CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40032

STATISTICAL REVIEW(S)

HFD-652

Statistical Review and Evaluation

Date: SEP 16 1994

ANDA #: 40-032

Applicant: Roxane Laboratories, Inc.

Name of Drug: Cyclophosphamide Tablets USP, 50 mg

Documents Reviewed:
1. ANDA 40-032, volume 2.1
2. Data from the Applicant's bioequivalence study, provided by the Applicant on computer diskette.

Lin-Whei Chuang, Ph.D. is the reviewer for this submission in the Division of Bioequivalence, Office of Generic Drugs.

The Applicant has conducted a bioequivalence study comparing their formulation of Cyclophosphamide 50 mg tablets (the Test product) to the Reference Product, Bristol Myers Cytoxan 50 mg tablets. Data from the study came from six different clinical sites. In addition, subjects participating in the study did not all receive the same dose. Rather, doses of 50 mg, 100 mg, 150 mg, and 200 mg were administered in the study (According to Dr. Chuang, the choice of dose was determined by the subject's body surface area). The Division of Bioequivalence has requested an analysis examining the possibility of site-by-treatment and/or dose-by-treatment statistical interaction.

The following table presents the subject numbers for each dose at each clinical site:

	dose			
	50 mg	100 mg	150 mg	200 mg
site #2	-	-	16 17-R	18-R
site #3	-	-	2 4 10 23-R	5 11 25
site #4	-	-	6 9	-
site #5	-	-	12-R 15	26
site #6	-	-	24	20-R 21
site #7	14-R	1 7 8 19 29	-	-

Site #1 did not yield any evaluable subjects for bioequivalence analysis.

In examining the table above, it is evident that there is sparse information on most of the combinations of site and dose. This

is further compounded by the fact that for many of the site-dose combinations, only one of the two administration sequences (Test followed by Reference, and Reference followed by Test) is present. This sparseness makes it difficult to carry out an overall analysis examining the effects of site and of dose simultaneously. It is evident that since the two lower doses (50 mg and 100 mg) occur only in site #7, and the two higher doses (150 mg and 200 mg) occur only in sites #2-6, any differences seen between the two lower doses and the two higher doses may be due to differences between site #7 and sites #2-6. However, other than this relationship, the analyses we have carried out show no evidence that the relationship between site and treatment depends on the dose, or that the relationship between dose and treatment depends on the site. For this reason, we have carried out separate analyses to examine the relationship between site and treatment, and to examine the relationship between dose and treatment.

When the analyses examining site and treatment are carried out, there is no evidence of site-by-treatment interaction for either log AUC or log Cmax. That is, there is no evidence that the average difference between the Test product and the Reference product depends on which of the six sites is considered.

When the analyses examining the relationship between dose and treatment are carried out, there is definite evidence ($p < .05$) of dose-by-treatment interaction in the case of log Cmax. There is some suggestion of dose-by-treatment interaction in the case of log AUC as well, but this seems to depend on how the period effects are characterized in the statistical model and is not consistent for all models. In the case of log Cmax, the statistical significance of dose-by-treatment interaction is consistent for all the statistical models used. We also carried out analyses deleting site #7, and analyses deleting sites #4 and #7, and the statistical significance of dose-by-treatment interaction was consistently present.

Based on these analyses, it appears that the ratio of the average Cmax for the Test product over the average Cmax for the Reference product differs for different doses. Figure 1 presents the individual Test/Reference Cmax ratios for each subject in the study, together with the observed geometric mean Cmax ratios for doses 100, 150, and 200 mg. The downward trend for decreasing dose is evident. In the case of the 100 mg dose, only one subject out of five had a Test/Reference ratio greater than 0.80.

