CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

50-763

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	50-763	SUBMISSION DATES March 20, 2002
DRUG NAME:	MITOExtra™ (mitomycin for injection)	
DOSAGE STRENGTH:	Solution for injection, 5 mg per vial	
APPPLICANT:	SuperGen, Inc. Two Annabel Lane, Suite 220, San Ramon, CA 94583	
REVIEWER:	John Duan, Ph.D.	
TEAM LEADER:	Atiqur Rahman, Ph.D.	
TYPE OF SUBMISSION:	NDA resubmission	

I. Executive Summary

MITOExtra has the same active ingredient, mitomycin, USP, as in the approved NDA 50-450, Mutamycin by Bristol-Myers Squibb. The proposed product differs from the approved drug product with respect to the inactive ingredient, hydroxypropyl-β-cyclodextrin (HPBCD) used as a vehicle to enhance solubility of mitomycin instead of Mannitol, USP. Currently mutamycin is approved for the treatment of disseminal adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed.

MITOExtra (NDA 50-763) was submitted on December 10, 1997. The information presented was found to be inadequate and the application was not approvable because there was insufficient evidence to conclude that MITOExtra was bioequivalent to Mutamycin. The Agency made several comments and requested for additional information in a resubmission. The Clinical Pharmacology and Biopharmaceutics request includes a reanalysis of the bioequivalence study using statistical procedures described in the Agency's guidance document and a pharmacokinetic study in consecutive cycles of therapy.

The current resubmission of NDA 50-763 presents a study report on the reanalysis of the bioequivalence study and a study report on a clinical study including the pharmacokinetic information in consecutive cycles of therapy. The reanalysis used two one-sided tests and one patient (#28) was excluded from the analysis. The results showed bioequivalence between MITOExtra and mutamycin. The pharmacokinetic study conducted in consecutive cycles showed similar pharmacokinetic behavior between different cycles. Based on these studies, the applicant fulfills the requirements in the nonapprovable letter from Clinical Pharmacology and Biopharmaceutics perspective.

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 50-763 resubmission and find the Clinical Pharmacology and Biopharmaceutics information acceptable. The following comments should be sent to the applicant.

1. The Clinical Pharmacology section of the package insert should be revised based on the results from bioequivalence study. Please see labeling recommendations.

2. The Clinical Pharmacology part of report for study ME2 was poorly generated. One example is that the graph of concentration time profile for patient OAR in cycle 1 was repeated for 202 times with bad quality.

Comments to the medical officer

The statistical procedure of two one-sided test was employed in the reanalysis as requested in the non-approvable letter. The bioequivalence between MITOExtra and Mutamycin was demonstrated after one patient (patient #28) was excluded from the analysis.

1. The exclusion of patient #28 from the analysis is reasonable based on the following considerations.

   - Mitomycin is extensively metabolized. It is rapidly inactivated in the liver and in adults, less than 10% of an IV dose is excreted in urine as active drug. Patient #28 had metastatic liver cancer and left hepatic lobectomy . The metabolic profile of this patient may be affected and different from other patient.

   - The patient had many coadministrated medications. These medications may affect the pharmacokinetics of mitomycin.

   - The patient was in unstable conditions during the bioequivalence study regarding the physical condition and laboratory tests.

   - In mitomycin C treatment cycle, the patient had Cmax and AUC values at 1.5 to 2 times the expected values. In MitoExtra treatment cycle, these values were 4 to 5 times higher.

2. The pharmacokinetic study conducted in consecutive cycles showed similar pharmacokinetic behavior between different cycles.

Labeling Recommendations

The Clinical Pharmacology Section should make the following changes.

draft

/S/

John Duan, Ph.D.
Reviewer
Division of Pharmaceutical Evaluation I

Date

/S/

Atiqur Rahman, Ph.D.
Team Leader
Division of Pharmaceutical Evaluation I

Date

CC: NDA 50-763 original
HFD-150 Division File
HFD-150 BAtkins

HFD-150 Nscher, DGriebel
HFD-860 MMehta, CSahajwalla, ARahman, JDuan
CDR

II. Table of Contents

III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

MITOExtra has the same active ingredient, mitomycin, USP, as in the approved NDA 50-450, Mutamycin by Bristol-Myers Squibb. Mutamycin (Mitomycin for injection, USP) has been approved and marketed in the US since 1973 for the treatment of disseminal adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed. Mitomycin is a highly toxic drug substance, which causes myelosuppression, thrombocytopenia, and leukopenia in cancer patients.

MITOExtra is a new parenteral formulation of mitomycin. In this new formulation inactive ingredient, hydroxypropyl-β-cyclodextrin (HPBCD) has substituted Mannitol, USP. The new formulation provides pharmaceutical advantages in terms of ease of reconstitution and more prolonged shelf life after reconstitution. The applicant referred to their preclinical pharmacokinetic and bioavailability studies in rats and mice where they have found that MITOExtra and Mutamycin were bioequivalent.

MITOExtra (NDA 50-763) was submitted on December 10, 1997. The applicant submitted a study to show the bioequivalence between MITOExtra and Mutamycin in patients with solid tumors. Both drugs were administered intravenously to 35 evaluable cancer patients in an open-label, two-way crossover study design with two treatment arms with 6-week wash-out period prior to crossover. The treatment arms were MITOExtra and Mutamycin administered as single dose infusions over approximately 30 minutes at a dose of 15 mg/m^2. Individual body weights and heights were obtained prior to dosing for calculation of body surface area. Blood samples were collected for serum preparation, and urine samples were collected. Only 25 evaluable patients received both formulation of mitomycin, these patients' data were used to perform the bioequivalence test.

The serum data were analyzed using noncompartemntal methods to determine the pharmacokinetics of mitomycin. The applicant reported various pharmacokinetic parameters AUC_t, AUC_∞, AUMC, C_{max}, CL_{tot}, V_{dss}, $T_{1/2}$, effective $T_{1/2}$, and MRT. For the analysis of bioequivalence, logtransformed AUC_t, AUC_∞, and C_{max} values were used. The applicant has reported that for the assessment of bioequivalence, SAS PROC GLM program with 20/20 rule was applied. The control stream as well as program output were not provided by the applicant, and it was unclear how the values of 90% confidence interval were obtained. Therefore, the previous reviewer performed the bioequivalence assessment test using SAS program for two-way, two-period, two-sequence, crossover study with washout period between two treatments (MITOExtra vs. Mutamycin).

Two one-sided t-test for bioequivalence failed to show bioequivalence of MITOExtra and Mutamycin based on comparisons of AUC_t (CI 96.6 - 129.4%), AUC_∞ (CI 97.3 - 130.9%), and C_{max} (CI 91.5 - 134.0%).

Variability of the pharmacokinetic parameters estimated by the applicant for the MITOExtra treatment arm was higher compared to Mutomycin treatment arm. Coefficients of variation (CV) for MITOExtra were 65% for AUC_t, 64% for AUC_∞, and 86% for C_{max}; whereas, for Mutamycin

CV were 31% for AUC_t, 32% for AUC_∞, and 44% for C_{max}. The mean values of AUC_∞ and C_{max} for MITOExtra were about 18% higher than Mutomycin.

