CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 040620

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	40-620
Drug Product Name	Methylprednisolone Acetate Injectable Suspension, USP
Strength	40 mg/mL & 80 mg/mL (Multi-Dose Vial)
Applicant Name	Sicor Pharmaceuticals
Address	Irvine, CA
Submission Date(s)	August 26, 2004
Amendment Date(s)	August 19, 2005
Reviewer	Connie T. Jung
First Generic	No
File Location	**V:\firmsnz\Sicor\ltrs&rev\40620N0804.doc**

I. Executive Summary

The firm submitted a single-dose, 2-way crossover fasting bioequivalence (BE) study comparing the test product, Methylprednisolone Acetate Injectable Suspension USP, 80 mg/mL (Multi-dose), with the RLD product, Pharmacia & Upjohn's Depo-Medrol® Suspension, 80 mg/mL (Multi-dose), at an intramuscular dose of 1 x 80 mg. Out of 170 subjects enrolled in 5 groups, 159 subjects completed the study. Twelve subjects were excluded from statistical analysis due to no or few detectable drug levels observed in one of the two periods, and one subject was excluded as he received test treatment in both periods. The statistical analysis using remaining 146 subjects showed a statistically significant GROUP*TREATMENT (GRP*TRT) interaction. The study meets BE criteria if the term is dropped. However, because GRP*TRT is significant, the individual groups must be analyzed separately, unless the firm present convincing evidence that all subjects were from the same study population and were enrolled at the same time. The data for the individual groups were also analyzed separately. Only group 1 met the BE criteria and the remaining 4 groups failed.

The firm submitted an amendment containing a re-dosing study of 12 subjects to evaluate nonresponders compared to responders from the original fasting BE study. The results from the re-dosing study were inconclusive. The firm increased the sensitivity of the analytical method and reanalyzed all samples from the original study. The reanalysis showed that 104 subjects had detectable drug levels at 0 hour and out of which 97 subjects had pre-dose drug levels greater than 5% of Cmax. Therefore these subjects were dropped from statistical analysis. The analysis using the remaining 61 subjects (97 dropped due to predose levels and 1 dropped due to receiving same treatment in both periods) showed significant GRP*TRT interaction for LAUCT. If this term is kept in the model, 90% CI could not be calculated. The firm dropped this term and calculated 90% CI. The firm's results (Summary in Section E) show that the study passes. The reviewer's results (Table 25) show that the 90% CI for LCmax are outside the acceptable limits. The discrepancy between the firm and reviewer's results may be because the data output shows incorrect plasma concentrations for the 0-hour time point for all subjects.

The reviewer also analyzed the data of each group separately. None of the individual groups pass the BE criteria. The fasting BE study is incomplete. The firm should address the deficiencies identified by the DBE before the DBE can determine whether it is acceptable to statistically analyze all the subjects together without the GRP*TRT term included.

The dissolution testing is acceptable, however, the firm should acknowledge its acceptance of the FDA-recommended dissolution method and specifications. The waiver for the 40 mg/mL strength is denied at this time, until the issues with the in vivo bioequivalence study are resolved.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Methylprednisolone Acetate Injectable Suspension USP (multi-dose vial), 40 mg/mL and 80 mg/mL
Reference Product	Depo-Medrol® (methylprednisolone acetate aqueous suspension) (multi-dose vial), 40 mg/mL and 80 mg/mL
RLD Manufacturer	Pharmacia & Upjohn Company
NDA No.	11-757
RLD Approval Date	09/09/75
Indication	An anti-inflammatory glucocorticoid used for intramuscular, intrasynovial, soft tissues or intralesional injection in treatment of endocrine disorders, rheumatic disorders, collagen diseases, dermatologic diseases, allergic states, ophthalmic diseases, gastrointestinal diseases, respiratory diseases, hematologic disorders, neoplastic diseases, edematous states and nervous system (acute exacerbations of multiple sclerosis).

B. PK/PD Information[1, 2, 3]

Bioavailability	Orally administered methylprednisolone is rapidly absorbed. The onset and duration of action of suspension are dependent on intra-articular or intramuscular injection and on the extent of local blood supply.
Food Effect	N/A
Tmax	Approximately 9 hours
Metabolism	The drug is extensively metabolized in the liver to inactive metabolites.
Excretion	The drug is excreted in the urine primarily as metabolites.
Half-life	Approximately 140 hours
Relevant OGD or DBE History	**Control Documents** # 01-154, # 01-569 (b) (4): For bioequivalence, the DBE recommended a single-dose, two-way crossover fasting bioequivalence study using intramuscular administration, which was considered adequate to cover all administration routes indicated in the RLD labeling, and measurement of plasma methylprednisolone only. # 02-298 (Gensia Sicor): Due to limited availability of the single-dose RLD product, the firm proposed conducting a bioequivalence study comparing its test multi-dose product to the single-dose RLD product. The DBE found this unacceptable since the RLD formulations are different for the single-dose and multi-dose products. The DBE recommended that the firm conduct BE studies that compare the single-dose product to the single-dose RLD product, and the multi-dose product to the multi-dose RLD product, respectively. **Protocols** # 00-049 (Gensia Sicor; 11/30/00): The firm submitted two acceptable protocols for *in vivo* bioequivalence studies comparing single-dose and multiple-dose vials, with the RLD product, single-dose and multiple-dose vials, respectively, using intramuscular administration. # 02-064 (Gensia Sicor; 12/12/02): The firm amended above Protocol # 00-049 with Protocol # 02-064 to include additional 48 subjects. The DBE agreed to allow the firm to amend the original protocol as requested with the following conditions: (a) the firm stopped the partial analysis of Period I samples of the study, (b) it had not started analysis of Period II samples, (c) only the first 78 completing subjects should be included in the study, and (d) the decision to enroll additional subjects is not based on the results obtained from the original part of the study. A DSI inspection was requested to inspect the study sites to ensure that the firm did not violate these conditions.

Relevant OGD or DBE History (continued)

For the statistical model used for the study, the firm used factors to account for dosing groups, sequences, subjects nested in dosing groups and sequences, periods nested in dosing groups and treatments. The DBE specifically requested the firm to incorporate the treatment by group (TRT*GRP) interaction term into the model used.

The firm subsequently included a second addition of 18 more subjects (for a total of 116 subjects) for the reason that it lost many samples in the sample transfer between (b) (4) (b) (4) to (b) (4) laboratory. The sample transfer was necessary since there were assay difficulties at the original site, and the assay method was not performing as validated. The firm did not consult with the DBE about this 18-subject addition before the addition was carried out. These data were submitted in ANDA #40-557 for methylprednisolone acetate injectable suspension, 80 mg/mL (single-dose vial).

03-011 (b) (4): The firm submitted an acceptable protocol for conducting a single-dose, two-way crossover BE study on the 80 mg/mL strength.

04-058 (b) (4): The firm submitted an acceptable protocol for conducting a single-dose, two-way crossover BE study on the 80 mg/mL strength. The 40 mg/mL and 20 mg/mL strengths may be eligible for a waiver of *in vivo* BE study requirements based on acceptable BE study on the 80 mg/mL strength, acceptable dissolution testing of all strengths, and proportionally similar formulation. The firm was asked to develop a dissolution method and conduct dissolution testing using the FDA recommended dissolution method on 12 different vials using 900 mL of water and Apparatus 2 (paddle) at 50 rpm. Sampling times were 1 and 4 hours.

ANDA currently listed in the Orange Book

40-557 (Sicor): The firm conducted an acceptable single-dose, crossover BE study on the 80 mg/mL (single-dose) strength. A waiver was granted for the 40 mg/mL (single-dose) strength. The application is for the single-dose, preservative free product.

ANDA's that have been either discontinued or withdrawn include: # 86-903 (Akorn), # 86-666, # 87-135, (b) (4) (b) (4) # 85-374, # 85-595, # 85-600, # 86-507, # 87-248, # 85-597 (Steris).

[1] Physicians' Desk Reference, http://pdrel.thomsonhc.com/pdrel/librarian, accessed 05/16/2005
[2] Clinical Pharmacology, http://cpip.gsm.com/, accessed 05/16/2005
[3] Electronic Orange Book: Approved Drug Products, current through March 2005, http://www.fda.gov/cder/ob/default.htm

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	Yes	2
Waiver requests	Yes	1
BCS Waivers	N/A	
Vasoconstrictor Studies	N/A	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	No	

D. Pre-Study Bioanalytical Method Validation

1. Original Study NA331 Method Validation

Vol. 1.7, pp. 11-593 to 11-647	**Parent**
(b) (4) Study Code: MX010_R	
Analyte name	Methylprednisolone
Internal Standard	(b) (4)
Method description	LC-MS/MS
QC range	4.00 - 40.0 ng/mL
Standard curve range	2.50 -50.0 ng/mL
Limit of quantitation	2.50 ng/mL
Average recovery of Drug (%)	76.8 %
Average Recovery of Int. Std (%)	89.8 %
Intraday precision range (%CV)	2.2 – 3.9 %
Intraday accuracy range (%)	100.2 – 106.4 %
Interday precision range (%CV)	2.5 – 4.8 %
Interday accuracy range (%)	100.6 – 102.5 %
Bench-top stability (hrs)	Not Reported
Stock stability (days)	Not Reported
Processed stability (hrs)	48 hours (under refrigeration) 72 hour (at room temperature)
Freeze-thaw stability (cycles)	Not Reported
Long-term storage stability (days)	Not Reported
Dilution integrity	4-fold: 101.9 %
Specificity	Yes
SOPs submitted	No
Bioanalytical method is acceptable	No

Comments: The firm did not provide bench-top stability data, stock stability data, freeze-thaw stability data, and long-term storage stability data in the original submission. This information was provided in an updated, more sensitive method validation below (MX010_A).

2. Re-Dosing Study of NA331 Method Validation

Vol. 4.2, Section IV, pp. 375-755 (b) (4) Study Code: MX010_R	**The same bioanalytical method validation was reported for the Re-Dosing Study as that which was reported for the Original Study NA331.**

3. Reanalysis of Original Study NA331 – More Sensitive Method Validation

Vol. 4.9, Section IV, pp. 4380-4447	
(b) (4) Study Code: MX010_A	**Parent**
Analyte name	Methylprednisolone
Internal Standard	(b) (4)
Method description	The assay method involves liquid-liquid extraction and chromatographic separation on a RP18 column and LC-MS/MS detection
Limit of Quantitation (ng/mL)	0.500
Average recovery of drug (%)	83.7
Average recovery of IS (%)	78.0
Standard curve concentrations (ng/mL)	0.500, 1.00, 2.50, 5.00, 10.0, 20.0, 30.0 50.0
QC concentrations (ng/mL)	1.50, 7.50, 37.5
QC intraday precision range (%)	1.4 to 4.9
QC intraday accuracy range (%)	102.2 to 107.2
QC interday precision range (%)	2.5 to 4.4
QC interday accuracy range (%)	102.9 to 104.2
Bench-top stability (hrs)	24 hours
Stock solution stability (days)	405 days at 5°C, 24 hours at RT
Processed stability (hrs)	72 hours at RT; 48 hours at 5° C
Freeze-thaw stability (cycles)	Up to 5 – **no data provided**
Long-term storage stability (days)	568 days at –20°C
Dilution integrity	Up to 5-fold
Selectivity	No interfering peaks noted in blank plasma samples
SOPs submitted	
Bioanalytical method is acceptable	

(Summary table provided by the firm.)

Reviewer Comments: This updated method validation has a LOQ of 0.50 ng/mL. The firm used this method to reanalyze study samples from Study NA331. The firm reported freeze-thaw stability of up to 5 cycles, however, no data were provided to support this claim.

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	NA331 (Protocol No. 03-0651-001)
Study Design	Single-Dose, 2-Way Crossover
No. of subjects enrolled	170
No. of subjects completing	159
No. of subjects analyzed	146*
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 84 Female: 75
Test product	Methylprednisolone Acetate Injectable Suspension USP, 80 mg/mL, Multi-Dose Vial (Sicor)
Reference product	Depo-Medrol® Injectable Suspension, 80 mg/mL Multi-Dose Vial (Pharmacia & Upjohn)
Strength tested	80 mg/mL
Dose	1 x 80 mg/mL

*Note: Of the 170 subjects enrolled, only 159 subjects completed the study. Subject # 82 data was not included in the analysis since this subject was given the Test treatment in both periods. The firm dropped an additional 12 subjects (Subjects # 3, 99, 158, 161, 166 received Test; Subjects # 80, 85, 87, 101, 151, 169 received Reference) from the analysis due to little or no systemic methylprednisolone levels observed in one of the two periods. The final analysis was done on 146 subjects.

Reviewer Results
Summary of Statistical Analysis (N=146)
Additional Information in Appendix, The following *PK analysis was conducted by the reviewer on 146 subjects, dropping the GRP*TRT interaction term from the model.*
Table 7 and Table 8

Parameter	Point Estimate	90% Confidence Interval
AUC_{0-t}	0.868	74.69 – 100.79 %
AUC_{∞}	-	-
C_{max}	0.973	88.06 – 107.52

Note: Reviewer's results reported above. SAS analysis included GROUP*TREATMENT interaction term. LS geometric means for AUC_{∞} was not estimated in the SAS analysis due to issues with Group 5 data (only 1 out of 5 subjects had reportable Kel value, therefore mean cannot be calculated).
The firm submitted results after dropping the statistically significant GROUP*TREATMENT term. The firm's results are reported below. Additional comments in the PK Analysis section.

Firm's Results Summary of Statistical Analysis (N=146)		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	0.949	85.1 – 105.8 %
AUC_{∞}	0.926	85.9 – 99.9 %
Cmax	0.988	91.9 – 106.2 %

Reanalysis of Study Samples (Vol. 1.3, page 7.25) Additional information in Appendix, Table 6								
Reasons 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**
No PK repeats were reported	0	0	0	0				
chromatogram was not evaluable	10	1	0.10	0.01	All reassay values were used.			
original concentration exceeded the upper limit of the calibrated working range (reanalyzed after dilution)	3	0	0.03	0				
Total	**13**	**1**	**0.13**	**0.01**				

Total number of samples analyzed: 10,475
(No summary tables provided by the firm)

2. Reanalysis of Fasting Study

The following results were reported by the firm after reanalysis using a more sensitive assay. It should be noted that the firm dropped the statistically significant GROUP*TREATMENT interaction term from its statistical model. The reviewer's results are reported in the Appendix Section.

Methylprednisolone 80 mg/mL sterile aqueous suspension Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Bioequivalence Study (All 158 Subjects)				
Parameter	**Test**	**Ref**	**Point Estimate**	**90% Confidence Interval**
AUC0-t	2505	2621	0.956	0.908, 1.007
AUC∞	3732	4045	0.923	0.868, 0.981
Cmax	7.46	7.77	0.960	0.891, 1.035
Bioequivalence Study (61 subjects - excludes subjects with positive pre-dose levels greater than 5% of their Cmax)				
Parameter	**Test**	**Ref**	**Point Estimate**	**90% Confidence Interval**
AUC0-t	2983	3190	0.935	0.873, 1.001
AUC∞	3608	3651	0.988	0.930, 1.050
Cmax	10.7	11.2	0.956	0.830, 1.101

Reason why assay was reported	**Study No. PA235 (Addendum 2 to NA331) Additional Information in Section III**							
	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**
Pharmacokinetic [1]	0	0	0.0	0.0	0	0	0.0	0.0
Inadequate LOQ for original bioanalytical assay leading to erroneous statistical assessment	(b) (4)		48.7	48.1	(b) (4)		48.7	48.1
Total			48.7	48.1			48.7	48.1

[1] If no repeats were preformed for pharmacokinetic reasons, insert "0.0" throughout table.

Total numbers samples analyzed: 10,145

(Summary tables provided by the firm.)

TABLE 1: Summary of Bioavailability Studies – 158 Subjects

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age, and Weight: (mean and range)	Mean Parameters (+/-SD)						Study Report Location
					Cmax (ng/mL)	Tmax (hour)	AUCt (ng-hr/mL)	AUC∞ (ng-hr/mL)	T½ (hour)	Ke (1/hour)	
PA235 **(Addendum 2 to NA331)**	An Open-Label, Randomized, Single-Dose Pharmacokinetic Study To Determine The Bioequivalence Of Injectable Methylprednisolone Acetate Suspensions	Randomized, Single-Dose, Crossover	**Test** methylpredn-isolone 80 mg/mL sterile aqueous suspension i.m. X02E603	158 (83 M/ 75 F) Healthy, normal 40.2 years old (18 - 73) 73.7 kg (52 - 108)	9.52 (± 9.38)	59.3	2725 (± 936)	3905 (± 1195)	281	0.0036	Section II, page 32
			Reference Depo-Medrol® 80 mg/mL sterile aqueous suspension i.m. 19JCS		9.39 (± 5.29)	55.0	2880 (± 1099)	4123 (± 1326)	288	0.0037	

TABLE 2: Summary of Bioavailability Studies – 61 Subjects
(excluding subjects with positive pre-dose levels greater than 5% of Cmax)

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age, and Weight: (mean and range)	Mean Parameters (+/-SD)						Study Report Location
					Cmax (ng/mL)	Tmax (hour)	AUCt (ng-hr/mL)	AUC∞ (ng-hr/mL)	T½ (hour)	Ke (1/hour)	
PA235 **(Addendum 2 to NA331)**	An Open-Label, Randomized, Single-Dose Pharmacokinetic Study To Determine The Bioequivalence Of Injectable Methylprednisolone Acetate Suspensions	Randomized, Single-Dose, Crossover	**Test** methylpredn-isolone 80 mg/mL sterile aqueous suspension p.o. X02E603	61 (42 M/ 19 F) Healthy, normal 44.0 years old (18 - 73) 75.5 kg (53 - 108)	13.4 (± 13.6)	47.9	3074 (± 878)	3747 (± 1020)	213	0.0042	Section II, page 13
			Reference Depo-Medrol® 80 mg/mL sterile aqueous suspension p.o. 19JCS		12.3 (± 5.63)	44.0	3277 (± 1054)	3954 (± 1067)	195	0.0048	

F. Formulation

Location in appendix	Section A.2, Page 24
Inactive ingredients within IIG Limits (yes or no)	Yes
If no, list ingredients outside of limits	
If a tablet, is the product scored? (yes or no)	N/A
If yes, which strengths are scored?	
Is scoring of RLD the same as test? (yes or no)	N/A
Formulation is acceptable (yes or no)	Yes

If not acceptable, why?

The test and reference formulations are identical, for both 40 mg/mL and 80 mg/mL, as shown in the Appendix, page 24.

