CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-655

BIOEQUIVALENCE REVIEW(S)

ANDA 74-655

JUL 31 1997

Geneva Pharmaceuticals, Inc.
Attention: Ms. Beth Brannan
2555 W. Midway Blvd.
P.O. Box 446
Broomfield, Colorado 80038-0446

Dear Ms. Brannan:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Ranitidine Hydrochloride Capsules, 150 mg and 300 mg.

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

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

for Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUL 28 1997

Ranitidine HCl Capsules
300 & 150 mg
ANDA #74-655
Reviewer: F. Nouravarsani
74655DA.697

Geneva Pharmaceuticals, Inc.
Broomfield, CO
Submission Date:
June 27, 1997

REVIEW OF A DISSOLUTION TESTING AMMENDMENT

In the current submission the firm has made references to the communication from the Division of Bioequivalence dated January 29, 1997, and phone conversation between OGD Chemist and Geneva (June 25, 1997). The firm stated that: "Geneva commits to incorporating the following dissolution testing into the stability and quality control programs:"

Medium: water, 900 mL at 37° C
Apparatus: paddle (2)
Rotation Speed: 50 rpm
Specifications:

Comment:

The firm incorporates the specifications of "NLT minutes" recommended by the Division of Bioequivalence. The firm had previously proposed specifications of "NLT minutes".

Recommendation:

No further action is required by the firm.

F . ani

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

RD INITIALED RMHATRE
FT INITIALED RMHATRE 7/14/97

Concur: for Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

Date: 7/28/97

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA: #74-655 SPONSOR: Geneva Pharmaceuticals, Inc
DRUG: Ranitidine HCl
DOSAGE FORM: Capsules
STRENGTH: 300 mg
TYPE OF STUDY: Single/Fasting
CLINICAL SITE: Phoenix International Life Sciences
ANALYTICAL SITE: Phoenix International Life Sciences

STUDY SUMMARY:

Twenty-six (26) healthy, male volunteers and two (2) alternate enrolled in the study. Twenty-five (25) subjects completed the study. Subject #4 withdrew from the study before period 2 for personal reasons. Blood samples were collected from 0.0 - 24.0 hours. Plasma levels of ranitidine was measured using HPLC 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 firm's proposed dissolution testing conducted on 12 units of the test and reference products are acceptable. Not Less Than labeled amount was dissolved in minutes

PRIMARY REVIEWER: F. Nouravarsani BRANCH: III

SIGNITURE: /S/ nsani DATE: 12/24/96

BRANCH CHIEF: R. Mhatre BRANCH: III

SIGNITURE: /S/ Mhatre DATE: 12/30/96

DIRECTOR: N. Fleischer
DIVISION OF BIOEQUIVALENCE:

SIGNITURE: /S/ DATE: 5/15/97

DIRECTOR:
OFFICE OF GENERIC DRUGS:

SIGNITURE: _____ DATE: _____

21

ANDA 74-655

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2555 W. Midway Blvd.
Broomfield 1 CO 80038-0446

JAN 29 1997

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Ranitidine Hydrochloride Capsule, 150 mg and 300 mg.

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

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following **tentative** specifications:

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

2 1

JAN 2 9 1997

Ranitidine HCl Capsules
300 & 150 mg
ANDA #74-655
Reviewer: F. Nouravarsani
74655ADW.796

Geneva Pharmaceuticals, Inc.
Broomfield, CO
Submission Date:
July 11, 1996

REVIEW OF A BIOEQUIVALENCE STUDY AMENDMENT, DISSOLUTION TESTING, A WAIVER REQUEST, AND RECOMMENDATIONS FOR APPROVAL

Deficiency #1:

(a) The long-term stability of ranitidine in plasma samples stored at -22° C was reported for 57 days. The study samples were stored at -22° C for 70 days. The firm was requested to submit data to support the stability of ranitidin in plasma during the storage of the study samples.

(b) The stability and comparison samples were prepared and stored at -20° C on 6/21/94 and 8/17/94, respectively. The firm was requested to clarify why the comparison samples were stored at -20° C, and when these samples were injected.

Response to Deficiency #1:

(a) The firm submitted stability data for samples stored for 83 days at -22° C.

(b) The comparison samples were prepared and stored overnight at -20° C, because they were scheduled to be extracted next day. It was difficult to complete the sample preparation, extraction, and injection in one working day.

The firm's response is acceptable.

Deficiency #2:

(a) The autosampler stability samples were found stable for 2.8 hours at 22° C. However, it was not clear whether injecting the samples for a duration of 2.8 hours covered the time that samples were kept on the autosampler.

(b) The autosampler stability study method was requested to be modified to obtain the deviation of each injected value at each time from the one injected at begining (0.0 time), instead of from mean of the all injected values.

Response to Deficiency #2:

(a) The firm has provided longer (4.4 hours) autosampler stability data at 20° C, which covers the period of samples

injection.

The response is acceptable.

(b) In reference to the modification of calculation to obtain the deviation of each injected value at each time from the mean of the all injected values, the firm responded that: the means of the quality control samples are the most representative of the nominal values.

The reviewer disagrees with using values of the mean data as the reference. The injection at each time should be from the same sample injected at zero hour, and deviation of each injected value at each time should be from the value of zero hour.

However, the autosampler stability data for this submission is acceptable, because the "Extracted Stability" study of ranitidine in human plasma was conducted at 22° C (+ 4° C) for 72 hours, and was found acceptable. The temperature for autosampler stability study was 20° C.