The application was not approvable because there was insufficient evidence to conclude that MITOExtra was bioequivalent to Mutamycin. The Agency made several comments and requested for additional information that should be addressed in a resubmission. Among the requests, the Clinical Pharmacology and Biopharmaceutics aspects include a reanalysis of the bioequivalence study using statistical procedures described in the Agency's guidance document and a pharmacokinetic study in consecutive cycles of therapy.

The current resubmission of NDA 50-763 presents a study report on the reanalysis of the bioequivalence study and a clinical study report including the pharmacokinetic information in consecutive cycles of therapy. The reanalysis used two one-sided tests and one patient (#28) was excluded from the analysis. The exclusion of this patient is reasonable because this patient had metastatic liver cancer and left hepatic lobectomy, and the metabolic profile of this patient may be affected and different from the other patients. In addition, this patient had many co-administered drugs and this patient was in an unstable condition during the bioequivalence study with regard to the physical condition and laboratory tests.

After exclusion of this patient, the results showed bioequivalence between MITOExtra and mutamycin based on comparisons of AUC_t (CI 93.2-121.8%), AUC_∞ (CI 93.9-123.4%), and C_{max} (CI 87.4-120.7%). Further, the variability of parameters for MITOExtra treatment is decreased to the similar extent with that for mutamycin treatment.

The pharmacokinetic study conducted in consecutive cycles showed similar pharmacokinetic behavior between different cycles. The study compared pharmacokinetic data for 23 patients completing cycles 1 and 2 and 10 patients completing cycles 1 and 3. The applicant performed an analysis to show the equivalence of AUC between cycles 1 and 2. Although the equivalence of AUC between cycles 1 and 3 had not been demonstrated, the pharmacokinetic behavior of the drug did not show dramatic differences.

Based on these studies, the applicant fulfills the requirements in the nonapprovable letter from Clinical Pharmacology and Biopharmaceutics perspective.

IV. Question Based Review

1. Why was the application submitted in December 1997 not approvable?

Because there was insufficient evidence to conclude that MITOExtra was bioequivalent to Mutamycin.

The applicant reported in the 1997 submission that statistical analysis was performed using SAS PROC GLM with the model for a two-way crossover design including the following factors: patient, sequence, patient with sequence, period, and treatment. Neither the statistical model (control stream) nor the program output was provided in the submission for review. Moreover, the applicant tested the bioequivalence of MITOExtra and Mutomycin based on 20/20 rule for the confidence interval. This is not an acceptable statistical test for bioequivalence assessment.

Two one-sided test procedure for bioequivalence applied to the pharmacokinetic parameters by the FDA reviewer failed to show bioequivalence of MITOExtra vs. Mutomycin based on comparisons of 90% confidence intervals for AUC_t (96.6 - 129.4%), AUC_∞ (97.3 - 130.9%), and C_{max} (91.5 - 134.0%).

Variability of the pharmacokinetic parameters estimated by the applicant for the MITOExtra treatment arm was higher compared to Mutomycin treatment arm. Coefficients of variation (CV) for MITOExtra were 65% for AUC_t, 64% for AUC_∞, and 86% for C_{max}; whereas, for Mutamycin CV were 31% for AUC_t, 32% for AUC_∞, and 44% for C_{max}. The mean AUC_∞ and C_{max} values for MITOExtra were about 18% higher than Mutomycin.

The applicant had intended to label MITOExta for at least 2-3 cycles of therapy. However, the pharmacokinetics of this new formulation had not been studied in the consecutive cycles of therapy.

Therefore, a nonapprovable letter was issued on December 11, 1998.

2. What additional information was requested from the Applicant if the application be resubmitted?

Following are the requests for additional information from the nonapprovable letter relevant to Clinical Pharmacology and Biopharmaceutics.

A. A re-analysis of study MEO01 should be perfonned using statistical procedures described in the Agency's guidance document entitled, "Statistical Procedures for Bioequivalence Studies Using a Standard Two- Treatment Crossover Design". Additional references include Schuinnann, D. J., J Pharmacokin Biopharm 1987: 715:657-680; and Rosner, B., Hypothesis Testing: Two-Sample Inference in Fundamentals of Biostatistics, PWS-Kent Publishing Co., Boston, MA, third edition. Patients considered outliers on statistical grounds should be further explored from a physiologic standpoint to provide justification for their exclusion from the re-analysis of this study. Alternatively, a new study demonstrating bioequivalence of MITOExtra™ and Mutamycin® should be performed.

B. The pharmacokinetics of MITOExtra™ should be studied in consecutive cycles of therapy as proposed in study ME2. Considering that MITOExtra™, if approved would be administered for multiple cycles and that circulating derivatives of 2-hydroxypropyl-β-cyclodextrin may influence the distribution and elimination of other co-administered drugs, you are encouraged to obtain blood samples for the pharmacokinetic evaluation of MITOExtra™ in the second and/or third cycles of treatment. Alternatively, a repeat cycle toxicology study in animals to confinn that MITOExtra™ does not pose a worse safety profile relative to Mutamycin® could be perfonned. This study should incorporate toxicokinetics.

C. A revised package insert should be submitted that describes the results of bioequivalence and other clinical studies performed with MITOExtra™.

3. Is the reanalysis for bioequivalence study acceptable?

Yes. Two one-sided test was used for the analysis as requested by the Agency. One patient (patient #28) was excluded from the analysis. This exclusion is reasonable based on following considerations.

- Mitomycin is extensively metabolized. It is rapidly inactivated in the liver and in adults, less than 10% of an IV dose is excreted in urine as active drug. Patient #28 had metastatic liver cancer and left hepatic loectomy. The metabolic profile of this patient may be affected and different from other patient.

- The patient had many coadministrated medications. These medications may affect the pharmacokinetics of mitomycin.

- The patient was in unstable conditions during the bioequivalence study regarding the physical condition and laboratory tests.

- In mitomycin C treatment cycle, the patient had Cmax and AUC values at 1.5 to 2 times the expected values. In MitExtra treatment cycle, these values were 4 to 5 times higher.

After the exclusion of this patient, the two formulations demonstrated bioequivalence. The following table shows the statistical results before and after the exclusion.

	N	90% Confidence Interval		
		AUCt	AUCinf	Cmax
Before	25	96.6-129.4	97.2-130.9	91.5-134.0
After	24	93.2-121.8	93.9-123.4	87.4-120.7

In addition, the variability for MITOExra treatment is decreased after the exclusion of the patient. The following tables show the point estimate analysis before and after the exclusion.

Table. Point Estimate Analysis before the Exclusion

Parameter	AUC_t (SD)	CV, %	AUC_∞ (SD)	CV, %	C_{max} (SD)	CV, %
MITOExtra	824 (534)	65	838 (533)	64	918 (791)	86
Mutamycin	701 (216)	31	709 (225)	32	778 (345)	44
Change in mean, %	17.5 ↑		18 ↑		18 ↑	

Table. Point Estimate Analysis after the Exclusion

Parameter	AUC_t (SD)	CV, %	AUC_∞ (SD)	CV, %	C_{max} (SD)	CV, %
MITOExtra	724 (195)	27	738 (198)	27	766 (233)	30
Mutamycin	687 (209)	30	695 (217)	31	774 (352)	45
Change in mean, %	5 .4↑		6.2 ↑		-1 ↑	

As can be seen from the tables, after the exclusion of patient #28, the variability of the parameters for the MITOExtra treatment is decreased and the differences of the means between two treatments are also decreased.