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	Firm
Medium	Water
Volume (mL)	900 mL
USP Apparatus type	USP Apparatus 2 (Paddle)
Rotation (rpm)	50 rpm
Firm's proposed specifications	Stage 1 and Stage 2 testing (see comments below): 4 hours : NLT (b) (4)
FDA-recommended specifications	For the 40 mg/mL strength: 1 hour: (b) (4) 4 hours: NLT (b) (4) For the 80 mg/mL strength: 1 hour: (b) (4) 4 hours: NLT (b) (4)
F2 metric calculated?	Yes
If no, reason why F2 not calculated	
Is method acceptable?	No
If not then why?	The firm should acknowledge the FDA recommended dissolution method and specifications.

Comments: The firm provided the following summary table of dissolution testing.

Product ID/ Batch No.	Dosage Form	Conditions	No. of Pooled Vials per Vessel	Collection Times Mean % Dissolution (Range) 0 hr	1 hr	2 hr	4 hr	Study Report Location
SICOR Cat. No. 0043 Lot #X02E603	40 mg/mL (5 mL)	Apparatus: (b) (4) dissolution tester Speed: 50 rpm Medium: water Volume: 900 mL Temp: 37.5 ± 0.5°C	(6 vessels) Stage I: 1 Stage II: 5	0	74	78	79 (b) (4)	Original ANDA Vol. 1 page 70-10
Depo-Medrol® Lot #19JCS				0	81	81	82 (b) (4)	
SICOR Cat. No. 0063 Lot # X02C605	80 mg/mL (5 mL)			0	81	86	92 (b) (4)	
Depo-Medrol® Lot #48HXS				0	81	84	87 (b) (4)	

It should be noted that the firm conducts Stage 1 and Stage 2 testing as defined below (refer to Sicor SOP No. QCP-1386):

Stage 1 testing – Use individual vials as one dosage unit
Stage 2 testing – Pool five(5) vials as one dosage unit

In this case, this terminology should not be confused with "stage 1 or stage 2 dissolution testing" which typically refers to dissolution testing involving multiple stages where a dissolution medium change occurs during the testing period or with multi-point sampling. The current dissolution specification will be determined based on dissolution testing using individual vials as one dosage unit (not pooled vials).

Currently there is no FDA-recommended dissolution method and specification for the drug product. Dissolution method was developed for the single-dose version of this drug product, previously submitted. Upon review of the data, the DBE recommended the following specifications for the single-dose product.

For the 40 mg/mL strength:
1 hour: (b) (4)
4 hours: NLT (b) (4)

For the 80 mg/mL strength:
1 hour: (b) (4)
4 hours: NLT (b) (4)

Based on review of the current data for the multi-dose product (n=6), the DBE is recommending the following dissolution specifications to accommodate both single-dose and multi-dose products. (See Consults in the Appendix Section.)

For the 40 mg/mL strength:
1 hour: (b) (4)
4 hours: NLT (b) (4)
For the 80 mg/mL strength:
1 hour: (b) (4)
4 hours: NLT (b) (4)

f_2 metric, lower strengths compared to highest strength			
Low strength	***Highest strength***	***f2 metric for test***	***f2 metric for RLD***
40 mg/mL	80 mg/mL	49.24	72.21

f_2 metric, Test compared to Reference	
Strength	***f_2 metric***
80 mg/mL	75.96
40 mg/mL	64.65

H. Waiver Request(s)

Strengths for which waivers requested	40 mg/mL
Regulation cited	21 CFR 320.22
Proportional to strength tested in vivo (yes or no)	Yes
Dissolution is acceptable (yes or no)	Yes, pending firm's acknowledgement of FDA-recommended method and specifications.
Waiver granted (yes or no)	No. See Deficiency Comments.

I. Deficiency Comments

1. The firm should explain why nearly 100 subjects showed significant predose drug levels in the fasting study.

2. The firm should provide all records and documentation of when (the dates) and at which clinical site that each subject was **recruited** for the fasting BE study.

3. The firm should provide all records and documentation of when (the dates) and at which clinical site that each subject was **enrolled** for the fasting BE study.

4. The firm should provide data to support the stability of methylprednisolone during five freeze-thaw cycles (bioanalytical method coded: MX010_A).

5. The firm should provide standard operating procedures (SOPs) for bio-analytical methods and those dealing with reassays, including their effective dates.

6. The firm should provide the potency of the reference drug used in the pivotal bioequivalence study NA331.

7. The plasma concentrations reported in the SAS statistical output (Reanalysis study PA235) do not match the data reported in the firm's analytical report and the electronic SAS data file. The firm should explain and correct this discrepancy. The firm should repeat and submit statistical analysis with the corrected data.

8. For the re-dosing study (Study OA369), the firm reported that the subjects in Group 2 received breakfast before Period 2 dosing. The firm should provide the exact time the breakfast was given and properly document this protocol deviation.

9. The firm should provide original subject medical records (pre-screening, clinical laboratory reports, study medical records). The Case Report Forms (CRFs) that have been submitted appear to be transcribed and typed. These CRFs do not document a person responsible for the record keeping (i.e. no signature or initials, and no date).

10. For future studies, the firm should submit serially selected chromatograms from 20% of the subjects. This should include all chromatograms from each period for each subject.

11. The dissolution specifications are determined based on dissolution testing using individual vials as one dosage unit (not pooled vials). The DBE does not agree with your proposed dissolution specifications. The DBE agrees with the following dissolution method:

    The dissolution testing should be conducted in 900 mL water using Apparatus 2 (Paddle) at 50 rpm. The test products should meet the following interim specifications:

    For the 40 mg/mL strength:
    1 hour: (b) (4)
    4 hours: NLT (b) (4)
    For the 80 mg/mL strength:
    1 hour: (b) (4)
    4 hours: NLT (b) (4)

    The firm should acknowledge its acceptance of the above FDA-recommended dissolution method and specifications.

    In addition, the firm should note that for future studies, the dissolution testing should be conducted using 12 units of the test and reference products.

J. Recommendations

1. The single-dose, fasting bioequivalence study (Study NA331) conducted by Sicor Pharmaceuticals, Inc. on its Methylprednisolone Acetate Injectable Suspension (Multi-dose), USP, 80 mg/mL (lot # X02C605P2) comparing it to Pharmacia & Upjohn's Depo Medrol® Injectable Suspension (Multi-dose), USP, 80 mg/mL (lot # 45HXS), is **not acceptable**.

2. The *in vitro* dissolution testing conducted by Sicor on its Methylprednisolone Acetate Injection Suspension (Multi-dose) , USP, 80 mg/mL, lot # X02C605P2, is acceptable.

   The dissolution testing should be conducted in 900 mL water using Apparatus 2 (Paddle) at 50 rpm. The test products should meet the following interim specifications:

   For the 40 mg/mL strength:
   1 hour: (b) (4)
   4 hours: NLT (b) (4)
   For the 80 mg/mL strength:
   1 hour: (b) (4)
   4 hours: NLT (b) (4)

   The firm should indicate if it accepts the FDA-recommended dissolution method and specifications.

3. The waiver of *in vivo* bioequivalence study requirements for the 40 mg/mL strength of the test product is denied at this time.

The firm should be informed of the above deficiencies and recommendations.

Connie T. Jung, Ph. D. — 11/23/2005
Reviewer, Branch IV

Kuldeep R. Dhariwal, Ph. D. — 11/23/2005
Team Leader, Branch IV

In — Dale P. Conner, Pharm. D. — 11/23/05
Director, Division of Bioequivalence
Office of Generic Drugs

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

Study Information						
Study Number	NA331 (Protocol No. 03-0651-001)					
Study Title	An Open-Label Randomized, Single-Dose Pharmacokinetic Study to Determine the Bioequivalence of Injectable Methylprednisolone Suspensions					
Clinical Site	SFBC Ft. Myers, Inc. 3745 Broadway Ave., Suite 100 Fort Myers, FL 33901					
Principal Investigator	Antonio Pizarro, M.D.					
Study/Dosing Dates	Period	Group 1	Group 2	Group 3	Group 4	Group 5
	I	12/03/03	12/30/03	01/21/04	01/27/04	02/17/04
	II	01/15/04	02/09/04	03/02/04	03/08/04	03/30/04
	n enrolled	39	42	56	26	7
	n completed	37	36	54	25	7
	n analyzed	36	35	50	20	5
	Subjects	1-26, 28-34, 36-41	42-79, 81-84	85-140	141-166	27, 35, 80, 167-170
Analytical Site	(b) (4)					
Analytical Director	(b) (6)					
Analysis Dates	January 23 – May 04, 2004					
Storage Period	154 days					

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Methylprednisolone Acetate Suspension (Multi-dose)	Depo-Medrol® Suspension (Multi-dose)
Manufacturer	Sicor Pharmaceuticals	Pharmacia & Upjohn
Batch/Lot No.	X02C605P2	48HXS
Manufacture Date	03/13/02	N/A
Expiration Date	Not Reported	05/2005
Strength	80 mg/mL	80 mg/mL
Dosage Form	Injectable Suspension	Injectable Suspension
Batch Size	(b) (4)	N/A
Potency	102.1%	Not provided
Content Uniformity	100.1-104.4%(RSD=1.4%)	Not provided
Formulation	See Appendix Section 2	
Dose Administered	1 x 80 mg	1 x 80 mg
Route of Administration	Intramuscular (thigh)	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	5
Washout Period	at least 42 days
Randomization Scheme	**A-B**: 2, 3, 5, 8, 11, 12, 15, 16, 17, 19, 21, 23, 26, 27, 30, 32, 33, 34, 37, 40, 47, 48, 50, 59, 60, 62, 63, 66, 68, 70, 72, 76, 77, 81, 83, 84, 86, 88, 89, 91, 93, 96, 97, 100, 101, 102, 105, 106, 109, 112, 113, 114, 117, 119, 121, 122, 126, 128, 130, 132, 133, 136, 137, 140, 142, 143, 145, 148, 150, 152, 155, 156, 157, 159, 161, 162, 165, 167, 170 **B-A**: 1, 4, 6, 7, 9, 10, 13, 14, 18, 20, 22, 24, 25, 28, 29, 31, 35, 36, 38, 39, 41, 42, 43, 44, 45, 46, 49, 51, 52, 53, 54, 55, 56, 57, 58, 61, 64, 65, 67, 69, 71, 73, 74, 75, 78, 79, 80, 85, 87, 90, 92, 94, 95, 98, 99, 103, 104, 107, 108, 110, 111, 115, 116, 118, 120, 123, 124, 125, 127, 129, 131, 134, 135, 138, 139, 141, 144, 146, 147, 149, 151, 153, 154, 158, 160, 163, 164, 166, 168, 169
Blood Sampling Times	Predose, 2.0, 4.0, 6.0, 8.0, 9.0, 10.0, 11.0, 12.0, 14.0, 16.0, 18.0, 24.0, 48.0, 72.0, 96.0, 120, 144, 168, 192, 216, 240, 264, 288, 312, 360, 408, 456, 504, 552, 600, 648 hours postdose
Blood Volume Collected/Sample	7 mL in tubes containing sodium heparin
Blood Sample Processing/Storage	Within 30 minutes of collection, samples were centrifuged at 4°C, and plasma was separated into polypropylene tubes. Plasma samples were stored at -70 °C or lower until analyzed.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	Approximately 10 hours prior to dosing until at least 4 hours postdose
Length of Confinement	Approximately 10 hours prior to dosing until 24 hours postdose, and returned for other blood sampling times
Safety Monitoring	Vital signs (blood pressure, heart rate, respiratory rate and temperature) were measured at screening and prior to dosing. Urine pregnancy tests were performed at screening and at check-in.

Table 1 Demographics of Study Subjects (n=159)

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.0	Male	52.8	Caucasian	38.4
Mean	40.14	Mean	73.6	18-40	52.8	Female	47.2	Afr.Amer.	6.3
SD	12.97	SD	10.7	41-64	42.1			Hispanic	55.3
Range	18	Range	51.8	65-75	5.0			Asian	0.0
	73		107.7	>75	0.0			Other	0.0

Notes: 159 subjects that completed the study; 146 subjects were analyzed. The demographic table provided by the firm was not used because it divided the subject data based on the randomization schedule and it is not clear how many subjects are summarized in the table.

Table 2 Dropout Information

Subject No	Reason	Period	Replaced?
9	Sponsor requested to drop subject after 648-hour blood draw (day 27, 12/30/03) due to missed blood draws.	1	**No**
32	Subject withdrew from the study on day 27 (12/30/03)	1	**No**
42	Subject withdrew from study after Period 1.	1	**No**
54	Subject withdrew from study after Period 1.	1	**No**
71	Subject withdrew from study after Period 1.	1	**No**
72	Subject withdrew from study after Period 1.	1	**No**
76	Subject withdrew from study on day 27.	1	**No**
77	Subject withdrew from study after Period 1.	1	**No**
88	Subject withdrew from Period 1 due to death in the family.	1	**No**
103	Subject was dropped from the study due to positive pregnancy test at check-in.	1	**No**
144	Subject withdrew from study on day 27.	1	**No**

Table 3 Study Adverse Events

System Class	Treatment Group		
COSTART	A	B	N/A (Pre-Dose)
Eye			
Pain Eye	(0.00%)	1 (1.41%)	(0.00%)
Gastr			
Diarrhea	5 (7.69%)	4 (5.63%)	(0.00%)
Dry mouth	(0.00%)	1 (1.41%)	(0.00%)
Dyspepsia	(0.00%)	2 (2.82%)	(0.00%)
Nausea	1 (1.54%)	(0.00%)	(0.00%)
Pharyngitis	1 (1.54%)	(0.00%)	(0.00%)
Stomatitis	1 (1.54%)	(0.00%)	(0.00%)
Stool abnorm	1 (1.54%)	(0.00%)	(0.00%)
Vomit	2 (3.08%)	2 (2.82%)	(0.00%)
Gen			
Asthenia	1 (1.54%)	1 (1.41%)	(0.00%)
Malaise	(0.00%)	1 (1.41%)	(0.00%)
Pain	2 (3.08%)	7 (9.86%)	(0.00%)
Sweat	2 (3.08%)	1 (1.41%)	(0.00%)
Vasodilat	2 (3.08%)	(0.00%)	(0.00%)
Infec			
Flu synd	1 (1.54%)	(0.00%)	(0.00%)
Food poisoning	(0.00%)	1 (1.41%)	(0.00%)
Infect	1 (1.54%)	(0.00%)	(0.00%)
Inj&P			
Atrophy inject site	(0.00%)	1 (1.41%)	(0.00%)
Edema	1 (1.54%)	1 (1.41%)	(0.00%)
Injury accid	2 (3.08%)	1 (1.41%)	(0.00%)
Pain	1 (1.54%)	(0.00%)	(0.00%)
Pain inject site	3 (4.62%)	2 (2.82%)	(0.00%)
Inv			
Fever	(0.00%)	2 (2.82%)	(0.00%)
Hyperglycem	(0.00%)	1 (1.41%)	(0.00%)
Liver Func Abnorm	(0.00%)	1 (1.41%)	(0.00%)
Hypotens	1 (1.54%)	(0.00%)	(0.00%)
Metab			
Appetite inc	1 (1.54%)	1 (1.41%)	(0.00%)
Musc			
Cramps Leg	2 (3.08%)	2 (2.82%)	(0.00%)
Neck Rigid	1 (1.54%)	(0.00%)	(0.00%)
Pain	(0.00%)	2 (2.82%)	(0.00%)
Pain Back	(0.00%)	(0.00%)	1 (50.00%)
Nerv			
Chills	(0.00%)	1 (1.41%)	(0.00%)
Dizziness	(0.00%)	4 (5.63%)	(0.00%)
Headache	12 (18.46%)	13 (18.31%)	1 (50.00%)

System Class	Treatment Group		
COSTART	A	B	N/A (Pre-Dose)
Hypesthesia	1 (1.54%)	1 (1.41%)	(0.00%)
Insomnia	1 (1.54%)	(0.00%)	(0.00%)
Migraine	1 (1.54%)	(0.00%)	(0.00%)
Paresthesia	(0.00%)	1 (1.41%)	(0.00%)
Syncope	(0.00%)	1 (1.41%)	(0.00%)
Vertigo	1 (1.54%)	(0.00%)	(0.00%)
Preg			
Pregn unintend	(0.00%)	1 (1.41%)	(0.00%)
Renal			
Cystitis	2 (3.08%)	(0.00%)	(0.00%)
Polyuria	1 (1.54%)	(0.00%)	(0.00%)
Urine abnorm	1 (1.54%)	(0.00%)	(0.00%)
Repro			
Vaginitis	1 (1.54%)	(0.00%)	(0.00%)
Resp			
Infect	2 (3.08%)	2 (2.82%)	(0.00%)
Pharyngitis	2 (3.08%)	2 (2.82%)	(0.00%)
Rhinitis	1 (1.54%)	3 (4.23%)	(0.00%)
Skin			
Atrophy skin	1 (1.54%)	(0.00%)	(0.00%)
Ecchymosis	(0.00%)	2 (2.82%)	(0.00%)
Pruritus	1 (1.54%)	2 (2.82%)	(0.00%)
Rash	3 (4.62%)	2 (2.82%)	(0.00%)
Skin discolor	1 (1.54%)	(0.00%)	(0.00%)
Tighness in skin	1 (1.54%)	(0.00%)	(0.00%)
Vasc			
Pallor	(0.00%)	1 (1.41%)	(0.00%)
TOTAL	**65 (100.00%)**	**71 (100.00%)**	**2 (100.00%)**

Comments: There were similar number of adverse events reported for the Test and Reference treatments. Although 4 vomiting episodes were reported, these occurred either prior to dosing or beyond 2 times the median Tmax. Therefore, no adjustments to the data were needed. Some of the adverse events were possibly/probably related to the study medication but most events were mild to moderate in severity. No serious adverse events were reported.

Table 4 Protocol Deviations

Type
Wash out period was 41 days (Subject No. 43-53, 55-70, 73-75, 78-79, 81-87, 89-102, 104-143, 145-166)
Blood samples not obtained
Blood sample centrifuged late
Concomitant medication
Subject No. 82 was given Test treatment for both periods.
Blood sample lost in transport
Blood sampling time deviations

Comments: Protocol deviations are listed in Table 4. Most of the deviations were minor and did not effect the study outcome. Subject No. 82 was given Test treatment for both periods and was removed from the statistical analysis. Further comments are located in the PK Analysis Section.