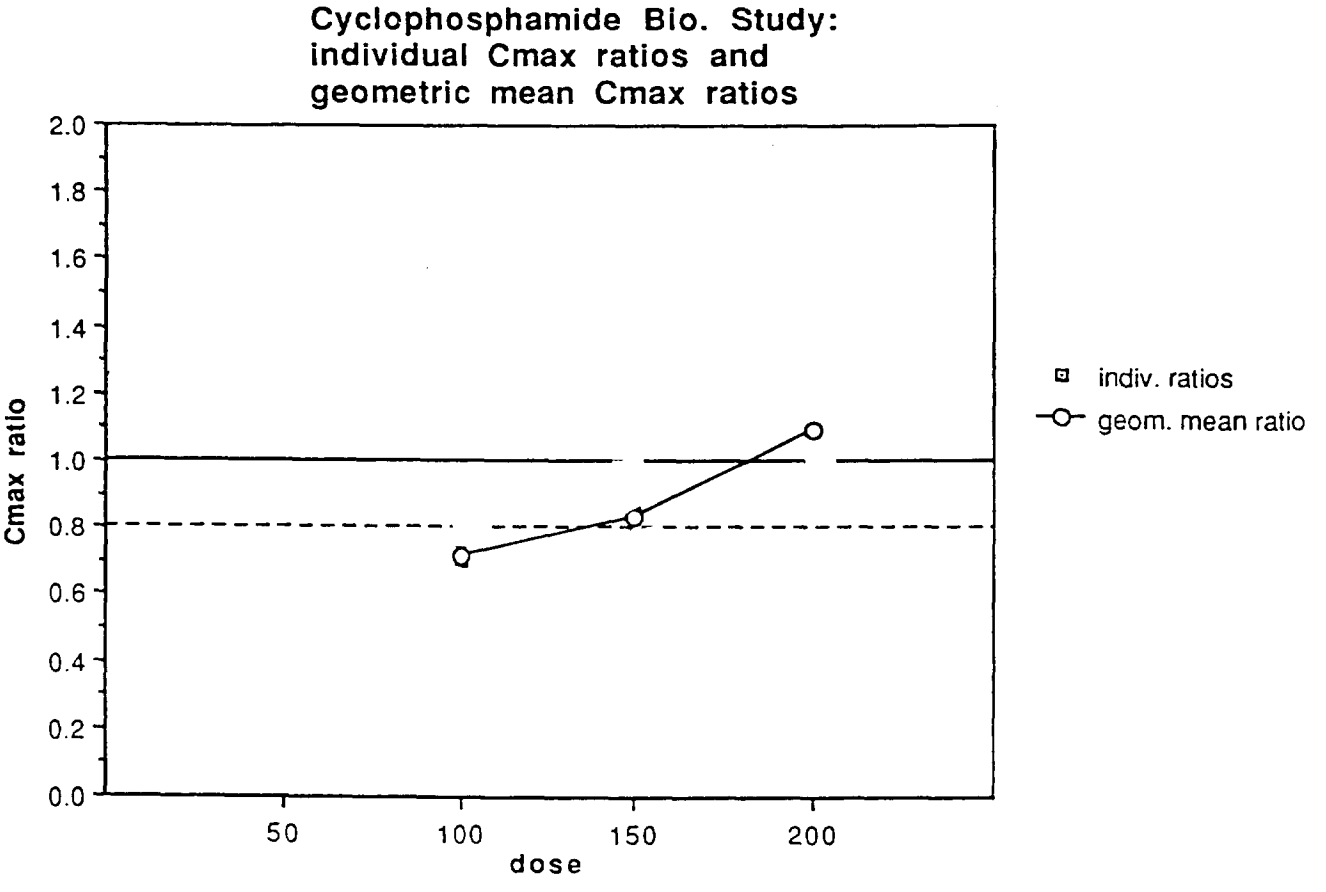

Figure 1: individual Cmax ratios and observed geometric mean ratios

Discussion

The 90% confidence interval (calculated using log-transformed data) for the ratio of the average Cmax for the Test product over the average Cmax for the Reference product, as reported by the Applicant, is 79.4% - 96.6%. This does not fall within the usual equivalence criterion limits of 80% to 125%. Aside from this fact is the statistically significant dose-by-treatment interaction, which raises the concern that the Test and Reference products might be equivalent for some doses, but not for others.

It is not clear what the regulatory requirements are in this circumstance. Must equivalence be shown for each dose individually? For this study, the log Cmax 90% confidence interval for the 200 mg dose falls within the limits of 80% to 125% only if we assume that the period effect depends on the dose. If we assume that the period effect depends on the site, or that the period effect is independent of dose and site, or that there is no period effect, then the upper limit of the 90% confidence interval exceeds 125%, regardless of whether we

analyze all of the data, the data from sites 2, 3, 4, 5, and 6 only, the data from sites 2, 3, 5, and 6 only, or only the 200 mg data. For the 100 mg and the 150 mg doses, the log Cmax 90% confidence interval does not fall within 80% to 125% for any statistical model or subset of the data. Since only one subject received the 50 mg dose, the study is inadequate to make inferences about the 50 mg dose.

Another concern is the question of the relative performance, with respect to Cmax, of the Test and Reference products at doses higher than those seen in this study.

In summary,

1. The overall log Cmax 90% confidence interval, as reported by the Applicant, does not fall within the limits of 80% to 125%.

2. There is no evidence of site-by-treatment interaction. However, dose-by-treatment interaction was statistically significant ($p < .05$) for log Cmax.