4. What information did the pharmacokinetic study conducted in consecutive cycles provide?

The pharmacokinetic study conducted in consecutive cycles showed similar pharmacokinetic behavior between different cycles. The study compared pharmacokinetic data for 23 patients completing cycles 1 and 2 and 10 patients completing cycles 1 and 3. The applicant performed an analysis to show the equivalence of AUC between cycles 1 and 2. Although the equivalence of AUC between cycles 1 and 3 had not been demonstrated, the pharmacokinetic behavior of the drug did not show dramatic differences.

5. Does the applicant fulfil the requirement in the non-approvable letter from the Clinical Pharmacology and Biopharmaceutics perspective?

Yes. The applicant performed a reanalysis for study ME1 using the statistical method requested in the non-approvable letter and demonstrated the bioeuqivalence between MITOExtra and mutamycin. A pharmacokinetic study was conducted in consecutive cycles as requested. The pharmacokinetics of mitomycin remained unchanged in subesequent cycles after MITOExtra administration. In addition, a revised package insert was submitted including the information of bioequivalence study. Therefore, the applicant has fulfilled the requirement from the Clinical Pharmacology and Biopharmaceutics perspective.

13 pages redacted from this section of the approval package consisted of draft labeling

APPENDIX II. INDIVIDUAL STUDY REVIEW

1. Study ME-001 reanalysis

STUDY TITLE: Addendum to report for a bioequivalence study of MitoExtra and Mutamycin in patients with solid tumors (Clinical study ME001).

REANALYSIS RESULTS:

Data exclusion:
Patient #28 was excluded from the reanalysis. The justification was provided in the following aspects.

Medical History:

- This patient was a 42 year old female with metastatic liver cancer (a history of liver cell carcinoma for more than 16 years) and left hepatic lobectomy (and chemotherapy) at age 26.
- This patient also had a history for more than 18 years of treated hypothyroidism and treated hypertension.
- She also had a history of seizures since age 23, myocardial infarction at age 24, and a hysterectomy at age 36. CT scan in March 1997 showed findings consistent with a previous infarction in the right middle cerebral artery distribution.
- Two years prior to study entry her liver cancer recurred and started to metastasize and she received 5-FU and radiation.
- During the study period she was on numerous concomitant medications (Lasix, Spironolactone for ascites among others, including on the days of pharmacokinetic studies).

Physical Conditions:
After the Mitomycin C dose on March 5, 1997 the patient deteriorated and was admitted on April 15 due to increased nausea/vomiting and tiredness, decreased oral intake. She was found "slightly dry" at physical examination, her serum creatin had risen from 0.8 to 1.5 fig/dL, her serum calcium had increased to 10.3 fig/dL and potassium to 6.4 mmol/L. Her spironolactone was discontinued, she was given IV fluids and furosemide. Three days later, on April18, when MitoExtra was dosed and blood drawn for the pharmacokinetic study, she was still on IV hydration and treated with furosemide. Her serum potassium was 5.4 mmol/L, serum creatin 1.3 fig/dL.

Pharmacokinetics:
In cycle 1 (Mitomycine C) she had Tmax and AUC values at 1.5-2 times the expected values. In cycle 2 (MitoExtra) she had Cmax and AUC values at 4-5 times the expected values.

Therefore, this patient was considered as an outlier.

Pharmacokinetics:

The outputs of the analysis are shown below.

SuperGen Protocol ME 001
Pharmacokinetic Analyses

SPECIFICATIONS

Date: **Thursday, January 14, 1999 at 18:25:43**

Data Set: pksum3x (24 Patients who completed both legs)

Analysis: Means 2x2 Crossover Multi Records/Subject

Subject:
Treatment: TRT (Test: ME)
Sequence: SEQ (Seq 1:TR)
Outcome: AUC

Note: This analysis assumes that there are no carry over effects.

Equivalence Parameter: Difference of Means (Log Scale)

Note: Results are presented for data transformed according to the natural logarithm (ln).

90.0000% Confidence Interval: (-0.0706, 0.1981)
Antilogged 90.0000% Confidence Interval: (0.9318, 1.2191)

Tests Bounds:

	Equivalence Bounds		
Lower Alpha Value	Lower	Upper	Upper Alpha Value
0.0500	-0.2231	0.2231	0.0500

DESCRIPTIVE STATISTICS

Descriptive Statistics:

	Test (Seq 1)	Reference (Seq 1)	Test (Seq 2)	Reference (Seq 2)
Mean	6.5797	6.5178	6.5109	6.4453
Standard Error (Mean)	0.0628	0.0679	0.1009	0.1207
Median	6.6240	6.5813	6.4999	6.5139
Standard Deviation	0.2350	0.2541	0.3190	0.3818
Variance	0.0552	0.0646	0.1018	0.1458
Min				
Max				
Range				

n	14	14	10	10

ANOVA RESULTS

Means:

Least Squares Means for Periods and Treatments:

	Test : ME	Reference : MMC	Test - Reference
Mean Period 1	6.5797	6.4453	0.1344
Std Deviation Period 1	0.2350	0.3818	
Mean Period 2	6.5109	6.5178	-0.0069
Std Deviation Period 2	0.3190	0.2541	

Least Squares Means across Periods by Sequence:

	n	Mean	Std Deviation
TR	14	6.5487	0.2422
RT	10	6.4781	0.3441

Least Squares Means across Sequences by Period:

	Mean	Std Deviation
Period 1	6.5125	0.3047
Period 2	6.5144	0.2763

Least Squares Means across Sequences by Treatment:

	Mean	Std Deviation
Test : ME	6.5453	0.2688
Reference : MMC	6.4815	0.3080
Test - Reference	0.0637	

Overall Mean: 6.5193
Overall Std. Deviation: 0.2877

Geometric Means:

Least Squares Geometric Means for Periods and Treatments:

	Test : ME	Reference : MMC	Test - Reference

SuperGen Protocol ME 001
Pharmacokinetic Analyses

Period 1	720.2897	629.7212	90.5685
Period 2	672.4586	677.1008	-4.6422

Least Squares Geometric Means across Periods by Sequence:

	n	Geo. Mean
TR	14	698.3614
RT	10	650.7391

Least Squares Geometric Means across Sequences by Period:

	Geo. Mean
Period 1	673.4847
Period 2	674.7757

Least Squares Geometric Means across Sequences by Treatment:

	Geo. Mean
Test : ME	695.9633
Reference : MMC	652.9814
Test - Reference	42.9819

Overall Geometric Mean: 678.1093

PARAMETRIC METHODS

Classical (shortest) Confidence Interval:

Point estimate of treatment effect = 0.0637

Confidence Bounds

	Specified	Observed	Within Equivalence Limits?
Lower [5.00]% Conf. limit	-0.2231	-0.0706	Yes
Upper [5.00]% Conf. limit	0.2231	0.1981	Yes

Antilogged point estimate = 1.0658

Antilogged Confidence Bounds

	Observed
Lower [5.00]% Conf. limit	0.9318
Upper [5.00]% Conf. limit	1.2191

SuperGen Protocol ME 001
Pharmacokinetic Analyses

Chow, S-C., Liu, J-P. (1992): Design and Analysis of Bioavailability and Bioequivalence Studies. Published by Marcel Dekker Inc., New York.