Table 5 Assay Validation – Within Study

	Methylprednisolone						
QC Conc. (ng/mL) (n=259)	4.00			16.0		40.0	
Inter day Precision (%CV)	5.3			3.9		3.3	
Inter day Accuracy (%)	102.0			100.4		99.9	
Cal. Standards Conc. (ng/mL) (n=88)	2.50	5.00	7.50	10.0	12.5	25.0	50.0
Inter day Precision (%CV)	4.3	3.4	3.8	3.0	3.0	2.6	1.3
Inter day Accuracy (%)	101.1	99.2	99.9	100.3	99.3	100.0	100.1
Linearity Range (range of R^2 values)	0.99259-0.99997						

Comments on Study Assay Quality Control: Acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes (only for 1 period of 2 for each subject)
Were chromatograms serially or randomly selected?	randomly (Period 1: Subjects 01, 02, 03, 04, 30, 31, 32, 33, 50, 51, 52, 53, 78, 79, 81, 82, 90, 91, 92, 93, 98, 99, 100, 101, 114, 115, 116, 117, 126, 127, 128, 129, 150, 151, 152, 153) (Period 2: Subjects 24, 25, 26, 28, 43, 44, 45, 46, 68, 69, 70, 73,

Chromatograms: The firm is advised to submit chromatograms of both periods in the future.

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

SOP No.	Date of SOP	SOP Title
		None Provided

Comments on repeat assays. All samples were repeated for analytical reasons only. No SOPs were provided.

The following PK analysis was conducted by the reviewer on 146 subjects, dropping the GRP*TRT interaction term from the model.

Table 7 Arithmetic Mean Pharmacokinetic Parameters (n=146)

Mean plasma concentrations are presented in Table 17 and Figure 1

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	ng.hr/mL	2498.84	44.98	2591.09	44.11	0.96
AUC∞	ng.hr/mL	4023.36	28.42	4265.89	25.19	0.94
Cmax	ng/mL	9.84	94.10	9.27	53.85	1.06
Tmax	Hrs	53.19	170.50	55.06	168.57	0.97
T1/2	Hrs	293.18	55.85	310.35	61.23	0.95
kel	hrs^{-1}	0.006	430.39	0.003	56.77	1.89

Table 8 Least Squares Geometric Means and 90% Confidence Intervals (n=146)

Parameter	Test	Reference	T/R	90% CI
AUC0-t	2007.70	2115.57	0.95	83.26 – 108.18 %
AUC∞	3802.35	4104.13	0.93	84.89 – 101.11 %
Cmax	8.13	8.23	0.99	90.54 – 107.75 %

Table 9 Additional Study Information for Analysis (n=146)

Root mean square error, AUC0-t	0.550402	
Root mean square error, AUC∞	0.272550	
Root mean square error, Cmax	0.365808	
Ke and AUCi determined for how many subjects?	A: 106	B: 103
Do you agree or disagree with firm's decision?	Agree	
Indicate the number of subjects with the following:		
-measurable drug concentrations at 0 hr	0	
-first measurable drug concentration as Cmax	2	
Were the subjects dosed as more than one group?	Yes (5 groups)	

Comments on Pharmacokinetic Analysis:

- Of the 159 subjects that completed the study, 12 subjects (Subjects # 3, 99, 158, 161, 166 received Test; Subjects # 80, 85, 87, 101, 151, 169 received Reference) were dropped from the statistical analysis due to no or few detectable drug levels observed in one of the two periods. In addition, Subject # 82 was given Treatment A (Test) in both periods, therefore this subject was not included in the analysis. The reviewer agrees with firm's decision. The firm analyzed data from 146 subjects.

- The firm conducted SAS statistical analysis using the General Linear Models (GLM) procedure including the terms for the effects of group, sequence, group-by-sequence, subject within group-by-sequence, period-within-group, treatment and group-by-treatment interaction in the statistical model. **A statistically significant ($p<0.05$) group-by-treatment interaction was observed for LAUCt.** The firm stated that since the study incorporated an adequate wash-out period, the subjects in each group were recruited from the same Ft. Myers – Tampa Bay area population, and each group was dosed within a reasonable time of the others, no clinical significance could be attributed to this statistical finding. The firm used this reasoning to drop the group-by-treatment (GRP*TRT) interaction term from the statistical model for bioequivalence evaluation.

- If the GRP*TRT interaction term is dropped from the statistical model, the reviewer's results are similar to the results reported by the firm. The 90% CI for LAUCt, LAUCi and LCmax are within the acceptable limits.

- The reviewer repeated the statistical analysis, dropping additional two subjects (Subjects # 125 and #135, n=144), as these subjects also did not have detectable methylprednisolone plasma levels in both periods. The statistical analysis was conducted dropping the GRP*TRT interaction term in the model. The results are very similar to the results observed analyzing 146 subjects (Table 8). The results using 144 subjects are listed in Table 10.

Table 10 Least Squares Geometric Means and 90% Confidence Intervals (n=144)

Parameter	Test	Reference	T/R	90% CI
AUC_{0-t}	2007.70	2115.57	0.95	83.26 – 108.18 %
AUC_{∞}	3802.35	4104.13	0.93	84.89 – 101.11 %
C_{max}	8.13	8.23	0.99	90.54 – 107.75 %

- Although all the subjects were dosed at the same clinical site, they were recruited from 2 different sites about 100 miles apart (Ft. Myers, FL and Tampa Bay, FL). The firm did not provide sufficient information about when and where the subjects were recruited and enrolled.

The following PK analysis was conducted by the reviewer on 146 subjects, keeping the GRP*TRT interaction term from the model.

- The reviewer repeated statistical analysis on 146 subjects including the GRP*TRT interaction term in the statistical model. **A statistically significant ($p<0.1$) GRP*TRT interaction was observed for LAUC∞ (compared to LAUCt, reported by the firm) and the 90% confidence interval for LAUCt were not within the acceptable limits.** The SAS program was not able to estimate the LS means for LAUC∞ due to the 5th group consisting of only 1 out of 5 subjects with a reportable Kel values for both the test and reference. The reviewer's results are reported in Table 11.

Table 11 Least Squares Geometric Means and 90% Confidence Intervals (n=146)

Parameter	Test	Reference	T/R	90% CI
AUC0-t	1919.322	2212.986	0.867	74.75 – 100.64 %
AUC∞	*	*	*	*
Cmax	8.071	8.295	0.973	88.06 – 107.52 %

*Not calculated

- Due to the statistically significant GRP*TRT interaction, the 5 dosing groups were analyzed separately. The following results were obtained:

Table 12 Least Squares Geometric Means and 90% Confidence Intervals GROUP 1 (n=36)

Parameter	Test	Reference	T/R	90% CI
AUC0-t	2949.16	2916.67	1.01	93.08 – 109.85 %
AUC∞	4213.49	4126.90	1.02	94.96 – 109.77 %
Cmax	10.37	10.06	1.03	89.52 – 118.57 %

Table 13 Least Squares Geometric Means and 90% Confidence Intervals GROUP 2 (n=35)

Parameter	Test	Reference	T/R	90% CI
AUC0-t	1717.70	1730.87	0.99	71.42 – 137.91 %
AUC∞	3629.35	4913.37	0.74	58.12 – 93.88 %
Cmax	7.92	7.56	1.05	93.41 – 117.46 %

Table 14 Least Squares Geometric Means and 90% Confidence Intervals GROUP 3 (n=50)

Parameter	Test	Reference	T/R	90% CI
AUC0-t	1963.55	1866.52	1.05	87.84 – 125.98 %
AUC∞	3676.30	3614.64	1.02	93.65 – 110.46 %
Cmax	7.68	7.70	1.00	85.34 – 116.62 %

Table 15 Least Squares Geometric Means and 90% Confidence Intervals GROUP 4 (n=20)

Parameter	Test	Reference	T/R	90% CI
AUC0-t	1594.94	2420.62	0.66	53.14 – 81.69 %
AUC∞	3238.24	3931.62	0.82	71.16 – 95.34 %
Cmax	6.85	8.48	0.81	69.09 – 94.45 %

Table 16 Least Squares Geometric Means and 90% Confidence Intervals GROUP (n=5)

Parameter	Test	Reference	T/R	90% CI
AUC0-t	1641.747	2326.921	0.706	16.77 – 296.76 %
AUC∞	-	-	-	-
Cmax	7.931	7.906	1.003	59.26 – 169.81 %

- Only Group 1 (n = 36) meets BE criteria. However, Group 3 with sample size of 50 did not result in acceptable confidence intervals for LAUCt, which leads to uncertainty of the power of the Group 1 analysis.

- It is noted that the firm previously conducted a bioequivalence study (# MA120) using 50 subjects (48 subjects completing). The 90% CI for all three parameters (LAUCt, LAUCi and LCmax) were outside the acceptable limits. The firm did not provide lot numbers of the test and reference products and therefore it is unknown if the same lots of the two products were used in the subsequent study. The firm concluded that this 50-subject study was statistically underpowered. Subsequently, the current study (# NA331) was powered with more subjects (170 enrolled/150 subjects to complete).

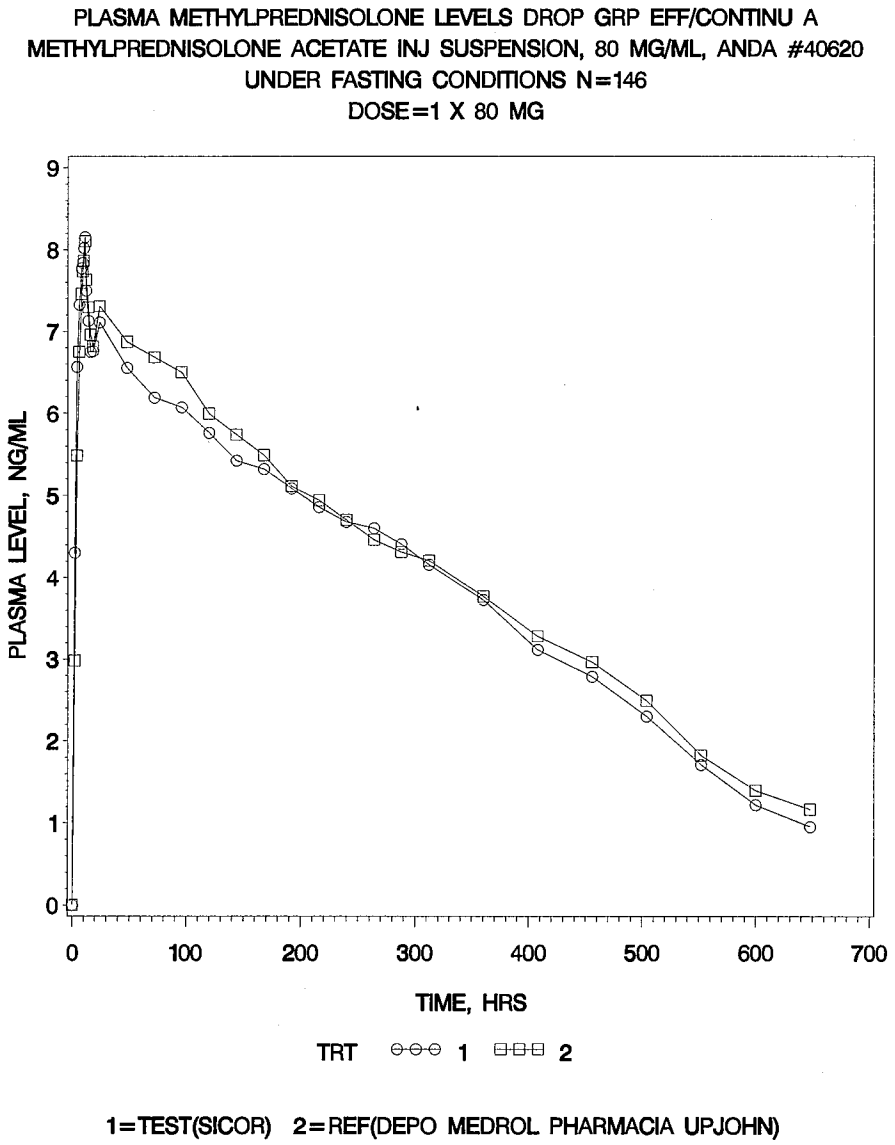
- It should be noted that the mean half-life for both the test and reference products determined from this study was more than twice the value estimated from a bioequivalence study conducted for the RLD product (140 hours). This study used a sampling schedule out to 27 days and an adequate washout period of 42 days. A half-life of about 286 hours for the test and 256 hours for the reference product was also observed in the other study submitted by Sicor on unit-dose product (ANDA #40-557).

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

Table 17 Mean Methylprednisolone Plasma Concentrations (ng/mL) Under fasting conditions, Groups 1-5 Analysis (n=146)

TIME (hour)	Test		Reference		T/R
	Mean	CV%	Mean	CV%	
0	0.00	.	0.00	.	.
2	4.302	174.980	2.983	90.950	1.442
4	6.565	128.730	5.483	57.690	1.197
6	7.328	89.540	6.749	57.500	1.086
8	7.774	71.980	7.460	57.660	1.042
9	7.839	72.830	7.734	58.090	1.014
10	8.020	67.470	7.864	57.820	1.020
11	8.154	67.630	8.101	58.780	1.006
12	7.500	67.790	7.634	60.960	0.982
14	7.130	67.730	7.293	60.020	0.978
16	6.751	66.000	6.958	60.960	0.970
18	6.758	64.710	6.817	57.190	0.991
24	7.111	58.580	7.310	53.110	0.973
48	6.553	58.110	6.873	60.370	0.953
72	6.191	55.940	6.683	59.220	0.926
96	6.073	54.400	6.499	53.630	0.934
120	5.762	50.750	5.994	50.430	0.961
144	5.423	52.670	5.738	48.870	0.945
168	5.320	49.270	5.489	48.490	0.969
192	5.085	47.880	5.110	47.530	0.995
216	4.858	48.520	4.942	45.230	0.983
240	4.679	49.220	4.702	48.000	0.995
264	4.602	49.580	4.460	49.220	1.032
288	4.408	45.880	4.312	46.400	1.022
312	4.156	49.230	4.205	48.160	0.988
360	3.726	53.960	3.769	56.440	0.989
408	3.116	56.290	3.280	62.250	0.950
456	2.786	64.930	2.965	70.060	0.940
504	2.299	78.370	2.491	90.730	0.923
552	1.709	100.960	1.821	105.970	0.938
600	1.220	130.250	1.396	122.650	0.874
648	0.956	159.030	1.168	137.470	0.818

Figure 1 Mean Methylprednisolone Plasma Concentrations (ng/mL) (n=146)



2. Single-dose Fasting Bioequivalence **Re-Dosing** Study

Study Information				
Study Number	OA369			
Study Title	An Open-Label Randomized, Single-Dose Pharmacokinetic Study to Determine the Bioequivalence of Injectable Methylprednisolone Suspensions in Selected Subjects			
Clinical Site	SFBC Ft. Myers, Inc. 3745 Broadway, Suite 100 Ft. Myers, FL 33901			
Principal Investigator	Antonio Pizarro, M.D.			
Study/Dosing Dates	Period	Group 1	Group 2	
	I	07/31/04	10/09/04	
	II	09/18/04	12/04/04	
	n enrolled	7	5	
	n completed	7	5	
	n analyzed	7	5	
	Subjects	1-7	8-12	
Analytical Site	(b) (4)			
Analytical Director	(b) (6)			
Analysis Dates	January 13-22, 2005			
Storage Period	176 days			

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Methylprednisolone Acetate Suspension (Multi-dose)	Depo-Medrol® Suspension (Multi-dose)
Manufacturer	Sicor Pharmaceuticals	Pharmacia & Upjohn
Batch/Lot No.	X02C605P2	48HXS
Manufacture Date	03/13/02	N/A
Expiration Date	3/2005 (based on stability testing)	05/2005
Strength	80 mg/mL	80 mg/mL
Dosage Form	Injectable Suspension	Injectable Suspension
Batch Size	(b) (4)	N/A
Potency	102.1%	Not provided
Content Uniformity	100.1-104.4%(RSD=1.4%)	Not provided
Formulation	See Appendix Section 2	
Dose Administered	1 x 80 mg	1 x 80 mg
Route of Administration	Intramuscular (thigh)	

Note: Study drugs were transferred from Study NA331.

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	2
Washout Period	at least 42 days
Randomization Scheme	**A-B**: 2, 4, 6, 8, 10 **B-A**: 1, 3, 5, 7, 9, 11, 12
Blood Sampling Times	Predose, 2.0, 4.0, 6.0, 8.0, 9.0, 10.0, 11.0, 12.0, 14.0, 16.0, 18.0, 24.0, 48.0, 72.0, 96.0, 120, 144, 168, 192, 216, 240, 264, 288, 312, 360, 408, 456, 504, 552, 600, 648 hours postdose Notes: 1) The 312-hour blood sample was not collected for Group 1 during Period 1 due to a category 4 hurricane (Charley) on August 13, 2004. 2) The 504-hour sample was not collected for Group 2 during Period 2 because it was scheduled on Christmas day.
Blood Volume Collected/Sample	7 mL in tubes containing sodium heparin
Blood Sample Processing/Storage	Within 30 minutes of collection, samples were centrifuged at 4°C, and plasma was separated into polypropylene tubes. Plasma samples were stored at -20 °C.
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 18
Length of Fasting	Approximately 10 hours prior to dosing until at least 4 hours postdose.
Length of Confinement	Subject reported to the clinical site in the afternoon of the day prior to study dosing. Subjects remained at the site until 24 hours postdose, and returned for other blood sampling times.
Safety Monitoring	Vital signs (blood pressure, heart rate, respiratory rate and temperature) were measured at screening and prior to dosing. Urine pregnancy tests (for female subjects) were performed at screening and at check-in.

Table 18 Demographics of Study Subjects (n=12)

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.0	Male	25.0	Caucasian	50.0
Mean	39.25	Mean	73.1	18-40	58.3	Female	75.0	Afr.Amer.	0.0
SD	13.14	SD	9.8	41-64	33.3			Hispanic	50.0
Range	26	Range	56.4	65-75	8.3			Asian	0.0
	72		89.3	>75	0.0			Other	0.0

Note: Firm did not provide electronic summary tab

No Dropouts

Table 19 Study Adverse Events

Adverse Event Description	# in Test Group	# in Reference Group
Rash	1	1
Paresthesia	4	1
Vasomotor response	1	0
Pallor	1	0
Headache	3	4
Rhinorrhea/Rhinitis	3	0
Back pain	1	0
Sore throat	1	0
Otalgia (ear pain)	1	1
Sneezing	1	0
Body aches	1	0
Ache on eye	1	0
Joint aches	1	0
Body chills	1	0
Bronchorrhea (inc. sputum)	1	0
Muscle spasm	0	1
Alopecia	0	1
Paresthesia of feet	0	1
Pruritus feet	0	1
Erythem on neck	0	1
Vertigo	0	1
Cramps in hand and feet	0	1
Dyspepsia	0	1
Pharyngitis	0	1
Upper respiratory infection	0	1
Tonsilitis	0	1
TOTAL	**22**	**19**

No summary table provided by the firm.

