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APPLICATION NUMBER: NDA 50-744

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

MAY 1 4 1997

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA 50-744	**SUBMISSION DATE:** 8/30/96, 3/17/97 4/2/97, 4/14/97 5/13/97
PRODUCT: Doxycycline hyclate	
BRAND NAME Periostat™	
SPONSOR: CollaGenex Pharmaceuticals, Inc. 301 South State Street Newtown, PA 18940	**REVIEWER:** Dan Wang, Ph.D.
	TYPE: Original

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW
NDA 50-744

BACKGROUND

Doxycycline is a member of the tetracycline class of antibiotics. It has been approved for approximately 30 years for use in the United State as an antibiotic for the treatment of a variety of infections caused by susceptible microorganisms. The usual initial dose of oral doxycycline for most antibiotic uses is 200 mg on the first day, followed by a daily maintenance dose of 100 mg for the next 7 to 10 days. Periostat™ is a capsule formulation of doxycycline hyclate equivalent to 20 mg of doxycycline, and is intended for oral administration twice daily. According to the applicant, at a dose of 20 mg BID, dexycycline acts as an inhibitor of collagenase and not as an antibiotic. As the subject of this NDA, Periostat™ is proposed for use as part of a professional oral health program to promote periodontal attachment level gain and reduce bone loss, pocket depth and bleeding upon probing in patients with adult periodontal disease.

As the pharmacokinetics of doxycycline has already been characterized at the higher antibiotic dose levels of currently marketed doxycycline products, the applicant has studied the bioavailability of Periostat™ relative to a commercially available product, Vibramycin™ 50mg by Pfizer. Doxycycline hyclate 20 mg capsules used in the clinical development program were produced by two manufacturers. produced capsules used in the three clinical efficacy trials. manufactured the formulation to be marketed. Therefore, the submission included three pivotal PK studies: Comparison of formulation to Vibramycin (Study CI-95-102); Comparison of Formulation to Vibramycin (Study 92-034); and Bioequivalence study for formulation (Study CI-95-101). Also submitted are 6- and 12-month plasma levels of a 12 month safety and efficacy study in chronic periodontal disease patients (Study 5732.11E).

The applicant also submitted a dissolution study and showed the dissolution of 20 mg capsules meet the USP dissolution specification for doxycycline capsules (% dissolved in min).

SYNOPSIS

As noted in the background section, the applicant has submitted results of three *in vivo* pharmacokinetic studies, plasma levels from a clinical trial and *in vitro* dissolution data. The pivotal study of this submission is study CI-95-101 which evaluated the bioequivalence between the product used in clinical efficacy trials (manufactured by) and the to be marketed product (manufactured by . The study demonstrated bioequivalence between these two products. Gender analysis was also conducted. The results showed that the extent of absorption (AUC), after normalized for body weight adjusted dose, was equivalent for males and females. However, females experienced higher peak plasma levels (Cmax, 30 to 38%). Study CI-95-102 evaluated the relative bioavailability of 20 mg Periostat™ (product, to be marketed) versus 50 mg Vibramycin™ at steady-state. The result showed that the bioavailability of 20 mg Periostat™ QD, after normalization for dose, is 75% and 79% of those of 50 mg Vibramycin™ based on AUC_τ and C_{max}^{ss}, respectively. The extent of absorption are equivalent following 20 mg doxycycline BID and 20 mg doxycycline QD based on steady-state AUC_τ values. The result of this study also showed a possible stronger food effect at 20 mg dose level than those at antimicrobial dose levels. Study CI-92-034 investigated the relative bioavailability of 20 mg Periostat™ product) versus 50 mg Vibramycin™. Due to the unstableness of plasma samples observed in this study, it was agreed between the applicant and the Agency that this study will not be used to support the approval of this NDA. However, this study did provide useful information regarding to food effect.

Plasma levels obtained from 12 month efficacy and safety trial in chronic periodontal disease patients are consistent with those observed from the PK studies summarized above.