Schuirmann OST/TOST:

Null Hypothesis L: Mean T- Mean R <= Lower Bound = -0.22
Null Hypothesis U: Mean T- Mean R >= Upper Bound = 0.22

	t-Value	One-sided p-value to reject non-equivalence		
	Specified	Observed	Specified	Observed
Null Hypothesis L t-statistic	1.7171	3.6663	0.0500	0.0007
Null Hypothesis U t-statistic	-1.7171	-2.0370	0.0500	0.0269

Chow, S-C., Liu, J-P. (1992): Design and Analysis of Bioavailability and Bioequivalence Studies. Published by Marcel Dekker Inc., New York.

NONPARAMETRIC METHODS

Hodges-Lehmann Interval:

Hodges-Lehmann estimate (median of all possible pairwise differences) = -0.0329

Confidence Bounds	Specified	Observed	Within Equivalence Limits?
Lower [5.00]% Conf. limit	-0.2231	-0.1823	Yes
Upper [5.00]% Conf. limit	0.2231	0.0800	Yes

Chow, S-C., Liu, J-P. (1992): Design and Analysis of Bioavailability and Bioequivalence Studies. Published by Marcel Dekker Inc., New York.

SuperGen Protocol ME 001
Pharmacokinetic Analyses

SPECIFICATIONS

Date: **Thursday, January 14, 1999 at 18:35:13**

Data Set: pksum3x (24 Patients who completed both legs)

Analysis: Means 2x2 Crossover Multi Records/Subject

Subject: [redacted]
Treatment: TRT (Test: ME)
Sequence: SEQ (Seq 1:TR)
Outcome: CMAX

Note: This analysis assumes that there are no carry over effects.

Equivalence Parameter: Difference of Means (Log Scale)

Note: Results are presented for data transformed according to the natural logarithm (ln).

90.0000% Confidence Interval: (-0.1356, 0.1888)
Antilogged 90.0000% Confidence Interval: (0.8732, 1.2078)

Tests Bounds:

	Equivalence Bounds		
Lower Alpha Value	Lower	Upper	Upper Alpha Value
0.0500	-0.2231	0.2231	0.0500

DESCRIPTIVE STATISTICS

Descriptive Statistics:

	Test (Seq 1)	Reference (Seq 1)	Test (Seq 2)	Reference (Seq 2)
Mean	6.6866	6.6219	6.4797	6.4911
Standard Error (Mean)	0.0730	0.1120	0.0895	0.1286
Median	6.6881	6.6382	6.3955	6.4610
Standard Deviation	0.2732	0.4192	0.2831	0.4066
Variance	0.0746	0.1758	0.0801	0.1653
Min	[redacted]			
Max	[redacted]			
Range	[redacted]			

SuperGen Protocol ME 001
Pharmacokinetic Analyses

n	14	14	10	10

ANOVA RESULTS

Means:

Least Squares Means for Periods and Treatments:

	Test : ME	Reference : MMC	Test - Reference
Mean Period 1	6.6866	6.4911	0.1954
Std Deviation Period 1	0.2732	0.4066	
Mean Period 2	6.4797	6.6219	-0.1422
Std Deviation Period 2	0.2831	0.4192	

Least Squares Means across Periods by Sequence:

	n	Mean	Std Deviation
TR	14	6.6542	0.3488
RT	10	6.4854	0.3410

Least Squares Means across Sequences by Period:

	Mean	Std Deviation
Period 1	6.5889	0.3414
Period 2	6.5508	0.3685

Least Squares Means across Sequences by Treatment:

	Mean	Std Deviation
Test : ME	6.5831	0.2905
Reference : MMC	6.5565	0.4103
Test - Reference	0.0266	

Overall Mean: 6.5839
Overall Std. Deviation: 0.3521

Geometric Means:

Least Squares Geometric Means for Periods and Treatments:

	Test : ME	Reference : MMC	Test - Reference

Period 1	801.5682	659.2795	142.2886
Period 2	651.7640	751.3629	-99.5989

Least Squares Geometric Means across Periods by Sequence:

	n	Geo. Mean
TR	14	776.0596
RT	10	655.5110

Least Squares Geometric Means across Sequences by Period:

	Geo. Mean
Period 1	726.9508
Period 2	699.7937

Least Squares Geometric Means across Sequences by Treatment:

	Geo. Mean
Test : ME	722.7955
Reference : MMC	703.8168
Test - Reference	18.9786

Overall Geometric Mean: 723.3477

PARAMETRIC METHODS

Classical (shortest) Confidence Interval:

Point estimate of treatment effect = 0.0266

Confidence Bounds

	Specified	Observed	Within Equivalence Limits?
Lower [5.00]% Conf. limit	-0.2231	-0.1356	Yes
Upper [5.00]% Conf. limit	0.2231	0.1888	Yes

Antilogged point estimate = 1.0270

Antilogged Confidence Bounds

	Observed
Lower [5.00]% Conf. limit	0.8732
Upper [5.00]% Conf. limit	1.2078

Chow, S-C., Liu, J-P. (1992): Design and Analysis of Bioavailability and Bioequivalence Studies. Published by Marcel Dekker Inc., New York.

Schuirmann OST/TOST:

Null Hypothesis L: Mean T- Mean R <= Lower Bound = -0.22
Null Hypothesis U: Mean T- Mean R >= Upper Bound = 0.22

	t-Value		One-sided p-value to reject non-equivalence	
	Specified	Observed	Specified	Observed
Null Hypothesis L t-statistic	1.7171	2.6439	0.0500	0.0074
Null Hypothesis U t-statistic	-1.7171	-2.0805	0.0500	0.0247

Chow, S-C., Liu, J-P. (1992): Design and Analysis of Bioavailability and Bioequivalence Studies. Published by Marcel Dekker Inc., New York.

NONPARAMETRIC METHODS

Hodges-Lehmann Interval:

Hodges-Lehmann estimate (median of all possible pairwise differences) = -0.0298

Confidence Bounds	Specified	Observed	Within Equivalence Limits?
Lower [5.00]% Conf. limit	-0.2231	-0.2096	Yes
Upper [5.00]% Conf. limit	0.2231	0.1449	Yes

Chow, S-C., Liu, J-P. (1992): Design and Analysis of Bioavailability and Bioequivalence Studies. Published by Marcel Dekker Inc., New York.

SPECIFICATIONS

Date: **Thursday, January 14, 1999 at 18:32:38**

Data Set: pksum3x (24 Patients who completed both legs)

Analysis: Means 2x2 Crossover Multi Records/Subject

Subject:	[redacted]
Treatment:	TRT (Test: ME)
Sequence:	SEQ (Seq 1:TR)
Outcome:	AUCI

Note: This analysis assumes that there are no carry over effects.

