

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**ANDA 76-553**

**BIOEQUIVALENCE REVIEW(S)**

## DIVISION OF BIOEQUIVALENCE REVIEW

<b>ANDA No.</b>	<b>76-553</b>
<b>Drug Product Name</b>	<b>Medroxyprogesterone Acetate Injectable Suspension</b>
<b>Strength</b>	<b>150 mg/mL in 1 ml Vial</b>
<b>Applicant Name</b>	<b>Gensia Sicor Pharmaceuticals</b>
<b>Address</b>	<b>Irvine, CA</b>
<b>Submission Date(s)</b>	<b>November 27, 2002</b>
<b>Amendment Date(s)</b>	<b>N/A</b>
<b>Reviewer</b>	<b>Nhan L. Tran</b>
<b>First Generic</b>	<b>Yes</b>
<b>File Location</b>	<b>V:\firmsam\Gensia Sicor\ltrs&amp;rev\76553N1102.doc</b>

### I. Executive Summary

Gensia Sicor is referencing Pharmacia's Depo-Provera<sup>®</sup> Injection Suspension, 150 mg/ml. The firm submitted one fasting bioequivalence (BE) study comparing its Medroxyprogesterone Acetate Injectable Suspension, 150 mg/mL Prefilled Syringe, with the RLD product, Pharmacia & Upjohn's Depo-Provera<sup>®</sup> (medroxyprogesterone acetate) Contraceptive Injection, 150 mg/mL (ANDA 76-552). The fasting study is a single-dose parallel study using 124 female normal healthy volunteers given a dose of 150 mg injected in the gluteal muscle. The results submitted by the firm (point estimate, 90% CI) of the fasting BE study are LAUC<sub>t</sub> of 0.96, 87 – 102%; LAUC<sub>i</sub> of 1.00, 94 – 106%; and LC<sub>max</sub> of 1.08, 82 – 118%. The firm used the same study as a basis for its Medroxyprogesterone Acetate Injectable Suspension, 150 mg/mL in 1 ml vial (ANDA 76-553). Since the formulation of Medroxyprogesterone Acetate Injectable Suspension, 150 mg/mL Prefilled Syringe is identical to the Medroxyprogesterone Acetate Injectable Suspension, 150 mg/mL in 1 ml vial, the cross-reference ANDA is acceptable. The study is incomplete due to several deficiencies. There is no FDA recommended dissolution testing for this drug product and the firm is requested to develop a dissolution method for its product. The application is therefore incomplete.

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### III. Submission Summary

#### A. Drug Product Information

<b>Test Product</b>	Medroxyprogesterone Acetate
<b>Reference Product</b>	Depo-Provera <sup>®</sup>
<b>RLD Manufacturer</b>	Pharmacia & Upjohn
<b>NDA No.</b>	20-246
<b>RLD Approval Date</b>	10/29/92
<b>Indication</b>	For the prevention of pregnancy

#### B. PK/PD Information

<b>Bioavailability</b>	Not available
<b>Food Effect</b>	Not applicable
<b>Tmax</b>	3 weeks
<b>Metabolism</b>	mainly in the liver
<b>Excretion</b>	excreted in the urine
<b>Half-life</b>	50 days
<b>Relevant OGD or DBE History</b>	See Attachment
<b>Agency Guidance</b>	N/A
<b>Drug Specific Issues (if any)</b>	None

#### C. Contents of Submission

<b>Study Types</b>	<b>Yes/No?</b>	<b>How many?</b>
Single-dose fasting	Yes	1
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	N/A	
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	No	

### D. Pre-Study Bioanalytical Method Validation

	Parent	Metabolite
	1	0
Analyte name	Medroxyprogesterone Acetate (MPA)	
Internal Standard	Megestrol Acetate	
Method description	GC/MS	
QC range	0.25 ng/ml To 75 ng/ml	
Standard curve range	0.1 ng/ml To 100 ng/ml	
Limit of quantitation	0.1 ng/ml	
Average recovery of Drug (%)	77.8%	
Average Recovery of Int. Std (%)	72.3%	
Intraday precision range (%)	4.07% To 11.81%	
Intraday accuracy range (%)	98.56% To 108.5%	
Interday precision range (%)	5.65% To 7.96%	
Interday accuracy range (%)	100.67% To 107.23%	
Bench-top stability (hrs)	Stable for 50 hrs	
Stock stability (days)	Stable for 28 days	
Processed stability (hrs)	Stable for 24 hrs	
Freeze-thaw stability (cycles)	3 cycles	
Long-term storage stability (days)	Not submitted	
Dilution integrity	Yes	
Specificity	Yes	
SOPs submitted	No	
Bioanalytical method is acceptable	No (no SOP & no long term stability data)	
20% Chromatograms included (Y/N)	Yes	
Random or Serial Selection of Chrom	Serial	

### E. In Vivo Studies

#### 1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	LA486
Study Design	Parallel
No. of subjects enrolled	124
No. of subjects completing	122
No. of subjects analyzed	122
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 0      Female: 124
Test product	Medroxyprogesterone Acetate
Reference product	Depo-Provera <sup>®</sup>
Strength tested	150 mg/mL
Dose	150 mg

Summary of Statistical Analysis (firm's data)		
Parameter	Point Estimate	90% Confidence Interval
AUC <sub>t</sub>	0.96	0.87-1.02
AUC <sub>∞</sub>	1.00	0.94-1.06
C <sub>max</sub>	1.08	0.82-1.18

Reanalysis of Study Samples Additional information in Appendix								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
For confirmatory	18	32	0.37	0.67	18	32	0.37	0.67
Higher than the upper limit	2	1	0.04	0.02	2	1	0.04	0.02
Poor chromatography	28	13	0.58	0.27	28	13	0.58	0.27
<b>Total</b>	<b>48</b>	<b>46</b>	<b>0.99</b>	<b>0.96</b>	<b>48</b>	<b>46</b>	<b>0.99</b>	<b>0.96</b>

Did use of recalculated plasma concentration data change study outcome? The reviewer has not calculated 90% CI pending the firm's response to the deficiencies.

2. Single-dose Fed Bioequivalence Study: N/A

#### F. Formulation

Location in appendix	Page 13
Inactive ingredients within IIG Limits (yes or no)	Yes
If no, list ingredients outside of limits	N/A
If a tablet, is the product scored? (yes or no)	N/A
If yes, which strengths are scored?	N/A
Is scoring of RLD the same as test? (yes or no)	N/A
Formulation is acceptable (yes or no)	Yes
If not acceptable, why?	N/A

The formulation of the test product is identical (Q1 and Q2) to that of the RLD product.

#### G. In-Vitro Dissolution Data:

Currently there is no FDA-recommended dissolution method and specification for the drug product. The firm is requested to develop a dissolution method for the product.

## H. Waiver Request(s): N/A

## I. Deficiency Comments:

1. The firm stated that subjects # 65 and # 101 were dropped after 83 days and 72 days respectively. Information submitted in the Analytical Report indicated that samples from subject # 65 and 101 were collected and assayed (See Analytical Report: 124 subjects x 39 samples/subject=4846 samples minus 33 undelivered samples = 4803). Since samples were collected long enough to properly characterize the absorption phase of the drug and were already assayed, the firm is requested to include plasma data from these subjects in the statistical analysis of AUC and Cmax.
2. The firm reported that Kel cannot be determined for 12 subjects. However, it appears that it is possible to estimate Kel for 8 subjects. Hence, it is requested that Kel and AUCi should be determined for the following subjects as follows:

<u>Subject #</u>	<u>Start time</u> (hrs)	<u>Stop time</u> (hrs)
8	1320	2664
11	1656	2856
18	1488	2856
20	1824	2856
30	1320	2856
41	1824	2856
76	984	2856
79	1320	2856

Please re-run ANOVA and calculate 90% C.I. limits on AUCi for all subjects, including subject # 8, 11, 18, 20, 30, 41, 76, and 79.

