CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-424

BIOEQUIVALENCE

Spironolactone Tablets
25 mg, 50 mg and 100 mg
ANDA 40-424
Reviewer: Moheb H. Makary
40424SDW.N00

Mylan Pharmaceuticals
Morgantown, WV

Submission Date: 11/13/00

Review of Bioequivalence Studies, Dissolution Data and Waiver Requests (Electronic Submission)

Introduction

Indication: Aldactone® is effective in lowering the systolic and diastolic blood pressure in patients with primary hyperaldosteronism.
Type of Submission: Electronic
Contents of Submission: Fasting and food studies on 100 mg tablet. Dissolution data on 25 mg, 50 mg and 100 mg tablets. Waiver requests for the 25 mg and 50 mg strengths.
RLD: Aldactone® 100 mg tablets (Searle) approved by the Agency under NDA #12151 on 12/30/83. It is also available in 25 mg and 50 mg strengths from G.D. Searle & CO.
Recommended Dose: For essential hypertension, an initial daily dosage of 50 to 100 mg of Aldactone administered in either single or divided doses is recommended

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

Protocol No.: **Single-Dose Fasting In Vivo Bioequivalence Study of Spironolactone Tablets (100 mg; Mylan) and Aldactone Tablets (100 mg; Searle) in Healthy Male Volunteers**

Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	CLINICAL AND PHARMACOLOGIC RESEARCH, INC
Medical Director:	
Scientific Director:	
Clinical Study Dates:	04/14/00 to 05/02/00
Analytical Facility	MYLAN PHARMACEUTICALS INC.
Analytical Study Dates:	05/09/00 to 06/07/00
Storage Period:	40 - 53 days

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Spironolactone tablets	Aldactone
Manufacturer:	Mylan Pharmaceuticals Inc.	G.D. Searle & Co.
Manufacture Date:	3/10/00	N/A
Expiration Date:	N/A	9/00
ANDA Batch Size:	J Tablets	N/A
Full Batch Size:	Tablets	N/A
Batch/Lot Number:	R1H0636	7L143
Potency:	99.8%	100.5%
Content Uniformity:	97.7%	99.4%
Strength:	100 mg	100 mg
Dosage Form:	tablet	tablet
Dose Administered:	100 mg	100 mg
Study Condition:	fasting	fasting
Length of Fasting:	10 hours	10 hours

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

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:**	35
Route of Administration:	oral	**No. of Subjects Completing:**	35
Dosing Interval:	hr	**No. of Subjects Plasma Analyzed:**	35
Number of Doses:	N/A	**No. of Dropouts:**	0
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:**	3

Dietary Restrictions: No vitamins, caffeine, alcohol or xanthine containing foods or beverages 48 hours prior to the initial dose of study medication. No change in dietary or exercise habits.

Activity Restrictions: Subjects engaged in normal activity for the first 12 hours after drug administration, avoiding both vigorous exertion and complete rest.

Drug Restrictions: No vitamins within 48 hours prior to the initial dose of study medication. No medication within the last 14 days prior to the initial dose of study medication. No use of any medication known to alter hepatic enzyme activity within 28 days of dosing.

Blood Sampling: Blood samples (1x10 mL) were collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 15, 24, 48, 60 and 72 hours post-dose. Plasma was stored in suitably labeled tubes at $-70^{o}C$ until analysis.

2) Analytical (Not to be Released Under FOI)

Pre-Study Assay Validation:

ANALYTE:	Canrenone
ASSAY METHOD:	
MATRIX:	plasma
INTERNAL STANDARD:	
SENSITIVITY:	5 ng/mL
STANDARD CURVE HIGHEST CONC.:	500 ng/mL
STANDARD CURVE LOWEST CONC.:	5 ng/mL
R2 IS GREATER THAN:	0.98
SPECIFICITY:	Y

Assay Validation

Recovery: The mean recovery for canrenone in human plasma was 83.7% and 80.4% at concentrations of 15.0 and 300.0 ng/mL, respectively.

Precision and Accuracy: Interday and intraday precision for quality control pre-study samples ranged from 2.8% to 7.7% and 0.93% to 4.93%, respectively, for Canrenone. Interday accuracy ranged from 99.0% to 102.2%.