Equivalence Parameter: Difference of Means (Log Scale)

Note: Results are presented for data transformed according to the natural logarithm (ln).

90.0000% Confidence Interval: (-0.0639, 0.2107)
Antilogged 90.0000% Confidence Interval: (0.9381, 1.2345)

Tests Bounds:

	Equivalence Bounds		
Lower Alpha Value	Lower	Upper	Upper Alpha Value
0.0500	-0.2231	0.2231	0.0500

DESCRIPTIVE STATISTICS

Descriptive Statistics:

	Test (Seq 1)	Reference (Seq 1)	Test (Seq 2)	Reference (Seq 2)
Mean	6.5970	6.5210	6.5324	6.4616
Standard Error (Mean)	0.0639	0.0694	0.1019	0.1246
Median	6.6306	6.5923	6.5671	6.5183
Standard Deviation	0.2390	0.2597	0.3223	0.3939
Variance	0.0571	0.0674	0.1039	0.1552
Min	[redacted]			
Max				
Range				

n	14	14	10	10

ANOVA RESULTS

Means:

Least Squares Means for Periods and Treatments:

	Test : ME	Reference : MMC	Test - Reference
Mean Period 1	6.5970	6.4616	0.1354
Std Deviation Period 1	0.2390	0.3939	
Mean Period 2	6.5324	6.5210	0.0114
Std Deviation Period 2	0.3223	0.2597	

Least Squares Means across Periods by Sequence:

	n	Mean	Std Deviation
TR	14	6.5590	0.2479
RT	10	6.4970	0.3522

Least Squares Means across Sequences by Period:

	Mean	Std Deviation
Period 1	6.5293	0.3125
Period 2	6.5267	0.2807

Least Squares Means across Sequences by Treatment:

	Mean	Std Deviation
Test : ME	6.5647	0.2720
Reference : MMC	6.4913	0.3158
Test - Reference	0.0734	

Overall Mean: 6.5332
Overall Std. Deviation: 0.2939

Geometric Means:

Least Squares Geometric Means for Periods and Treatments:

	Test : ME	Reference : MMC	Test - Reference

Period 1	732.8923	640.0579	92.8344
Period 2	687.0499	679.2641	7.7858

Least Squares Geometric Means across Periods by Sequence:

	n	Geo. Mean
TR	14	705.5689
RT	10	663.1378

Least Squares Geometric Means across Sequences by Period:

	Geo. Mean
Period 1	684.9040
Period 2	683.1459

Least Squares Geometric Means across Sequences by Treatment:

	Geo. Mean
Test : ME	709.6010
Reference : MMC	659.3697
Test - Reference	50.2313

Overall Geometric Mean: 687.5689

PARAMETRIC METHODS

Classical (shortest) Confidence Interval:

Point estimate of treatment effect = 0.0734

Confidence Bounds

	Specified	Observed	Within Equivalence Limits?
Lower [5.00]% Conf. limit	-0.2231	-0.0639	Yes
Upper [5.00]% Conf. limit	0.2231	0.2107	Yes

Antilogged point estimate = 1.0762

Antilogged Confidence Bounds

	Observed
Lower [5.00]% Conf. limit	0.9381
Upper [5.00]% Conf. limit	1.2345

SuperGen Protocol ME 001
Pharmacokinetic Analyses

Chow, S-C., Liu, J-P. (1992): Design and Analysis of Bioavailability and Bioequivalence Studies. Published by Marcel Dekker Inc., New York.

Schuirmann OST/TOST:

Null Hypothesis L: Mean T- Mean R <= Lower Bound = -0.22
Null Hypothesis U: Mean T- Mean R >= Upper Bound = 0.22

	t-Value		One-sided p-value to reject non-equivalence	
	Specified	Observed	Specified	Observed
Null Hypothesis L t-statistic	1.7171	3.7096	0.0500	0.0006
Null Hypothesis U t-statistic	-1.7171	-1.8728	0.0500	0.0372

Chow, S-C., Liu, J-P. (1992): Design and Analysis of Bioavailability and Bioequivalence Studies. Published by Marcel Dekker Inc., New York.

NONPARAMETRIC METHODS

Hodges-Lehmann Interval:

Hodges-Lehmann estimate (median of all possible pairwise differences) = -0.0278

Confidence Bounds			
	Specified	Observed	Within Equivalence Limits?
Lower [5.00]% Conf. limit	-0.2231	-0.1915	Yes
Upper [5.00]% Conf. limit	0.2231	0.0574	Yes

Chow, S-C., Liu, J-P. (1992): Design and Analysis of Bioavailability and Bioequivalence Studies. Published by Marcel Dekker Inc., New York.

COMMENTS:

1. The statistical procedure of two one-sided t test was employed in the reanalysis as required in the non-approvable letter.

2. After one patient (patient #28) was excluded from the analysis, the bioequivalence between MITOExtra and Mutamycin was demonstrated.

3. The exclusion of patient #28 from the analysis is reasonable based on the following considerations.

   - Mitomycin is extensively metabolized. It is rapidly inactivated in the liver and in adults, less than 10% of an IV dose is excreted in urine as active drug. Patient #28 had metastatic liver cancer and left hepatic loectomy. The metabolic profile of this patient may be affected and different from other patient.

   - The patient had many coadministrated medications. These medications may affect the pharmacokinetics of mitomycin.

   - The patient was in unstable conditions during the bioequivalence study regarding the physical condition and laboratory tests.

   - In mitomycin C treatment cycle, the patient had Cmax and AUC values at 1.5 to 2 times the expected values. In MitExtra treatment cycle, these values were 4 to 5 times higher.

2. Study ME2

STUDY TITLE: Tolerance and Efficacy of MitoExtra™ in Patients with Solid Tumors who Have Failed Previous Therapy (ME2).

INVESTIGATORS AND CLINICAL SITES: multicenter trial

STUDY PERIOD: October 7, 1998 to September 8, 2000

OBJECTIVES:

- To evaluate the occurrence/severity of toxicities and tumor response rates with MitoExtra treatment.
- To investigate the pharmacokinetics of mitomycin administered as MitoExtra, comparing successive course of treatment, in a limited number of patients.

DOSAGES: MitoExtra was given once every six weeks. The initial dose was 15-20 mg/m^2 given in a 30-minute intravenous infusion. Subsequent doses were adjusted according to the tolerability of the previous doses. The maximum allowed cumulative dose was 60 mg/m^2 of mitomycin.