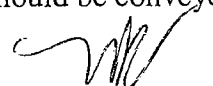
3. a) The firm should include objective criteria in its Standard Operating Procedures (SOPs) for reassay of samples for confirmation of the first analysis. The SOP should include procedures and acceptance criteria for handling reassay values. The data should be analyzed using both original as well as reassay values. Without objective criteria, established prior to the beginning of the study for the determination of which samples are to be reassayed, these reassay values will not be accepted b) in addition to those subjects selected by the firm, based on irregularities observed in the plasma concentration-time profiles, the firm should provide justification for not selecting the following subjects for confirmation of the first analysis: Subject # 8, 41, 54, 82, 83, 85, 99, 100 and 124, and c) the firm should provide a theoretical/statistical basis for using  $2\sqrt{2}CV$  as an acceptance criterion for confirmation of the first measurement.
4. SOP for reassays due to values higher than the ULOQ and reassays due to poor chromatography should be provided, along with criteria for selection of reported values. A table of original values and reported values should be submitted for review.

5. The firm is requested to include a table with explanation for all missing samples.
6. The firm is requested to provide long term stability data. Long term stability should exceed the time of first sample collection and the time of the last sample analysis.
7. The firm should provide content uniformity/potency of the test and reference products.
8. The firm is requested to develop a dissolution method for its product. The following guidance can be used as a guide in developing a dissolution methodology and setting specifications: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In-Vivo/In-Vitro Correlations.
9. The firm should provide a table of AUC/AUC<sub>i</sub> ratios, mean and range for all subjects.

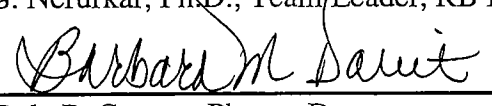
#### J. Recommendations

The single-dose, fasting bioequivalence study conducted by Gensia Sicor Pharmaceuticals, on its Medroxyprogesterone Acetate Injectable suspension, 150mg/ml (lot #X01P613P1), comparing it to Pharmacia & Upjohn's Depo-Provera® Injectable Suspension, 150mg/ml (lot #11HCC), has been found incomplete by the Division of Bioequivalence due to above deficiencies.

Deficiencies should be conveyed to the firm.

 1/28/04  
\_\_\_\_\_  
Nhan L. Tran, Ph.D., Review Branch II

 1/28/2004  
\_\_\_\_\_  
S. Nerurkar, Ph.D., Team Leader, RB II

 1/29/04  
\_\_\_\_\_  
Dale P. Conner, Pharm. D.  
Director, Division of Bioequivalence  
Office of Generic Drugs

## IV. Appendix

### A. Individual Study Reviews

#### 1. Single-dose Fasting Bioequivalence Study

Study Information	
Study Number	LA486
Study Title	A PIVOTAL STUDY TO EVALUATE THE BIOEQUIVALENCE OF 150MG/ML MEDROXYPROGESTERONE ACETATE INJECTION IN POSTMENOPAUSAL WOMEN
Clinical Site	_____
Principal Investigator	_____, MD
Study/Dosing Dates	Group 1(#1-64): 04/19/02, Group 2 (#65-119): 04/27/02, Group 3 (#120-124): 05/24/02
Analytical Site	_____
Analytical Director	_____, Ph.D.
Analysis Dates	April 29, 2002 to October 01, 2002
Storage Period (no. of days from first sample to final analysis)	160 days

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Medroxyprogesterone Acetate	Depo-Provera <sup>®</sup>
Manufacturer	Gensia Sicor	Pharmacia & Upjohn
Batch/Lot No.	X01P613P1	11HCC
Expiration Date	November 2002	July 2005
Strength	150 mg/1 ml	150 mg/ 1 ml
Dosage Form	Injectable Suspension	Injectable Suspension
Batch Size	_____	N/A
Potency	Not submitted	Not submitted
Content Uniformity	Not submitted	Not submitted
Formulation	See Appendix Page 13	
Dose Administered	150 mg/1 ml	
Route of Administration	IM Injection (in gluteal muscle).	



No. of Sequences	1
No. of Periods	1
No. of Treatments	2
No. of Groups	3
Washout Period	N/A
Randomization Scheme	Test (A):1,4,6,7,9,11,14,15,17,20,2124,25,28,29,31,34,36,38,3941,43,46,47,49,51,54,56,58,60,61,64,66,67,69,72,74,75,77,80,82,83,85,87,90,91,94,96,98,100,102,103,105,108,109,111,113,115,117,120,121,123 Ref (B):2,3,5,8,10,12,13,16,18,19,22,23,26,27,30,32,33,35,37,40,42,44,45,48,50,52,53,55,57,59,62,63,65,68,70,71,73,76,78,79,81,84,86,88,89,92,93,95,97,99,101,104,106,107,110,112,114,116,118,119,122,124
Blood Sampling Times	0,0.5,1,2,4,6,8,12,24,48,72,96,120,144,168,192,216,240,264,288,312,360,432,504,576,648,816,984,1152,1320,1488,1656,1824,1992,2160,2328,2496,2664,2856 hrs.
Blood Volume Collected/Sample	10 ml
Blood Sample Processing/Storage	At -20 <sup>0</sup> C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	10 hrs
Length of Confinement	24 hrs
Safety Monitoring	Y

Table 1 Demographics of Study Subjects (124 subjects)

Age (year)		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0			Caucasian	100%
Mean	56.7	Mean	67.8	18-40	0	Male	0%	Afr. Amer.	0%
SD	6.7	SD	9.7	41-64	88.7	Female	100%	Hispanic	0%
Range	45-77	Range	47-94	65-75	10.5			Asian	0%
				>75	0.8			Others	0%

## Study Results

Table 2 Dropout Information

Subject No	65	101
Reason	Accident on study day 83-- required hospitalization.	Accident on study day 72-- required hospitalization.
Period	Reference Drug	Reference Drug
Replacement	No	No

Table 3 Study Major Adverse Events

Adverse Event Description	# in Test Group	# in Reference Group
Headache	53	38
Hot flushes	17	12
Spotting bleeding	13	15
Weight gain	7	4
Total:	90	69

**Table 4 Protocol Deviations**

The original protocol was to enroll 128 subjects and consisted of two groups with 64 subjects/group. However, the contract laboratory had difficulties in recruiting subjects. As a result, the present study was conducted in 124 subjects divided in three groups: Group 1 (subj. #1-64), Group 2 (subj. #56-119) and Group 3 (subj. #120-124).

**Comments:** The adverse events and protocol deviations did not compromise the integrity of study.

**Table 5 Assay Validation – Within Study (Vol.1.2, pages 5-251)**

	Parent								Metabolite
QC Conc. (pg/mL)	250		1500		15000		N/A		
Inter day Precision (% CV)	8.1		6.8		7.5		N/A		
Inter day Accuracy (%)	102.3		100.9		101.9		N/A		
Cal. Standards Conc. (pg/mL)	100	200	500	1000	2000	5000	10000	20000	N/A
Inter day Precision (% CV)	3	5.8	4.8	4.7	3.9	3.6	3.7	4.6	N/A
Inter day Accuracy (%)	102	97.6	96.8	97.3	99.1	101	102.3	103.9	N/A
Linearity Range (range of R <sup>2</sup> )	0.98781 – 0.99960								N/A

**Chromatograms:** Any interfering peaks? No

**Table 6 SOP's dealing with analytical repeats of study samples:**

No complete SOP along with SOP Number and/or the Date of the SOP was submitted. But in the Analytical Report Section of the application (Vol. 2 page 5-218: ANALYTICAL STUDY REPORT), the firm has mentioned “**Criteria for Batch Acceptance**” (page 5-244) and “**Criteria for Reassay**” (pages 5-244-245).