Comments: There were similar number of adverse events reported for the Test and Reference treatments. Some of the adverse events were possibly/probably related to the study medication but most events were mild to moderate in severity. No serious adverse events were reported.

Table 20 Protocol Deviations

Type	Subject No.
Due to delayed dosing, the sponsor gave permission for Group 2, Period 2 to receive breakfast prior to dosing in Period 2	
Blood samples not obtained	numerous
Blood sample centrifuged late	numerous
Concomitant medication	9, 3
Blood sampling time deviations	numerous

Comments: Most of the deviations were minor and did not effect the study outcome. The firm reported that Group 2, Period 2, received breakfast before dosing during Period 2. Based on the Schedule of Events provided, dosing of this group started at 12:45 pm.(12/04/2004). This schedule does not show what time breakfast was given. Although food in this case, may not effect the absorption of the study medication since it is being administered intramuscularly, the firm should properly document this protocol deviation.

Table 21 Assay Validation – Within Study

	Methylprednisolone						
QC Conc. (ng/mL) (n=22)	4.00			16.0		40.0	
Inter day Precision (%CV)	7.7			3.2		3.6	
Inter day Accuracy (%)	101.3			101.3		100.3	
Cal. Standards Conc. (ng/mL) (n=8)	2.50	5.00	7.50	10.0	12.5	25.0	50.0
Inter day Precision (%CV)	5.9	8.8	4.4	1.3	4.5	1.7	1.5
Inter day Accuracy (%)	100.4	99.8	99.6	99.2	100.5	100.9	99.6
Linearity Range (range of R^2 values)	0.9967 – 0.9996						

Comments on Study Assay Quality Control: Acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes)
Were chromatograms serially or randomly selected?	randomly (Subjects 11, 12, 1, 2)

Chromatograms: The chromatograms are acceptable.

Table 22 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
		None Provided

Comments on repeat assays. No samples were repeated. No SOPs were provided.

Comments on Pharmacokinetic Analysis: Statistical analysis was not conducted for the re-dosing study. The firm did not provide an electronic data file of the plasma concentrations. PK parameters of AUCt and Cmax were calculated and summarized below.

AUC VALUES

Subject No. from original study NA331	Original Study NA331			Re-dosing Study OA369		
	Test	Reference	AUCt Ratio	Test	Reference	AUCt Ratio
3*	0.00	817	**0.00**	2053	2.53	**811**
5	2769	2801	**0.989**	0.00	1008	**0.00**
23	3782	3918	**0.965**	3344	1525	**2.19**
25	3800	3338	**1.14**	3491	4226	**0.826**
44	2259	2384	**0.947**	2956	3236	**0.913**
45	3325	3236	**1.03**	2939	2999	**0.980**
85*	1569	0.00	**.**	0.00	1275	**0.00**
99*	0.00	16.1	**0.00**	0.00	0.00	**.**
101*	1910	0.00	**.**	2491	3179	**0.784**
108	3228	3691	**0.875**	1533	2427	**0.631**
165*	0.00	1834	**0.00**	36.7	2949	**0.012**
166*	2.57	3711	**0.001**	4481	3860	**1.16**

CMAX VALUES

Subject No. from original study NA331	Original Study NA331			Re-dosing Study OA369		
	Test	Reference	Cmax Ratio	Test	Reference	Cmax Ratio
3*	0.00	3.31	**0.00**	8.19	2.53	**3.24**
5	9.28	8.50	**1.09**	0.00	3.37	**0.00**
23	9.18	12.9	**0.712**	7.76	4.03	**1.93**
25	9.61	7.18	**1.34**	11.7	15.7	**0.745**
44	9.53	8.83	**1.08**	11.1	19.2	**0.578**
45	11.3	11.1	**1.02**	12.3	19.9	**0.618**
85*	5.14	0.00	**.**	0.00	3.42	**0.00**
99*	0.00	2.75	**0.00**	0.00	0.00	**.**
101*	7.40	0.00	**.**	12.6	12.9	**0.977**
108	14.1	8.32	**1.70**	5.55	4.87	**1.14**
165*	0.00	3.56	**0.00**	3.06	6.13	**0.499**
166*	2.57	11.4	**0.225**	13.2	15.0	**0.880**

"." Reference value was 0.00

Subject No. from Re-Dosing Study (OA369)	Subject No. from original study (NA331)	
1	23	Control
2	99	Control
3	108	Enigmatic
4	85	Enigmatic
5	5	Control
6	3	Enigmatic
7	165	Enigmatic
8	166	Enigmatic
9	101	Enigmatic
10	44	Control
11	45	Control
12	25	Control

Firm's Conclusion: The profiles were highly variable, and there was not adequate evidence for classifying the 12 subjects that were dropped from the original study analysis as representing outlier behavior.

Reviewer Comments: The reviewer agrees with the firm's conclusion.

3. Reanalysis of Original Study NA331 Data

Many plasma concentration values in the redosing study were near the LOQ. The firm developed a more sensitive bioanalytical assay (LOQ of 0.50 ng/mL instead of 2.50 ng/mL).

The samples from the original study were reanalyzed using this more sensitive assay. Reanalysis of study samples occurred on May 10 – June 09, 2005. This analysis was conducted 554 days after the first collection of the study samples. Bioanalytical method validation data supports long-term stability of study samples for up to 568 days.

Upon reanalysis, the firm found that 104 subjects had measurable drug levels in the predose samples and out of which 97 subjects had pre-dose plasma concentrations of methylprednisolone greater than 5% of the Cmax. These subjects were dropped from the statistical analysis leaving 61 subject for the final reanalysis. Although the firm found a statistically significant GROUP*TREATMENT interaction for LAUCt in its analysis, it dropped this term from the analysis providing the same reasons as for the original study.

Table 23 Assay Validation – Within Study

	Methylprednisolone							
QC Conc. (ng/mL) (n=244)	1.50		7.50		37.5			
Inter day Precision (%CV)	5.9		4.5		4.9			
Inter day Accuracy (%)	99.5		101.0		100.1			
Cal. Standards Conc. (ng/mL) (n=82)	0.500	1.00	2.50	5.00	10.0	20.0	30.0	50.0
Inter day Precision (%CV)	4.8	3.7	4.5	3.3	3.3	2.8	2.6	1.7
Inter day Accuracy (%)	101.1	99.6	98.3	101.1	100.2	99.9	99.9	100.1
Linearity Range (range of R^2 values)	0.99651 – 0.99998							

Comments on Study Assay Quality Control: Acceptable

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	randomly (Period 1 & 2): Subjects 8, 10, 19, 20, 34, 35, 43, 44, 49, 50, 62, 63, 78, 79, 95, 96, 108, 109, 114, 115, 116, 117, 120, 121, 122, 123, 124, 125, 153, 154, 165, 166

Chromatograms: The chromatograms are acceptable.

No Repeat Assays were reported.

The reviewer's results are presented in the following tables

Table 24 Arithmetic Mean Pharmacokinetic Parameters (n=61)

Mean plasma concentrations are presented in Table 31 and Figure 2

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	ng.hr/mL	3074.48	28.57	3284.99	32.31	0.94
AUC∞	ng.hr/mL	3747.46	27.21	3954.30	26.98	0.95
Cmax	ng/mL	13.44	100.98	12.36	45.61	1.09
Tmax	hrs	47.85	178.86	44.44	192.56	1.08
T1/2	hrs	212.77	51.23	194.67	52.15	1.09
kel	hrs^{-1}	0.004	58.29	0.005	68.54	0.89

Comments: The reviewer repeated SAS statistical analysis using 61 subjects including the GRP*TRT interaction term in the statistical model (Table 22). A statistically significant ($p<0.1$) GRP*TRT interaction was observed for LAUCt. The SAS program was not able to estimate the LS means and 90% confidence intervals due problems with the group analysis. Some of the study groups have very small number of subjects, for example, Group 5 now has 2 subjects. When this occurs, the LS geometric means cannot be estimated.

Table 25 Additional Study Information for Analysis (n=61)

Root mean square error, AUC0-t	0.198600	
Root mean square error, AUC∞	0.147409	
Root mean square error, Cmax	0.439089	
Ke and AUCi determined for how many subjects?	A: 107	B: 104
Do you agree or disagree with firm's decision?	Agree	
Indicate the number of subjects with the following:		
-measurable drug concentrations at 0 hr	97 subjects	
-first measurable drug concentration as Cmax	1	
Were the subjects dosed as more than one group?	Yes (5 groups)	

Comments on Pharmacokinetic Analysis:

- The firm conducted SAS statistical analysis using the General Linear Models (GLM) procedure including the terms for the effects of group, sequence, group-by-sequence, subject within group-by-sequence, period-within-group, treatment and group-by-treatment interaction in the statistical model. A statistically significant ($p<0.05$) group-by-treatment interaction was observed for LAUCt. The firm stated that since the study incorporated an adequate wash-out period, the subjects in each group were recruited from the same Ft. Myers – Tampa Bay area population, and each group was

dosed within a reasonable time of the others, no clinical significance could be attributed to this statistical finding. The firm used this reasoning to drop the group-by-treatment (GRP*TRT) interaction term from the statistical model for bioequivalence evaluation.

- If the GRP*TRT interaction term is dropped from the statistical model, the reviewer's results (Table 25) do not agree with those reported by the firm. The 90% CI for LCmax is not within the acceptable limits.

NO GRP*TRT TERM

Table 26 Least Squares Geometric Means and 90% Confidence Intervals (n=61)

Parameter	Test	Reference	T/R	90% CI
AUC_{0-t}	2977.86	3182.24	0.94	84.50 – 103.63 %
AUC_{∞}	3607.64	3651.02	0.99	91.37 – 106.86 %
C_{max}	10.81	11.37	0.95	76.94 – 117.38 %

- The firm only states that prospective subjects were initially screened by telephone. These candidates for enrollment were screened by clinical laboratories exams (11/12/2003 – 02/13/2004). The subjects selected to participate in the study were instructed to report to the dormitory to begin the study. The firm does not provide any documents that report which subjects were recruited at which site and when each subject was recruited. We cannot be certain that the subjects were enrolled at the same time.

- According to the protocol, subjects were recruited at more than one clinical site. The firm does not report specific locations, but in the Statistical Summary states that the subjects were recruited from the Ft. Myers-Tampa Bay area. These two areas are approximately 100 miles apart. Clinical screening of subjects occurred from 11/12/2003 – 02/13/2004.

Group #	Dosing Dates (Period 1, Period 2)
1	12/03/2003, 01/15/2004
2	12/30/2003, 02/09/2004
3	01/21/2004, 03/02/2004
4	01/27/2004, 03/08/2004
5	02/17/2004, 03/30/2004

Most of the clinical screenings of prospective subject were conducted shortly before dosing for each group. For example, subjects in group 1 were screened (lab work) sometime in November and dosed on December 3rd; subjects in group 5 were screened in late January/early February and dosed on February 17th. It is the usual practice to have physical exam within 30-60 days of dosing and therefore we do not know if all subjects were enrolled at the same time and then asked to come for their physical examination at different times.

- Due to the statistically significant GRP*TRT, the dosing groups were analyzed separately. Analysis on Group 5 was not conducted because it consisted of only 2 subjects. The following results were obtained:

Table 27 Least Squares Geometric Means and 90% Confidence Intervals GROUP 1 (n=17)

Parameter	Test	Reference	T/R	90% CI
AUC0-t	3221.33	3407.12	0.95	87.94 – 101.65 %
AUC∞	4018.18	3892.21	1.03	94.80 – 112.42 %
Cmax	12.20	13.91	0.88	70.93 – 108.44 %

Table 28 Least Squares Geometric Means and 90% Confidence Intervals GROUP 2 (n=15)

Parameter	Test	Reference	T/R	90% CI
AUC0-t	3242.38	3363.78	0.96	87.09 – 106.69 %
AUC∞	3840.18	3681.21	1.04	92.86 – 117.19 %
Cmax	10.64	11.60	0.92	75.59 – 111.28 %

Table 29 Least Squares Geometric Means and 90% Confidence Intervals GROUP 3 (n=19)

Parameter	Test	Reference	T/R	90% CI
AUC0-t	2926.83	2811.58	1.04	89.43 – 121.17 %
AUC∞	3297.48	3616.25	0.91	80.37 – 103.45 %
Cmax	11.24	9.45	1.19	83.08 – 170.23 %

Table 30 Least Squares Geometric Means and 90% Confidence Intervals GROUP 4 (n=8)

Parameter	Test	Reference	T/R	90% CI
AUC0-t	2282.84	3280.24	0.70	51.64 – 93.79 %
AUC∞	.	.	.	.
Cmax	8.01	11.05	0.72	44.82 – 117.23 %

- When analyzed individually, all groups resulted in confidence intervals which are **not** with acceptable limits.

- The age, body weight, and gender did not differ significantly among the 5 groups. Groups 1 and 3 had similar ethnic characteristics. Groups 2, 4, and 5 has similar ethnic characteristics. The summary tables are provided below. These tables summarize the demographics of those subjects that completed the study (n=159). Subjects that were not included in the statistical analysis are included in theses summaries. The values would not change significantly if the excluded subjects were taken into account.

GROUP 1 (n=37)

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.0	Male	59.5	Caucasian	45.9
Mean	41.95	Mean	74.6	18-40	48.6	Female	40.5	Afr.Amer.	8.1
SD	14.71	SD	11.3	41-64	43.2			Hispanic	45.9
Range	18	Range	58.2	65-75	8.1			Asian	0.0
	73		98.2	>75	0.0			Other	0.0

GROUP 2 (n=36)

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.0	Male	55.6	Caucasian	27.8
Mean	44.67	Mean	73.1	18-40	33.3	Female	44.4	Afr.Amer.	5.6
SD	13.23	SD	10.3	41-64	55.6			Hispanic	66.7
Range	18	Range	52.3	65-75	11.1			Asian	0.0
	72		107.7	>75	0.0			Other	0.0

GROUP 3 (n=54)

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.0	Male	48.1	Caucasian	46.3
Mean	38.26	Mean	75.3	18-40	61.1	Female	51.9	Afr.Amer.	3.7
SD	11.42	SD	11.3	41-64	38.9			Hispanic	50.0
Range	19	Range	51.8	65-75	0.0			Asian	0.0
	63		100.5	>75	0.0			Other	0.0

GROUP 4 (n=25)

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.0	Male	52.0	Caucasian	28.0
Mean	34.64	Mean	67.0	18-40	72.0	Female	48.0	Afr.Amer.	12.0
SD	12.35	SD	9.4	41-64	24.0			Hispanic	60.0
Range	19	Range	52.7	65-75	4.0			Asian	0.0
	72		88.2	>75	0.0			Other	0.0

GROUP 5 (n=7)

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.0	Male	42.9	Caucasian	28.6
Mean	41.57	Mean	65.9	18-40	42.9	Female	57.1	Afr.Amer.	0.0
SD	6.48	SD	5.6	41-64	57.1			Hispanic	71.4
Range	34	Range	60.0	65-75	0.0			Asian	0.0
	50		77.3	>75	0.0			Other	0.0

- The plasma concentration reported in the SAS output do not match the data reported in the firm's analytical report and the electronic SAS data file (Vol. 4.3 pp. 1103-1206). Specifically, all the concentrations listed for the 0-hour time point are not correct. The firm should explain or correct this discrepancy.

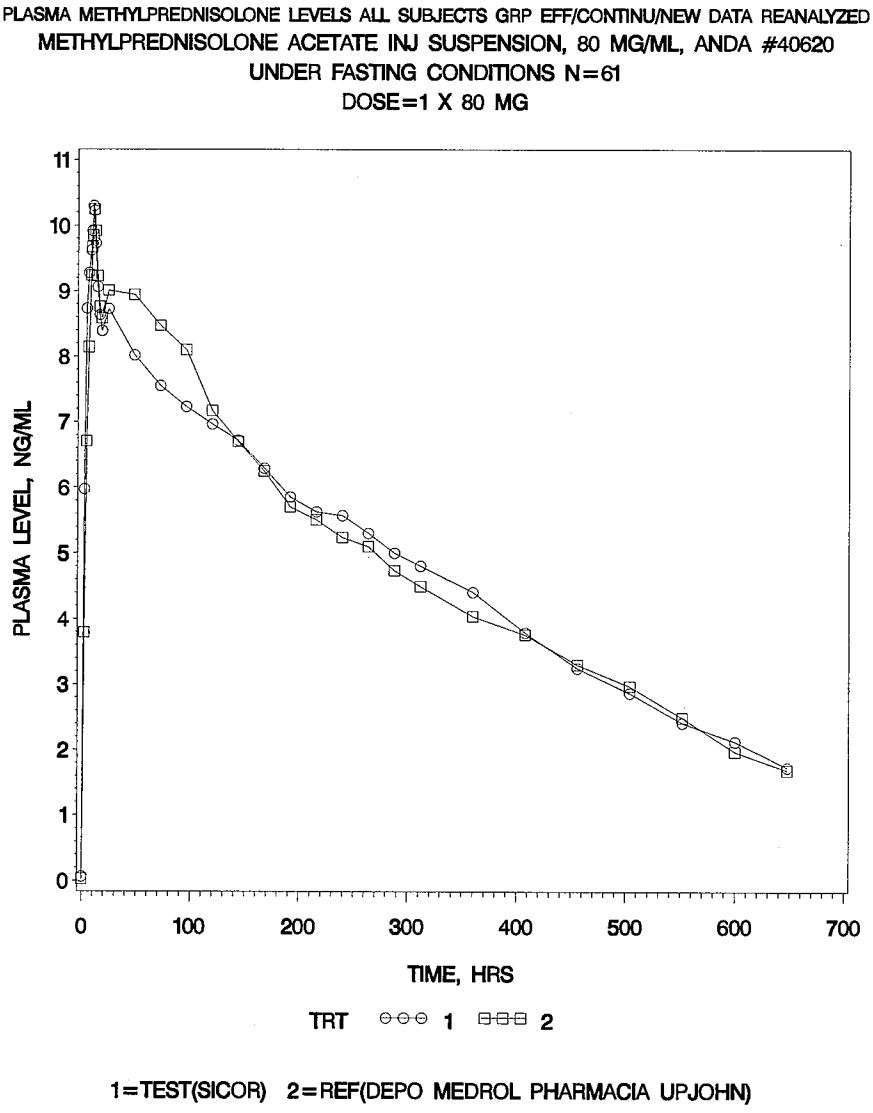
- The firm's reanalysis using a more sensitive assay method resulted in 97 subjects (50 in period 1 and 47 in period 2) having pre-dose plasma levels of methyprednisolone. These subjects were dropped from the statistical analysis. The firm did not provide an explanation for the high incidence of pre-dose levels of a non-endogenous compound.