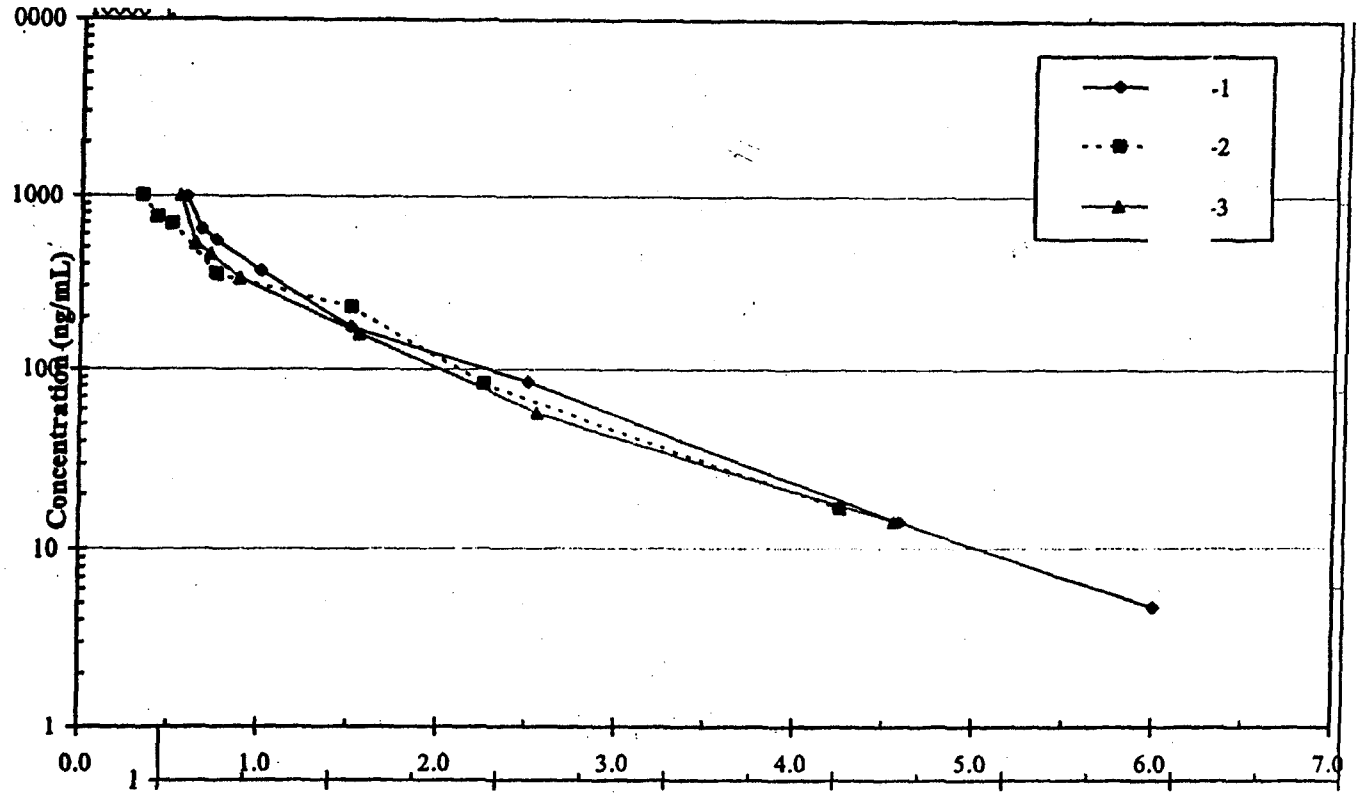
SUBJECT: Men or women (not pregnant or lactating and taking an approved method of birth control), 18 years of age or older. Individuals with a histologically proven solid malignant tumor and who were refractory to or relapsed after other chemotherapy and were not candidates for treatment of higher efficacy or priority. Enrolled, 123; treated, 116 (with at least one course) Pharmacokinetic data were evaluable for 23 patients completing cycles 1 and 2 and 10 patients completing cycles 1 and 3.

STUDY DESIGN:
This was an open trial of at least three consecutive courses of study medication given every six weeks. Treatment was to continue until disease progression or treatment-limiting toxicity was observed, or the patient withdrew consent, or the maximum cumulative dose was reached. The bioequivalence between cycles 1 and 2 and between 1 and 3 was assessed by comparing their area under the curve (AUC), terminal half-life (THALF), and clearance (Cl). All Pharmacokinetic analyses were performed with the statistical package EquivTest Ver. 1.0.

RESULTS:

Assay methods:
The information is not provided.

Pharmacokinetics:
Pharmacokinetic evaluation of consecutive treatment cycles demonstrated equivalence for AUC and Cl between treatment cycles 1 and 2. The pharmacokinetic behavior between cycles 1 and 3 are similar, although the equivalence has not been demonstrated. Some of the graphical comparisons of the concentration time profiles between different cycles are shown below.