<b>SOP No.</b>	<b>Date of SOP</b>	<b>SOP Title</b>
Not Available	Not Available	Not Available
Not Available	Not Available	Not Available
Not Available	Not Available	Not Available

**Comments on repeat assays.**

According to the study sample reassay criteria, 94 samples (out of total 4803 samples or 1.95%) were reanalyzed for a variety of reasons as follows:

- 50 samples for confirmation of the first analysis (36 subjects)
- 3 samples due to values higher than the upper limit of quantitation (3 subjects)
- 41 samples due to poor chromatography (27 subjects).

**Comments on Within-Study Validation: None**

**Conclusion:** Analytical method is not acceptable for the following reasons:

Analytical SOP and SOP for sample repeats are not submitted.  
 Long term stability data is missing.  
 Explanations for missing samples were not provided.

Mean plasma concentrations are presented in Table 10 and Figure 1.

Table 7 Arithmetic Mean Pharmacokinetic Parameters (firm's analysis)

Parameter	Units	Test		Reference		T/R
		Mean	% CV	Mean	% CV	
AUC <sub>t</sub>	pg*hr/ml	3357479.81	26.44	3509326.09	22.41	0.95
AUC <sub>i</sub>	pg*hr/ml	4089922.93	19.75	4083124.98	18.76	1.00
C <sub>max</sub>	pg/ml	4836.93	85.80	4486.00	58.72	1.07
T <sub>max</sub>	Hr	118.32	120.42	162.14	127.84	0.73
T <sub>1/2</sub>	Hr	1056.82	66.08	865.41	60.55	1.22
K <sub>el</sub>	1/hr	0.0010	62.55	0.0011	53.48	0.91

Table 8 Geometric Means and 90% Confidence Intervals (firm's analysis)

Parameter	Test Mean	Reference Mean	T/R	90% CI
AUC <sub>t</sub>	3401768	3552885	0.96	0.876-1.02
AUC <sub>i</sub>	4094937	4084980	1.00	0.94-1.06
C <sub>max</sub>	4771	4414	1.08	0.82-1.18

Table 9 Additional Study Information

Root mean square error, AUC	0.244
Root mean square error, C <sub>max</sub>	0.592
mean ratio AUC <sub>t</sub> /AUC <sub>i</sub>	Not Available
Range of values, ratio AUC <sub>t</sub> /AUC <sub>i</sub>	Not Available

**Comments:** (on pharmacokinetic analysis)

- The firm stated that subject # 65 and # 101 were dropped after 83 days and 72 days respectively. Information provided indicated that samples from those subjects were collected and assayed (See Analytical Report: 124 subjects x 39 samples/subject=4846 samples minus 33 undelivered samples=4803). Since samples were collected long enough to properly characterize the absorption phase of the drug in those two subjects, the firm is requested to include plasma data from those subjects in the statistical analysis of AUC and C<sub>max</sub>.

- The firm reported that Kel cannot be determined for 12 subjects. However, it appears that it is possible to estimate the Kel for 8 subjects. Hence, it is requested that Kel and AUCi should be determined for the following subjects as follows:

Subject #	Start time (hrs)	Stop time (hrs)
8	1320	2664
11	1656	2856
18	1488	2856
20	1824	2856
30	1320	2856
41	1824	2856
76	984	2856
79	1320	2856

Please re-run ANOVA and calculate 90% C.I. for AUCi including subject # 8, 11, 18, 20, 30, 41, 76, and 79.

- Indicate the number of subjects with the following:
  - measurable drug concentrations at 0 hr: None
  - first scheduled post-dose sampling time as Tmax: None
  - first measurable drug concentration as Cmax: None.
- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations? The reviewer has not calculated 90% C.I. pending the firm's response to the deficiencies.
- Were there statistically significant sequence or period effects? If so, did these affect the integrity of the study? The reviewer has not run SAS ANOVA pending the firm's response to the deficiencies.
- Are the 90% confidence intervals for AUCt, AUCi, and Cmax within the acceptable limits of 80-125%? The reviewer has not calculated 90% C.I. limits pending the firm's response to the deficiencies.
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect. Subjects were dosed in three groups and the reviewer will use appropriate model for statistical analysis.

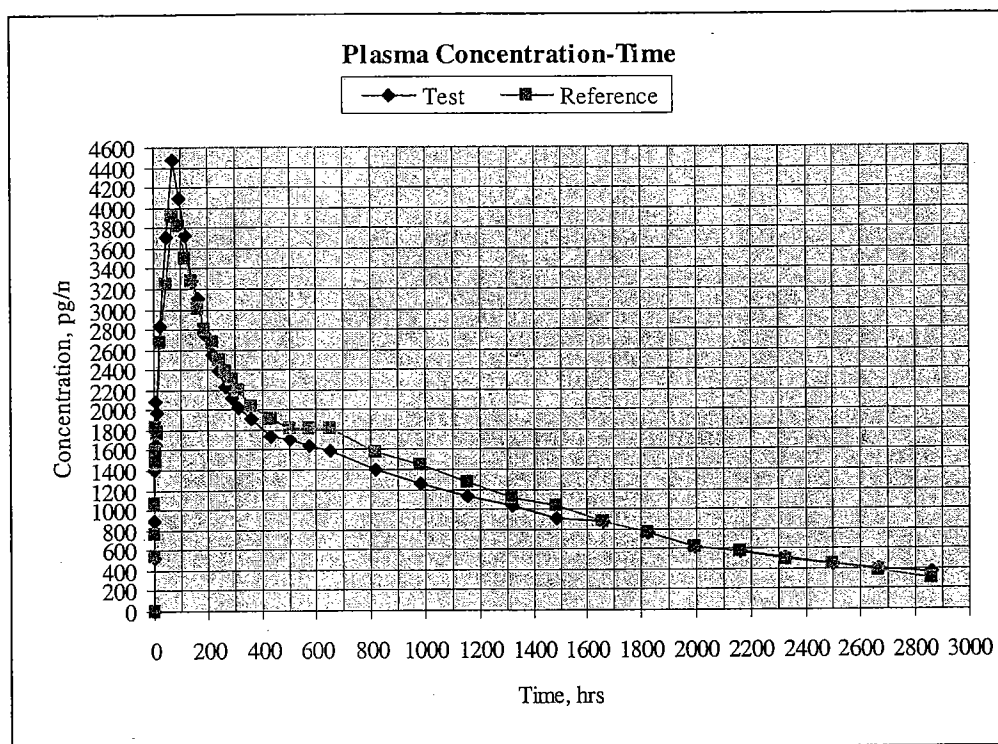
**Conclusion:** The single-dose fasting bioequivalence study is incomplete.

