES:

1. The samples from all 26 subjects were assayed by error, but the data from 24 subjects were analyzed statistically. The firm should submit the data for all of the subjects, and conduct statistical data analyses using all 26 subjects.

2. Limit Of Quantification (LOQ) was set at ng/mL. The firm should be advised to increase the LOQ to a higher value, since significant interference was observed for the following subject samples:

For example the original values for the following samples should be reported:

4. The waiver request for bioequivalence study requirements for 150 mg Ranitidine HCl Tablets may not be granted, since the bio-study conducted on 300 mg Tablets has been found incomplete.

5. It was stated that samples will be stored frozen until 5/25/94, then they will be discarded. The samples were stored less than one year, since the clinical study was started on October 8, 1993. The firm should be informed for the future studies that the storage period should be increased to at least one year.

RECOMMENDATIONS:

1. The bioequivalence study conducted by Geneva Pharmaceuticals, Inc. on its Ranitidine HCl Tablets, 300 mg, lot #6493066, comparing it to Zantac Tablets, 300 mg has been found incomplete by the Division of Bioequivalence.

2. The dissolution testings conducted by the Geneva Pharmaceuticals, Inc. on its Ranitidine HCl Tablets, 300 mg, lot #6493066, and Ranitidine HCl Tablets, 150 mg, lot #6493065 are acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37° C using USP XXII apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

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

The firm should be informed of the DEFICIENCIES and the RECOMMENDATIONS.

/S/

Farahnaz Nouravarsani, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE /S/

Concur: /S/ Date: 12/9/94
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

Table 1:

Mean (CV%) Serum Concentrations (ng/mL) of Ranitidine, N=24:

Time, hr	Test Product		Reference Product	
0.00	0.000	(--)	0.000	(--)
0.33	158.4	(96)	108.8	(69)
0.50	322.9	(63)	292.9	(52)
0.67	414.5	(47)	386.7	(43)
1.00	600.3	(50)	510.2	(41)
1.33	746.0	(71)	607.5	(50)
1.50	721.2	(61)	682.1	(52)
1.67	686.9	(61)	692.5	(54)
2.00	811.0	(56)	747.9	(60)
2.50	880.1	(50)	751.4	(53)
3.00	836.7	(40)	834.4	(36)
3.50	751.0	(38)	772.7	(41)
4.00	668.1	(33)	694.3	(35)
5.00	549.6	(28)	560.2	(32)
6.00	399.1	(30)	410.0	(28)
8.00	250.5	(28)	244.8	(25)
10.00	134.5	(29)	142.0	(26)
12.00	72.1	(30)	73.8	(26)
16.00	29.3	(37)	29.7	(31)
24.00	7.7	(40)	7.5	(40)

Table 2:

Comparison of Mean (CV%) Ranitidine Pharmacokinetic Parameters Obtained for 300 mg Tablets of the Test and Reference Products, N=24:

Parameters	Test Product		Reference Product	
AUC(0-T) hr*ng/mL	5284.1	(24.5)	5182.1	(23.2)
AUC(0-Inf) hr*ng/mL	5323.7	(24.2)	5217.7	(23.0)
C(Max) ng/mL	1171.0	(41.8)	1124.9	(38.3)
T(Max) hr	2.527	(34.1)	2.417	(35.5)
K(Elm) 1/hr	0.223	(14.9)	0.222	(11.1)
T(1/2) hr	3.17	(14.6)	3.16	(12.1)

Table 3: AUC(0-T)/AUC(0-Inf) Percentage

Subject	Test	Reference
01		
02		
03		
04		
05		
06		
07		
08		
09		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		
23		
24		
Mean%	99.2	99.3
CV%	0.6	0.4
Range%	%	%

Table 4: Ratio Analysis of the Parameters

	(Test/Reference) Percentage		
Subject	AUC(0-T)	AUC(0-Inf)	C(Max)
01			
02			
03			
04			
05			
06			
07			
08			
09			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
Mean%	103.7	103.7	107.1
CV%	22.0	21.9	32.3
Range%			

Table 5:

Drug (Generic Name):Ranitidine HCl Tablets, USP
Dose Strength: 300 mg, 150 mg
ANDA: #74-467m: Geneva Pharmaceuticals, Inc
Submission Date: February 16, 1994

In Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXII Basket ___ Paddle X RPM 50 No. Units Tested 12

Medium: Water at 37° C Volume: 900 mL

Reference Drug, (Manuf.) Zantac, (Glaxo)

Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times	Test Product Lot # 6493066			Reference Product Lot # Z10203BP		
Minutes	Strength (mg) 300			Strength (mg) 300		
	Mean%	Range%	(CV%)	Mean %	Range%	(CV%)
15	88.0	-	(08.8)	70.0	-	(11.7)
30	100.0	-	(01.8)	93.0	-	(04.4)
45	100.0	-	(01.9)	97.0	-	(02.5)
60	101.0		(01.7)	99.0	-	(01.9)

Sampling Times	Test Product Lot # 6493065			Reference Product Lot # Z10773FP		
Minutes	Strength (mg) 150			Strength (mg) 150		
	Mean%	Range%	(CV%)	Mean %	Range%	(CV%)
15	84.0	-	13.1)	41.0	-	(12.4)
30	98.0	-	01.6)	72.0	-	(06.0)
45	99.0	-	01.6)	89.0	-	(07.5)
60	99.0	-	(01.7)	94.0	-	(04.1)

Figure I

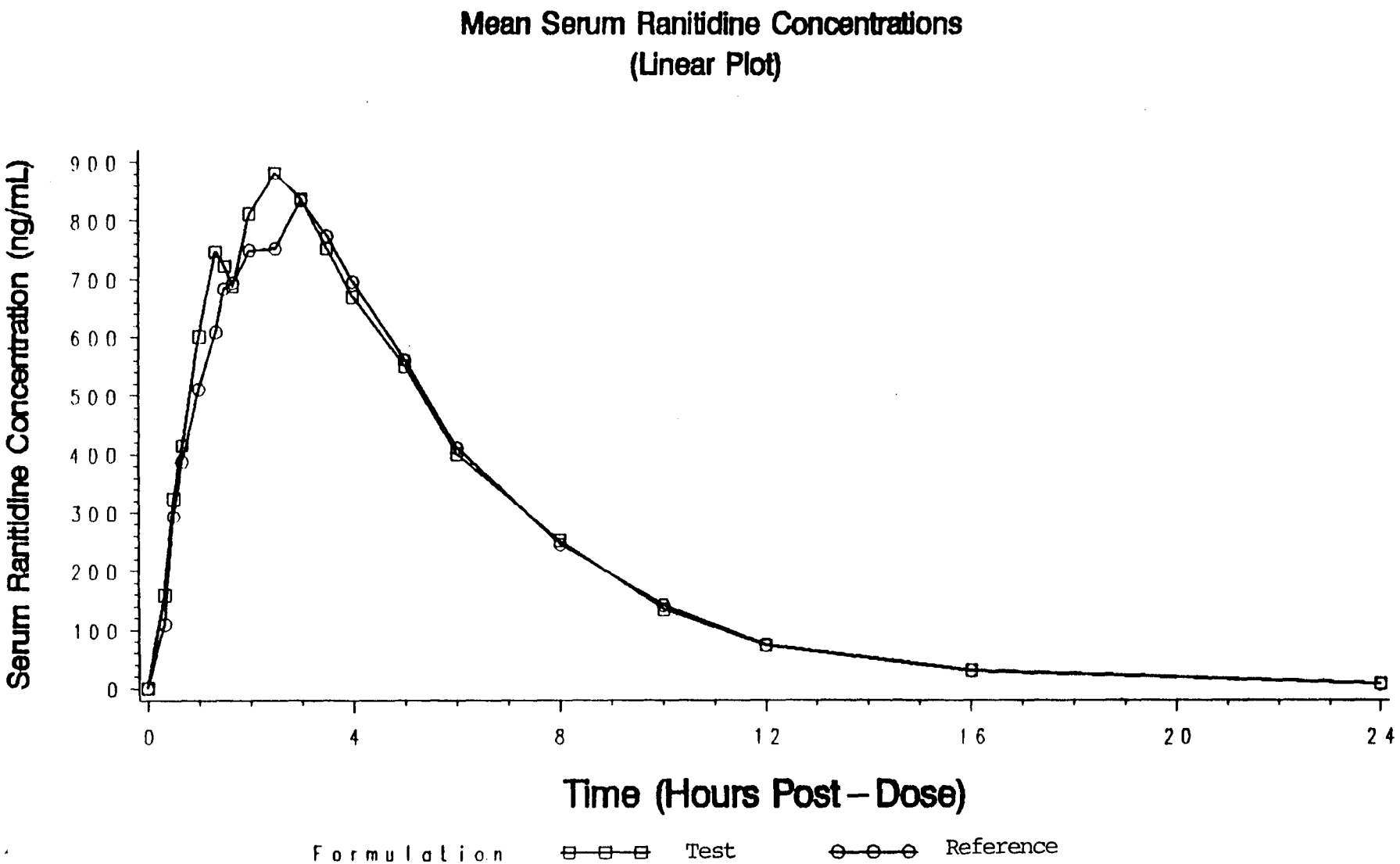
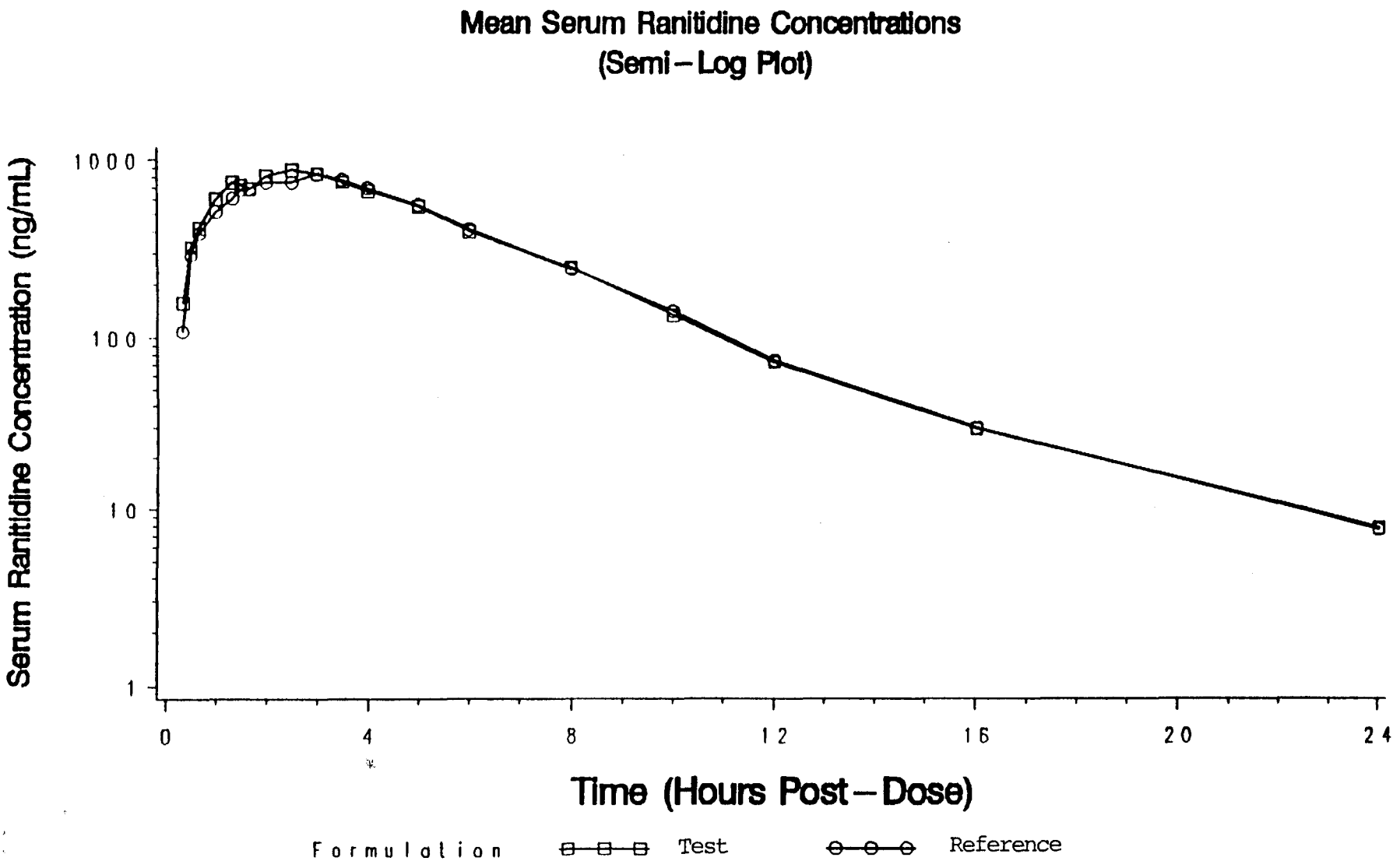

Mean Serum Ranitidine Concentrations
(Linear Plot)
Serum Ranitidine Concentration (ng/mL)
900
800
700
600
500
400
300
200
100
0
0
4
8
12
16
20
24
Time (Hours Post – Dose)
Formulation
Test
Reference

Figure II


Mean Serum Ranitidine Concentrations
(Semi-Log Plot)
Serum Ranitidine Concentration (ng/mL)
1000
100
10
1
0
4
8
12
16
20
24
Time (Hours Post-Dose)
Formulation
Test
Reference