Stability: Long Term Frozen Stability: Canrenone was stable for a period of 19 days in human plasma at -70°C.
Freeze-Thaw: Canrenone was stable after three freeze-thaw cycles in human plasma.

Precision and Accuracy: Interday precision for quality control within-study samples ranged from 4.5% to 5.6% for Canrenone. Interday accuracy ranged from 98.3% to 99.7%.

Statistical Methods

AUCT, AUCI, CMAX, TMax, KEL and T1/2 were calculated from the individual concentration versus time data for canrenone. Analysis of variance was performed on each pharmacokinetic parameter using SAS GLM procedure.

Study Results

1) Clinical
Adverse Events: Three subjects during the study experienced a total of 3 post-dose adverse events. All events were listed mild in intensity. Adverse events are summarized on page 10, Vol. 1.4. There were no serious or life threatening adverse events reported in the study.

The plasma concentrations and pharmacokinetic parameters for canrenone are summarized in Table I.

Table I

Time(hours)	A Test Mean ng/mL (%CV)	B Ref Mean ng/mL (%CV)	T/R Ratio (A)/(B)
0	0.00 (0.00)	0.00 (0.00)	**
0.25	0.00 (0.00)	0.00 (0.00)	**
0.5	4.24 (149.07)	4.84 (205.76)	0.88
1.0	41.58 (45.41)	54.00 (58.50)	0.77
1.5	63.89 (40.50)	85.93 (43.83)	0.74
2.0	77.25 (34.65)	99.77 (33.92)	0.77
2.5	84.46 (30.27)	102.01 (29.36)	0.83
3.0	87.46 (25.32)	101.38 (27.04)	0.86
3.5	86.26 (24.37)	97.99 (26.97)	0.88
4.0	85.29 (23.37)	93.57 (25.90)	0.91
4.5	88.69 (24.73)	97.45 (26.70)	0.91
5.0	82.30 (25.39)	85.87 (25.41)	0.96
6.0	68.28 (26.80)	71.32 (25.44)	0.96
7.0	60.92 (27.31)	61.35 (25.12)	0.99
8.0	56.02 (26.86)	55.51 (26.21)	1.01
10	47.12 (26.63)	46.92 (26.14)	1.00
12	40.89 (27.51)	40.44 (26.03)	1.01
15	33.77 (29.00)	33.58 (29.04)	1.01
24	17.36 (29.24)	17.01 (29.75)	1.02
36	12.97 (29.57)	12.34 (27.87)	1.05
48	7.25 (41.56)	6.78 (51.58)	1.07
60	4.02 (84.92)	3.48 (103.10)	1.16
72	0.71 (288.35)	1.00 (242.91)	0.71

Mean Plasma PK Parameters

Parameter	Test Mean	Ref Mean	T/R Ratio (A)/(B) Geometric Mean
AUCT	1422.9 (23.0)	1465.8 (23.6)	0.97
AUCI	1610.6 (20.1)	1637.8 (21.7)	0.99
CMAX	97.0 (25.0)	112.4 (27.4)	0.87
TMAX	3.3	2.7	
KEL	0.04	0.04	
THALF	20.0	18.3	

	Root MSE	90% CI
LnAUCT	0.078	94.2-100.3%
LnAUCI	0.087	95.3-102.3%
LnCMAX	0.132	82.3- 91.6%

1. The mean canrenone plasma levels peaked at 2.5 and 3 hours for the reference and the test products, respectively, following their administration under fasting conditions.

2. For Mylan's spironolactone, the mean AUCT, AUCI and CMAX values for canrenone were 2.9%, 1.7% and 13.7% lower, respectively, than those for the reference product values under fasting conditions. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUCT, AUCI and CMAX.