**Table 10 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study**

Time, hrs	Test (n=62 )		Reference (n=60 )		T/R
	Mean Conc.	% CV	Mean Conc.	% CV	
0	0	0	0	0	0
0.5	0520.80	106.35	547.41	112.72	0.95

1	890.58	95.61	760.58	93.52	1.17
2	1401.35	87.14	1072.75	90.24	1.30
4	2077.27	84.72	1831.50	87.31	1.13
6	1660.21	77.82	1463.63	72.74	1.13
8	1845.16	74.83	1587.21	65.72	1.16
12	1977.79	69.86	1772.00	61.54	1.11
24	2826.50	67.91	2677.41	54.87	1.05
48	3707.98	81.17	3246.30	61.36	1.14
72	4480.24	91.69	3910.68	64.72	1.14
96	4090.64	83.87	3817.88	67.62	1.07
120	3716.77	78.11	3503.68	59.01	1.06
144	3272.58	65.89	3285.51	53.98	0.99
168	3099.16	58.37	3000.46	50.07	1.03
192	2752.25	54.65	2796.53	45.25	0.98
216	2545.97	51.81	2677.84	46.39	0.95
240	2392.32	48.74	2498.67	41.19	0.95
264	2231.47	46.68	2387.58	41.57	0.93
288	2117.95	46.33	2300.98	38.95	0.92
312	2025.43	43.10	2189.47	39.30	0.92
360	1907.95	41.77	2038.60	34.04	0.93
432	1742.45	43.59	1913.61	35.99	0.91
504	1698.80	44.81	1808.56	36.73	0.93
576	1640.82	49.09	1815.94	42.51	0.90
648	1595.17	44.40	1809.82	43.01	0.88
816	1406.03	55.88	1579.98	41.65	0.88
984	1253.77	40.19	1451.50	36.28	0.86
1152	1136.35	38.59	1279.85	31.52	0.88
1320	1034.11	39.24	1111.30	36.36	0.93
1488	914.54	37.63	1032.88	38.89	0.88
1656	877.55	61.42	875.44	38.97	1.00
1824	761.11	40.31	770.88	39.81	0.98
1992	624.72	43.61	619.18	42.27	1.00
2160	565.46	46.23	580.89	49.00	0.97
2328	505.18	50.00	490.64	57.68	1.02
2496	453.42	55.24	439.91	62.40	1.03
2664	390.32	55.10	379.22	66.50	1.02
2856	362.00	54.66	310.35	72.99	1.17

**Figure 1 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study**



2. Single-dose Fed Bioequivalence Study: N/A

### B. Formulation Data

Ingredients	Test (mg/ml)	**Reference (mg/ml)
Medroxyprogesterone Acetate, USP	150.0 mg	150.0 mg
Polyethylene Glycol 3350, NF	28.9 mg	28.9 mg
Polysorbate 80, NF	2.41 mg	2.41 mg
Sodium Chloride, USP	8.68 mg	8.68 mg
Methylparaben, NF	1.37 mg	1.37 mg
Propylparaben, NF	0.150 mg	0.150 mg
Sodium Hydroxide, NF	To adjust pH	To adjust pH
Hydrochloric Acid, NF	To adjust pH	To adjust pH
Water For Injection, NF	q.s to 1 ml	q.s to 1 ml

\*\*From COMIS database

The formulation of the test product is identical (Q1 and Q2) to that of the RLD product.

### C. Dissolution Data:

Currently there is no FDA-recommended dissolution method and specification for the drug product. The firm is requested to develop a dissolution method for the product.

**D. Consult Reviews: None**

**E. SAS Outputs: Not Available at this time.**

**F. Additional Attachments**

**Relevant DBE/NDA History:**

1. Control Document # \_\_\_\_\_ : The DBE recommended the following: A single-dose parallel intramuscular bioequivalence study is requested. No food study is necessary. Only medroxyprogesterone should be measured for the study. 90% confidence interval approach is applied to log-transformed CMAX, AUCt and AUCi of medroxyprogesterone.
2. Control Document #00-548 (Pharmacia & Upjohn; 12/18/00): The DBE confirmed that a single-dose bioequivalence study is requested for the drug product. In addition, the test and reference products should be identical quantitatively and qualitatively (Q1 & Q2 sameness).
3. Control Documents # \_\_\_\_\_ : The same recommendations as in CD # \_\_\_\_\_ were given. Q1 and Q2 sameness between the test and reference formulations is required.
4. Control Document # \_\_\_\_\_ : The DBE recommended that a separate bioequivalence study for each strength, 400 mg/ml and 150 mg/mL. For a 50 mg/mL strength, a Suitability Petition should be submitted according to 21 CFR 314.93 to request a change in dosage strength from that of the RLD product. *In vivo* bioequivalence testing is also necessary for this strength to establish the relative bioavailability of the proposed product to the product designated for comparison.
5. Three other protocols have been submitted for the drug product: P# \_\_\_\_\_ and P#01-057 (Gensia Sicor; 11/14/01). All three protocols were for a single-dose parallel design bioequivalence study in healthy male or postmenopausal and/or sterile female volunteers. Only medroxyprogesterone was to be measured for the studies.

**APPEARS THIS WAY  
ON ORIGINAL**

## BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-553

APPLICANT: GENSIA SICOR

DRUG PRODUCT: Medroxyprogesterone Acetate Injectable Suspension, 150 mg/ml.

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. You stated that subjects # 65 and # 101 were dropped after 83 days and 72 days respectively. Information submitted in the Analytical Report indicated that samples from these subjects were collected and assayed (See Analytical Report: 124 subjects x 39 samples/subject=4846 samples minus 33 undelivered samples = 4803). Since samples were collected long enough to properly characterize the absorption phase of the drug and were already assayed, please include plasma data from these subjects in the statistical analysis of  $AUC_t$ ,  $AUC_i$  and  $C_{max}$ .
2. You reported that  $K_{el}$  cannot be determined for 12 subjects. However, it appears that it is possible to estimate  $K_{el}$  for 8 of these subjects. Please determine  $K_{el}$  and  $AUC_i$  for the following subjects as follows:

<u>Subject #</u>	<u>Start time</u> (hrs)	<u>Stop time</u> (hrs)
8	1320	2664
11	1656	2856
18	1488	2856
20	1824	2856
30	1320	2856
41	1824	2856
76	984	2856
79	1320	2856

Please re-run the ANOVA and calculate 90% C.I. on  $AUC_i$  for all subjects.

3. The following comments pertain to reassays of plasma samples in the bioequivalence study
  - a. Please include criteria for selection of samples for the reassay for confirmation of the first analysis in your Standard Operating Procedures

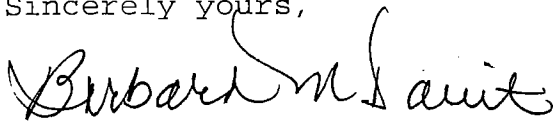


(SOPs). The SOP should include procedures for the determination of which samples are to be reassayed and acceptance criteria for handling reassay values. The data should be analyzed using both original as well as reassay values. Without objective criteria established prior to the beginning of the study, these reassay values will not be accepted.

- b. Based on the irregularities observed in the plasma concentration-time profiles, please provide justification for not selecting the following subjects for confirmation of the first analysis: Subject # 8, 41, 54, 82, 83, 85, 99, 100 and 124.
  - c. Please provide a theoretical/statistical basis for using  $2\sqrt{2}CV$  as an acceptance criterion for confirmation of the first measurement in your repeat assays.
- 4. The SOP for reassays due to values higher than the upper limit of quantitation and the reassays due to poor chromatography should be provided, along with criteria for selection of reported values. Please submit a table of original values and reported values for review.
  - 5. Please include a table with explanations for all missing samples.
  - 6. Please provide long term stability data. Long term stability should exceed the time of first sample collection and the time of the last sample analysis.
  - 7. Please provide content uniformity/potency of the test and reference products.
  - 8. Please develop a dissolution method for your product. The following CDER guidance can be used as a guide in developing a dissolution methodology and setting specifications: "Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In-Vivo/In-Vitro Correlations".