The applicant used USP dissolution method for doxycycline capsules for 20 mg Periostat™. The USP dissolution specification is Q % in minutes. For the to be marketed product, doxycycline is dissolved more than % in minutes. This causes for a modification of the current USP dissolution method and specification for the product that is the subject of this NDA.

RECOMMENDATION

The applicant has adequately demonstrated bioequivalence between the to be marketed product and the product used in clinical trials In addition, the applicant has also evaluated the relative bioavailability of 20 mg Periostat™ versus 50 mg Vibramycin™ at steady-state. Gender difference and food effect were also analyzed. This information has been summarized in SYNOPSIS section of the review. In conclusion, the Human Pharmacokinetics and Biopharmaceutics section of the NDA is acceptable for meeting the requirements of 21 CFR 320 provided comments #2 to #7 on page 19-20 are adequately addressed.

TABLE OF CONTENTS Page No.

FORMULATIONS

Periostat™ (doxycycline hyclate capsules USP), 20 mg is a white capsule printed with black ink.

The quantitative composition of the Periostat™ dosage form is:

Ingredient	mg/Capsule
Doxycycline Hyclate, USP	
Microcrystalline Cellulose, NF	
Magnesium Stearate, NF	
Capsules: White Opaque, Size 2, Printed with Periostat™ 20 mg	
Full Weight	

*Equivalent to 20.0 mg Doxycycline

Other formulation information and their relationship to phase I, II and III clinical trials are gathered in Tables A and B in appendix.

SUMMARY OF *IN VIVO* PHARMACOKINETIC TRIALS

TITLE: A double-blind, single-dose, two-period crossover study evaluating pharmacokinetic bioequivalence of capsules of doxycycline hyclate manufactured by and capsules of doxycycline hyclate manufactured by in healthy volunteers.

STUDY NO: CI-95-101 VOLUME: 2.14-16

INVESTIGATOR:

BACKGROUND: The formulation used in clinical studies 92-034, 5732.11E, 5732.11F and 5732.11G was produced by . Subsequent lots were produced by and will be the formulation to be marketed. This study was a bioequivalence trial to compare was produced with a % manufacturing overage. Future lots will be produced at the labeled strength.

OBJECTIVE: To compare the safety and pharmacokinetics of a single dose of doxycycline hyclate (equivalent to 20 mg doxycycline) manufactured by . to a single dose of doxycycline hyclate (equivalent to 20 mg doxycycline) manufactured by administered orally to healthy adult volunteers.

FORMULATIONS: 1) Test formulation - 20 mg capsules of doxycycline hyclate manufactured by Reference formulation - 20 mg capsules of doxycycline hyclate manufactured by

STUDY DESIGN: This is a double-blind, single-dose, randomized, two-period, two-treatment crossover study. Forty-two subjects, 25 males and 17 females, with mean age of 26.2 (ranged from yrs.) were screened and randomized to one of two treatment regimens:

Group A	-	product during study period I	- test, treatment A
	-	product during study period II	- reference, treatment B
Group B	-	product during study period I	- reference, treatment B
	-	product during study period II	- test, treatment A

Each of the two study periods lasted approximately 76 hours and were separated by a four-day period. The washout period between the two dose administrations was seven days. On the evening of Day -1, at approximately 7:00 PM, all subjects were given a standard meal with fluids. No additional food was permitted on Day -1 and on Day 1 before administration of study drug. Study drug was administered at approximately 8:00 AM on Day 1. Each subject was given one capsule of doxycycline hyclate (either the product or the product). Study drug was taken orally and administered with approximately 8 oz. of water. Subjects may not drink fluids for 2 hours after dosing and have any food at least 4 hours after dosing.

Plasma samples were collected at pre-dose, and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 10, 15, 24, 30, 36, 48 and 72 hours post dose for pharmacokinetic analysis and information concerning adverse events were also collect at these time points.