0000
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Concentration (ng/mL)
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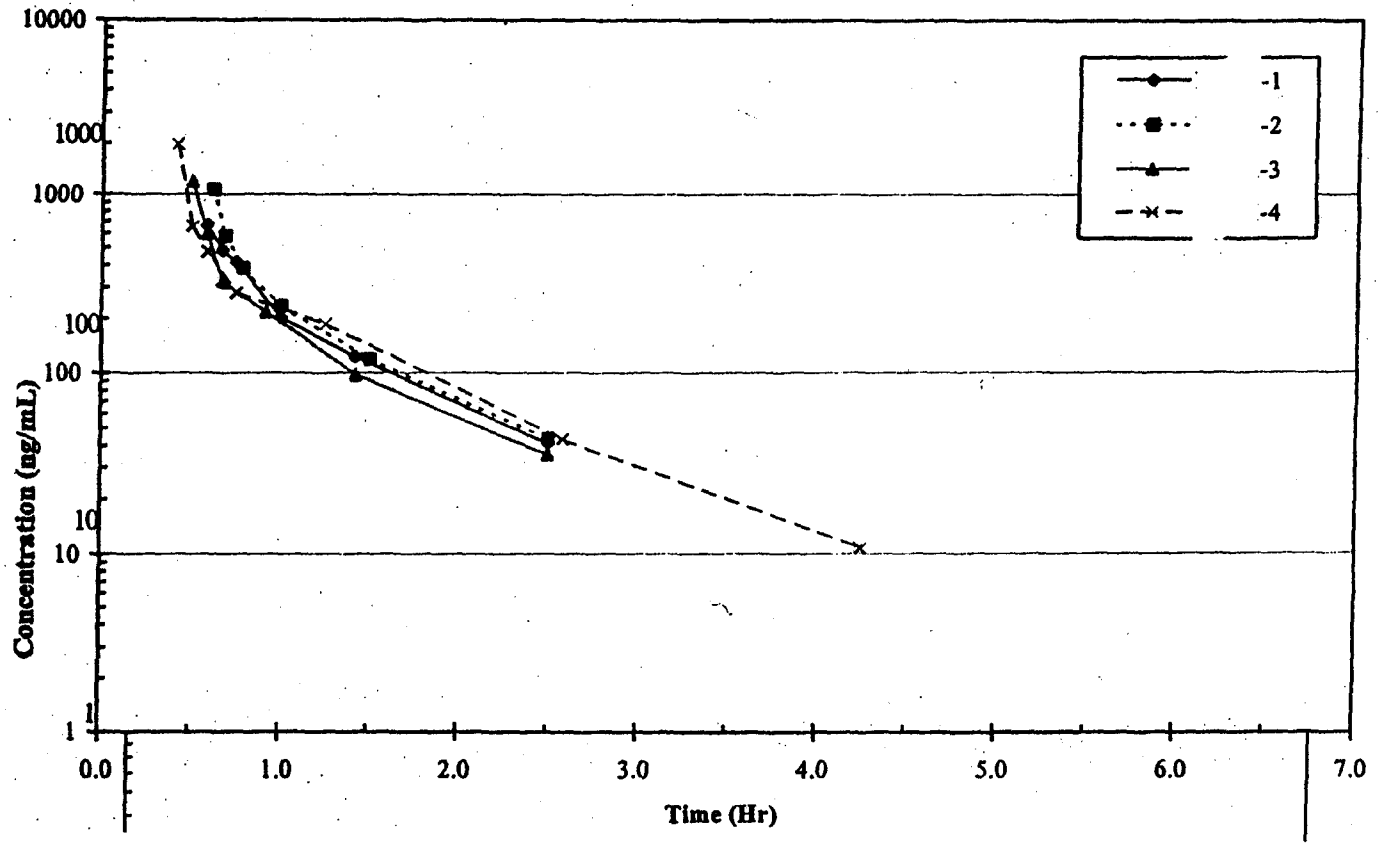
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5.0
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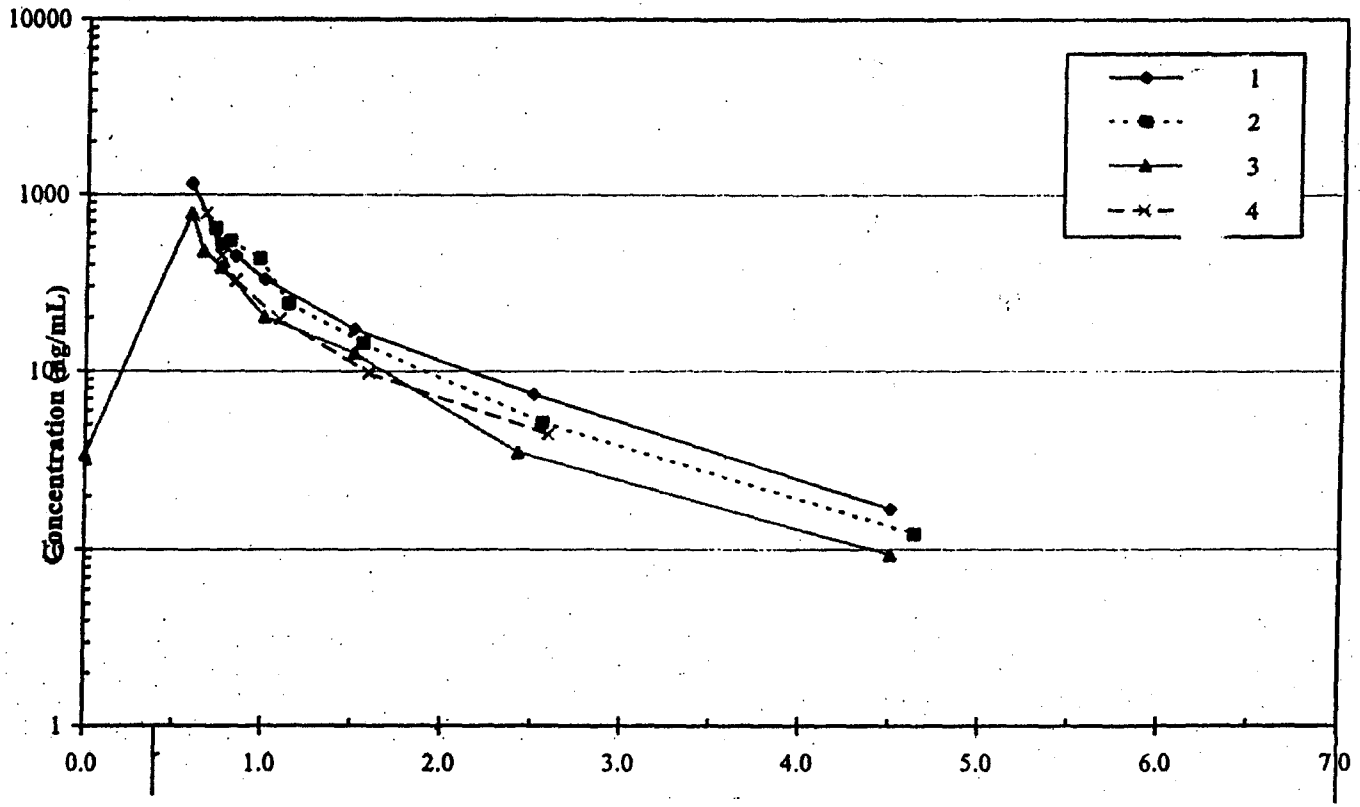
7.0
Concentration (ng/mL)
Time (Hr)
-1
-2
-3
-4