Conclusion: The single-dose fasting bioequivalence study remains **not acceptable.**

Table 31 Mean Methylprednisolone Plasma Concentrations (ng/mL)
Under fasting conditions, GRP*TRT interaction included
n=61

TIME (hour)	Test		Reference		T/R
	Mean	CV%	Mean	CV%	
0	0.06	344.24	0.03	556.84	2.51
2	5.97	203.38	3.79	50.76	1.58
4	8.73	153.00	6.70	52.31	1.30
6	9.28	94.87	8.14	58.12	1.14
8	9.62	67.36	9.24	57.82	1.04
9	9.92	60.22	9.67	59.12	1.03
10	10.30	58.68	9.85	56.11	1.05
11	10.23	53.85	10.24	59.03	1.00
12	9.73	56.62	9.92	54.85	0.98
14	9.06	50.07	9.23	55.93	0.98
16	8.64	51.65	8.76	54.84	0.99
18	8.39	49.51	8.58	60.60	0.98
24	8.73	50.05	9.01	58.56	0.97
48	8.02	44.71	8.94	54.41	0.90
72	7.55	45.46	8.47	54.83	0.89
96	7.23	42.12	8.10	49.40	0.89
120	6.96	39.44	7.17	40.56	0.97
144	6.72	37.68	6.70	43.31	1.00
168	6.29	33.83	6.25	40.52	1.01
192	5.85	36.38	5.70	37.02	1.03
216	5.63	34.24	5.51	39.01	1.02
240	5.57	37.30	5.24	37.62	1.06
264	5.30	38.95	5.10	36.97	1.04
288	5.00	36.45	4.73	37.90	1.06
312	4.81	36.18	4.49	38.21	1.07
360	4.41	34.78	4.04	44.17	1.09
408	3.79	32.16	3.76	52.68	1.01
456	3.25	38.56	3.30	53.62	0.98
504	2.87	37.92	2.97	62.42	0.97
552	2.41	42.86	2.49	55.21	0.97
600	2.13	56.46	1.97	54.21	1.08
648	1.73	60.94	1.69	54.06	1.03

Figure 2 Mean Methylprednisolone Plasma Concentrations (ng/mL) (n=61)



B. Formulation Data

The formulation of the 80 mg/mL and 40 mg/mL strengths of the test product is identical to that of the 80 mg/mL and 40 mg/mL of the reference product, Depo-Medrol® Injection Suspension.

Formulation for Sicor's Methylprednisolone Acetate Inj. Suspension, USP (Multi-Dose Vial)

Component	Function	80 mg/mL Vial 5 mL fill		40 mg/mL Vial 5 mL fill		40 mg/mL Vial 10 mL fill
		amount	%	amount	%	amount
Methylprednisolone Acetate, USP	Active	400 mg	(b) (4)	200 mg	(b) (4)	400 mg
Polyethylene Glycol 3350	(b) (4)	141 mg		146 mg		291 mg
Benzyl Alcohol, NF		44.4 mg		45.8 mg		91.6 mg
Polysorbate 80, NF		9.4 mg		9.7 mg		19.4 mg
Sodium Chloride, USP	Isotonicity Agent					(b) (4)
Monobasic Sodium Phosphate, (b) (4) USP	(b) (4)	33 mg	(b) (4)	34 mg	(b) (4)	68 mg
Dibasic Sodium Phosphate, (b) (4) USP		6.9 mg		7.1 mg		14.2 mg
Sodium Hydroxide, NF	pH adjuster	pH adjust	-	pH adjust	-	pH adjust
Hydrochloric Acid, NF	pH adjuster	pH adjust	-	pH adjust	-	pH adjust
(b) (4)						

(Reviewer generated table, since the table provided by the firm did not contain %wt.)

C. Dissolution Data

Dissolution Method: Apparatus II (Paddle)
Speed: 50 rpm
Medium: Water
Volume: 900 mL **Units: 6**
Firm's Proposed Specification: NLT (b) (4) (Q) in 4 hours

Table 1 Comparative Dissolution Profiles for Methylprednisolone Acetate Injection Suspension 80 mg/mL, Mulit-Dose Vials

Sampling Time (hour)	TEST Methylprednisolone Acetate Injection Suspension USP 80 mg/mL (Sicor) Lot No. X02C605			REFERENCE Depo-Medrol® Injection Suspension USP 80 mg/mL (Pharmacia & Upjohn) Lot No. 48HXS (exp. 05/2005)		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
0	0.0			0		
1	81.5	11.4	(b) (4)	81.0	6.9	(b) (4)
2	86.3	10.6		84.0	6.1	
4	92.0	8.1		87.7	5.4	
f2 metric			75.96			pass

Table 2 Comparative Dissolution Profiles for Methylprednisolone Acetate Injection Suspension 40 mg/mL, Mulit-Dose Vials

Sampling Time (hour)	TEST Methylprednisolone Acetate Injection Suspension USP 40 mg/mL (Sicor) Lot No. X02E306			REFERENCE Depo-Medrol® Injection Suspension USP 40 mg/mL (Pharmacia & Upjohn) Lot No. 19JCS (exp. Not reported)		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
0	0.0			0		
1	73.7	4.9	(b) (4)	80.5	6.1	(b) (4)
2	77.7	1.8		81.3	6.0	
4	78.5	2.4		82.3	6.5	
f2 metric			64.65			pass

D. Attachment

Summary of the studies submitted in this ANDA:

1. **Study # MA120** - The firm states that it conducted a BE study in 50 subjects (48 completed). The 90% CI for all three parameters (LAUCt, LAUC∞ and LCmax) were outside the acceptable limits. The statistical analysis and other details of this study were not submitted to the Agency. The firm did not provide lot numbers of the test and reference products and therefore it is unknown if the same lots of the two products were used in the subsequent study. The firm states that this study was under powered and therefore repeated the study with more subjects.

2. **Study # NA331** - One hundred and seventy subjects were dosed in five groups. One hundred and fifty nine subjects completed the study. Twelve subjects were dropped from statistical analysis due to no or a few detectable drug levels observed in one of the two periods. One subject was given the test product in both periods. Therefore 13 subjects were not included in the statistical analysis. The firm's statistical analysis using the remaining 146 subjects showed significant GRP*TRT interaction for LAUCt. In addition, a significant GRP*TRT interaction was observed for LAUC∞. The firm states that GRP*TRT interaction term can be dropped from the model as the subjects were from Ft. Myers-Tampa Bay area and all subjects were dosed within a reasonable time. It may be noted that Ft. Myers and Tampa Bay are about 100 miles apart and the subjects were dosed between 12/3/03 and 3/30/04.

   If the GRP*TRT term is dropped from the model and if all groups are analyzed together, the study passes.

3. The firm dropped 12 subjects due to no or a few detectable drug levels observed in one of the two periods. However, there were 2 more subjects falling in this category but were not dropped. The reviewer reanalyzed the data after dropping these two additional subjects (n=144). The GRP*TRT interaction was statistically significant for LAUC∞.
   According to the DBE policy, if the GRP*TRT is statistically significant, then data from all groups cannot be statistically analyzed together, unless the firm provides convincing evidence that all study subjects were from the same population and were enrolled at the same time.

4. Since the GRP*TRT term was significant, the reviewer also analyzed each group separately:
   GRP 1, n=36 - Study passes
   GRP 2, n=35 - AUCt and AUC∞ outside the acceptable limits
   GRP 3, n=50 - AUCt outside the acceptable limits
   GRP 4, n=20 - AUCt, AUC∞ and Cmax outside the acceptable limits
   GRP 5, n=5 - AUCt and Cmax fails, AUC∞ could not be calculated

5. The firm conducted a re-dosing study to evaluate if the 12 subjects who did not have plasma levels in one of the two periods in the original study were outliers. However, the firm could recruit only 6 of these 12 subjects. The 6 'outliers' were re-dosed along with 6 control subjects also from the original study. The plasma concentration profiles in the re-dosing study were variable and not significantly different from the original study. See page 37 for detailed data from the re-dosing study. The T/R ratios in the two studies are given below:

Subject No. from original study NA331	Origianl Study NA331 Test/Reference		Redosing Study OA369 Test/Reference	
	AUCt	Cmax	AUCt	Cmax
3	0.00	0.00	811	3.24
5	0.989	1.09	0.00	0.00
23	0.965	0.712	2.19	1.93
25	1.14	1.34	0.826	0.745
44	0.947	1.08	0.913	0.578
45	1.03	1.02	0.980	0.618
85	.	.	0.00	0.00
99	0.00	0.00	.	.
101	.	.	0.784	0.977
108	**0.875**	**1.70**	**0.631**	**1.14**
165	0.00	0.00	0.012	0.499
166	0.001	0.225	1.16	0.880

"." Reference value was 0.00

Subject No. from Re-Dosing Study (OA369)	Subject No. from original study (NA331)	
1	23	Control
2	99	Control
3	108	Enigmatic
4	85	Enigmatic
5	5	Control
6	3	Enigmatic
7	165	Enigmatic
8	166	Enigmatic
9	101	Enigmatic
10	44	Control
11	45	Control
12	25	Control

From these data, it cannot be concluded if the 12 subjects were outliers. The firm also observed that many values in the re-dosing study were near the LOQ. Therefore, the firm developed a more sensitive assay using a LOQ of 0.50 ng/mL instead of 2.5 ng/mL.

6. **Reanalysis Study PA235** - Using the more sensitive assay, all samples of the original study were reanalyzed (firm demonstrated long-term stability of the drug in the storage samples). The reanalysis showed that 104 subjects had detectable drug levels at 0-hour and out of which 97 subjects had pre-dose drug levels greater than 5% of Cmax. Therefore these subjects were dropped from statistical analysis. The analysis using remaining 61 subjects (97 dropped due to predose levels and 1 dropped due to same treatment in both periods) showed significant GRP*TRT interaction for LAUCt. If this term is kept in the model, 90% CI could not be calculated. The firm dropped this term and calculated 90% CI. The firm's results (Summary table, Section E) show that the study passes. The reviewer results (Table 25) show that the 90% CI for LCmax are outside the acceptable limits. The discrepancy between the firm and reviewer's results may be because the data output shows incorrect plasma concentrations for the 0-hour time point for all subjects. The reviewer also analyzed the data of each group separately. None of the individual groups pass the BE criteria.

E. Consults

1. Dissolution Consult with DBE Dissolution Focal Point, Dr. Nahn Tran and OGD Chemistry

-----Original Message-----
From: Tran, Nhan L
Sent: Tuesday, August 16, 2005 8:39 AM
To: Jung, Connie
Subject: RE: ANDA 40620 Methylpredn Inj Suspension

I think your proposed specs are very reasonable and wide enough to accommodate future changes in the products under different storage conditions such as temperature and time.

Thanks,

-----Original Message-----
From: Jung, Connie
Sent: Tuesday, August 16, 2005 8:30 AM
To: Tran, Nhan L
Subject: FW: ANDA 40620 Methylpredn Inj Suspension

Hi Tran:
Attached below is the response that I got from the chemist regarding the CMC. I also did not see any significant differences except their proposed spec for dissolution is NLT (b) (4) at 4 hours for the multi-dose product.

If we decide to change the spec to accommodate both single and multi-dose products, do you agree with the proposed: (changes to single-dose spec are **bold**)

For the 40 mg/mL
1 hour: (b) (4)
4 hour: NLT (b) (4)

For the 80 mg/mL
1 hour: (b) (4)
4 hour: NLT (b) (4)

(Please refer to previous emails for the data and specs for ANDA 40-557(single-dose, already approved) and ANDA 40-620 (multi-dose, the one that I am reviewing). Thanks!-Connie

-----Original Message-----
From: Lim, Benjamin
Sent: Tuesday, August 16, 2005 7:55 AM
To: Jung, Connie
Subject: RE: ANDA 40620 Methylpredn Inj Suspension

Connie,
the tests and the specs appears to be fairly similar. The tests and specs for particle size distribution, particle size and osmolality are identical for both submission. However, the sedimentation volume, sedimentation rate and viscosity are slightly less for the single-dose product (I can't tell why this may be the case). The multi-dose uses benzyl alcohol as the (b) (4) while single-dose does not. Single-dose uses Myristyl-Gamma Picolinium Chloride (b) (4) as the (b) (4) while multi-dose uses polysorbate 80 as the (b) (4) (the composition of the drug product is based on the RLD). The single dose does not use any (b) (4) while the multi-dose utilizes monobasic sodium phosphate (b) (4) and dibasic sodium phosphate (b) (4) as the (b) (4) This allows the multi-dose to be in the (b) (4) of the drug product specs but the sinlge-dose (b) (4) (b) (4) The compounding steps are quite similar for both the drug products.

I hope this helps, let me know if you need anything specific.

I will ge on a plant trip from 23-26 and work from home on Wed and Thr (no access to FDA resources).

Ben

2. Dissolution consult with Dr. Nhan Tran

-----Original Message-----
From: Jung, Connie
Sent: Monday, August 15, 2005 11:53 AM
To: Tran, Nhan L
Subject: RE: 40-620 Methylprednisolone Inj Susp (Sicor) Multi-dose vial

Hi Tran!

Do your recommendations change based on the comment I made previously about the 80 mg strength:

> As for the 80 mg strength, there was one that was (b) (4) dissolved at 1 hour which would be outside of the (b) (4) spec.
>
> -----Original Message-----
> **From:** Tran, Nhan L
> **Sent:** Friday, August 12, 2005 2:20 PM
> **To:** Jung, Connie
> **Subject:** RE: 40-620 Methylprednisolone Inj Susp (Sicor) Multi-dose vial
>
> Based on data submitted, my suggestion is that you need to modify the spec for the multiple dose strength (40 mg/ml), only at 1 hr time point as (b) (4), and keep the 4 hrs unchanged. There is no problem with the 80 mg/ml multiple dose. Just keep the same spec as the single dose.

Another option is to recommend a new spec for the single and multiple dose 40 mg/ml strength. By doing this we may be able to avoid having too many specs for the same product and it will not look good. I propose the new spec for the 40 mg/ml will be (b) (4) at 1 hr time point. And I prefer this option.

Are you sure the formulation, manufacturing and control the same for the single and multiple dose? Did you check with the chemist?

-----Original Message-----
From: Jung, Connie
Sent: Friday, August 12, 2005 1:03 PM
To: Tran, Nhan L
Subject: 40-620 Methylprednisolone Inj Susp (Sicor) Multi-dose vial

Hello Tran:

This consult is the regarding the Methylprednisolone application that I spoke to you about his morning. Unfortunately, the dissolution data submitted for the multi-dose vials do not meet the specs set for this firm's single dose vials at L1 level. (Specs are listed below).

The 40 mg/mL strength multi-dose dissolves slightly slower than the single-dose product.
And the 80 mg/mL strength multi-dose dissolve slightly faster than the single-dose product.

Should we set different specs for the multi-dose product?

The dissolution data for ANDA 40-620, Multi-dose vials are listed below:

Sampling Time (hour)	TEST Methylprednisolone Acetate Injection Suspension USP 40 mg/mL (Sicor) Lot No. X02E306			REFERENCE Depo-Medrol® Injection Suspension USP 40 mg/mL (Pharmacia & Upjohn) Lot No. 19JCS		
	Mean	%CV	Range	Mean	%CV	Range
0	0.0			0		
1	73.7	4.9	(b) (4)	80.5	6.1	(b) (4)
2	77.7	1.8		81.3	6.0	
4	78.5	2.4		82.3	6.5	
f2 metric			64.65			pass

Sampling Time (hour)	TEST Methylprednisolone Acetate Injection Suspension USP 80 mg/mL (Sicor) Lot No. X02C605			REFERENCE Depo-Medrol® Injection Suspension USP 80 mg/mL (Pharmacia & Upjohn) Lot No. 48HXS		
	Mean	%CV	Range	Mean	%CV	Range
0	0.0			0		
1	81.5	11.4	(b) (4)	81.0	6.9	(b) (4)
2	86.3	10.6		84.0	6.1	
4	92.0	8.1		87.7	5.4	
f2 metric			75.96			pass

The information from ANDA 40-557 (Sicor) Methylprednisolone Acet. Inj. Suspensions:
From v:firmsnz\sicor\ltrs&rev\40557A1104.doc

Sampling Time (min)	Test Product, Strength 40 mg Lot No. X02K617			Reference Product, Strength 40 mg Lot No. 70KMW		
	Mean	%CV	Range	Mean	%CV	Range
15	84.8	1.3	(b) (4)	85.5	5.4	(b) (4)
30	88.1	2.6		86.4	3.9	
45	89.9	2.2		87.7	4.5	
60	88.3	4.2		87.5	4.3	
120	88.5	3.0		88.2	4.2	
240	89.2	3.5		89.4	5.8	
Sampling Time (min)	**Test Product, Strength 80 mg Lot No. X02C603**			**Reference Product, Strength 80 mg Lot No. 17HSU**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
15	72.4	8.5	(b) (4)	71.5	5.1	(b) (4)
30	78.3	6.0		80.3	3.2	
45	80.0	6.8		83.9	3.9	
60	81.4	6.3		83.5	2.4	
120	82.6	7.5		85.3	2.1	
240	84.1	7.7		84.3	2.8	

FDA-Recommend Specifications for the single-dose product:

For the 40mg strength:
1 hr: (b) (4)
4 hrs: NLT (b) (4)

For the 80 mg strength:
1 hr: (b) (4)
4 hrs: NLT (b) (4)

Your recommendation would be greatly appreciated.
Thanks!
Connie

F. SAS Output

FASTING STUDY ANALYSIS	DATA	SAS PROGRAM	SAS OUTPUT
(N=146) GRP*TRT interaction included	 40620Data.xls	 GRP_DROPSUBJ146_CONTINUA_PR	 GRP_DROPSUBJ146_CONTINUA_OU
(N=146) no GRP*TRT term			 NOGRP_DROPSUBJ146_CONTINUA_

FASTING STUDY ANALYSIS	SAS OUTPUT
GROUP 1 (N=36)	 GROUP1analysis.txt
GROUP 2 (N=35)	 GROUP2analysis.txt
GROUP 3 (N=50)	 GROUP3analysis.txt
GROUP 4 (N=20)	 GROUP4analysis.txt
GROUP 5 (N=5)	 GROUP5analysis.txt

FASTING STUDY REANALYSIS	DATA	SAS PROGRAM	SAS OUTPUT
(N=61) GRP*TRT interaction included	40260NEWDATA158.xls	GRP_NEWDATAS UBJ61SASprog.txt	GRP_NEWDATAS UBJ61OUTPUT.txt
(N=61) no GRP*TRT term			NOGRP_NEWDATASUBJ61_OUTPUT

FASTING STUDY REANALYSIS	SAS OUTPUT
GROUP 1 (N=17)	GRP1_NEWDATA OUTPUT.txt
GROUP 2 (N=15)	GRP2_NEWDATA OUTPUT.txt
GROUP 3 (N=19)	GRP3_NEWDATA OUTPUT.txt
GROUP 4 (N=8)	GRP4_NEWDATA OUTPUT.txt
GROUP 5 (N=2)	not conducted

BIOEQUIVALENCE DEFICIENCIES

ANDA: 40-620 APPLICANT: Sicor Pharmaceuticals

DRUG PRODUCT: Methylprednisolone Acetate Injectable Suspension (Multi-dose) USP, 40 mg/mL and 80 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. Please explain why nearly 100 subjects showed significant predose drug levels in the fasting study.