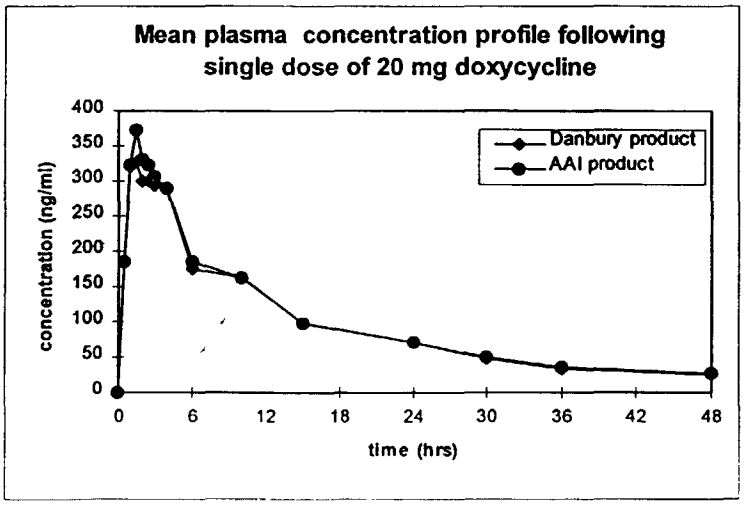
Following the washout period, subjects returned for study period II. The procedures conducted during study period II were identical to those conducted during study period I except the treatment.

Safety parameters were collected before and after the treatment.

DATA ANALYSIS: Non-compartmental analysis was performed to obtain Cmax, AUC and tmax using sponsor's in-house developed software The calculated AUC value and Cmax, tmax values had been randomly checked by the reviewer and were found to be correct. The apparent terminal rate-constant (λz) was estimated by linear regression of the logarithmically transformed concentration versus time data using a minimum of three data points. Statistical analysis was conducted for AUC_{∞}, AUC_{last}, Cmax, λz, $t_{1/2}$ and tmax using SAS (version 6.09).

ASSAY:

RESULT: Forty-two subjects were enrolled into the study and forty-one subjects completed the study. One subject (subject withdrew on the third day of study period II due to an adverse event (intermittent stomach ache). This subject was not replaced as it was considered that sufficient data had been collected during this period to enable pharmacokinetic parameters to be calculated. Individual plasma levels and pharmacokinetic parameters are listed in appendix. The mean plasma concentrations for each treatment are plotted below.



The sponsor indicated that one subject (subject was included in the safety analysis but excluded from the pharmacokinetic analyses of AUC_∞, λz and $t_{1/2}$ for Treatment A as a linear, apparent terminal phase could not be identified following Treatment A. However, the inspection of individual plasma concentration-time profile found that the decline pattern of Subject plasma concentration at terminal phase was similar to several other subjects. Therefore, the applicant is requested by the Agency to estimate Subject terminal half-life and AUC_∞ values as with other subjects. The applicant re-analyzed the data including Subject The results of re-analysis were submitted only for AUC_∞, but not for λz and $t_{1/2}$ values. Summarized below are the results of this bioequivalence study.

Summary Statistics for Pharmacokinetic Parameters

Parameter	n	Geometric LS mean (A[1])	Geometric LS mean (B[1])	Ratio of treatment (A/B)	90% C.I. for ratio of treatment means
AUC_∞ (ng.h/ml)	42	5136.7	5384.6	95%	(91%, 100%)
AUC_{last} (ng.h/ml)	42	4504.3	4711.5	96%	(91%, 100%)
Cmax (ng/ml)	42	348.7	378.9	92%	(86%, 98%)
λz (h^{-1})	41	0.04125	0.03945	105%	(98%,111%)
$t_{1/2}$ (h)	41	16.80	17.57	96%	(90%, 102%)
Parameter	n	Median (A)	Median (B)		Median difference (A-B)
Tmax (h)	42	1.50	1.50	0.00	(-0.25, 0.25)

[1] A represent Treatment A, the product (the product used in clinical trials).
[1] B represent Treatment B, the product (the to be marketed product).

Inclusion of Subject does not change the statistical analysis result from previous analysis. The results show that 90% confidence intervals for ratios of both mean AUC_∞ and Cmax values of the test product versus reference product are within the range of %. Therefore, this two products are considered bioequivalent.