Deficiency #3:

The stock solutions of ranitidine and astemizole in methanol, stored at -22° C for 138 days and 30 days, respectively, were found stable. However, the firm was informed that method of obtaining the percentage difference between the stability and comparison samples was found incorrect. The percentage difference should have been determined by dividing the difference between means of the stability samples and comparison samples by mean of the comparison samples, instead of dividing them by "mean" of the stability and comparison samples.

Response to Deficiency #3:

The firm has responded that the formula used for the calculation of percentage difference between the comparison and stability samples was unintentionally incorrect. However, the formula used in the program to calculate the percentage difference was correct.

The response is acceptable.

Deficiency #4:

Thirty-one (31) samples with code B (lost in process) were reanalyzed. The firm was requested to clarify how these samples were lost in process.

Response to Deficiency #4:

The firm has responded that a solid phase extraction was used to

extract the samples. In most cases samples were lost due to high content of insoluble compounds in the plasma samples, therefore blocking the cartridges. Low or zero volume were eluted from the blocked cartridges. The samples coded 'lost in processing' were reassayed.

The firm's response is acceptable.

Deficiency #5:

The firm was requested to submit the SOP used for Analytical Method Validation (AL-G-1521-04).

Response to Deficiency #5:

The firm has submitted the SOP used for the Analytical Method Validation.

The firm's response is acceptable.

Deficiency #6:

The dissolution of the test products were faster than the reference products. At 15 minutes, a mean of 96% and 99% were dissolved for the test products, 300 mg and 150 mg Capsules, respectively, compared with 58% and 67% for GELdose Capsules, 300 mg and 150 mg, respectively.

The firm was requested to submit comparative dissolution testings data conducted on 12 units of test and reference products in 900 mL water at 37° C, using both USP paddle at 50 RPM, and basket at 100 RPM. Sampling times of 10, 20, 30, and 45 minutes was recommended instead of 15, 30, 45, and 60 minutes.

Response to Deficiency #6:

The firm has submitted dissolution testings data conducted on 12 units of each the test, and reference products in 900 mL water at 37° C using apparatus 1 (basket) at 100 rpm, and apparatus 2 (paddle) at 50 rpm. The sampling times were at 10, 20, 30, and 45 minutes (Table 1). The proposed specifications are

The dissolution data were similar using either paddle at 50 rpm, or basket at 100 rpm. Percent dissolved for the test and reference products were similar and above 80% at 20, 30, and 45 minutes using either apparatus (Table 1). Percent dissolved at 10 minutes was higher for the test product compard with the reference product using either apparatus (Table 1).

Table 2 compares two different lots of the reference products,

lot #4B333 (300 mg) and lot #5M330 (300 mg). Lot #4B333, which was previously used for the bio-study and dissolution testing had been expired at the time of the new dissolution testing. The data show similarity between the two lots at all the times except for 20 minutes.

Table 2 also compares two different lots of the reference products, lot #4B356 (150 mg) and lot #6ZPC001 (150 mg). The data show similarity between the two lots at all the times.

The response is acceptable.

Deficiency #7:

The firm had requested a waiver of bioequivalence study for its test product, Ranitidine Capsules, 150 mg. However, the firm's bio-study for its 300 mg strength had been found incomplete. The firm has also requested a waiver in this submission.

Response to Deficiency #7:

The firm has responded to the bio-study deficiencies for its higher strength, 300 mg Capsules, and the study is acceptable. The dissolution testing conducted on both strengths are acceptable. The test products' compositions for 150 mg and 300 mg Capsules are propertionally similar (Table 3).

The response is acceptable.

COMMENT:

In reference to the deficiency #2 (b), the modification of calculation to obtain the deviation of each injected value at each time from the mean of the all injected values, the firm responded that: the means of the quality control samples are the most representative of the nominal values.

The firm should be informed for the future that, the Division disagrees with using values of the mean data as the reference. The injection at each time should be from the same sample injected at zero hour, and deviation of each injected value at each time should be from the value of zero hour.

DEFICIENCY: None.

RECOMMENDATIONS:

1. The bioequivalence study conducted by Geneva Pharmaceuticals, Inc. on its Ranitidine HCl Capsules, 300 mg, lot #6494023, comparing it to Zantac Capsules, 300 mg, lot #4B333 has been found acceptable by the Division of Bioequivalence. The study demonstrates that Geneva's ranitidine HCl, 300 mg Capsules is

manufactured by Glaxo Pharmaceuticals.

2. The dissolution testing conducted by Geneva Pharmaceuticals on its Ranitidine HCl, 300 mg Capsules, lot #6494023 is 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 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following **tentative** specifications:

[illegible] rug

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.

5. The dissolution testing conducted by Geneva Pharmaceuticals on its drug, 150 mg Ranitidine HCl Capsules, lot #6494022 is acceptable. The firm has conducted an acceptable in vivo bioequivalence study comparing its 300 mg Capsules of the test product with 300 mg Capsules of the reference product Zantac manufactured by Glaxo Pharmaceuticals. The formulation of the 150 mg strength is proportionally similar to the 300 mg strength of the test product which underwent bioequivalency testing. The waiver of in vivo bioequivalence study requirements for the 150 mg Capsules of the test product is granted. The 150 mg Capsules of the test product is therefore deemed bioequivalent to the 150 mg Capsules of Zantac manufactured by Glaxo Pharmaceuticals.