2. Please provide all records and documentation of when (the dates) and at which clinical site that each subject was **recruited** for the fasting BE study.

3. Please provide all records and documentation of when (the dates) and at which clinical site that each subject was **enrolled** for the fasting BE study.

4. Please provide data to support the stability of methylprednisolone during five freeze-thaw cycles (bioanalytical method coded: MX010_A).

5. Please provide standard operating procedures (SOPs) for bio-analytical methods and those dealing with reassays, including their effective dates.

6. Please provide the potency of the reference drug used in the pivotal bioequivalence study NA331.

7. The plasma concentrations reported in the SAS statistical output (Reanalysis study PA235) do not match the data reported in your analytical report and the electronic SAS data file. Please explain and correct this discrepancy. Please repeat and submit statistical analysis with the corrected data.

8. For the re-dosing study (Study OA369), you reported that the subjects in Group 2 received breakfast before Period 2 dosing. Please provide the exact time the breakfast was given and properly document this protocol deviation.

9. Please provide original subject medical records (pre-screening, clinical laboratory reports, study medical records). The Case Report Forms (CRFs) that have been submitted appear to be transcribed and typed. These CRFs do not document a person responsible for the record keeping (i.e. no signature or initials, and no date).

10. For future studies, please submit serially selected chromatograms from 20% of the subjects. This should include all chromatograms from each period for each subject.

11. The dissolution specifications are determined based on dissolution testing using individual vials as one dosage unit (not pooled vials). The DBE does not agree with your proposed dissolution specifications. The DBE agrees with the following dissolution method:

    The dissolution testing should be conducted in 900 mL water using Apparatus 2 (Paddle) at 50 rpm. The test products should meet the following interim specifications:

    For the 40 mg/mL strength:
    1 hour: (b)(4)
    4 hours: NLT (b)(4)
    For the 80 mg/mL strength:
    1 hour: (b)(4)
    4 hours: NLT (b)(4)

    Please acknowledge your acceptance of the above FDA-recommended dissolution method and specifications.

    In addition, please note that for future studies, the dissolution testing should be conducted using 12 units of the test and reference products.

Sincerely yours,

Barbara M. Davit

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

CC: ANDA 40-620
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Final with Dates)
HFD-650/ C.T. Jung CTJ 11/23/2005
HFD-650/ K.R. Dhariwal KRD 11/23/05
HFD-650/ D. Conner DJC 11/23/05

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Printed in final on 11/23/2005

BIOEQUIVALENCE - INCOMPLETE

Submission date: 08/26/2004

✓**1. FASTING STUDY (STF)**

Strength: 80 mg/mL
Outcome: IC

Clinical: SFBC Ft. Myers, Inc.
3745 Broadway Ave., Suite 100
For Myers, FL 33901

Analytical: (b) (4)

(b) (4)

✓**2. WAIVER REQUEST (WAI)**

Strength: 40 mg/mL
Outcome: IC

✓**3. STUDY AMENDMENT (STA)**

Submission date: 08/19/2005
Strength: 80 mg/mL
Outcome: AC

Clinical: SFBC Ft. Myers, Inc.
3745 Broadway Ave., Suite 100
For Myers, FL 33901

Analytical: (b) (4)

(b) (4)

OUTCOME DECISIONS: **IC** - Incomplete

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	40-620
Drug Product Name	Methylprednisolone Acetate Injectable Suspension, USP
Strength	40 mg/mL & 80 mg/mL (Multi-Dose Vial)
Applicant Name	Sicor Pharmaceuticals
Address	Irvine, CA
Submission Date(s)	December 22, 2005
Amendment Date(s)	
Reviewer	Connie T. Jung
First Generic	No
File Location	**V:\firmsnz\Sicor\ltrs&rev\40620A1205.doc**

REVIEW OF AN AMENDMENT

I. Executive Summary

The firm previously submitted a single-dose, 2-way crossover fasting bioequivalence (BE) study comparing the test product, Methylprednisolone Acetate Injectable Suspension USP, 80 mg/mL (Multi-dose), with the RLD product, Pharmacia & Upjohn's Depo-Medrol® Suspension, 80 mg/mL (Multi-dose), at an intramuscular dose of 1 x 80 mg. Out of 170 subjects enrolled in 5 groups, 159 subjects completed the study. Twelve subjects were excluded from statistical analysis due to no or few detectable drug levels observed in one of the two periods, and one subject was excluded as he received test treatment in both periods. The application was incomplete due to several deficiency comments. This amendment contains the firm's responses to deficiencies issued by the Division of Bioequivalence.

The firm improved the sensitivity of the analytical method and reanalyzed all samples from the original study. The reanalysis showed that 104 subjects had detectable drug levels at 0 hour and out of which 97 subjects had pre-dose drug levels greater than 5% of Cmax. Therefore these subjects were dropped from statistical analysis. The analysis using the remaining 61 subjects showed a statistical significant group-by-treatment (GRP*TRT) interaction for LAUCT. The DBE does not agree with the firm's justification for dropping the GRP*TRT term from the model. Since the GRP*TRT interaction is statistically significant, the 5 groups were evaluated separately. When analyzed individually, all groups resulted in confidence intervals which are not within acceptable limits. Therefore, the single-dose, fasting bioequivalence study (Study NA331) is not acceptable. The firm should repeat the study and submit its results to the agency for review.

The comparative dissolution testing is acceptable. However, the waiver request for the 40 mg/mL strength is denied because the BE study on the 80 mg/mL strength is still incomplete.

II. Table of Contents

III. Submission Contents

A. Response to Deficiencies

1. Please explain why nearly 100 subjects showed significant predose drug levels in the fasting study.

Firm's Response: The firm states that to further evaluate the bioequivalence of test and reference products, the re-dosing study was conducted (August 19, 2005 amendment) to evaluate previous non-responders compared to responders. Based on the outcome of this re-dosing study, the analytical method was re-examined, and a more sensitive assay was developed (LOQ of 0.5 ng/mL compared to 2.5 ng/mL). Re-analysis of the subject's study samples with the more sensitive assay resulted in predose drug levels now observed in Period 2. The firm explains these predose drug levels were due to carryover from Period 1.

Reviewer's Comment: The firm response is acceptable. After re-analysis using the more sensitive assay, 104 subjects had predose drug levels. Of these, 94 subject were dropped from the statistical analysis since these predose levels were > 5% of the Cmax. It was incorrectly reported by the reviewer in the original review (40620N0804.doc) that approximately 50% of these predose drugs levels were observe in each Period. The correct number is all except one of the predose drug levels were observed in Period 2. For those subjects that demonstrated predose levels in Period 2, each exhibited drug levels at that last time points of Period 1. The reviewer agrees with the firm's explanation of carryover from Period 1 for these predose drug levels.

2. Please provide all records and documentation of when (the dates) and at which clinical site that each subject was recruited for the fasting BE study.

Firm's Response: The firm provided a table which lists the recruitment site and recruitment date for each subject.

Reviewer's Comment: The firm's response is acceptable.

3. Please provide all records and documentation of when (the dates) and at which clinical site that each subject was enrolled for the fasting BE study.

Firm's Response: The firm provided a table which lists the enrollment date for each subject.

Reviewer's Comment: The firm has reported enrollment dates which correspond to dosing dates for each subject. The firm's response is acceptable.

Additional Comments on Subject Recruitment and Enrollment:
Although all subjects were treated at the same clinical site, the subjects were recruited from 2 different recruitment sites. In the original submission, the statistical analysis of the re-analysis study data (PA235) resulted in a significant group by treatment (GRP*TRT) interaction term for LAUCT. The reviewer examined the possible group differences by looking at recruitment and enrollment information provided in this amendment. The subjects were recruited from 2 different sites, Fort Myers (FM) and Temple Terrance (TT), which are approximately 100 miles apart. Although the reviewer found differences in the subjects recruited from each of these sites, the study subjects from each of the recruitment sites were used in each group (except for Group 5). All study subjects were dosed at the same clinical site, but just on different dates. Review of the recruitment documents showed that most of the subjects recruited from the FM site were Caucasian, and most of the subject recruited from the TT site were Hispanic (Table 1).

TABLE 1 Demographics of recruits from each site (n=61)

Percent from site:	Fort Myers (FM)	Temple Terrace (TT)
Caucasian	37.7 %	3.3 %
African American	1.6 %	1.6 %
Hispanic	11.5 %	44.3 %

The number of subjects used from each recruitment site for each group are shown in Table 2. The firm used subjects from both sites to compose Groups 1-4. Group 5 was only made up of 2 subjects that were recruited from the TT site.

TABLE 2 Subjects recruited from Fort Myers (FM) or Temple Terrace (TT) site in each Group

SITE	TYPE			TOTALS
	caucasian	african american	hispanic	
GROUP 1				
FM	9	1	1	11
TT	0	0	6	6
GROUP 2				
FM	4	0	3	7
TT	1	0	7	8
GROUP 3				
FM	8	0	2	10
TT	0	1	8	9
GROUP 4				
FM	2	0	1	3
TT	1	0	4	5
GROUP 5				
FM	0	0	0	0
TT	0	0	2	2

The demographic profile of each study group are summarized in Tables 3A-3E. Mean values for age and weight are similar between groups. There are slight differences in age groups, gender and race categories.

TABLE3A Demographics of Group 1 (n =17)

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.0	Male	70.6	Caucasian	52.9
Mean	49.24	Mean	75.4	18-40	35.3	Female	29.4	Afr.Amer.	5.9
SD	14.89	SD	12.1	41-64	47.1			Hispanic	41.2
Range	26	Range	59.1	65-75	17.6			Asian	0.0
	73		98.2	>75	0.0			Other	0.0

TABLE 3B Demographics of Group 2 (n = 15)

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.0	Male	73.3	Caucasian	33.3
Mean	48.20	Mean	77.8	18-40	20.0	Female	26.7	Afr.Amer.	0.0
SD	14.11	SD	12.7	41-64	60.0			Hispanic	66.7
Range	18	Range	57.7	65-75	20.0			Asian	0.0
	72		107.7	>75	0.0			Other	0.0

TABLE 3C Demographics of Group 3 (n =19)

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.0	Male	63.2	Caucasian	42.1
Mean	38.26	Mean	76.2	18-40	57.9	Female	36.8	Afr.Amer.	5.3
SD	10.55	SD	9.6	41-64	42.1			Hispanic	52.6
Range	19	Range	58.2	65-75	0.0			Asian	0.0
	60		93.6	>75	0.0			Other	0.0

TABLE 3D Demographics of Group 4 (n = 8)

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.0	Male	62.5	Caucasian	37.5
Mean	37.75	Mean	70.2	18-40	50.0	Female	37.5	Afr.Amer.	0.0
SD	11.77	SD	9.2	41-64	50.0			Hispanic	62.5
Range	20	Range	52.7	65-75	0.0			Asian	0.0
	52		81.8	>75	0.0			Other	0.0

TABLE 3E Demographics of Group 5 (n = 2)

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.0	Male	100.0	Caucasian	0.0
Mean	46.00	Mean	72.5	18-40	0.0	Female	0.0	Afr.Amer.	0.0
SD	4.24	SD	6.8	41-64	100.0			Hispanic	100.0
Range	43	Range	67.7	65-75	0.0			Asian	0.0
	49		77.3	>75	0.0			Other	0.0

4. Please provide data to support the stability of methylprednisolone during five freeze-thaw cycles (bioanalytical method coded: MX010_A).

Firm's Response: The firm provided Amendment II to the Validation Study Report : Determination of Methylprednisolone in Human Plasma by High Performance Liquid Chromatography and UV Detection. This report contains data for freeze-thaw stability for 1 and 5 cycles for three QC concentrations (4.00, 16.0 and 40.0 ng/mL). The results after 5 cycles had a CV% range of 0.9 – 2.5%, and accuracy range of 98.2 – 102.7 %.

Reviewer's Comment: The firm's response is acceptable.

5. Please provide standard operating procedures (SOPs) for bio-analytical methods and those dealing with reassays, including their effective dates.

Firm's Response: The firm submitted copies of the following SOPs and effective dates:

SOP	Title	Used During		Effective Date
		Original Analysis	Re-Analysis	
MOP_MX010_R	Determination of Methylprednisolone in Plasma by LC-MS	X	---	01/22/2004
MOP_MX010_A	Determination of Methylprednisolone in Plasma by LC-MS/MS	---	X	4/25/2005
SOP BAS_RMT_02	Selection Criteria for Reanalyses	---	X	4/15/2001
SOP BAS_RMT_03	Further use of measured values after reinjection or reanalysis of a sample	---	X	5/15/2003

Reviewer's Comment: The firm's response is acceptable.

6. Please provide the potency of the reference drug used in the pivotal bioequivalence study NA331.

Firm's Response: The firm reports the potency of the reference product, Depo-Medrol® Lot No. 48HXS (expiry 05/2005) used in the bioequivalence study (NA331) was 100.1% using Sicor's SOP QCP-1326 "Assay and Impurities Determination for Methylprednisonlone Acetate in the Drug Substance and Drug Product by HPLC."

Reviewer's Comment: The firm's response is acceptable.

7. The plasma concentrations reported in the SAS statistical output (Reanalysis study PA235) do not match the data reported in your analytical report and the electronic SAS data file. Please explain and correct this discrepancy. Please repeat and submit statistical analysis with the corrected data.

Firm's Response: The firm states that the bioanalytical statistical analysis (Reanalysis study PA235) and electronic SAS data file provided in the August 19, 2005 amendment are correct. Due to a printing issue, the original data listing provided was not representative of the data provided in the SAS data file. The firm provided a reprinted data list, which is consistent with the SAS data file.

Reviewer's Comment: The firm submitted a corrected data list, and has confirmed that the statistical analysis was conducted on this data set. The firm's response is acceptable.

8. For the re-dosing study (Study OA369), you reported that the subjects in Group 2 received breakfast before Period 2 dosing. Please provide the exact time the breakfast was given and properly document this protocol deviation.

Firm's Response: The firm provided a summary of the subjects and time that breakfast was given to subjects in Group 2 of the re-dosing study (Study OA369). The firm also provided copies of updated clinical report and case report forms, which document this protocol deviation.

Subject No.	Date	Time Pre-dose meal started	Time subject was dosed
8	10/09/2004	7:03 AM	12:45 PM
9	10/09/2004	7:06 AM	12:48 PM
10	10/09/2004	7:09 AM	12:51 PM
11	10/09/2004	7:12 AM	12:54 PM
12	10/09/2004	7:15 AM	12:57 PM

Reviewer's Comment: Since this drug product is administered via intramuscular injection, it is unlikely that this protocol deviation affected the integrity of the study. The firm's response is acceptable.

9. Please provide original subject medical records (pre-screening, clinical laboratory reports, study medical records). The Case Report Forms (CRFs) that have been submitted appear to be transcribed and typed. These CRFs do not document a person responsible for the record keeping (i.e. no signature or initials, and no date).

Firm's Response: The firm states that on the last page of each subject's CRF, the Principal Investigator, Antoniao R. Pizarro, M.D. or one of the sub-investigators listed on the Form FDA 1572. provides his/her signature along with the date the form was signed. This is consistent with the requirements under 21 CFR 312.62(b), which states that the clinical "investigator is require to prepare and maintain adequate and accurate case histories...including case report forms..."

Sicor has confirmed with the contract research organization, SFBC Ft. Myers, Inc., that the transcription of medical information onto the CRFs and signed by the Investigator (only) has been their practice for the last 5-10 years, and is consistent with industry practice.

Reviewer's Comment: The firm's response is acceptable.

10. For future studies, please submit serially selected chromatograms from 20% of the subjects. This should include all chromatograms from each period for each subject.

Firm's Response: The firm concurs with this comment, and states that in future submissions, it will submit serially selected chromatograms from 20% of the subjects.

Reviewer's Comment: The firm's response is acceptable.

11. The dissolution specifications are determined based on dissolution testing using individual vials as one dosage unit (not pooled vials). The DBE does not agree with your proposed dissolution specifications. The DBE agrees with the following dissolution method:

The dissolution testing should be conducted in 900 mL water using Apparatus 2 (Paddle) at 50 rpm. The test products should meet the following interim specifications:

For the 40 mg/mL strength:
1 hour: (b) (4)
4 hours: NLT (b) (4)
For the 80 mg/mL strength:
1 hour: (b) (4)
4 hours: NLT (b) (4)

Please acknowledge your acceptance of the above FDA-recommended dissolution method and specifications.

In addition, please note that for future studies, the dissolution testing should be conducted using 12 units of the test and reference products.

Firm's Response: The firm states that it will comply with the FDA-recommended dissolution method and specifications. The firm provided revised Finish Product Specifications and Data Sheets reflecting the accepted specifications. The firm also acknowledges the for future studies, it commits to using 12 units of test and reference drug products for dissolution testing.

Reviewer's Comment: The firm's response is acceptable.

B. Additional comments on statistical data analysis

SAS statistical analysis conducted by the reviewer on the re-analyzed data (n=61) showed a statistically significant ($p<0.1$) group-by-treatment (GRP*TRT) interaction for LAUCt. The firm also observed a statistically significant difference for the GRP*TRT, however the firm justified dropping this term from the statistical model for the following reasons: 1) it had incorporated an adequate washout period, 2) the subjects in each group were recruited from the same Ft. Myers – Tampa Bay area population, 3) each group was dosed within a reasonable time of the others, and 4) no clinical significance could be attributed to this statistical finding.