The reviewer also requested the applicant to analyze gender difference in this study. The result of this analysis follows.

It is observed that the extent of absorption is % higher and peak concentration is 61 to 70% higher in females than males. Since the dose for this NDA (20 mg) is only 1/5 to 2/5 of the marketed doxycycline dose as an antibiotics, the higher concentration in females at 20 mg dose level is not unlikely to cause safety problem. However, the treatment period of Periostat is up to one year which is much longer than the treatment of doxycycline as an antibiotics. In case adverse event does occur, concerns should be more for females than males based on pharmacokinetic results. Vice versa, the lower concentrations in males need to be considered if

efficacy concern exists.

Summary Statistics for Gender Difference

Parameter	n	Geometric LS mean (female)	n	Geometric LS mean (male)	Ratio of gender (female/male)	90% C.I. for ratio of gender means
AUC_{∞} (ng.h/ml),A	16	5829.0	25	4642.5	126%	(113%, 140%)
AUC_{last} (ng.h/ml),A	17	5347.6	25	4099.4	133%	(120%, 148%)
Cmax (ng/ml),A	17	478.2	25	281.3	170%	(149%, 194%)
AUC_{∞} (ng.h/ml),B	17	5827.2	25	5103.1	114%	(102%, 127%)
AUC_{last} (ng.h/ml),B	17	5235.7	25	4385.3	119%	(107%, 134%)
Cmax (ng/ml),B	17	502.4	25	312.7	161%	(142%, 181%)

[1]A is for treatment A, the product, and B is for treatment B, the product.

The reviewer also requested the applicant to conduct statistical analysis for gender difference using body weight normalized AUC and Cmax. In NDA 50-744 supplement submitted on March 12, 1997, body weight normalized pharmacokinetic parameter analysis had been done using observed PK parameters (AUC and Cmax) divided by body weight. The purpose of this analysis is to eliminate the effect of body weight on PK parameters. The approach used by the applicant does not serve this purpose. The correct method is to compare the PK parameters per (dose/body weight). This comment was faxed to the applicant on April 11, 1997. The applicant re-analyzed data using the above recommended method. The results are shown below.

Summary Statistics for Gender Difference based on body weight adjusted dose

Parameter	n	Geometric LS mean (female)	n	Geometric LS mean (male)	Ratio of gender (female/male)	90% C.I. for ratio of gender means
AUC_{∞}[1], A[2]	16	41772.8	25	40945.6	102%	(90%, 115%)
AUC_{last}, A	17	38177.4	25	35596.4	108%	(96%, 122%)
Cmax[1], A	17	3428.9	25	2489.9	138%	(120%, 158%)
AUC_{∞}, B[2]	17	41772.8	25	45251.9	93%	(82%, 104%)
AUC_{last}, B	17	37421.5	25	38948.7	97%	(87%, 108%)
Cmax, B	17	3604.7	25	2779.4	130%	(117%, 145%)

[1] The unit for AUC is (ng.h/ml)/(mg/lb), and the unit for Cmax is (ng./ml)/(mg/lb).
[2] A is for treatment A, the product, and B is for treatment B, the product.

The analysis results indicated that the difference in AUC between males and females before normalized for body weight adjusted dose may be attributed to the difference of body weight

between males and females. However, females still experienced higher peak plasma levels even when body weight difference is considered although the magnitude is reduced.

CONCLUSION:

1. Doxycycline hyclate (equivalent to 20 mg doxycycline) manufactured by is bioequivalent to doxycycline hyclate (equivalent to 20 mg doxycycline) manufactured by The 90% confidence intervals for test product versus reference product are 91 to 100% and 86 to 98% for mean AUC value and Cmax value, respectively.

2. Following single dose of 20 mg doxycycline, female subjects experienced a higher extent of absorption %) and peak plasma concentration (61 to 70%) compared to male subjects. When normalized for body weight adjusted dose, the extent of absorption was equivalent between females and males. However, higher peak plasma levels (30 to 38%) were still observed in females after correction for body weight difference.