3. The log Cmax data from the study cannot consistently establish the equivalence of the Test and Reference products at the 200 mg dose, and it cannot establish the equivalence of Test and Reference at the 50 mg, 100 mg, or 150 mg doses under any circumstances.

4. It is not clear what the regulatory requirements are for a multi-dose bioequivalence study exhibiting dose-by-treatment interaction.

/S/

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Mathematical Statistician

Concur: /S/ 9/15/94

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HFD-715/DRU 2.5 ANDA 40-032 Roxane Labs Cyclophosphamide Tablets USP, 50 mg - Bio. study with multiple doses and sites
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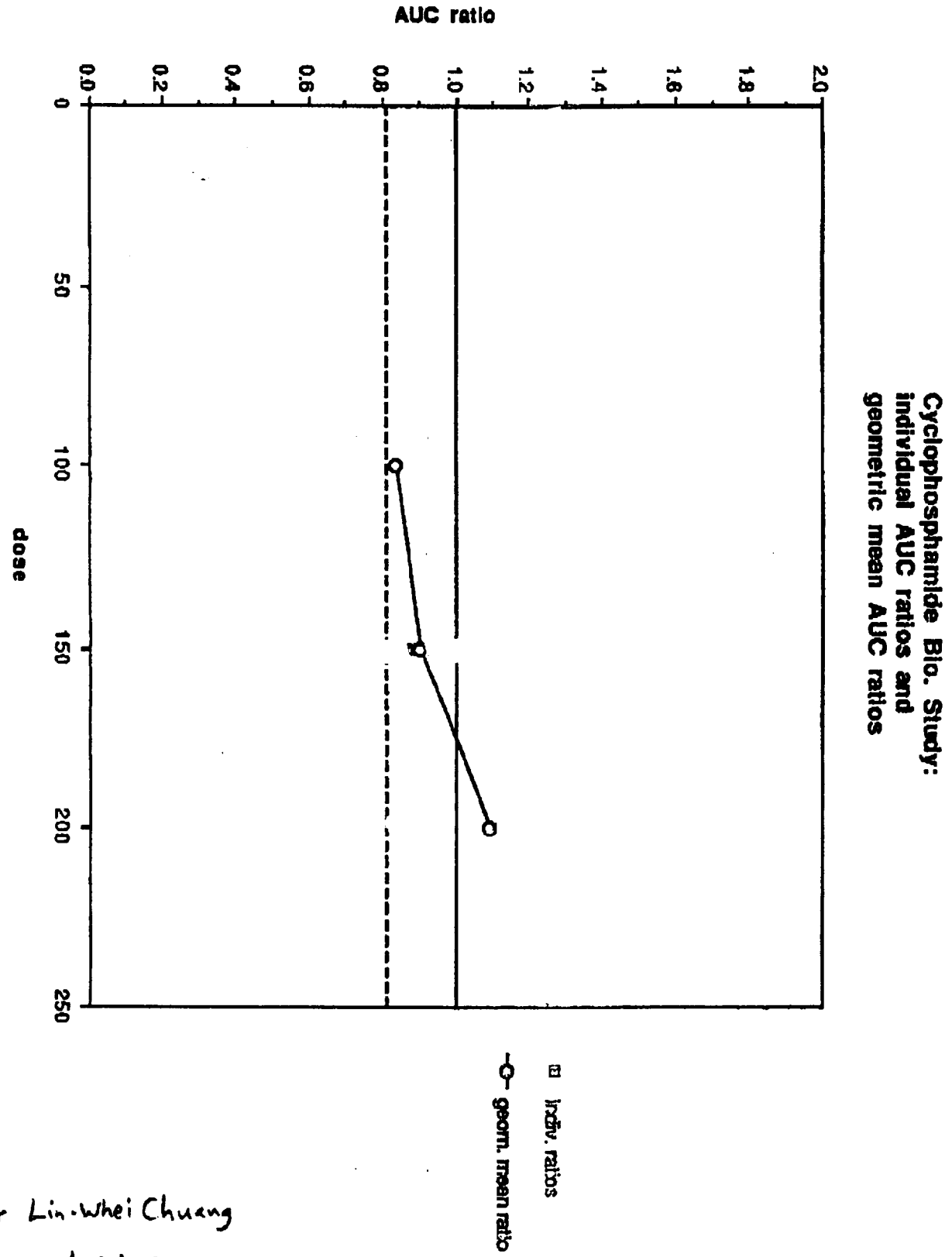

Graph for Lin-Whei Chuang
om Donald Schuirmann