Protocol No.: , **Single-Dose Food In Vivo Bioequivalence Study of Spironolactone Tablets (100 mg; Mylan) and Aldactone Tablets (100 mg; Searle) in Healthy Male Volunteers**

Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	CLINICAL AND PHARMACOLOGIC RESEARCH, INC
Medical Director:	
Scientific Director:	
Clinical Study Dates:	04/18/00 to 05/20/00
Analytical Facility	MYLAN PHARMACEUTICALS INC.
Analytical Study Dates:	06/12/00 to 06/26/00
Storage Period:	55 - 68 days

TREATMENT INFORMATION

Treatment ID:	A	B	C
Test or Reference:	T	R	T
Product Name:	Spironolactone tablets	Aldactone	Spironolactone tablets
Manufacturer:	Mylan Pharmaceuticals Inc.	G.D. Searle & Co.	Mylan Pharmaceuticals Inc.
Manufacture Date:	3/10/00	N/A	3/10/00
Expiration Date:	N/A	9/00	N/A
Batch/Lot Number:	R1H0636	7L143	R1H0636
Strength:	100 mg	100 mg	100 mg
Dosage Form:	tablet	tablet	tablet
Dose Administered:	100 mg	100 mg	100 mg
Study Condition:	fed	fed	fasting
Length of Fasting:	N/A	N/A	10 hours
Standardized Breakfast:	Y	Y	N
Breakfast Specifics:	1 buttered English muffin, 1 fried egg, 1 slice American cheese, 1 slice Canadian bacon, 1 serving of hashed brown potatoes, 6 ounces of orange juice and 8 ounces of whole milk	1 buttered English muffin, 1 fried egg, 1 slice American cheese, 1 slice Canadian bacon, 1 serving of hashed brown potatoes, 6 ounces of orange juice and 8 ounces of whole milk	N/A

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	crossover
No. of Sequences:	6	**Replicated Treatment Design:**	N
No. of Periods:	3	**Balanced:**	N
No. of Treatments:	3	**Washout Period:**	14 days

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:**	19
Route of Administration:	oral	**No. of Subjects Completing:**	15
Dosing Interval:	hr	**No. of Subjects Plasma Analyzed:**	15
Number of Doses:	N/A	**No. of Dropouts:**	4
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:**	4

Dropouts:

SUBJECT NO.:	10	17	18	19
REASON:	did not report for Period 3 due to personal reasons not study related	dropped out of Period 1 due to the number of blood collections	dropped out during Period 1 due to personal reasons that were not study related	dropped out during Period 2 due to adverse experiences not study related
PERIOD:	3	1	1	2
REPLACEMENT:	N	N	N	N

Analytical (Not to be Released Under FOI)

Same as the fasting study

Stability: Long Term Frozen Stability: Canrenone was stable for a period of 110 days in human plasma at -70^{o}C.
Freeze-Thaw: Canrenone was stable after three freeze-thaw cycles in human plasma.

Precision and Accuracy: Interday precision for quality control study samples ranged from 5.0% to 5.9% for Canrenone. Interday accuracy ranged from 97.2% to 98.5%.

Study Results

Four subjects during the study experienced a total of 4 post-dose adverse events. All events were listed mild in intensity. Adverse events are summarized on page 9, Vol. 1.6. There were no serious or life threatening adverse events reported in the study.

The plasma concentrations and pharmacokinetic parameters for canrenone are summarized in Table II.

Table II

Time(hours)	A Test Mean ng/mL (%CV)	B Ref Mean ng/mL (%CV)	C Test Mean ng/mL (%CV)	T/R Ratio (A)/(B)
0	0.00 (0.0)	0.00 (0.0)	0.00 (0.0)	**
.25	0.00 (0.0)	0.00 (0.0)	0.00 (0.0)	**
.5	1.31 (387.3)	2.21 (387.3)	7.03 (171.1)	0.59
1.0	27.05 (68.3)	26.82 (91.3)	46.31 (65.4)	1.01
1.5	67.27 (49.2)	63.97 (63.3)	69.45 (49.3)	1.05
2.0	93.40 (35.5)	86.03 (52.2)	79.12 (41.3)	1.09
2.5	108.36 (31.1)	97.43 (41.5)	80.96 (36.5)	1.11
3.0	119.10 (25.2)	107.22 (34.4)	86.71 (34.2)	1.11
3.5	121.51 (25.7)	110.76 (30.5)	84.72 (29.2)	1.10
4.0	120.19 (25.2)	113.88 (27.4)	87.85 (27.7)	1.06
4.5	124.24 (27.8)	118.72 (26.6)	90.08 (27.3)	1.05
5.0	111.97 (27.7)	110.80 (28.3)	85.56 (27.8)	1.01
6.0	97.86 (29.2)	93.45 (29.1)	72.66 (35.1)	1.05
7.0	85.59 (27.6)	83.42 (27.2)	66.35 (37.3)	1.03
8.0	77.75 (26.8)	76.19 (29.0)	60.29 (40.9)	1.02
12	53.17 (24.3)	50.47 (32.8)	42.53 (42.8)	1.05
15	38.51 (29.1)	39.95 (24.1)	31.06 (38.5)	0.96
24	22.60 (36.1)	23.01 (30.4)	16.95 (37.8)	0.98
36	15.03 (39.0)	14.78 (38.5)	10.84 (52.7)	1.02
48	7.47 (82.1)	8.20 (62.1)	6.49 (76.6)	0.91
60	5.69 (94.0)	5.48 (89.6)	4.06 (95.7)	1.04
72	3.34 (123.3)	2.94 (127.7)	1.61 (175.4)	1.14