9. Please provide a table of AUCt/AUCi ratios mean and range for all subjects.

Sincerely yours,

*for* 

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

**APPEARS THIS WAY  
ON ORIGINAL**

CC: ANDA #76-553  
ANDA DUPLICATE  
DIVISION FILE  
HFD-651/ Bio Drug File  
HFD-655/ Reviewer  
HFD-655/ Bio team Leader

Endorsements: (Final with Dates)

HFD-655/Tran *W 11/18/04*

HFD-655/Nerurkar

HFD-650/ D. Conner *BWD 1/29/04*

*[Signature]* 1/28/04

*for* BIOEQUIVALENCE - INCOMPLETE

Submission date: 11/27/2002

1. Fasting Study (STF)

Strength: 150 mg/ml

Clinical Site: \_\_\_\_\_

*✓* Outcome: IC

Analytical Site: \_\_\_\_\_

Outcome: IC

Outcome Decisions: IC - INCOMPLETE

APPEARS THIS WAY  
ON ORIGINAL

## DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-552 (Prefilled Syringe) and 76-553 ( 1mL Vial)
Drug Product Name	Medroxyprogesterone Acetate Injectable Suspension
Strength	150 mg/mL
Applicant Name	Gensia Sicor Pharmaceuticals
Address	Irvine, CA
Submission Date(s)	November 27, 2002
Amendment Date(s)	February 23, 2004
Reviewer	Nhan L. Tran
First Generic	Yes
File Location	V:\firmsam\Gensia\ltrs&rev\76552A0204.doc

### I. Executive Summary

The firm submitted a single dose, fasting BE study with a suspension Medroxyprogesterone Acetate (MPA) in Prefilled Syringe (76-552) on November 27, 2002 (original submission). Since, in these two ANDAs, the suspension of MPA is identical, the firm submitted the same BE study in ANDA 76-553 (for MPA suspension in 1 ml Vial). The Division of Bioequivalence (DBE) reviewed the BE study and found it deficient. The DBE communicated the identical deficiencies to both ANDAs. As a response to the DBE deficiencies, the firm has submitted an amendment for ANDA 76-552 and another for 76-553. The firm's response in these two amendments is also identical. Instead of writing two separate and identical documents for these two ANDAs, the DBE is generating one document for both ANDAs. The DBE has determined that of nine (9) deficiencies, the firm did not satisfactorily respond to two (2) deficiencies and therefore both ANDAs are still incomplete.

The previous reviews are stored on V:\firmsam\Gensia\ltrs&rev\76552N1102.doc and V:\firmsam\Gensia\ltrs&rev\76553N1102.doc

### II. Review of the responses (Note the original deficiencies are in *italic*)

Deficiency 1: *You stated that subjects # 65 and # 101 were dropped after 83 days and 72 days respectively. Information submitted in the Analytical Report indicated that samples from these subjects were collected and assayed (See Analytical Report: 124 subjects x 39 samples/subject=4846 samples minus 33 undelivered samples = 4803). Since samples were collected long enough to properly characterize the absorption phase of the drug and were already assayed, please include plasma data from these subjects in the statistical analysis of AUC<sub>t</sub>, AUC<sub>i</sub> and C<sub>max</sub>.*

Firm's response: Although all collected samples were assayed, the firm stated that data from subject # 65 and 101 were not included in the statistical analysis because:

1. Per protocol, these subjects were dropped from the study due to “serious adverse event” requiring hospitalization, and hence no samples were scheduled for pharmacokinetic assessment
2. The concentration-time profiles for subject #65 and 101 had 5 consecutive missing samples. The inclusion of those subjects therefore would result in an inaccurate and biased assessment of the study.

FDA Comment: The reviewer does not agree with the firm’s response because:

1. The serious adverse event requiring hospitalization for Subject #65 and 101 was not due to the drug under investigation. Subject #65 was hospitalized because she broke her leg on Day 83 of 119 for the study while subject # 101 was in a horse drawn carriage accident on Day 72 of 119 for the study. Both subjects were hospitalized due to an accident but not due to the drug under investigation.
2. Due to the accident, the subject # 65 (reference trt) has the last six (6) samples missing while the subject # 101(reference trt) had last seven (7) samples missing. The DBE calculated AUC (0-1656 hrs) and AUC (0-1824 hrs) from the reference mean plasma profile which were 85% and 81% of the AUC (0-2856) from the mean reference plasma profile. The DBE also computed the reference mean AUC (0-t) by including these two subjects. The T/R ratio of the arithmetic means of AUC (0-t) changed from 0.9567 to 0.9619. The DBE is aware of the fact that the actual AUC (0-t) values for these two subjects may be different from the values calculated above. For that reason it is essential that you provide the DBE with the plasma data and values of PK parameters for these two subjects. Moreover, from the plasma profiles we will determine whether these two subjects have feasible AUC (0-inf) values. Additionally, these two subjects will provide accurate values for Cmax and therefore the inclusion of these two subjects is essential for the statistical analysis of the Cmax value. Thus, based on our calculations, the DBE does not believe the inclusion of those subjects would result in an inaccurate and biased assessment of Cmax (definitely) and AUC (0-t), AUC (0-inf) (possibly). Therefore, the firm is requested to provide plasma data for these two subjects and provide statistical analyses of the PK parameters including these two (2) subjects.

Deficiency 2: *You reported that Kel cannot be determined for 12 subjects. However, it appears that it is possible to estimate Kel for 8 of these subjects. Please determine Kel and AUCi for the following subjects as follows:*

<u>Subject #</u>	<u>Start time (hrs)</u>	<u>Stop time (hrs)</u>
8	1320	2664
11	1656	2856
18	1488	2856
20	1824	2856
30	1320	2856
41	1824	2856
76	984	2856
79	1320	2856

*Please re-run the ANOVA and calculate 90% C.I. on AUCi for all subjects.*

Firm's response: The firm has provided data as requested. There was no change in the outcome of the statistical analysis of the AUCinf.

FDA Comment: The reviewer has reviewed the data and concurred with the firm. The response is acceptable.

Deficiency 3:

*3. a. The following comments pertain to reassays of plasma samples in the bioequivalence study:*

*Please include criteria for selection of samples for the reassay for confirmation of the first analysis in your Standard Operating Procedures (SOPs). The SOP should include procedures for the determination of which samples are to be reassayed and acceptance criteria for handling reassay values. The data should be analyzed using both original as well as reassay values. Without objective criteria established prior to the beginning of the study, these reassay values will not be accepted.*

Firm's response: The SOP was provided as requested

FDA Comment: The reviewer has reviewed the information submitted and the firm's response is acceptable

*3. b: Based on the irregularities observed in the plasma concentration-time profiles, please provide justification for not selecting the following subjects for confirmation of the first analysis: Subject # 8, 41, 54, 82, 83, 85, 99, 100 and 124.*

Firm's response: The firm stated that subjects # 8, 41, 54, 82, 83, 85, 99, 100 and 124 were not selected for reassay because those subjects did not meet the criteria for the reassay as stated in the firm's SOP.

FDA Comment: The firm's response was found acceptable.

*3. c: Please provide a theoretical/statistical basis for using  $2\sqrt{2}CV$  as an acceptance criterion for confirmation of the first measurement in your repeat assays.*

Firm's response: The firm provided an explanation for using  $2\sqrt{2}CV\%$  as an acceptance criterion for confirmation of the first measurement.

FDA Comment: The explanation provided by the firm is acceptable since the firm is using 10% as an acceptable %CV.

Deficiency 4: *The SOP for reassays due to values higher than the upper limit of quantitation and the reassays due to poor chromatography should be provided, along with criteria for selection of reported values. Please submit a table of original values and reported values for review.*

Firm's Response: The SOP and related data were provided as requested.

FDA Comment: SOP and data were reviewed and found satisfactory

Deficiency 5: *Please include a table with explanations for all missing samples.*

Firm's Response: Data with explanation were submitted.

FDA Comment: Acceptable

Deficiency 6: *Please provide long term stability data. Long term stability should exceed the time of first sample collection and the time of the last sample analysis.*

Firm's Response: Long term stability data were provided to indicate samples were stable for at least 157 days under storage conditions.

FDA Comment: Data were reviewed and found acceptable.