10000
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Concentration (ng/mL)
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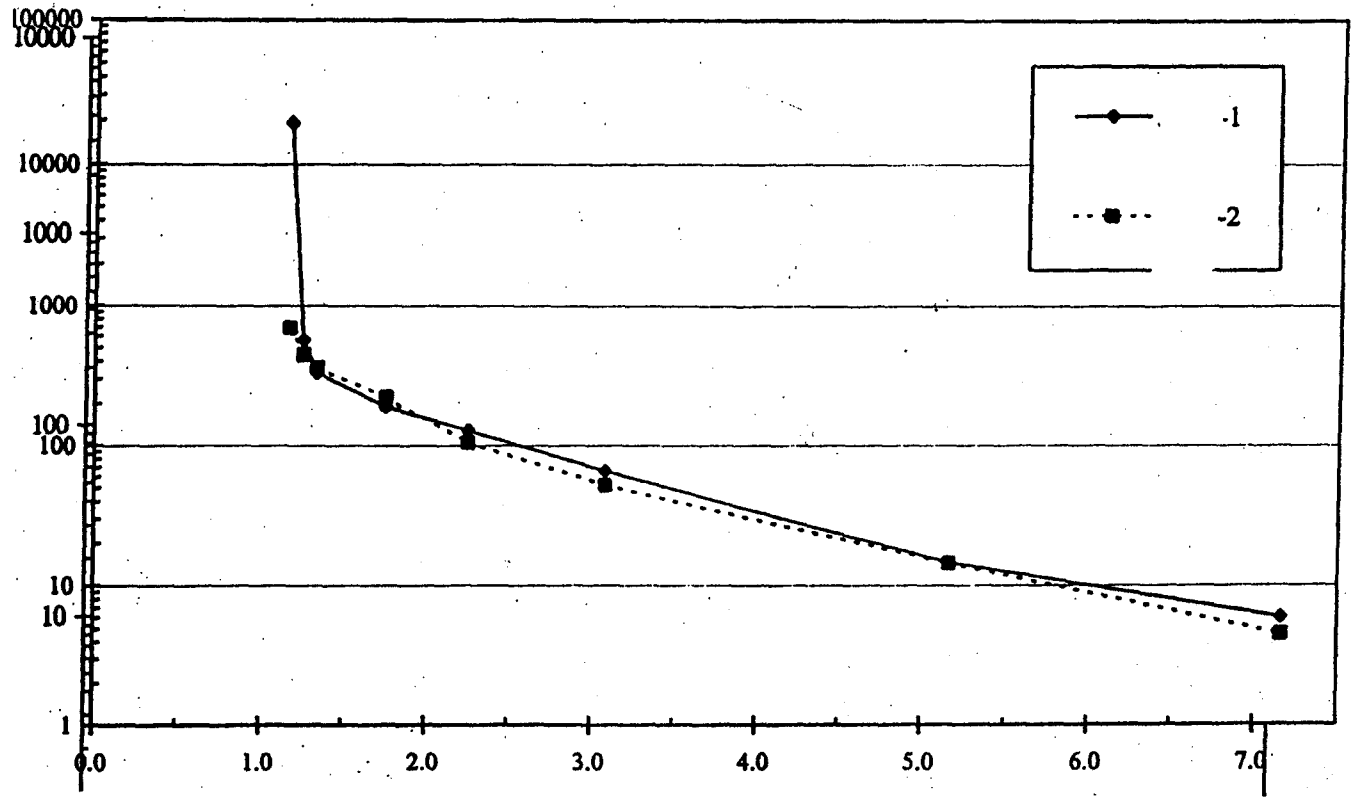
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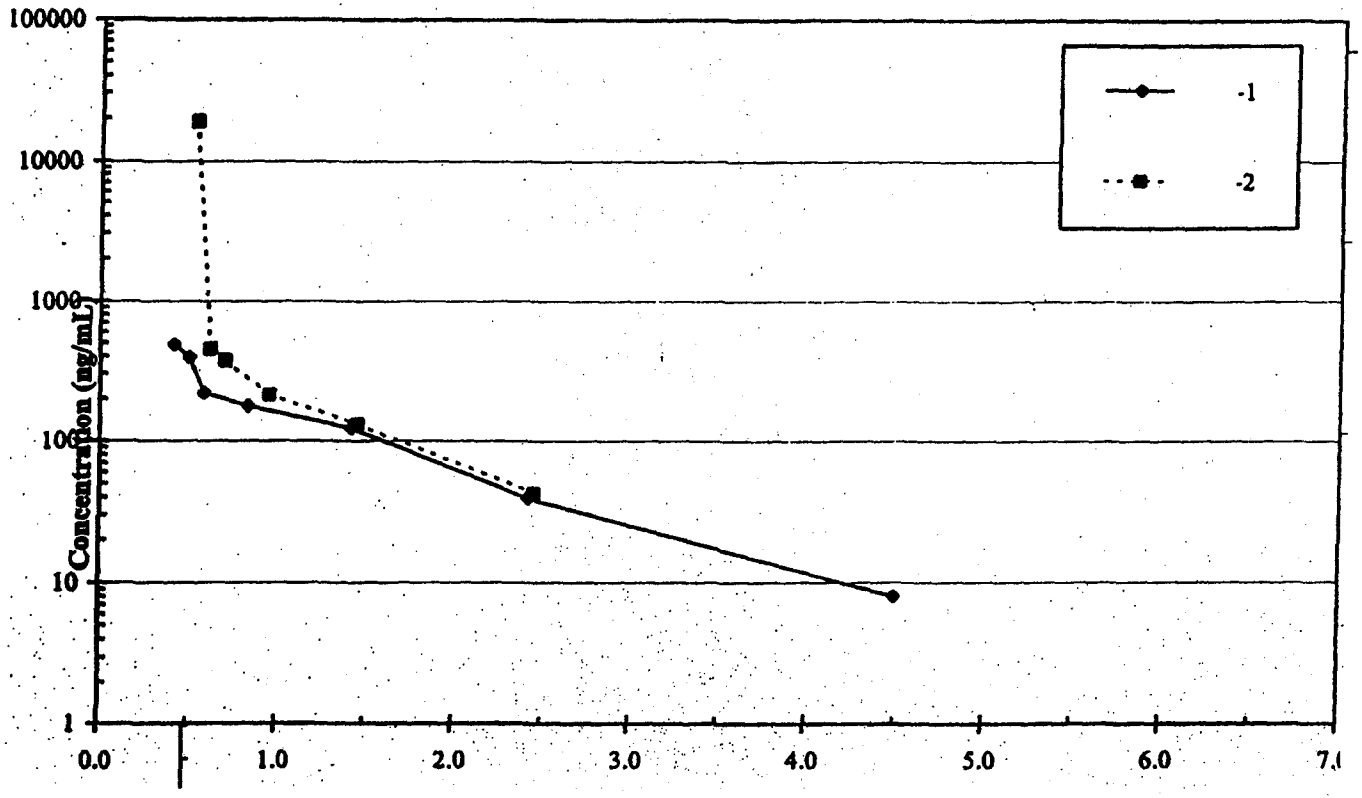
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1
Concentration (ng/mL)
0.0
1.0
2.0
3.0
4.0
5.0
6.0
-1
-2

As can be seen from the graphs, the concentration-time profiles are similar although there are varibilities between different occasions.

COMMENTS:

1. The study showed similar pharmacokinetic behavior of MITOExtra between different cycles.

2. The study report was poorly generated.

   - Tables, figures and appendix were wrongly referred in the text.
   - Figures were poorly generated and arranged, e.g. the concentration time profile for patient OAR in cycle 1 was repeated 202 times (from page 1192 to 1392).

3. The assay description and validation information is missing.

Appendix III

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	50-763	Brand Name	MITOExtra
OCPB Division (I, II, III)	I	Generic Name	Mitamycin C
Medical Division	Oncology Drug Products	Drug Class	Antineoplastic
OCPB Reviewer	John Duan	Indication(s)	Stomach or pancreas cancer
OCPB Team Leader	Atique Rahman	Dosage Form	Injection
		Dosing Regimen	20 mg/m^2
Date of Submission	3/20/02	Route of Administration	IV
Estimated Due Date of OCPB Review	8/31//02	Applicant	SuperGen
PDUFA Due Date	11/14/02	Priority Classification	3S
Division Due Date	11/14/02		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
acute dose:				
chronic dose:				
Patients-				
acute dose:				
chronic dose:	1	1	1	
Dose proportionality -				
Fasting / non-fasting acute dose:				
Fasting / non-fasting chronic dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				

PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
Alternate formulation as reference:				
Bioequivalence studies -				
Traditional design; acute / multi dose:	X	1	1	
Replicate design; acute / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		2	2	

Filability and QBR comments

	"X" if yes	***Comments***
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	N/A	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**1. Does the application fulfill the requirement posted in the nonapprovable letter?**	
Other comments or information not included above		
Primary reviewer Signature and Date	**John Duan 8/1/02**	
Secondary reviewer Signature and Date	**Atique Rahman 8/1/02**	

CC: NDA 50-763, HFD-850 (Electronic Entry or Lee), HFD-150 (CSO), HFD-860 (Rahmana, Mehta), CDR

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John Duan
9/10/02 09:36:03 AM
BIOPHARMACEUTICS

Atiqur Rahman
9/12/02 04:01:30 PM
BIOPHARMACEUTICS