Mean Plasma PK Parameters

Parameter	Test Mean	Ref Mean	Test Mean	T/R Ratio (A)/(B)
AUCT	1852.01 (22.7)	1787.72 (22.6)	1422.67 (30.3)	1.04
AUCI	2071.35 (21.6)	1994.84 (20.6)	1599.00 (28.5)	1.04
CMAX	131.45 (24.1)	127.27 (25.4)	101.90 (23.6)	1.03
TMAX	4.00	3.67	3.57	
KEL	0.042	0.042	0.045	
THALF	20.15	19.74	19.71	

	A/B Geometric Mean
AUCT	1.04
AUCI	1.04
CMAX	1.04

1. The canrenone plasma levels peaked at 4.5 hours for both the test and reference products under nonfasting conditions and for the test product under fasting conditions.

2. For Mylan's spironolactone, the mean AUC(0-t), AUCinf and Cmax values for canrenone were 3.6%, 3.8% and 3.3% higher, respectively, than the reference product values under nonfasting conditions. The ratios of the geometric means are within the acceptable 0.8-1.25 range for AUCT, AUCI and CMAX.

3. For the test product, the mean AUC(0-t), AUCinf and Cmax values were increased by about 30.2%, 29.5% and 29.0%, respectively, when dosed under nonfasting conditions compared to fasting conditions.

Formulations (Not to be released under FOI)

Ingredient	Strength 100 mg	Strength 50 mg	Strength 25 mg
SPIRONOLACTONE, USP	100	50	25
CALCIUM SULFATE DIHYDRATE			
FLAVOR			
COLLOIDAL SILICON DIOXIDE			
CROSCARMELLOSE SODIUM,			
CROSPOVIDONE,			
LACTOSE MONOHYDRATE,			
MG STEAR/NA LAURYL SULFATE			
POVIDONE,			
PREGELATANIZED STARCH,			
PURIFIED WATER,			
Total			75

Dissolution Testing: (USP method)

Method:	USP 24 apparatus I I(paddle) at 75 rpm
Medium:	1000 mL of 0.1N HCl containing 0.1% SLS
Number of Tablets:	12
Test products:	Mylan's Spironolactone Tablets USP 100 mg, lot #R1H0636 50 mg, lot #R1H0635 25 mg, lot #R1H0634
Reference Products:	G.D. Searle's Aldactone^{R} Tablets 100 mg, lot #7L143 50 mg, lot #8B377 25 mg, lot#5D216

Specifications: NLT in 60 minutes

The dissolution testing results are shown in Table III.

Comments:

1. The firm's single-dose bioequivalence study #SPIR-0013 under fasting conditions, conducted on its 100 mg spironolactone tablet is acceptable. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of 80-125% for canrenone.

2. The firm's bioequivalence study under fasting and nonfasting conditions, conducted on its 100 mg spironolactone tablet is acceptable. The ratios of the geometric means for canrenone are within the acceptable 0.8-1.25 range for AUC(0-t), AUCinf and Cmax under nonfasting conditions.

3. The dissolution testing conducted by the firm on its spironolactone Tablets, 100 mg, 50 mg and 25 mg, lot #R1H0636, lot #R1H0635 and lot # R1H0634, respectively, is acceptable.