6. The firm should be informed of the COMMENT.

/S/

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

RD INITIALED RMHATRE
FT INITIALED RMHATRE /S/ 12/4/96

Concur: /S/ Date: 12/27/96
Rabindra Pathak, Ph.D.
Acting Director
Division of Bioequivalence

FNouravarsani/12-01-96/74655ADW.796

Table 1:

Drug (Generic Name): Ranitidine HCl Capsules
Dose Strength: 300 mg, 150 mg
ANDA: #74-655: Geneva Pharmaceuticals, Inc
Submission Date: July 11, 1996

In Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXII Basket ___ Paddle __ RPM ___ No. Units Tested 12

Medium: Water at 37° C Volume: 900 mL

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

Assay Methodology:

II. Results of In Vitro Dissolution Testing:

A. Paddle at 50 rpm, 300 mg Capsules

Sampling Times Minutes	Test Product Lot # 6494023 Strength (mg) 300			Reference Product Lot # 4B333 Strength (mg) 300		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
10	59.0		(14.9)	4.0		(55.0)
20	98.0		(4.1)	94.0		(6.9)
30	102.0		(3.0)	100.0		(2.8)
45	102.0		(3.0)	101.0		(3.0)

B. Basket at 100 rpm, 300 mg Capsules

Sampling Times Minutes	Test Product Lot # 6494023 Strength (mg) 300			Reference Product Lot # 4B333 Strength (mg) 300		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
10	46.0		(11.7)	5.0		(96.0)
20	82.0		(6.2)	96.0		(5.0)
30	94.0		(4.5)	99.0		(3.6)
45	96.0		(4.0)	99.0		(3.3)

C: Paddle at 50 rpm, 150 mg Capsules

Sampling Times Minutes	Test Product Lot # 6494022 Strength (mg) 150			Reference Product Lot # 4B356 Strength (mg) 150		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
10	59.0		(23.2)	3.0		(60.0)
20	96.0		(4.9)	94.0		(6.8)
30	100.0		(2.1)	101.0		(2.3)
45	100.0		(2.5)	101.0		(1.8)

D: Basket at 100 rpm, 150 mg Capsules

Sampling Times Minutes	Test Product Lot # 6494022 Strength (mg) 150			Reference Product Lot # 4B356 Strength (mg) 150		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
10	49.0		(17.6)	4.0		(30.0)
20	93.0		(7.0)	96.0		(9.0)
30	99.0		(2.7)	102.0		(3.1)
45	100.0		(2.0)	102.0		(2.0)

Table 2: Comparison of Two Lots of the Reference Product

A. Paddle at 50 rpm, 300 mg Capsule

Sampling Times Minutes	Reference Product Lot # 5M330 Strength (mg) 300			Reference Product Lot # 4B333 Strength (mg) 300		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
10	6.0		(41.7)	4.0		(55.0)
20	74.0		(14.1)	94.0		(6.9)
30	100.0		(2.4)	100.0		(2.8)
45	101.0		(1.7)	101.0		(3.0)

B. Basket at 100 rpm, 300 mg Capsules

Sampling Times Minutes	Reference Product Lot # 5M330 Strength (mg) 300			Reference Product Lot # 4B333 Strength (mg) 300		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
10	7.0		(101)	5.0		(96.0)
20	69.0		(12.2)	96.0		(5.0)
30	93.0		(3.8)	99.0		(3.6)
45	99.0		(1.4)	99.0		(3.3)

C: Paddle at 50 rpm, 150 mg Capsules

Sampling Times Minutes	Reference Product Lot # 6ZPC001 Strength (mg) 150			Reference Product Lot # 4B356 Strength (mg) 150		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
10	4.0		(52.5)	3.0		(60.0)
20	94.0		(4.9)	94.0		(6.8)
30	101.0		(1.9)	101.0		(2.3)
45	102.0		(1.5)	101.0		(1.8)

D: Basket at 100 rpm, 150 mg Capsules

Sampling Times Minutes	Reference Product Lot # 6ZPC001 Strength (mg) 150			Reference Product Lot # 4B356 Strength (mg) 150		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
10	9.0		(101)	4.0		(30.0)
20	96.0		(5.3)	96.0		(9.0)
30	101.0		(2.5)	102.0		(3.1)
45	102.0		(2.5)	102.0		(2.0)

Table 3:

Formulation Comparison:

Ingredients	150 mg Capsule	300 mg Capsule
see package insert for labeling		
[illegible] NF	1 750 mg	[illegible] mg
		[illegible]
Total Capsule Weight		

(a) Equivalent to 150 mg ranitidine base.

(b) Equivalent to 300 mg ranitidine base.

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA: #74-655 SPONSOR: Geneva Pharmaceuticals, Inc
DRUG: Ranitidine HCl
DOSAGE FORM: Capsules
STRENGTH: 300 mg
TYPE OF STUDY: Single/Fasting
CLINICAL SITE:
ANALYTICAL SITE

STUDY SUMMARY:

Twenty-six (26) healthy, male volunteers and two (2) alternate enrolled in the study. Twenty-five (25) subjects completed the study. Subject #4 withdrew from the study before period 2 for personal reasons. Blood samples were collected from 0.0 - 24.0 hours. Plasma levels of ranitidine was 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. THE DISSOLUTION AMENDMENT (6.27.97) IS ACCEPTABLE (SEE REVIEW BY F. NOURAVARSANI 7.28.97) 11/18/97

DISSOLUTION:

The firm's proposed dissolution testing conducted on 12 units of the test and reference products are acceptable. Not Less Than

PRIMARY REVIEWER: F. Nouravarsani /S/ BRANCH: III

SIGNITURE: DATE: 12/24/96

BRANCH CHIEF: R. Mhatre BRANCH: III

SIGNITURE: /S/ DATE: 12/30/96

DIRECTOR: N. Fleischer
DIVISION OF BIOEQUIVALENCE:

SIGNITURE /S/ DATE: 5/15/97

DIRECTOR:
OFFICE OF GENERIC DRUGS:

SIGNITURE: DATE:

1:1 D. Amoine

ANDA 74-655

MAY 10 1996

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2555 W. Midway Blvd.
Post Office Box 446
Broomfield, CO 80038-0446

Dear Ms. Brannan:

Reference is made to the amendment dated April 16, 1996, in response to our January 22, 1996 correspondence for Ranitidine Hydrochloride Capsules, 150 mg and 300 mg.