Deficiency 7: *Please provide content uniformity/potency of the test and reference products.*

Firm's Response: For the test product, the average (6 samples) content uniformity was 101.3% and for the reference product, the average was 99%

FDA Comment: Acceptable

Deficiency 8: *Please develop a dissolution method for your product. The following CDER guidance can be used as a guide in developing a dissolution methodology and setting specifications: "Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In-Vivo/In-Vitro Correlations".*

Firm's Response: A dissolution method for the product was developed by the firm as follows: Apparatus II (Paddle) at 50 RPM, 900 ml 0.35% — in water. The proposed tolerances were: 15 min: NMT —%, 60 min: —%, 2880 min (48 Hrs): NLT —%

FDA Comment: The firm did not provide dissolution data for individual dosage units. A Prefilled Syringe or a Vial is an individual dosage unit. The dissolution testing should be conducted by emptying the contents of one dosage unit into the dissolution medium at a time and repeating the process for 12 such individual units. The DBE requests the following additional information:

- a. Please, provide individual dissolution data for 12 dosage units using the above mentioned method. Please, submit the mean percent dissolution, CV% and range (minimum and maximum) of the dissolution.
- b. Please repeat the dissolution testing using the above mentioned method at 25 rpm.

c. Please use additional sampling times of 12 hrs and 24 hrs in Sections "a" and "b" above.

Deficiency 9: *Please provide a table of  $AUC_t/AUC_{\infty}$  ratios, mean and range for all subjects.*

Firm's Response: The firm provided data as requested. Using original data, the mean and range (minimum and maximum) of  $AUC_t/AUC_{\infty}$  ratios were 0.8472, 0.3620 and 0.9900 respectively. Using reassay values, the mean and range (minimum and maximum) of  $AUC_t/AUC_{\infty}$  ratios were 0.8459, 0.3620 and 0.9920 respectively.

FDA Comment: The response is acceptable.

### III. Deficiency Comments:

1. The serious adverse event requiring hospitalization for Subject #65 and 101 was not due to the drug under investigation. Subject #65 was hospitalized because she broke her leg on Day 83 of 119 for the study while subject # 101 was in a horse drawn carriage accident on Day 72 of 119 for the study. Both subjects were hospitalized due to an accident but not due to the drug under investigation. Due to the accident, the subject # 65 (reference trt) has the last six (6) samples missing while the subject # 101(reference trt) had last seven (7) samples missing. The DBE calculated AUC (0-1656 hrs) and AUC (0-1824 hrs) from the reference mean plasma profile which were 85% and 81% of the AUC (0-2856) from the mean reference plasma profile. The DBE also computed the reference mean AUC (0-t) by including these two subjects. The T/R ratio of the arithmetic means of AUC (0-t) changed from 0.9567 to 0.9619. The DBE is aware of the fact that the actual AUC (0-t) values for these two subjects may be different from the values calculated above. For that reason it is essential that you provide the DBE with the plasma data and values of PK parameters for these two subjects. Moreover, from the plasma profiles we will determine whether these two subjects have feasible AUC (0-inf) values. Additionally, these two subjects will provide accurate values for C<sub>max</sub> and therefore the inclusion of these two subjects is essential for the statistical analysis of the C<sub>max</sub> value. Thus, based on our calculations, the DBE does not believe the inclusion of those subjects would result in an inaccurate and biased assessment of C<sub>max</sub> (definitely) and AUC (0-t), AUC (0-inf) (possibly). Therefore, the firm is requested to provide plasma data for these two subjects and provide statistical analyses of the PK parameters including these two (2) subjects.
2. The firm did not provide dissolution data for individual dosage units. The DBE requests the following additional information:
  - a. Please, provide individual dissolution data for 12 dosage units using the above mentioned method. Please, submit the mean percent dissolution, CV% and range (minimum and maximum) of the dissolution.




- b. Please repeat the dissolution testing using the above mentioned method at 25 rpm.
- c. Please use additional sampling times at 12 hrs and 24 hrs in Sections "a" and "b" above.

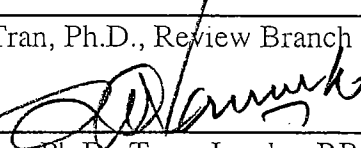
#### J. Recommendations

The single-dose, fasting bioequivalence study conducted by Gensia Sicor Pharmaceuticals, on its Medroxyprogesterone Acetate Injectable suspension, 150mg/ml (lot #X01P613P1), comparing it to Pharmacia & Upjohn's Depo-Provera® Injectable Suspension, 150mg/ml (lot #11HCC), has been found incomplete by the Division of Bioequivalence due to above deficiencies.

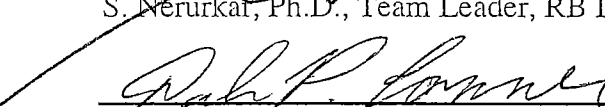
Deficiencies should be conveyed to the firm.

  
\_\_\_\_\_  
Nhan L. Tran, Ph.D., Review Branch II

3/24/04

  
\_\_\_\_\_  
S. Nerurkar, Ph.D., Team Leader, RB II

3/24/2004

  
\_\_\_\_\_  
Dale P. Conner, Pharm. D.  
Director, Division of Bioequivalence  
Office of Generic Drugs

3/24/04

## BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-552 & 76-553

APPLICANT: GENSIA SICOR

DRUG PRODUCT: Medroxyprogesterone Acetate Injectable  
Suspension, 150 mg/ml.

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The serious adverse event requiring hospitalization for Subject #65 and 101 was not due to the drug under investigation. Due to the accident, the subject # 65 (reference trt) has the last six (6) samples missing while the subject # 101(reference trt) had last seven (7) samples missing. The DBE calculated AUC (0-1656 hrs) and AUC (0-1824 hrs) from the reference mean plasma profile which were 85% and 81% of the AUC (0-2856) from the mean reference plasma profile. The DBE also computed the reference mean AUC (0-t) by including these two subjects. The T/R ratio of the arithmetic means of AUC (0-t) changed from 0.9567 to 0.9619. The DBE is aware of the fact that the actual AUC (0-t) values for these two subjects may be different from the values calculated above. For that reason it is essential that you provide the DBE with the plasma data and values of PK parameters for these two subjects. Moreover, from the plasma profiles we will determine whether these two subjects have feasible AUC (0-inf) values. Additionally, these two subjects will provide accurate values for Cmax and therefore the inclusion of these two subjects is essential for the statistical analysis of the Cmax value. Thus, based on our calculations, the DBE does not believe the inclusion of those subjects would result in an inaccurate and biased assessment of Cmax (definitely) and AUC (0-t), AUC (0-inf) (possibly). Therefore, you are requested to provide plasma data for these two subjects and provide statistical analyses of the PK parameters including these two (2) subjects.
3. You did not provide dissolution data for 12 individual dosage units (a Prefilled Syringe or a Vial is an individual dosage unit). The DBE requests the following additional information:

- a. Please, provide dissolution data for 12 individual dosage units using the method you have proposed in this submission. Please, submit the mean percent dissolution, CV% and range (minimum and maximum) of the dissolution.
- b. Please repeat the dissolution testing using your proposed method but with the paddle speed at 25 rpm.
- c. Please use additional sampling times at 12 hrs and 24 hrs in Sections "a" and "b" above.