4. The formulations of the 50 mg and 25 mg strengths are proportionally similar to the 100 mg strength.

5. It should be noted that Mylan Pharmaceuticals Inc. currently manufactures and markets spironolactone Tablets USP, 25 mg under ANDA #87-086. This application, supported by both fasting and nonfasting bioequivalence studies, is independent of ANDA #87-086 and provides for the manufacture and marketing of 25 mg, 50 mg and 100 mg spironolactone tablets, USP. The firm indicated that the formulation and manufacturing process for the spironolactone tablets contained in this application have been revised to enhance manufacturing efficiency.

Recommendations:

1. The bioequivalence studies under fasting and nonfasting conditions conducted by Mylan Pharmaceuticals Inc., on its Spironolactone Tablet, 100 mg, lot # R1H0636, comparing it to Aldactone^{R} Tablet, 100 mg, manufactured by G.D. Searle & Co., have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Mylan's Spironolactone Tablet, 100 mg, is bioequivalent to the reference product, Aldactone^{R} Tablet, 100 mg, manufactured by G.D. Searle., under fasting and nonfasting conditions.

2. The dissolution testing conducted by the firm on its spironolactone Tablets, 100 mg, 50 mg and 25 mg, lot #R1H0636, lot #R1H0635 and lot # R1H0634, respectively, is acceptable. The formulations of the 50 mg and 25 mg strengths are proportionally similar to the 100 mg strength which underwent acceptable bioequivalence testing. The waivers of *in vivo* bioequivalence study requirements for the 50 mg and 25 mg tablets of the test products are granted. The Division of Bioequivalence deems Spironolactone Tablets, 50 mg and 25 mg, manufactured by Mylan Pharmaceuticals Inc., to be bioequivalent to Aldactone^{R} Tablets, 50 mg and 25 mg, respectively, manufactured by G.D. Searle & Co.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 1000 mL of 0.1N HCl containing 0.1% SLS at 37^{o}C using USP 24 apparatus II (paddle) at 75 rpm. The test product should meet the following specification:

> Not less than of the labeled amount of the drug in dosage form is dissolved in 60 minutes.

The firm should be informed of the above recommendations.

4. Consistent with the CDER Guidance for Industry "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations", posted 10/27/00, the Division of Bioequivalence now requests that spironolactone be assayed in plasma and analyzed using a confidence interval approach. This criteria will be applied to any bioequivalence studies of spironolactone initiated after the guidance was issued. Since spironolactone can be reliably measured in plasma, canrenone need not be assayed.

Moheb H. Makary

Moheb H. Makary, Ph.D. Date:
Review Branch III
Division of Bioequivalence

BDAVIT 2/15/01

RD INITIALLED BDAVIT
FT INITIALLED BDAVIT Barbara M. Davit Date: 2/15/01

Concur: Dale P. Conner Date: 2/19/2001

for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

cc: ion File.

Table III

Mean Dissolution Data

Test				REFERENCE		
Lot No.: R1H0634				Lot No.: 5D216		
Strength: 25 mg				Strength: 25 mg		
No. of Units: 12				No. of Units: 12		
Time(minutes)	Mean	Range	%CV	Mean	Range	%CV
15	84.67		2.82	78.33		15.37
30	94.00		1.81	94.00		4.40
45	96.92		2.31	98.08		2.66
60	97.42		1.72	98.75		1.62

Mean Dissolution Data

Test				REFERENCE		
Lot No.: R1H0635				Lot No.: 8B377		
Strength: 50 mg				Strength: 50 mg		
No. of Units: 12				No. of Units: 12		
Time(minutes)	Mean	Range	%CV	Mean	Range	%CV
15	85.67		3.80	72.42		13.04
30	96.50		2.48	93.83		3.43
45	100.00		1.91	99.92		2.61
60	100.00		1.54	101.17		1.97