TITLE: An open-label, multiple-dose, three-period crossover study evaluating pharmacokinetic dose-proportionality of the following drug formulations in healthy volunteers: 20 mg doxycycline hyclate administered QD; 20 mg doxycycline hyclate administered BID; 50 mg Vibramycin administered QD

STUDY NO: CI-95-102 VOLUME: 2.12

INVESTIGATOR:

OBJECTIVES: The objective of the study was to compare the steady-state pharmacokinetic profiles of repeated doses of 20 mg doxycycline hyclate administered QD, 20 mg doxycycline hyclate administered BID, and 50 mg Vibramycin administered QD

FORMULATION: 1) 20 mg capsules of doxycycline hyclate manufactured by
2) 50 mg capsules (Vibramycin®) by

STUDY DESIGN: This is an open-label, randomized, multiple dose, three-period, three-treatment crossover study. The three treatments were as follows:

A	20 mg QD	20 mg doxycycline hyclate (Periostat™) administered QD
B	20 mg BID	20 mg doxycycline hyclate (Periostat™) administered BID
C	50 mg QD	50 mg Vibramycin® administered QD

were administered over seven days for each treatment.

A total of 30 normal subjects, 27 males and 3 females, age ranged from yrs (mean 31.6 yrs), were enrolled in the study. Subjects were randomly assigned to one of the three treatments. Each treatment lasted for 7 days and there was no washout period between the treatments. On the evening of Day -1, at approximately 7:00 PM, all subjects were given a standard meal with fluids. No additional food was permitted on Day -1 and on Day 1 before administration of study drug. Study drug was administered at approximately 7:00 AM and 7:00 PM (BID dosage group only) on Days 1 through 21. Study drug was taken orally and administered with approximately 8 oz. of water. All subjects were served the same controlled diet from the postdosing meal though discharge on Day 22. Postdosing meals were provided to all subjects as follows:

Breakfast at approximately 6:00 AM except on Days 7, 14, and 21.

Lunch at approximately 12:00 PM. On Days 7, 14, and 21, this was after the 5-hour post-dosing evaluations.

Dinner at approximately 6:30 PM.

Plasma samples were collected at pre-dose on Days 5, 6, 7, 12, 13, 14, 19, 20, and 21 to assess the achievement of steady-state. On Days 7, 14, and 21, blood samples were also taken at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 16, and 24 hours after the morning dose for pharmacokinetic analysis and information concerning adverse events were also collect at these time points.

ASSAY:

DATA ANALYSIS: Non-compartmental analysis was performed to obtain Cmax, AUC and tmax, C_{av}^{ss}, and DF (degree of fluctuation, = $(100*(Cmax^{ss}-Cmin^{ss})/C_{av}^{ss})$ using sponsor's in-house developed software Statistical analysis was conducted for AUC_{τ}, Cmax, C_{av}^{ss}, and DF (degree of fluctuation) using SAS. The effect of carryover was tested for at the 10% level. There was evidence of a significant carryover effect in the analysis of DF and hence the results of DF are based on the model including carryover. The analysis of tmax was

performed using Wilcoxin signed rank test.

RESULTS: All 30 subjects completed the study. The following supportive data can be found in Appendix I. Individual plasma levels are listed in Tables 8.2.1.0 to 8.2.1.2. Summary statistics for plasma doxycycline concentrations for all treatments given in Table 3. The individual PK parameters for each treatment, together with their summary statistics, are given in Tables 3.1 to 3.5, respectively. The comparative statistics of log transformed and untransformed PK parameters are given in Tables 4.0 and 4.1, respectively.