With respect to the submitted amendment the following comment is provided for your consideration:

> The April 16, 1996 amendment fails to address all concerns expressed in the January 22, 1996 correspondence and is thus not complete for review. Since the amendment is not a complete response it will not be reviewed. You are advised to resubmit the amendment when the data is available.

Should you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

for Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-655

JAN 22 1996

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2555 W. Midway Blvd.
Post Office Box 446
Broomfield, CO 80038-0446

Dear Ms. Brannan:

Reference is made to the Abbreviated New Drug Application submitted on March 31, 1995, for Ranitidine Hydrochloride Capsules, 150 mg and 300 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. The long-term stability of ranitidine in plasma samples stored at -22°C was reported for 57 days. The study samples were stored at -22° C for 70 days. The firm should submit data to support the stability of ranitidine in plasma for a period equivalent to the longest time the study samples remained under storage.

   Furthermore, the stability and comparison samples were prepared and stored at -20°C on 6/21/94 and 8/17/94, respectively. Please clarify why the comparison samples were stored at -20°C, and when the samples were injected.

2. The autosampler stability samples were found stable for 2.8 hours at 22°C. However, it is not clear whether injecting the samples for a duration of 2.8 hours covered the time that samples were kept on the autosampler.

   Furthermore, the autosampler stability study method should be modified to obtain the deviation of each injected value at each time from the one injected at beginning (0.0 time), instead of from mean of the all injected values.

3. The stock solutions of both ranitidine and astemizole in methanol, stored at -22°C for 138 days and 30 days, respectively, were found stable. However, the method of obtaining the percent difference between the stability and comparison samples was incorrect. The percent difference should be determined by dividing the difference between the means of the stability samples and comparison samples by the mean of the comparison sample, instead of dividing them by "mean" of the stability and comparison samples.

4. Thirty-one (31) samples with code B (lost in process) were reanalyzed. Clarify how these samples were lost in process.

5. Submit the SOP used for Analytical Method Validation (AL-G-1521-04).

6. The dissolution results of the test products were faster than those of the reference products. At 15 minutes, means of 96% and 99% were attained for the test capsules, 300 mg and 150 mg, respectively, compared with 58% and 67% for GELdose Capsules, 300 mg and 150 mg, respectively.

   Submit comparative dissolution data conducted on 12 units each of both the test and reference products in 900 mL water at 37°C, using both USP apparatus 2 (paddle) at 50 RPM, and apparatus 1 (basket) at 100 RPM. Sampling times of 10, 20, 30, and 45 minutes is recommended instead of 15, 30, 45, and 60 minutes.

7. The request for a waiver of bioequivalence study requirements for the 150 mg strength cannot be considered at this time. Please resubmit your waiver request with the information requested to complete your study requirements.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

Keith M. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DEC 19 1995

Ranitidine HCl Capsules
300 & 150 mg
ANDA #74-655
Reviewer: F. Nouravarsani
74655SDW.395

Geneva Pharmaceuticals, Inc.
Broomfield, CO
Submission Date:
March 31, 1995

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 Capsules, 300 mg, and Zantac GELdose Capsules, Ranitidine Hydrochloride, 300 mg, manufactured by Glaxo Pharmaceuticals (NDA #20095-002, March 08, 1994) 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 49, 1995).

Zantac GELdose capsules, 150 and 300 mg are soft gelatin capsules in a nonaqueous matrix of and

BIOEQUIVALENCE

Objectives:

1. Determine the bioequivalency of the test product, Ranitidine Hydrochloride Capsules, 300 mg and the reference product, Zantac GELdose Capsules, 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 Capsules, 150 mg.

Sponsor: Geneva Pharmaceuticals, Inc., Broomfield, CO

Manufactured by: Geneva Pharmaceuticals, Inc.
Contract Facility:
Montreal, [redacted]ada
Principal Investigator:
Pharmacokinetics and Clinical Pharmacology

Treatments:

Treatment A (test Product): A single dose of Ranitidine Capsules, 300 mg, lot #6494023, expiration date: 8/96, actual batch size [redacted] psules.

Treatment B (reference Product): A single dose of Zantac GELdose Capsules, 300 mg, lot #4B333, expiration date: 8/95

Study Design:

A single dose of treatment A and B were administered randomly to healthy volunteers in a two - way crossover study design (protocol/report No. 941143).

Clinical Study Dates:

Phase I: September 28, 1994
Phase II: October 5, 1994
Washout period: 7 days.

Subjects:

Twenty-six (26) healthy male volunteers were enrolled. Two subjects served as alternates. Twenty-five subjects completed the study. Subject #4 withdrew from the study before the period 2, for personal reasons. This subject, who was in sequence BA, was unintentionally replaced by alternate subject #25 in sequence AB, instead of subject #26, who was in sequence BA. Data from 24 subjects were used for statistical data analyses.