The DBE does not agree with the firm's reasoning for dropping the GRP*TRT interaction term. Based on the observed predosed levels in period 2, the washout period of 42 days may not be adequate for this test product. The recruitment information suggests that there are demographic differences in the subjects recruited from the 2 recruitment sites. All subjects were treated at the same clinical site, therefore statistical analysis examining the site-by-treatment interaction was not necessary.

The statistical analysis of the subject data indicates significant differences between the treatment groups. If the GRP*TRT interaction is statistically significant, then the groups should be evaluated separately. When analyzed individually, all groups resulted in confidence intervals which are **not within acceptable limits**. The firm has not provided sufficient information to convince the DBE to examine the groups together.

C. Deficiency Comments

1. The DBE does not agree with the firm's reasoning for dropping the GRP*TRT interaction term. SAS statistical analysis conducted on the re-analyzed data (n=61) showed a statistically significant ($p<0.1$) group-by-treatment (GRP*TRT) interaction for LAUCt and 90% confidence intervals which are not within acceptable limits for LCmax. Since the GRP*TRT interaction is statistically significant, the 5 groups were examined separately. When analyzed individually, all groups resulted in confidence intervals which are not with acceptable limits. The single-dose, fasting bioequivalence study (Study NA331) is not acceptable. The firm should repeat the study and submit its results to the agency for review.

D. Waiver Request(s)

Strengths for which waivers requested	40 mg/mL
Regulation cited	21 CFR 320.22
Proportional to strength tested in vivo (yes or no)	Yes
Dissolution is acceptable (yes or no)	Yes
Waiver granted (yes or no)	No (BE study is incomplete)

E. Recommendations

1. The single-dose, fasting bioequivalence study conducted by Sicor Pharmaceuticals, Inc. on its Methylprednisolone Acetate Injectable Suspension (Multi-dose), USP, 80 mg/mL (lot # X02C605P2) comparing it to Pharmacia & Upjohn's Depo Medrol® Injectable Suspension (Multi-dose), USP, 80 mg/mL (lot # 45HXS), is incomplete.

2. The *in vitro* dissolution testing conducted by Sicor on its Methylprednisolone Acetate Injection Suspension (Multi-dose) USP, 80 mg/mL, lot # X02C605P2, is **acceptable**.

   The dissolution testing should be conducted in 900 mL water using Apparatus 2 (Paddle) at 50 rpm. The test products should meet the following interim specifications:

   For the 40 mg/mL strength:
   1 hour: (b) (4)
   4 hours: NLT (b) (4)
   For the 80 mg/mL strength:
   1 hour: (b) (4)
   4 hours: NLT (b) (4)

3. The waiver of *in vivo* bioequivalence study requirements for the 40 mg/mL strength is denied.

The firm should be informed of the above deficiency and recommendations.

Connie T. Jung, Ph. D. — 03/13/2006
Reviewer, Branch IV — Date

Yih-Chain Huang, Ph. D. — 3/14/2006
Team Leader, Branch IV — Date

Dale P. Conner, Pharm. D. — 3/15/06
Director, Division of Bioequivalence — Date
Office of Generic Drugs

IV. APPENDIX

A. Summary of Statistical Analysis of (Study NA331)

Due to the statistically significant GRP*TRT, the dosing groups were analyzed separately. Analysis on Group 5 was not conducted because it consisted of only 2 subjects. The results are summarized in Tables 1-4:

Table 1 Least Squares Geometric Means and 90% Confidence Intervals GROUP 1 (n=17)

Parameter	Test	Reference	T/R	90% CI
AUC0-t	3221.33	3407.12	0.95	87.94 – 101.65 %
AUC∞	4018.18	3892.21	1.03	94.80 – 112.42 %
Cmax	12.20	13.91	0.88	70.93 – 108.44 %

Table 2 Least Squares Geometric Means and 90% Confidence Intervals GROUP 2 (n=15)

Parameter	Test	Reference	T/R	90% CI
AUC0-t	3242.38	3363.78	0.96	87.09 – 106.69 %
AUC∞	3840.18	3681.21	1.04	92.86 – 117.19 %
Cmax	10.64	11.60	0.92	75.59 – 111.28 %

Table 3 Least Squares Geometric Means and 90% Confidence Intervals GROUP 3 (n=19)

Parameter	Test	Reference	T/R	90% CI
AUC0-t	2926.83	2811.58	1.04	89.43 – 121.17 %
AUC∞	3297.48	3616.25	0.91	80.37 – 103.45 %
Cmax	11.24	9.45	1.19	83.08 – 170.23 %

Table 4 Least Squares Geometric Means and 90% Confidence Intervals GROUP 4 (n=8)

Parameter	Test	Reference	T/R	90% CI
AUC0-t	2282.84	3280.24	0.70	51.64 – 93.79 %
AUC∞	.	.	.	.
Cmax	8.01	11.05	0.72	44.82 – 117.23 %

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-620 APPLICANT: Sicor Pharmaceuticals

DRUG PRODUCT: Methylprednisolone Acetate Injectable Suspension (Multi-dose) USP, 40 mg/mL and 80 mg/mL

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

1. The DBE does not agree with your reasoning for dropping the group-by-treatment interaction (GRP*TRT) term from your statistical analysis. SAS statistical analysis conducted on the re-analyzed data (n=61) showed a statistically significant ($p<0.1$) group-by-treatment (GRP*TRT) interaction for LAUCt and 90% confidence intervals which are not within acceptable limits for LCmax. Since the GRP*TRT interaction is statically significant, the 5 groups were examined separately. When analyzed individually, all groups resulted in confidence intervals which are not with acceptable limits. The single-dose, fasting bioequivalence study (Study NA331) is not acceptable. Please repeat the study and submit your results to the agency for review.

Sincerely yours,

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

CC: ANDA 40-620
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Final with Dates)
HFD-650/ C.T. Jung CJ 03/13/2006
HFD-650/ Y.C. Huang YH 3/14/2006
HFD-650/ D. Conner DC 3/15/06
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Printed in final on 03/13/2006

BIOEQUIVALENCE -DEFICIENCY

Submission date: 12/22/2005

1. STUDY AMENDMENT (STA)

OIC

Strength: 80 mg/mL and 40 mg/mL
Outcome: IC

OUTCOME DECISIONS: **IC - Incomplete**

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	40-620
Drug Product Name	Methylprednisolone Acetate Injectable Suspension, USP
Strength	40 mg/mL & 80 mg/mL (Multi-Dose Vial)
Applicant Name	Sicor Pharmaceuticals
Address	Irvine, CA
Submission Date(s)	April 12, 2006
Amendment Date(s)	
Reviewer	Connie T. Jung
First Generic	No
File Location	**V:\firmsnz\Sicor\ltrs&rev\40620A0406.doc**

REVIEW OF AN AMENDMENT

I. Executive Summary

This amendment contains the firm's response to deficiencies issued by the Division of Bioequivalence. The firm previously submitted a single-dose, 2-way crossover fasting bioequivalence (BE) study comparing the test product, Methylprednisolone Acetate Injectable Suspension USP, 80 mg/mL (Multi-dose), with the RLD product, Pharmacia & Upjohn's Depo-Medrol® Suspension, 80 mg/mL (Multi-dose). Final statistical analysis was conducted on 61 subject that were dosed as 5 groups. The analysis showed a statistically significant group-by-treatment (GRP*TRT) interaction for LAUCt only. Based on evaluations of potential group differences, the DBE feels that the firm made sufficient efforts to randomize all subjects in each group and that there is no specific cause for the group effects observed. The DBE accepts the statistical analytical results of LAUCt, retaining the GRP*TRT interaction term in the statistical model, and statistical analytical results of LAUC∞ and LCmax, excluding the GRP*TRT interaction term. The results in the fasting study were (point estimate, 90% CI) LAUCt of 0.90, 82.8 – 98.5%, AUC∞ of 0.99, 91.4 – 106.9%, and LCmax 0.96, 80.8 – 113.4% for methylprednisolone. The single-dose, fasting bioequivalence study (Study NA331) is acceptable.

The firm previously submitted acceptable dissolution testing on both strengths, and the 40 mg/mL test product is proportional to the 80 mg/mL test product which has undergone acceptable bioequivalence testing. The waiver request for the 40 mg/mL strength is granted. The submission is acceptable pending the outcome of the DSI inspection.

II. Table of Contents

III. Submission Contents

A. Response to Deficiencies

1. ***The DBE does not agree with your reasoning for dropping the group-by-treatment interaction (GRP*TRT) term from your statistical analysis. SAS statistical analysis conducted on the re-analyzed data (n=61) showed a statistically significant (p<0.1) group-by-treatment (GRP*TRT) interaction for LAUCt and 90% confidence intervals which are not within acceptable limits for LCmax. Since the GRP*TRT interaction is statically significant, the 5 groups were examined separately. When analyzed individually, all groups resulted in confidence intervals which are not with acceptable limits. The single-dose, fasting bioequivalence study (Study NA331) is not acceptable. Please repeat the study and submit your results to the agency for review.***

Firm's Response: Sicor reported the following response from the contract research organization , (b) (4) that conducted Study NA331.

Statistical analysis was initially conducted by (b) (4) including the group-by-treatment interaction term in the statistical model for subjects without significant pre-dose levels (n=61). A statistically significant group-by-treatment interaction was observed for LAUCt, but not with LAUC∞ and LCmax. (b) (4) states that it believes inclusion of the group-by-treatment interaction term in the statistical model for LAUCt is the correct and led to a 90% confidence interval for geometric mean test-to-reference ratio of 82.7 to 98.5 %, demonstrating bioequivalence of the test and reference products.

(b) (4) feels that it is statistically correct to exclude the group-by-treatment interaction term from the statistical model for the evaluations of LAUC∞ and LCmax, resulting in 90% confidence intervals on the geometric mean test-to-reference ratios within the bioequivalence limits of 80-125 %.

[redacted] further evaluated reasons for the statistically significant group-by-treatment interaction for LAUCt by examining all permutations of excluding one of the five dosing groups in the statistical analysis. It found that when Group 4 was excluded from the analysis, that the significance of the group-by-treatment interaction term disappeared ($p>0.05$). [redacted] did not determine any demographic characteristics that differentiated the 8 subjects in Group 4 compared to the other subjects in the other groups. Further inspection of the individual AUCt test-to-reference ratios in Group 4, showed that Subject # 158 represented an extreme case, and the [redacted] referred to this as a statistical anomaly. This was evaluated by conducting statistical analysis of the larger dosing groups (Groups 1, 2, and 3) including Subject # 158 in each. When this subject was moved to the larger groups, in all three analyses, the group-by-treatment interaction term was not detected as statistically significant. [redacted] explains that the statistical significance in the group-by-treatment interaction term for LAUCt was due to the influence of a single subject (in this case, Subject # 158) upon a small dosing group. If this subject, by chance, had been dosed in one of the larger groups, no group-by-treatment interaction issues would have been raised. [redacted] stated that statistical analyses conducted with conducted without the group-by-treatment interaction term and excluding Group 4 showed that the test and reference products are bioequivalent.

Based on this information, Sicor contends that its bioequivalence study (NA331) demonstrates bioequivalence and that it does not need to repeat the study. (Note: the firm did not submit any of the above listed statistically data in the submission)

Reviewer's Comment: Current DBE statistical practices for analyzing LAUCt, LAUC∞ and LCmax of bioequivalence studies with multiple treatment groups include:

1) *conduct statistical analysis including the group-by-treatment interaction term*
2) *if no significant group-by-treatment interaction is observed, the group-by-treatment interaction may be dropped from the statistical modes*
3) *if a significant group-by-treatment interaction is observed, the group-by-interaction term should remain in the model*
    - *Reviews conducted on a case-by-case basis will determine whether there is sufficient statistical reasoning to accept the data*
    - *FDA will decide whether the test product has met bioequivalence criteria based on statistical analysis of one of the groups*

Previous reviews and amendments of this submission have followed this procedure. The DBE concurs with the firm's statement that statistical analysis of the 61 qualifying subjects resulted in a statistically significant group-by-treatment (GRP*TRT) effect for LAUCt only (not for LAUC∞ and LCmax). Due this significance, the 5 dosing groups were analyzed separately by the reviewer, and resulted in none of the groups passing the 90% confidence intervals limits. The reviewer evaluated potential group differences in the December 2005 amendment review (40620A1205.doc). Although different recruitment sites were used (Fort Myers, FM and Temple Terrace, TT), all subject were enrolled and dosed at the same clinical site. The evaluation of each group showed that each group (except for Group 5 that only had 2 subjects from TT) were comprised of

subjects from both recruitment sites, and that the firm made a decent attempt to mixed these subjects in each group. A thorough breakdown of the subject demographics were also examined for each group. Mean values of age and weights were similar between groups, and only slight differences were observed in gender and race categories. The majority of the subjects were male, and either Caucasian or Hispanic race. Based on these evaluations, the DBE feels that the firm made sufficient efforts to randomize all subjects in each group and that there is no specific cause for the group effects observed.

The DBE accepts the statistical analytical results of LAUCt, retaining the GRP*TRT interaction term in the statistical model, and statistical analytical results of LAUC∞ and LCmax, excluding the GRP*TRT interaction term. The 90% confidence intervals from this analyses are summarized below:

Parameter	Test	Reference	T/R	90% CI
AUC0-t	2932.17	3245.94	0.90	82.84 – 98.50 %

Parameter	Test	Reference	T/R	90% CI
AUC∞	3607.64	3651.02	0.99	91.37 – 106.86 %
Cmax	10.67	11.17	0.96	80.80 – 113.04 %

More detailed information of the statistical analyses are available in the Appendix of this review or from previous reviews. Based on these results, the 90% confidence intervals for the test to reference ratios of the natural long-transformed parameters, AUCt, AUC∞, and Cmax are within acceptable limits of 80-125%. The single-dose fasting bioequivalence study on Methylprednisolone Acetate Injection Suspension (80 mg/mL) is now acceptable.

Additional Reviewer Comments: Further inspection and statistical analysis conducted by (b) (4) manipulating data of Group 4 and Subject # 158, is not valid. The FDA discourages the deletion of statistical anomalies or outliers, due to these subjects could indicate product failure or the applicant may be biased in selecting and excluding potential outliers. The applicant can demonstrate that a response is truly aberrant by conducting a re-dosing study. It should be noted that the Re-Dosing Study # OA369 previously submitted by Sicor did not include Subject # 158, had highly variable results and was inconclusive.

D. Waiver Request(s)

Strengths for which waivers requested	40 mg/mL
Regulation cited	21 CFR 320.22
Proportional to strength tested in vivo (yes or no)	Yes
Dissolution is acceptable (yes or no)	Yes
Waiver granted (yes or no)	Yes

Note: Dissolution testing and the formulations were previously reviewed and found acceptable. The formulation has been included in the Appendix Section.

E. Recommendations

1. The single-dose, fasting bioequivalence study conducted by Sicor Pharmaceuticals, Inc. on its Methylprednisolone Acetate Injectable Suspension (Multi-dose), USP, 80 mg/mL (lot # X02C605P2) comparing it to Pharmacia & Upjohn's Depo Medrol® Injectable Suspension (Multi-dose), USP, 80 mg/mL (lot # 45HXS), is **acceptable**.

2. The *in vitro* dissolution testing conducted by Sicor on its Methylprednisolone Acetate Injection Suspension (Multi-dose) , USP, 80 mg/mL, lot # X02C605P2, is acceptable.

   The dissolution testing should be conducted in 900 mL water using Apparatus 2 (Paddle) at 50 rpm. The test products should meet the following **interim specifications:**

   For the 40 mg/mL strength:
   1 hour: (b) (4)
   4 hours: NLT (b) (4)
   For the 80 mg/mL strength:
   1 hour: (b) (4)
   4 hours: NLT (b) (4)

   The specifications listed above are for these test products only.

3. The 40 mg/mL strength (multi-dose) test product is proportionally similar to the 80 mg/mL (multi-dose) strength test product which has undergone acceptable in vivo bioequivalence testing. The waiver of *in vivo* bioequivalence study requirements for the 40 mg/mL strength is granted.

The firm should be informed of the above recommendations.

Connie T. Jung, Ph. D. — 07/27/2006
Reviewer, Branch IV — Date

Yih-Chain Huang, Ph. D. — 7/27/2006
Team Leader, Branch IV — Date

Dale P. Conner, Pharm. D. — 7/31/06
Director, Division of Bioequivalence — Date
Office of Generic Drugs

IV. Appendix

A. Summary of Statistical Analysis of (Study NA331) conducted by reviewer

1. Results of group statistical analysis including group-by-treatment interaction term (GRP*TRT) in the statistical model are listed in Table 1. A statistically significant (p = 0.0318) GRP*TRT interaction was found for LAUCt. The 90 % confidence for LCmax does not fall within the acceptable limits of 80-125%. If the GRP*TRT term is dropped from the model, the 90% confidence intervals for LAUCt, LAUC∞, and LCmax would be within the acceptable limits. (NOTE: When the term is statistically significant, under the current DBE practice, it is not appropriate to drop it from the statistical analysis.). The results are summarized in Table 1. It should be noted that the 90% CI results for LAUCt are within the acceptable limits of 80-125%.

Table 1 Least Squares Geometric Means and 90% Confidence Intervals (n=61)

Parameter	Test	Reference	T/R	90% CI
AUC0-t	2932.17	3245.94	0.90	82.84 – 98.50 %
AUC∞	.	.	.	.
Cmax	10.60	11.24	0.94	77.93 – 114.28 %

2. Due to the statistically significant GRP*TRT, the dosing groups were analyzed separately. Analysis on Group 5 was not conducted because it consisted of only 2 subjects. The results are summarized in Tables 2-5. For Groups 1-3, the 90% confidence intervals for LCmax do not fall within the acceptable limits. For Group 4, neither LAUCt or LCmax resulted in 90% confidence interval which fell within the acceptable limits. The reviewer previously examined demographic and recruitment site information, and did not find any significant differences in these factors. All subjects were treated at the same clinical site. No specific cause for the group effect could be determined after review of the clinical and demographic data.