1. Achievement of steady-state

The mean pre-dose doxycycline concentrations (ng/ml) (SD) are summarized below:

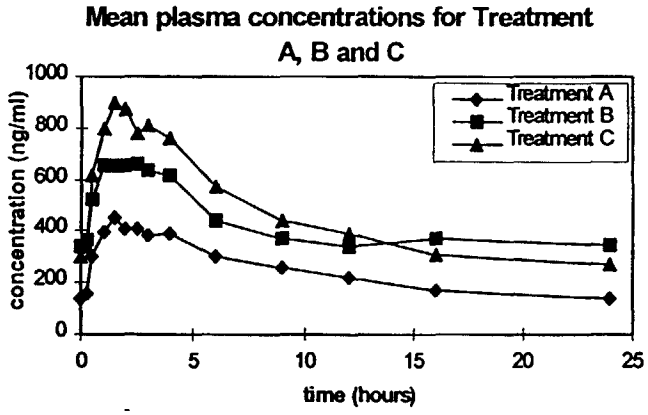
Treatment	Day 5	Day 6	Day 7
A	140 (90.7)	132 (116)	137 (77.6)
B	319 (124)	326 (147)	340 (138)
C	251 (103)	251 (92.7)	305 (175)

Treatment A=20 mg Periostat™ QD for 7 days; Treatment B=20 mg Periostat™ BID for 7 days; Treatment C=50 mg Vibramycin® QD for 7 days.

Result of ANOVA showed that steady-state had been achieved by Day 7 for each treatment.

2. Treatment comparison

The following figure shows steady-state mean plasma concentration profiles after treatment A, B and C:



Treatment A=20 mg Periostat™ QD for 7 days; Treatment B=20 mg Periostat™ BID for 7 days; Treatment C=50 mg Vibramycin® QD for 7 days.

The result of statistical comparison for pharmacokinetic parameters of three treatments is summarized below:

Parameter	Least Squares Geometric Mean			Ratio of Treatment Means (90% Confidence Interval)			
	A	B	C	B/A	C/B	C/A	C/A[1]
AUC_τ (ng.h/ml)	5386.2	5539.2	10037.9	103% (93%,114%)	91%[2] (82%, 100%)	186%** (168%, 207%)	75%** (67%, 83%)
C_{av}^{ss} (ng/ml)	224.4	461.6	418.2	103%[3] (93%, 114%)	91% (82%, 100%)	186%** (168%, 207%)	-
C_{max}^{ss} (ng/ml)	489.7	746.4	961.1	152%** (136%, 171%)	129%** (115%, 144%)	196%** (175%, 220%)	79%** (70%, 88%)
DF(%)	166.8	101.2	187.3	61%** (55%, 67%)	185%** (166%, 206%)	112%* (102%, 124%)	-
	Median			Ratio of Median Difference (90% Confidence Interval)			
	A	B	C	B-A	C-B	C-A	
Tmax (h)	1.50	2.00	1.5	0.24 (-0.25, 1.00)	-0.25 (-1.00, 0.01)	0.00 (-0.5, 0.25)	

No. of Subjects = 30
A=20 mg Periostat™ QD for 7 days; B=20 mg Periostat™ BID for 7 days; C=50 mg Vibramycin® QD for 7 days.
[1] = Comparison based on 2.5 x Treatment A; [2] = Comparison of AUC_τ based on 2 x Treatment B; [3] = Comparison of C_{av}^{ss} based on 2 x Treatment A
** = Significant at the 0.001 level; * = Significant at the 0,05 level

The results show that the relative bioavailability of 50 mg Vibramycin QD versus 20 mg Periostat QD, after normalized for dose, is 75% and 79% based on AUC_τ and C_{max}^{ss}, respectively. This result is unexpected and disagrees with the result of study 92-034 which showed similar bioavailability of 50 mg Vibramycin and 20 mg doxycycline hyclate (manufactured by

The extent of absorption are equivalent following 20 mg doxycycline BID and 20 mg doxycycline QD based on steady-state AUC_τ values. As expected, Cmax value is higher following BID regimen than that following QD regimen.