Subjects [redacted], 5, 7, 9, 11, 12, 14, 15, 17, 20, 21, and 25 received treatment A in period I. The rest of the volunteers (2, 4, 6, 8, 10, 13, 16, 18, 19, 22, 23, 24, and 26) were dosed treatment A in period II.

The Mean (CV%) and range of the subjects' age, weight, and height are summarized as following:

	Mean (CV%)	Range
Age	28.8 (27.7%) years	
Weight	72.8 (8.4%) kg	
Height	174.8 (3.5%) cm	

Housing, Fasting, Food and Fluid Intake:

All volunteers were housed in the
from 12 hours prior to the administration of the dose until after last blood sample collection at 24 hours. The subjects fasted overnight prior to the dosing until 5 hours after the dose. Standard meals were served at 5 and approximately 10 hours after the dose. Except for 240 mL taken with the dose, water was not allowed from 2 hours before the dose, until 5 hours after.

Blood Samples:

Blood samples were collected at predose, and 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 after the dose.

Analytical Procedures:

A
detection method of assay was developed and validated for measurement of ranitidine in human plasma at
The study samples were assayed on 23 calibration curves run. A total of 959 samples were analyzable. Samples were stored at -22° C for 70 days.

Specificity:

Human plasma, and stock solutions of ranitidine and internal standard were screened by chromatography for any interfering compounds.

Predose samples containing internal standard were used to determine any endogenous or contaminant substances at the retention time of ranitidine.

To determine any interference at the retention time of the internal standard, subject samples with concentrations close to highest levels of ranitidine were extracted and injected.

Accuracy:

(a) From the standard samples, interday-
concentration range of 2.52-1007.20 ng/mL: 95.0%-104.2%

(b) From the quality control samples, interday-
concentration of 7.03 ng/mL: 97.5% (N=46)
concentration of 200.72 ng/mL: 100.5% (N=45)
concentration of 802.89 ng/mL: 96.4% (N=44)

Precision:

(a) From the standard samples, interday-
concentration range of 2.52-1007.20 ng/mL: 4.2%-7.6%

(b) From the quality control samples, interday-
concentration of 7.03 ng/mL: 8.7% (N=46)
concentration of 200.72 ng/mL: 7.7% (N=45)
concentration of 802.89 ng/mL: 7.1% (N=44)

Internal Standard:

Limit of Quantitation:

The lower limit of quantitation was set at 2.5 ng/mL (the lowest non-zero concentration of a standard sample).

Assay Range: 2.52-1007.2 ng/mL, using Ln polynomial regression.

Stability Studies:

Long-Term Frozen: samples stored at -20° C for 57 days were found stable.

Short-Term (benchtop): samples kept at 22° C for 7.5 hours were found stable.

Freeze-Thaw: samples were found stable after three freeze-thaw cycles.

Autosampler: quality control samples at 4 different concentrations were injected at various times. Mean value was determined for each concentration. Percent deviation of each injection at each time from the mean was calculated. The percentage deviations were plotted against time. The samples were found stable at 22° C for 2.8 hours.

Repeat Analysis:

1. Analysis of eight samples (0.8% of the total samples) were repeated (duplicates) as suspected pharmacokinetic outliers. The median values were reported for seven of them. One sample (18-2.5-2) was reported as "not reportable", since there was only one repeated assay. The second repeated assay was outside the range. There was insufficient sample volume for reanalysis.

2. Thirty-one samples (3.2%) were lost in processing.

3. Seventeen samples (1.8%) were reassayed, because they were outside the standard concentrations range. The original values for the samples "outside range" were not submitted.

Data 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 ln-transformed parameters of AUC(0-t), AUC(0-Inf), and C(Max) obtained from the test and reference products.

Medical Event:

The only non-serious, mild, and probably drug related medical event was headache, reported by subject #19.

Results:

The mean plasma 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 1 and 2. The pharmacokinetic parameters are compared in Table 2.

The AUC(0-T) for the test product, 4404.8 hr*ng/mL, is comparable with the AUC(0-T) of 4143.7 hr*ng/mL for the reference product.

The AUC(0-Inf) for the test product, 4438.5 hr*ng/mL, is comparable with the one obtained for the reference product, 4189.7 hr*ng/mL.

The C(Max) for the test product, 859.93 ng/mL, is comparable with the C(Max) of 775.88 ng/mL for the reference product.

Mean AUC(0-T)/AUC(0-Inf) ratios for the test and reference products were 99.3% and 98.9%, respectively (Table 3).

Mean test/reference ratios for AUC(0-T), AUC(0-Inf), and C(Max), were 107.5%, 107.1%, and 116.5%, respectively (Table 4).

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

The 90% CIs calculated for the ln-transformed parameters fall in the required range of 80 - 125% (Table 2).

IN VITRO STUDIES:

Dissolution Testing:

Results of the dissolution testing conducted on 12 units of the test product, Ranitidine Capsules, 300 mg (lot #6494023)

and the reference product, Zantac Capsules, 300 mg (lot #4B333) are shown in Table 5.

The dissolution testing was conducted in water at 37° C using USP XXII paddle at 50 RPM. The firm has proposed a specification of "Not less than amount

Not less than (mean of 12 units) of the labeled amount of ranitidine was dissolved in minutes" for the test or reference product. The dissolution of no unit was less than Q - 15% at 45 minutes.