Mean Dissolution Data

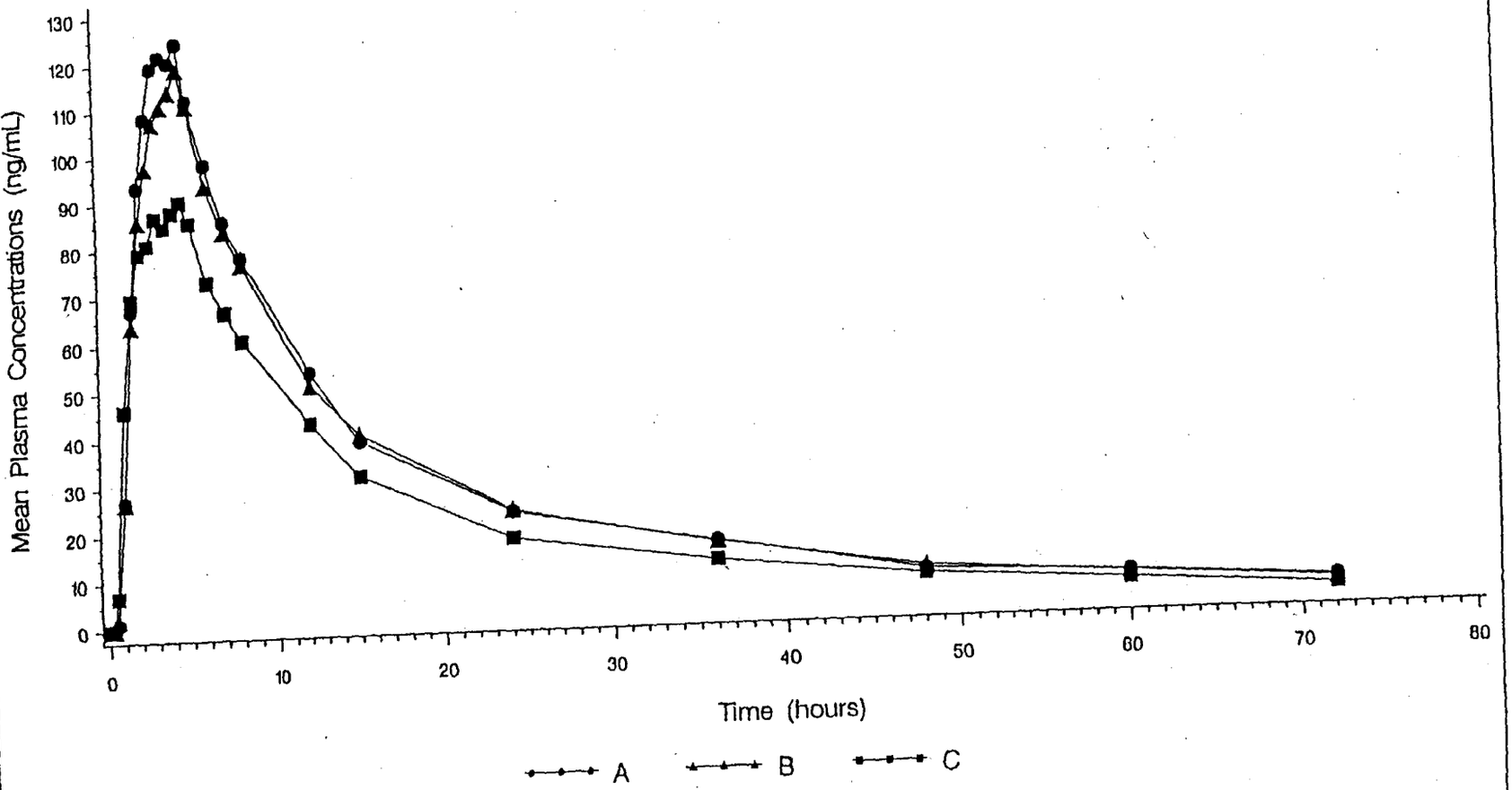
Test				REFERENCE		
Lot No.: R1H0636				Lot No.: 7L143		
Strength: 100 mg				Strength: 100 mg		
No. of Units: 12				No. of Units: 12		
Time(minutes)	Mean	Range	%CV	Mean	Range	%CV
15	78.83		2.15	64.92		12.33
30	88.17		1.17	84.00		4.22
45	92.08		0.73	90.33		3.28
60	93.75		0.66	93.08		2.49

SPIRONOLACTONE (SPIR—0014)