Table 2 Least Squares Geometric Means and 90% Confidence Intervals GROUP 1 (n=17)

Parameter	Test	Reference	T/R	90% CI
AUC0-t	3221.33	3407.12	0.95	87.94 – 101.65 %
AUC∞	4018.18	3892.21	1.03	94.80 – 112.42 %
Cmax	12.20	13.91	0.88	70.93 – 108.44 %

Table 3 Least Squares Geometric Means and 90% Confidence Intervals GROUP 2 (n=15)

Parameter	Test	Reference	T/R	90% CI
AUC0-t	3242.38	3363.78	0.96	87.09 – 106.69 %
AUC∞	3840.18	3681.21	1.04	92.86 – 117.19 %
Cmax	10.64	11.60	0.92	75.59 – 111.28 %

Table 4 Least Squares Geometric Means and 90% Confidence Intervals
GROUP 3 (n=19)

Parameter	Test	Reference	T/R	90% CI
AUC0-t	2926.83	2811.58	1.04	89.43 – 121.17 %
AUC∞	3297.48	3616.25	0.91	80.37 – 103.45 %
Cmax	11.24	9.45	1.19	83.08 – 170.23 %

Table 5 Least Squares Geometric Means and 90% Confidence Intervals
GROUP 4 (n=8)

Parameter	Test	Reference	T/R	90% CI
AUC0-t	2282.84	3280.24	0.70	51.64 – 93.79 %
AUC∞	.	.	.	.
Cmax	8.01	11.05	0.72	44.82 – 117.23 %

3. Results of statistical analysis excluding the group-by-treatment interaction term (GRP*TRT) in the statistical model are listed in Table 6. The 90 % confidence for LAUC∞ and LCmax fall within the acceptable limits of 80-125%.

Table 6 Least Squares Geometric Means and 90% Confidence Intervals (n=61)

Parameter	Test	Reference	T/R	90% CI
AUC0-t	2983.15	3190.47	0.94	86.22 – 101.40 %
AUC∞	3607.64	3651.02	0.99	91.37 – 106.86 %
Cmax	10.67	11.17	0.96	80.80 – 113.04 %

B. SAS Analysis

	SAS Program	SAS Data	SAS Output
Fasting Study NA331 (n=61) Including GRP*TRT term	GRP_NEWDATASUB61_DEC05AMENDprogr	40260NEWDATA158.xls	GRP_NEWDATASUBJ61_DEC05AMEND.txt
Fasting Study NA331 (n=61) Excluding GRP*TRT term	NOGRP_NEWDATASUB_DEC05AMENDpro		NOGRP_NEWDATASUBJ61_DEC05AMEND

C. Formulation Data

Formulation for Sicor's Methylprednisolone Acetate Inj. Suspension, USP (Multi-Dose Vial)

Component	Function	80 mg/mL Vial 5 mL fill		40 mg/mL Vial 5 mL fill		40 mg/mL Vial 10 mL fill
		amount	%	amount	%	amount
Methylprednisolone Acetate, USP	Active	400 mg	(b) (4)	200 mg	(b) (4)	400 mg
Polyethylene Glycol 3350	(b) (4)	141 mg		146 mg		291 mg
Benzyl Alcohol, NF		44.4 mg		45.8 mg		91.6 mg
Polysorbate 80, NF		9.4 mg		9.7 mg		19.4 mg
Sodium Chloride, USP	Isotonicity Agent	(b) (4)				
Monobasic Sodium Phosphate, (b) (4) USP	(b) (4)	33 mg	(b) (4)	34 mg	(b) (4)	68 mg
Dibasic Sodium Phosphate, (b) (4) USP		6.9 mg		7.1 mg		14.2 mg
Sodium Hydroxide, NF	pH adjuster	pH adjust	-	pH adjust	-	pH adjust
Hydrochloric Acid, NF	pH adjuster	pH adjust	-	pH adjust	-	pH adjust
(b) (4)						

(Reviewer generated table, since the table provided by the firm did not contain %wt.)

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 40-620 APPLICANT: Sicor Pharmaceuticals

DRUG PRODUCT: Methylprednisolone Acetate Injectable Suspension (Multi-dose) USP, 40 mg/mL and 80 mg/mL

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

The DBE concurs with the following dissolution method and specifications.

The dissolution testing should be conducted in 900 mL water using Apparatus 2 (Paddle) at 50 rpm. The test products should meet the following **interim specifications**:

For the 40 mg/mL strength:
1 hour: (b) (4)
4 hours: NLT (b) (4)
For the 80 mg/mL strength:
1 hour: (b) (4)
4 hours: NLT (b) (4)

Please note that the specifications listed above are for these test products only.

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,

Richard M Davit

for

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

CC: ANDA 40-620
ANDA DUPLICATE
DIVISION FILE
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DRUG FILE

Endorsements: (Final with Dates)
HFD-650/ C.T. Jung CTJ 07/27/2006
HFD-650/ Y.C. Huang YH 7/27/2006
HFD-650/ D. Conner BMD 7/31/06

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Printed in final on 07/27/2006

BIOEQUIVALENCE - ACCEPTABLE

Submission date: April 12, 2006

1. STUDY AMENDMENT (STA) OK

Strength: 80 mg/mL and 40 mg/mL
Outcome: AC

OUTCOME DECISIONS: **AC – Acceptable**

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	40-620
Drug Product Name	Methylprednisolone Acetate Injectable Suspension, USP
Strength	40 mg/mL & 80 mg/mL (Multi-Dose Vial)
Applicant Name	Sicor Pharmaceuticals
Address	Irvine, CA
Submission Date(s)	August 06, 2006
Amendment Date(s)	
Reviewer	Connie T. Jung
First Generic	No
File Location	**V:\firmsnz\Sicor\ltrs&rev\40620O0806.doc**

REVIEW OF A DSI REPORT

I. Executive Summary

This amendment is a review of the findings by the Division of Scientific Investigations (DSI) during a for-cause inspection of the clinical site, SFBC (Ft. Myers and Temple Terrace, FL), used for Study NA331. DSI found several inconsistencies in record keeping and documentation, enrollment of subject that were unwilling to adhere to the protocol, failure to document frozen storage of study blood samples, and failure to ensure condition of study blood samples during transfer. DSI concludes that the integrity of out patient study samples collected at the Temple Terrace site were not assured and should be excluded from the bioequivalence determination. The reviewer agreed with the recommendations from DSI to exclude subject data collected at this site from the re-analysis. Final statistical analysis was conducted on 36 subjects. The results of the single-dose, 2-way crossover fasting bioequivalence (BE) study (point estimate, 90% CI) are LAUCt of 1.00, 89.38 – 112.10%, AUC∞ of 0.97, 90.52 – 104.24%, and LCmax 1.01, 84.60 – 119.96% for methylprednisolone. The fasting BE study (Study NA331) was previously found to be acceptable (40620A0406.doc). Re-analysis based on the DSI recommendations to exclude data samples collected at Temple Terrace shows that the fasting BE study remains acceptable. No further action is needed.

II. Table of Contents

III. DSI Findings

1. Numerous documentation inconsistencies were found. For example:

a. the pre-dose blood samples for Subject 049 was centrifuged one minute prior to the sample being collected

b. the pre-dose blood sample for Subject 137 was collected 8 minutes post-dose

c. study forms to summarize medication use and adverse events were not completed until approximately two months after the last PK sample was drawn (Subjects 045, 064, 083, 120, 124, 158, 159)

d. records of blood sample processing on 02/17/2004 list the subject but not the sample number/time point that were processed for Subjects 145-149 and 152-162)

In SFBC's May 05, 2006 response, the firm stated that documentation errors occurred and the clinic staff did not realize prior to dosing that a pre-dose sample was not drawn for Subject 137 (item 1b), and the subject was a last minute alternate. In light of the time discrepancies for Subject 049 and 137, the period 1 pre-dose samples on 12/30/2003 and 01/21/2004 respectively, should not be considered valid. The firm needs to improve their record keeping practices.

2. Subjects were enrolled although they were unwilling to adhere to the protocol
The protocol required subjects to abstain from strenuous physical activity for at least seven days after each drug administration (Section IVB.B.2.b(5)). When asked "Are you willing to avoid strenuous physical activity?", the documented answer for Subjects 011 through 016 was "no" (included in the report as an attachment, Exhibit 1). In SFBC's May 05, 2006 response, SFBC suggested that the clinic staff inadvertently checked "no" instead of "yes" because the preceding questions on the check-in form required an answer of "no" for study participation.

Additional Issues

- Statistical analysis of the study data (n=146 subjects) by FDA found significant group-by-treatment interaction for LAUCinf (compared to LAUCt reported by the sponsor). The FDA investigator reports that no evidence was found to suggest that recruitment procedure differed between the two sites. Subjects screened at Temple Terrance were not re-screened at Ft. Myers. Also, no discrepancies were observed between the source data and case report forms (CRFs) for demographic information and recent participation in other studies.

- The study report indicated that Subject 082 received the test treatment for both periods. SFBC informed the FDA investigator that they made an error and documented it as a protocol deviation. This was documented and the reviewer did not include this subject in the analysis.
- The OGD reviewer expressed concern regarding the firm's procedure for recording source data since the submitted CRFs lacked dated signatures/initials. The investigator found the source data was recorded manually with entries signed and dated, and were transcribed to the electronic forms.

3. Failure to document frozen storage of pharmacokinetic (PK) blood samples
Although Temple Terrance began collecting study samples for Study NA331 on 12/02/2003, the site did not keep a freezer log of sample storage until 03/02/2004. Furthermore, the freezer charts did not recorded degrees in Celsius or Fahrenheit. Although the site stated that the temperatures should be recorded in Celsius, the investigator found that the records were in Fahrenheit. The clinic staff informed the investigator that the freezer was not working properly, and for the duration of outpatient PK sample collection, there were consistent warmer temperatures spikes every 8 hours ranging from 0 to -10° (included in the report as an attachment, Exhibit 2). Also the firm lacked calibration records to reflect actual freezer conditions. Due to these deficiencies, the actual storage conditions of the PK samples collected at the Temple Terrance site cannot be assured. The clinical site promised corrective action for future studies.

4. No record regarding the transfer of PK samples from Temple Terrace to Ft. Myers
The conditions of the PK sample during shipment and upon receipt to Ft. Myers is unknown.

5. Inconsistencies in source documentation
Examples of the inconsistencies included 1) blood sample collection times occurred when subjects were not documented as present in the facility, 2) samples were processed and frozen prior to the documented blood sample collection time, 3) processing records were incomplete or missing for some samples. The accuracy of the blood collection and processing times cannot be assured.

6. Issues regarding electronic CRFs
SFBC recorded source data manually and transcribed the information into electronic CRFs. The FDA investigator found that the CRF database ((b) (4)) was not validated and users could bypass the audit trail function. There was no documentation to indicate that the verified CRFs were the version sent to the study sponsor. It should be noted that the investigator did not find any significant discrepancies between the source data and the CRFs. According to the SFBC's February 24, 2006 response, they have stopped using the (b) (4) CRF database.

7. Procedure for documenting start and stop dates for medication or medical history is deficient

SFBC would document an arbitrary date, if a subject could not recall the precise date of a medical event. SFBC responded that they will revise their procedure and enter "unknown, year".

DSI Conclusions: DSI concluded that the integrity of the outpatient PK samples collected at Temple Terrace was not assured (items 3 and 4) and should be excluded from the bioequivalence determination. Furthermore, the accuracy of times recorded for various study events at the Temple Terrance site is questionable due to inconsistencies in source documentation (item 5). DSI also recommended that the reviewer consider the impact of subjects that did not commit to abstention from strenuous physical activity within 7 days post-dose on study outcomes (item 2).

IV. Reviewer Comments:

1. The DBE previously found the fasting study (NA331) acceptable, based on statistical analysis of 61 subjects (40620A0406.doc).

2. Based on the DSI findings, it is clear that the firm did not correctly report that the clinical portions of the study were carried out at both sites, Ft. Myers and Temple Terrance. In its original submission, the firm stated that the clinical site was only Ft. Myers. Although all subjects were dosed at the Ft. Myers site, outpatient samples were collected at the Temple Terrace site. These outpatient samples are considered part of the clinical study.

3. The reviewer agrees with the recommendation from DSI to exclude the PK samples collected at the Temple Terrace site due to the inconsistencies in documentation, failure to ensure proper frozen storage conditions, and failure to ensure proper transfer of sample from Temple Terrance to Ft. Myers. The reviewer will re-analyze the study data and report results in Section IV.

4. Although clinic staff at SBFC has provided inadequate excuses for their failure to adhere to study protocol (i.e. pre-screening questioning), the reviewer feels that the protocol deviation potential of Subjects 011 through 016 not willing to abstain from strenuous physical activity within 7 days post-dose would not affect the study outcome, therefore no adjustment in the analysis is needed for this factor.

5. Since the investigator did not find any significant discrepancies between the source data and the electronic CRFs, there are no further concerns regarding electronic CRFs for this study.

V. Reanalysis Based on DSI Recommendations

Based on the recommendations from DSI, the following samples that were collected at the Temple Terrace site for Periods 1 and 2 (48-648 hours post-dose) were excluded from the statistical analysis (Table 1). It should be noted that some of these subjects have already been excluded from the analysis due to pre-dose drug levels greater than 5% of the Cmax.

Table 1 PK Samples Excluded (48-648 hrs post dose)

GROUP	Subject
1	11-19
2	58-79, 81-83
3	111-130
4	145-162
5	168-170

After excluding the PK samples mentioned above, the reviewer determined that 25 subjects were not eligible for statistical analysis due to insufficient sampling for characterizing the pharmacokinetic profile. Based on the study results for this product and for the firm's single-dose product (ANDA # 40-557), the apparent Tmax is approximately 40-50 hours. If samplings at 48-648 hours are excluded, the last sampling time point for those subjects affected was at 24 hours, which was likely before the Tmax was reached. Therefore, final statistical analysis was conducted on 36 subjects. Since there was no indication of differences in recruitment procedures and no obvious demographic differences between the two recruitment sites, the group-by-treatment (GRP*TRT) interaction term was dropped from the statistical model. Statistical analysis was conducted using the PK parameters and concentration data provided by the firm, and the results are summarized in Tables 2-4.

Table 2 Arithmetic Mean Pharmacokinetic Parameters (n=36)

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC_{0-t}	ng.hr/mL	2982.60	30.68	3114.78	34.58	0.96
AUC_{∞}	ng.hr/mL	3649.33	27.05	3834.88	27.97	0.95
Cmax	ng/mL	11.94	52.60	11.40	38.22	1.05
Tmax	hrs	57.64	173.10	55.31	192.93	1.04
kel	hrs^{-1}	0.004	47.38	0.005	78.86	0.86
$T_{1/2}$	hrs	195.80	47.48	198.70	57.66	0.99

Table 3 Least Squares Geometric Means and 90% Confidence Intervals (n=36)

Parameter	Test	Reference	T/R	90% CI
AUC0-t	2881.80	2878.98	1.00	89.38 – 112.10 %
AUC∞*	3533.41	3637.48	0.97	90.52 – 104.24 %
Cmax	10.36	10.29	1.01	84.60 – 119.96 %

*See Comments Below

Table 4 Additional Study Information for Analysis

Root mean square error, AUC0-t	0.267850
Root mean square error, AUC∞	0.138788
Root mean square error, Cmax	0.412995
Ke and AUCi determined for how many subjects?	25
Do you agree or disagree with firm's decision?	Agree

Comments on Pharmacokinetic Analysis:
After excluding the 25 subjects affected, the 90% CI for LAUCt, LAUCi, and LCmax remain within the acceptable limits.

Conclusion: The single-dose fasting bioequivalence study is acceptable.

VI. Recommendations

1. The single-dose, fasting bioequivalence study conducted by Sicor Pharmaceuticals, Inc. on its Methylprednisolone Acetate Injectable Suspension (Multi-dose) USP, 80 mg/mL (lot # X02C605P2) comparing it to Pharmacia & Upjohn's Depo Medrol® Injectable Suspension (Multi-dose) USP, 80 mg/mL (lot # 45HXS), remains acceptable after exclusion of study samples collected at the Temple Terrance site. No further action is required..

Connie T. Jung, Ph. D. — Date 09/19/2006
Reviewer, Branch IV

Yih-Chain Huang, Ph. D. — Date 9/19/2006
Team Leader, Branch IV

Dale P. Conner, Pharm. D. — Date 9/19/06
Director, Division of Bioequivalence
Office of Generic Drugs

VII. Appendix

A. SAS Data

FASTING STUDY	SAS DATA	SAS PROGRAM	SAS OUTPUT
Reanalysis post DSI (n=36) no GRP*TRT interaction term	 40260NEWDATA158 postDSI.xls	 SASProgramPOSTDSI .txt	 POSTDSIDROPADDL. TXT

CC: ANDA 40-620
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Final with Dates)
HFD-650/ C.T. Jung CTJ 09/19/2006
HFD-650/ Y.C. Huang YCH 9/19/2006
HFD-650/ D.P. Conner DPC 9/19/06

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Printed in final on 09/19/2006

BIOEQUIVALENCE - ACCETABLE Submission date: August 09, 2006

1. OTHER (OTH) OIC Strength: 80 mg/mL and 40 mg/mL
Review of DSI Report **Outcome: AC**

US Document (with additional statistical data analysis)

OUTCOME DECISIONS: **AC** - Acceptable

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 40-620	**SPONSOR:** Sicor Pharmaceuticals
DRUG & DOSAGE FORM:	Methylprednisolone Acetate Injection Suspension USP
STRENGTH(S):	80 mg/mL and 40 mg/mL
TYPES OF STUDIES:	Fasting BE study
CLINICAL STUDY SITE(S):	SFBC Ft. Myers, Inc. 3745 Broadway Ave., Suite 100, Fort Myers, FL 33901
ANALYTICAL SITE(S):	(b) (4)
STUDY SUMMARY:	Acceptable fasting BE study
DISSOLUTION:	Acceptable dissolution testing method and interim specification: 900 mL water using Apparatus 2 (Paddle) at 50 rpm. The test products should meet the following **interim specifications:** For the 40 mg/mL strength: 1 hour: (b) (4) 4 hours: NLT (b) (4) For the 80 mg/mL strength: 1 hour: (b) (4) 4 hours: NLT (b) (4)
WAIVER(S):	Waiver is granted for the 40 mg/ml strength Methylprednisolone Acetate Injection Suspension

DSI INSPECTION STATUS

Inspection needed:	NO	**Inspection status:**	**Inspection results:**
First Generic	NO	Clinical site was inspected in 2006. Analytical site was last inspected on April 2004.	
New facility			
For cause			
Other			

Proposed Dissolution Method and Specifications from Original Submission Acceptable?

Yes _____ No X (If no, project Manager should verify and sign below when acknowledgement amendment is received)

DBE Dissolution Method and Specifications acknowledged by firm? N/A Yes X No ___

AMENDMENT DATE: December 22, 2005

PROJECT MANAGER: _____ **DATE:** _____

PRIMARY REVIEWER: Connie T. Jung, Ph. D **BRANCH:** IV
INITIAL: CTJ DATE: 09/19/2006

TEAM LEADER: Yih-Chain Huang, Ph. D **BRANCH:** IV
INITIAL: YCH DATE: 9/19/2006

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.
INITIAL: DPC DATE: 9/22/06