Results of the dissolution testing conducted on 12 units of the test product, 150 mg Capsules (lot #6494022) and reference product, 150 mg Zantac Capsules (lot #4B356) are shown in Table 5. Not less than (mean of 12 units) of the labeled amount of ranitidine was dissolved in inutes for the test or reference product. The dissolution of no unit was less than

Potency:

The assayed potencies of the test products, Ranitidine HCl Capsules, 300 mg, and 150 mg were 100.9% (CV = 0.9%, N=10) and 99.1% (CV = 0.8%, N=10) of the labeled amount claimed, respectively. The assayed potencies of the reference products was reported as 99.6% (CV = 1.2%, N=3)) for the 300 mg capsules, and 100.1% (CV =1.1%, N = 3) for 150 mg capsules.

Content Uniformity:

Values of 100.4% (CV = 1.5%, N=10) and 100.7% (CV = 2.3%, N=10) were obtained as means of percentage of the labeled amount claimed for 10 Ranitidine HCl Capsules, 300 mg, and 150 mg, respectively. The content uniformities of the reference products were 101.8% (CV = 1.8%, N=10) for 300 mg Capsules, and 99.8% (CV = 2.1% N=10) for 150 mg Capsules.

Waiver Request for Ranitidine HCl Capsules, 150 mg:

The firm has requested a waiver of bioequivalence study requirements for its Ranitidine HCl Capsules, 150 mg based on similar formulations of the products (Table 6), dissolution testing for the 150 mg strength (Table 5), and in-vivo bio-study conducted on the 300 mg strength.

COMMENTS:

1. Lots #6494023 (test product) and #4B333 (reference product) were used for both the bioequivalence study and the dissolution testing. Theoretical batch size was

2. The 90% CIs calculated for the ln-transformed parameters fall in the required range of 80 - 125%.

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

4. Multiple peaks are observed for both test and reference products in most of the subjects.

5. Sample at 0.5 hour, period 1, treatment B could not be collected for subject #13.

6. Plasma level could not be reported for subject #18, at 2.5 hour, period 2, test product due to insufficient sample volume for reanalysis.

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

DEFICIENCIES:

1. The long-term stability of ranitidine in plasma samples stored at -22° C was reported for 57 days. The study samples were stored at -22° C for 70 days. The firm should submit data to support the stability of ranitidin in plasma during the storage of the study samples.

Furthermore, the stability and comparison samples were prepared and stored at -20° C on 6/21/94 and 8/17/94, respectively. The firm should clarify why the comparison samples were stored at -20° C, and when these samples were injected.

2. The autosampler stability samples were found stable for 2.8 hours at 22° C. However, it is not clear whether injecting the samples for a duration of 2.8 hours covered the time that samples were kept on the autosampler.

Furthermore, the autosampler stability study method should be modified to obtain the deviation of each injected value at each time from the one injected at begining (0.0 time), instead of from mean of the all injected values.

3. The stock solutions of ranitidine and astemizole in methanol, stored at -22° C for 138 days and 30 days, respectively were found stable. However, the firm should be informed that method of obtaining the %difference between the stability and comparison samples was found incorrect. The %difference should be determined by dividing the difference between means of the stability samples and comparison samples by mean of the comparison samples, instead of dividing them by "mean" of the stability and comparison samples.

4. Thirty-one (31) samples with code B (lost in process) were

reanalyzed. The firm should clarify how these samples were lost in process.

5. The firm should submit the SOP used for Analytical Method Validation (AL-G-1521-04).

6. The dissolution of the test products were faster than the reference products. At 15 minutes, a mean of 96% and 99% were dissolved for the test products, 300 mg and 150 mg Capsules, respectively, compared with 58% and 67% for GELdose Capsules, 300 mg and 150 mg, respectively.

The firm should submit comparative dissolution testings data conducted on 12 units of test and reference products in 900 mL water at 37° C, using both USP paddle at 50 RPM, and basket at 100 RPM. Sampling times of 10, 20, 30, and 45 minutes is recommended instead of 15, 30, 45, and 60 minutes.

RECOMMENDATION:

The bioequivalence study conducted by Geneva Pharmaceuticals, Inc. on its Ranitidine HCl Capsules, 300 mg, lot #6494023, comparing it to Zantac Capsules, 300 mg, lot #4B333 has been found incomplete by the Division of Bioequivalence.

The firm should be informed of the DEFICIENCIES.

/S/

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

RD INITIALED [redacted]
FT INITIALED [redacted]

/S/ 12/19/95

Concur: /S/ Date: _____
Keith Chan, Ph.D.
Director
Division of Bioequivalence

FNouravarsani/11-22-95/74655SDW.395

Table 1:

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

Time, hr	Test Product	Reference Product
0.00	0.000 (--)	0.000 (--)
0.33	48.96 (75)	21.38 (174)
0.50	174.52 (48)	132.09 (82)
0.67	289.27 (38)	242.70 (53)
1.00	373.19 (39)	356.73 (57)
1.33	408.71 (36)	412.00 (38)
1.50	404.25 (37)	420.79 (39)
1.67	426.14 (39)	441.84 (36)
2.00	586.32 (63)	517.12 (52)
2.50	700.89 (50)	560.57 (35)
3.00	693.40 (30)	583.26 (31)
3.50	684.50 (31)	586.17 (33)
4.00	645.08 (35)	564.33 (36)
5.00	518.73 (37)	497.79 (34)
6.00	400.08 (37)	390.78 (42)
8.00	210.07 (36)	212.71 (33)
10.00	113.86 (41)	121.01 (33)
12.00	65.33 (37)	69.38 (32)
16.00	23.09 (43)	26.56 (38)
24.00	6.16 (58)	7.64 (69)

Table 2:

Comparison of Mean (CV%) Ranitidine Pharmacokinetic Parameters, and 90% CI Obtained for 300 mg Capsules of the Test and Reference Products, N=24:

Parameters	Test	Reference	90% CI (ln-trans.)
AUC(0-T) hr*ng/mL	4404.8(26.3)	4143.7(21.2)	95.3 - 113.0
AUC(0-Inf) hr*ng/mL	[illegible]5(26.4)	4189.7(21.2)	95.1 - 112.6
C(Max) ng/mL	859.9 (39.4)	775.9 (32.7)	92.3 - 123.8
T(Max) hr	3.132 (29.8)	3.315 (39.0)	
K(Elm) 1/hr	0.218 (17.4)	0.210 (22.1)	
T(1/2) hr	3.26 (14.9)	3.50 (28.5)	

Table 3: AUC(0-T)/AUC(0-Inf) Percentage, N=24:

Subject	Test	Reference
01		
02		
03		
05		
06		
07		
08		
09		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		
23		
24		
25		
Mean%	99.25	98.93
CV%	0.3	1.1
Range%		

Table 4: Ratio Analysis of the Parameters, N=24:

	(Test/Reference) Percentage		
Subject	AUC(0-T)	AUC(0-Inf)	C(Max)
01			
02			
03			
05			
06			
07			
08			
09			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
Mean%	107.50	107.06	116.47
CV%	22.5	22.1	37.2
Range%			

[redacted]

Table 5:

Drug (Generic Name): Ranitidine HCl Capsules
Dose Strength: 300 mg, 150 mg
ANDA: #74-655; Geneva Pharmaceuticals, Inc
Submission Date: March 31, 1995

In Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXII Basket ___ Paddle X (with sinkers) RPM 50 No. Units Tested 12

Medium: Water at 37° C Volume: 900 mL

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

Assay Methodology:

Proposed Specifications:

II. Results of In Vitro Dissolution Testing:

Sampling Times Minutes	Test Product Lot # 6494023 Strength (mg) 300			Reference Product: Zantac Capsules Lot # 4B333 Strength (mg) 300		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
15	96.0		(3.3)	58.0		(29.3)
30	102.0		(1.8)	98.0		(3.9)
45	102.0		(2.0)	99.0		(3.8)
60	103.0		(1.6)	99.0	89..	(4.1)

Sampling Times Minutes	Test Product Lot # 6494[illegible] Strength (mg) 150			Reference Product: Zantac Capsules Lot # 4B356 Strength (mg) 150		
	Mean%	Range%	(CV%)	Mean%	Range%	(CV%)
15	99.0		(3.3)	67.0		(27.2)
30	99.0		(3.3)	99.0		(2.4)
45	100.0		(2.9)	101.0		(2.0)
60	102.0		(2.7)	101.0		(2.0)

Table 6:

Formulation Comparison:

Ingredients	150 mg Capsule	300 mg Capsule
[illegible]	see package insert labeling.	
D		
Total Capsule Weight	222.000 mg	428.000 mg

(a) Equivalent to 150 mg ranitidine base.

(b) Equivalent to [illegible] mg ranitidine base.