Total Dose: 100mg (1x100mg Tablets), Study Type: Fed

Mean Canrenone Plasma Concentrations

N= 15



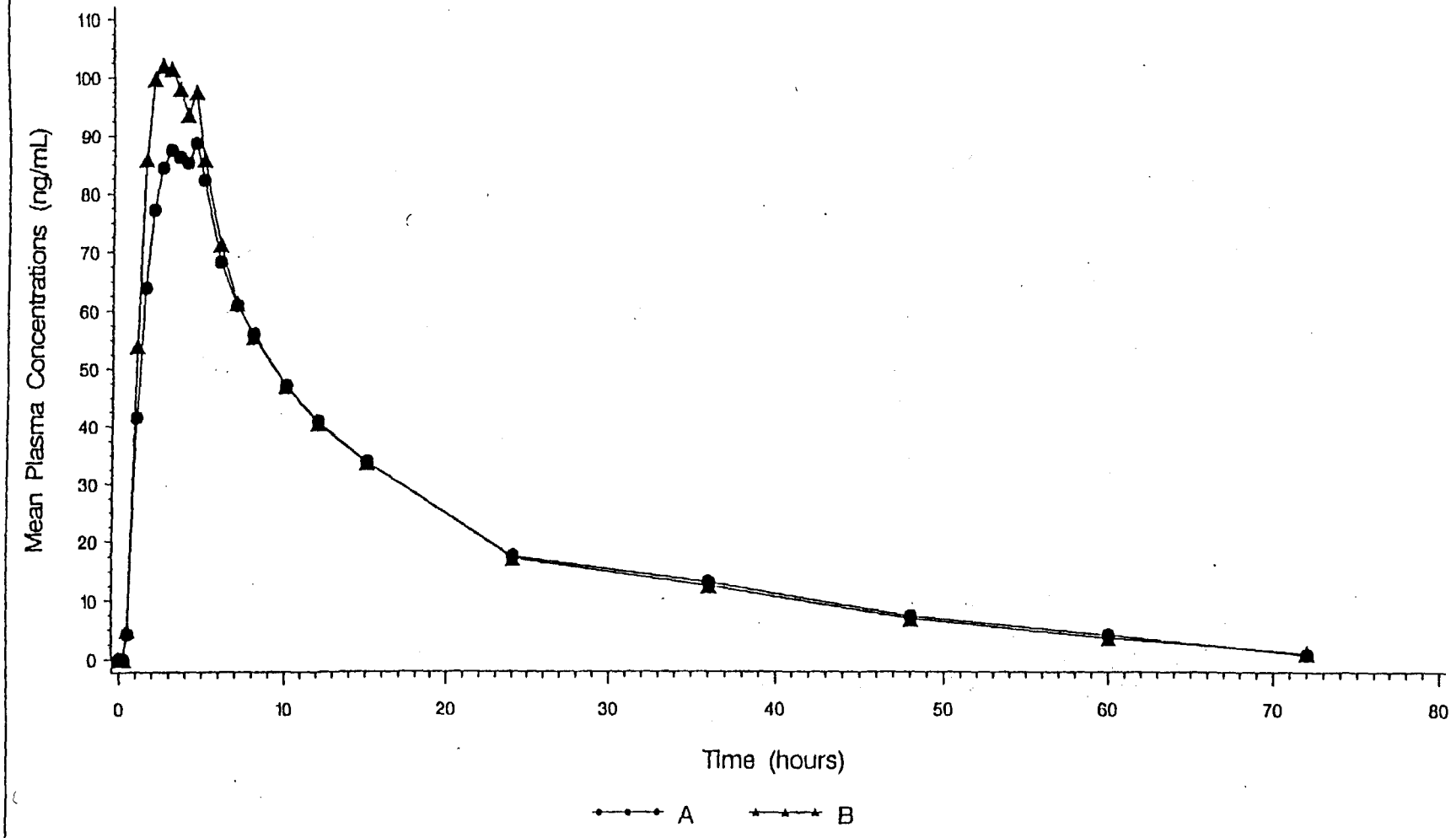
Treatment A is A (Spironolactone #R1H0636 -- fed)
Treatment B is B (Aldactone #7L143 -- fed)
Treatment C is C (Spironolactone #R1H0636 -- fast)

SPIRONOLACTONE (SPIR–0013)

Total Dose: 100mg (1x100mg Tablets), Study Type: Fasting

Mean Canrenone Plasma Concentrations

N= 35



Treatment A is A (Spironolactone #R1H0636)

Treatment B is B (Aldactone #7L143)