Sincerely yours,



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

CC: ANDA #76-552 & 76-553  
ANDA DUPLICATE  
DIVISION FILE  
HFD-651/ Bio Drug File  
HFD-655/ Reviewer  
HFD-655/ Bio team Leader

Endorsements: (Final with Dates)

HFD-655/Tran *TV* 3/24

HFD-655/Nerurkar

HFD-650/ D. Conner *AM* 3/24/04

*[Signature]* 3/24/04

BIOEQUIVALENCE - INCOMPLETE

Submission date: 02/23/2004

1. Study Amendment (STA)

✓ Strength: 150 mg/ml  
(Prefilled Syringe)

Clinical Site: \_\_\_\_\_

Outcome: IC

Analytical Site: \_\_\_\_\_

Outcome: IC

2. Study Amendment (STA)

✓ Strength: 150 mg/ml  
(Single Dose Vial)

Clinical Site: \_\_\_\_\_

Outcome: IC

Analytical Site: \_\_\_\_\_

Outcome: IC

Outcome Decisions: IC - INCOMPLETE

MAY 11 2004

OFFICE OF GENERIC DRUGS  
DIVISION OF BIOEQUIVALENCE

ANDA #: 76-552/76-553 SPONSOR : Gensia

DRUG AND DOSAGE FORM : Medroxyprogesterone Acetate Injectable Suspension  
STRENGTH(S) : 150 mg/ml  
TYPES OF STUDY : Fasting  
CLINICAL STUDY SITE(S) : \_\_\_\_\_  
ANALYTICAL SITE: \_\_\_\_\_

STUDY SUMMARY : Fasting study on 150 mg/ml Prefilled Syringe is acceptable.

DISSOLUTION : The dissolution testing is acceptable.

DSI INSPECTION STATUS

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

PRIMARY REVIEWER : Nhan L. Tran, Pharm.D.

BRANCH : I

for INITIAL : 

DATE : 5/11/2004

TEAM LEADER : S. Nerurkar (For YC Huang, Ph.D.)

BRANCH : I

INITIAL : 

DATE : 5/11/2004

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

INITIAL : 

DATE : 5/11/04

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-552 & 76-553

APPLICANT: GENSIA SICOR

DRUG PRODUCT: Medroxyprogesterone Acetate Injectable Suspension,  
150 mg/ml.

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

We agree with your proposed dissolution method and specification  
as follows:

Apparatus: USP Apparatus II (paddle)  
Medium: 0.35% SLS in water at 37 °C  
Volume: 900 mL  
Speed: 50 rpm.

Times	Tolerances
15 min (0.25 hr)	NMT —%
60 min (1 hr)	——%,
2880 min (48 hrs)	NLT —%

Please note that the bioequivalence 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 bioequivalence  
information and/or studies, or may result in a conclusion  
that the proposed formulation is not approvable.

Sincerely yours,



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

## DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-552 (Prefilled Syringe) and 76-553 ( 1mL Vial)
Drug Product Name	Medroxyprogesterone Acetate Injectable Suspension
Strength	150 mg/mL
Applicant Name	Gensia Sicor Pharmaceuticals
Address	Irvine, CA
Submission Date(s)	November 27, 2002
Amendment Date(s)	February 23, 2004 April 15, 2004
Reviewer	Nhan L. Tran
First Generic	Yes
File Location	V:\firmsam\Gensia\ltrs&rev\76552A0404.doc

**I. Executive Summary**

The firm submitted a single dose, fasting BE study with a suspension Medroxyprogesterone Acetate (MPA) in Prefilled Syringe (76-552) on November 27, 2002 (original submission). Since, in these two ANDAs, the suspension of MPA is identical, the firm submitted the same BE study in ANDA 76-553 (for MPA suspension in 1 ml Vial). The Division of Bioequivalence (DBE) reviewed the BE study and found it deficient. The DBE communicated the identical deficiencies to both ANDAs. As a response to the DBE deficiencies, the firm has submitted an amendment for ANDA 76-552 and another for 76-553. The firm's responses in these two amendments are also identical. Instead of writing two separate and identical documents for these two ANDAs, the DBE is generating one document for both ANDAs. The DBE has determined that, the firm satisfactorily responded to the deficiencies and therefore both ANDAs are acceptable with no deficiencies.

The previous reviews are stored on V:\firmsam\Gensia\ltrs&rev\76552N1102.doc and V:\firmsam\Gensia\ltrs&rev\76552N0204.doc

**II. Review of the responses** (Note the original deficiencies are in *italic*)

Deficiency 1: *The serious adverse event requiring hospitalization for Subject #65 and 101 was not due to the drug under investigation. Due to the accident, the subject # 65 (reference trt) has the last six (6) samples missing while the subject # 101 (reference trt) had last seven (7) samples missing. The DBE calculated AUC (0-1656 hrs) and AUC (0-1824 hrs) from the reference mean plasma profile which were 85% and 81% of the AUC (0-2856) from the mean reference plasma profile. The DBE also computed the reference mean AUC (0-t) by including these two subjects. The T/R ratio of the arithmetic means of AUC (0-t) changed from 0.9567 to 0.9619. The DBE is aware of the fact that the actual AUC (0-t) values for these two subjects may be different from the values calculated above. For that reason it is essential that you provide the DBE with the plasma data and values of PK parameters for these two subjects. Moreover, from the plasma profiles we will determine whether these two*

subjects have feasible AUC (0-inf) values. Additionally, these two subjects will provide accurate values for Cmax and therefore the inclusion of these two subjects is essential for the statistical analysis of the Cmax value. Thus, based on our calculations, the DBE does not believe the inclusion of those subjects would result in an inaccurate and biased assessment of Cmax (definitely) and AUC (0-t), AUC (0-inf) (possibly). Therefore, you are requested to provide plasma data for these two subjects and provide statistical analyses of the PK parameters including these two (2) subjects.

Firm's response: The firm provided plasma data for all subjects including the two subjects requested by the Division of Bioequivalence (Subjects # 65 and 101). Statistical analyses of the PK parameters including these two (2) subjects are within acceptable limits (LAUC 0.87-1.01%, LAUCinf 0.92-1.05% and LCmax 0.8-1.15%)

The DBE Comment: The reviewer has reviewed the information submitted and the firm's response is acceptable.

Deficiency 2: You did not provide dissolution data for 12 individual dosage units (a Prefilled Syringe or a Vial is an individual dosage unit). The DBE requests the following additional information:

- Please, provide dissolution data for 12 individual dosage units using the method you have proposed in this submission. Please, submit the mean percent dissolution, CV% and range (minimum and maximum) of the dissolution.
- Please repeat the dissolution testing using your proposed method but with the paddle speed at 25 rpm.
- Please use additional sampling times at 12 hrs and 24 hrs in Sections "a" and "b" above.

Firm's Response:

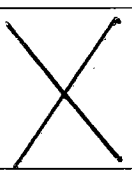

- Dissolution data for 12 individual dosage units using the firm's method are provided below:

USP Apparatus II (Paddle)

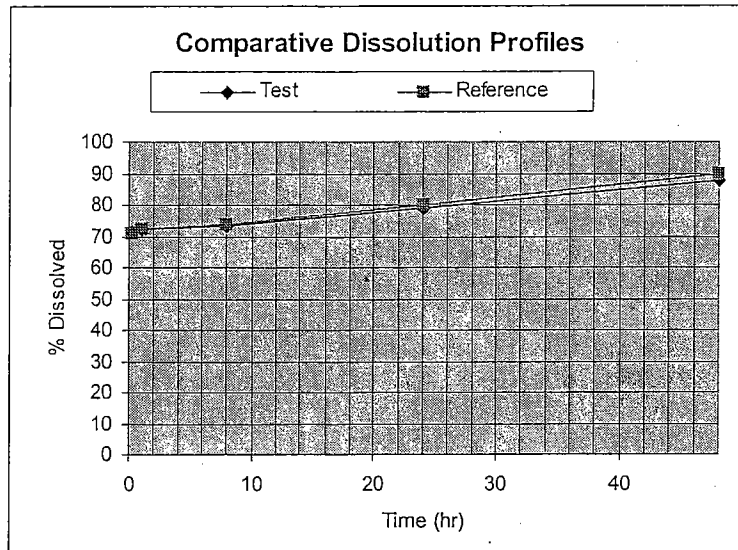
Speed: 50 RPM

Medium: 0.35% — in Water, 900 ml

Results are shown in tables below:

Sampling Time (hrs)	Test Product, strength 150 mg/ml Lot No. X01P613 (Biolot)			Reference Product, Strength 150 mg Lot No. 11HCC (Biolot)		
	Mean	%CV	Range	Mean	%CV	Range
0	0	-	-	-	-	-
0.25	71.20	3.82		71	3.68	
1	72.54	4.61		72.55	4	
8	73.39	6.43		73.94	5.68	
24	79.22	3.84		80	4.83	
48	87.75	6.04		90	6.25	
F2	92.46					





The firm proposed the following tolerances:

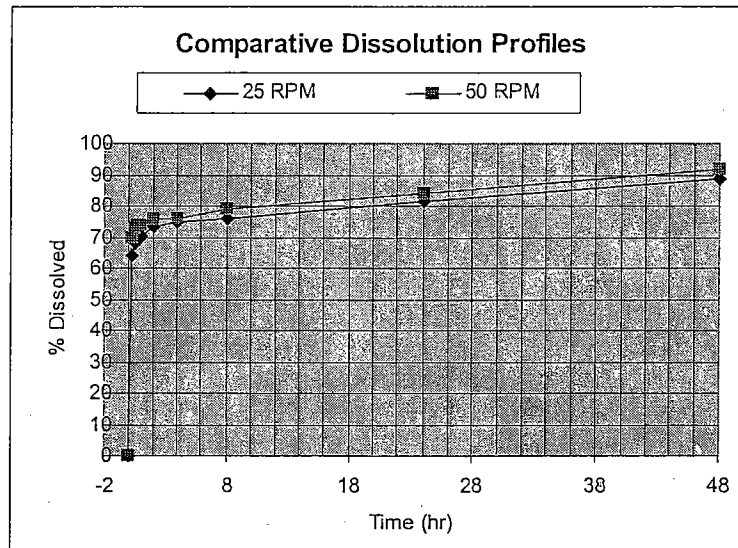
Times	Tolerances
15 min (0.25 hr)	NMT —%
60 min (1 hr)	——%,
2880 min (48 hrs)	NLT —%

The DBE Comment: The dissolution testing method and specifications are acceptable.

**APPEARS THIS WAY  
ON ORIGINAL**

- b. Data on dissolution testing using the firm's method but with the paddle speed at 25 rpm are provided. Based on the data, the firm concluded that there is not a significant difference between 25 RPM and 50 RPM.

Times	25 RPM	Range	50 RPM	Range
0	0	--	--	--
0.25	64.22		70	
0.5	68.01		73	
0.75	69.88		74	
1	70.51		74	
2	73.42		76	
4	74.99		76	
8	75.90		79	
24	81.67		84	
48	88.75		92	



The DBE Comment: Acceptable.

### III. Recommendations

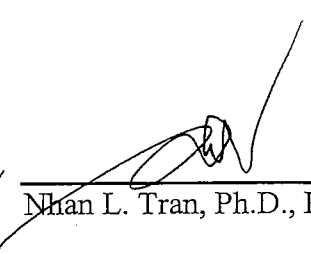
1. The single-dose, fasting bioequivalence study conducted by Gensia Sicor Pharmaceuticals, on its Medroxyprogesterone Acetate Injectable suspension, 150mg/ml (lot #X01P613P1), comparing it to Pharmacia & Upjohn's Depo-Provera® Injectable Suspension, 150mg/ml (lot #11HCC), has been found acceptable by the Division of Bioequivalence.

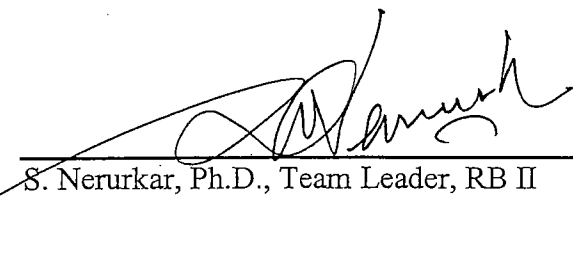
2. The in-vitro dissolution testing method and the specification are acceptable. The firm should conduct dissolution testing in 900 ml of water containing 0.35% Sodium Lauryl Sulfate using USP apparatus 2 (paddle) at 50 rpm with the following specifications.

15 minutes: NLT — %  
60 minutes: — %  
48 hours: NLT — %

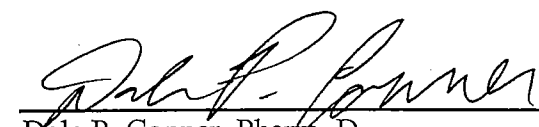
3. The ANDA is acceptable.

for

  
\_\_\_\_\_  
Nhan L. Tran, Ph.D., Review Branch I

  
\_\_\_\_\_  
S. Nerurkar, Ph.D., Team Leader, RB II

5/11/2004

  
\_\_\_\_\_  
Dale P. Conner, Pharm. D.  
Director, Division of Bioequivalence  
Office of Generic Drugs

5/11/04

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-552 & 76-553

APPLICANT: GENSIA SICOR

DRUG PRODUCT: Medroxyprogesterone Acetate Injectable Suspension,  
150 mg/ml.

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

We agree with your proposed dissolution method and specification  
as follows:

Apparatus: USP Apparatus II (paddle)  
Medium: 0.35% SLS in water at 37 °C  
Volume: 900 mL  
Speed: 50 rpm.

Times	Tolerances
15 min (0.25 hr)	NMT —%
60 min (1 hr)	——%,
2880 min (48 hrs)	NLT —%

Please note that the bioequivalence 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 bioequivalence  
information and/or studies, or may result in a conclusion  
that the proposed formulation is not approvable.

Sincerely yours,



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

CC: ANDA #76-552 & 76-553  
ANDA DUPLICATE  
DIVISION FILE  
HFD-651/ Bio Drug File  
HFD-655/ Reviewer  
HFD-655/ Bio team Leader

Endorsements: (Final with Dates)  
HFD-655/Tran  
HFD-655/Nerurkar  
HFD-650/ D. Conner

*[Signature]* 5/11/04

*[Signature]* 5/11/04

BIOEQUIVALENCE - ACCEPTABLE

Submission date: 04/15/2004

1. Study Amendment (STA)

Strength: 150 mg/ml  
(Prefilled Syringe)

Clinical Site: \_\_\_\_\_ Outcome: AC  
Analytical Site: \_\_\_\_\_ / Outcome: AC

2. Study Amendment (STA)

Strength: 150 mg/ml  
(Single Dose Vial)

Clinical Site: \_\_\_\_\_ Outcome: AC  
Analytical Site: \_\_\_\_\_ / Outcome: AC

Outcome Decisions: AC - ACCEPTABLE

**OFFICE OF GENERIC DRUGS  
DIVISION OF BIOEQUIVALENCE**

ANDA # : 76-552/76-553 SPONSOR : Gensia

DRUG AND DOSAGE FORM : Medroxyprogesterone Acetate Injectable Suspension  
STRENGTH(S) : 150 mg/ml  
TYPES OF STUDY : Fasting  
CLINICAL STUDY SITE(S) : \_\_\_\_\_  
ANALYTICAL SITE: \_\_\_\_\_

STUDY SUMMARY : Fasting study on 150 mg/ml Prefilled Syringe is acceptable.

DISSOLUTION : The dissolution testing is acceptable.

**DSI INSPECTION STATUS**

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

PRIMARY REVIEWER : Nhan L. Tran, Pharm.D.

BRANCH : I

INITIAL : 

DATE : 5/11/2004

TEAM LEADER : S. Nerurkar (For YC Huang, Ph.D.)

BRANCH : I

INITIAL : 

DATE : 5/11/2004

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

INITIAL : 

DATE : 5/11/04