Figure 1

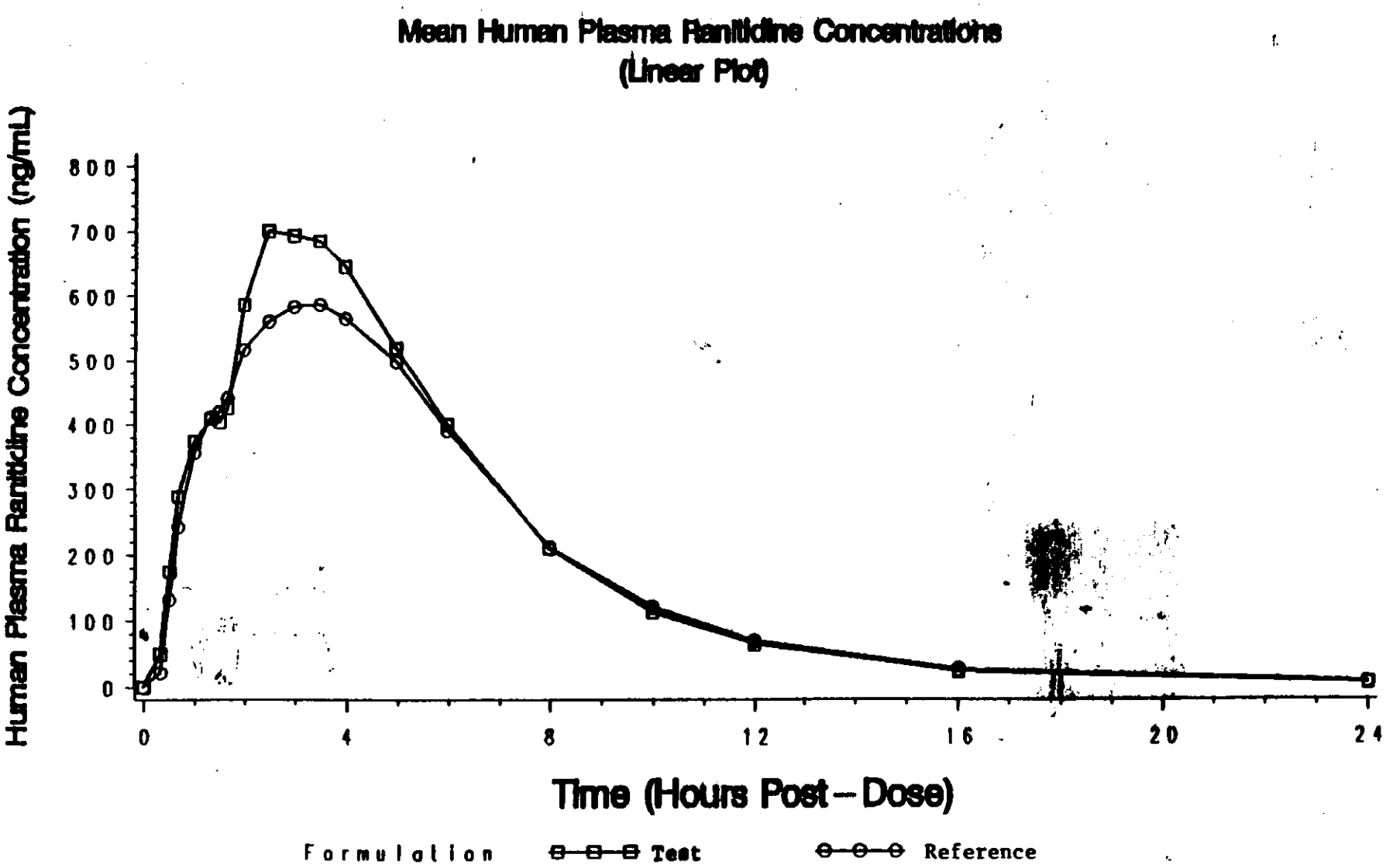
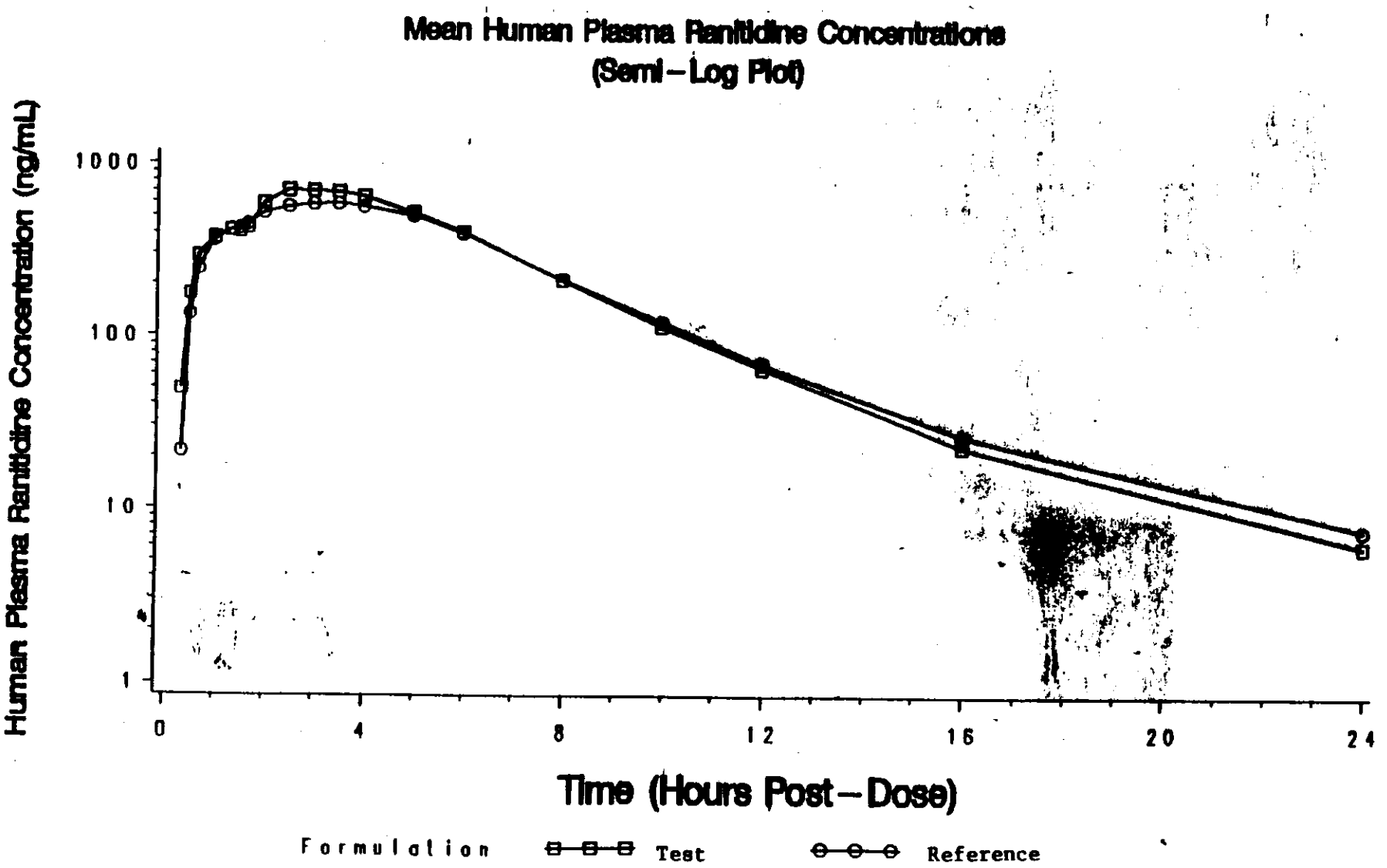

Mean Human Plasma Ranitidine Concentrations
(Linear Plot)
Human Plasma Ranitidine Concentration (ng/mL)
800
700
600
500
400
300
200
100
0
0
4
8
12
16
20
24
Time (Hours Post-Dose)
Formulation
Test
Reference

Figure 2


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