The comparison between Treatment B and Treatment C is not valid. In sponsor's fax dated 12/17/96, the sponsor stated in item #1 that comparison between Treatment C (50 mg QD) and B (20 mg BID) was used to illustrate the difference in drug exposure following proposed Periostat labeling compared with the established doxycycline labeling for antimicrobial indications. This comparison was made by comparing $AUC_{0\text{-}24h}$ (C) to $2xAUC_{0\text{-}12h}$ (B). According to the result of study 92-034 and previous publications, food delayed and reduced absorption of doxycycline. Therefore, simply doubling the exposure under the fasted condition ($AUC_{0\text{-}12h}$ after morning

dose) could lead to overestimation of the drug exposure following BID regimen and is, therefore, inappropriate.

3. Possible stronger food effect at 20 mg dose level

Published studies on influence of food on doxycycline absorption at antibacterial dose levels (100-200 mg) show that maximum decrease in bioavailability caused by food is about 20% and the increase of tmax is from approximately 2-3 hrs. to 4-5 hrs. In this submission, study 92-034 also indicates 16% decrease in AUC and 31% in Cmax, and increase of tmax from 1.46 to 5.85 hrs when 20 mg doxycycline was given 2.5 hrs after meal compared to under fasting condition. With the similar pharmacokinetics changes observed from published studies and study 92-034 caused by food effect, the result from study 92-034 seems to indicate a stronger food effect at lower dose level since the drug was given 2.5 hrs after meal rather than immediately after the meal in high dose level studies.

In treatment B of this study, the first dose was given under fasted condition and the second dose was given 0.5 hours after meal. The mean tmax value after the first dose was 2 hours. As the first and second samples after the second dose were taken 4 and 12 hours after dosing, the concentration-time profile following the second dose could not be defined. However, based on previous experience with doxycycline pharmacokinetics under fed and fasting condition, it would be reasonable to expect a shift of tmax toward a longer time (more than 2hrs). Following this line of speculation and assuming tmax is increased from 2 hours to 4 hours as observed in previous studies, the concentration at 4 hours should be 70 to 80% of the Cmax value after the morning dose considering 20 to 30% reduction of Cmax caused by food effect. In this study, the concentration at 4 hours would therefore be 0.7-0.8xCmax, i.e. 522.5 to 597.1 ng/ml. Contrasting with what expected, the plasma concentration at 4 hours after the second dose (mean of 371.3 ng/ml) was much lower. When compared to the C_{4hr} after the morning dose (619 ng/ml), the C_{4hr} after the evening dose was 40% lower. The reviewer suspects that the lower C_{4hr} after the evening dose with meal may suggest a possible stronger food effect on doxycycline absorption for 20 mg BID dose regimen compared to that seen at higher dose levels.

CONCLUSION:

1. Steady-state was achieved by Day 7 for each treatment.

2. In contrast with that observed in study 92-034, the relative bioavailability of 50 mg Vibramycin QD versus 20 mg Periostat QD, after normalized for dose, is 75% and 79% based on AUC_τ and C_{max}^{ss}, respectively.

3. The extent of absorption are equivalent following 20 mg doxycycline BID and 20 mg doxycycline QD based on steady-state AUC_τ values. Cmax value is higher following BID regimen than that following QD regimen.

4. The result of this study showed a possible stronger food effect at 20 mg dose level than those at antimicrobial dose levels. The applicant indicated in their Mar. 17, 1997 and April 2, 1997 submissions that during the May 15, 1995 pre-NDA meeting, the issue of food effect on doxycycline was discussed with Mr. John Hunt, the then Biopharmaceutist. It was agreed that if the applicant was willing to include dosing instructions in the product labeling similar to the pivotal clinical trials, a waiver for conducting a food effect study could be provided. The current reviewer of this NDA discussed the issue of food effect with Mr. Hunt after reviewed studies in this NDA submission. Mr. Hunt indicated that the agreement that the Agency made with the applicant in May 15, 1995 pre-NDA meeting was based on the fact that there were no data at 20 mg doxycycline dose level available at that time. As none of the studies in current submission addressed this problem satisfactorily, a well designed food effect study is needed.

TITLE: A bioavailability and Dose Proportionality Study of Three Dosing Levels of Doxycycline Capsules in Normal Healthy Male

STUDY NO: 92-034 VOLUME: 2.13

INVESTIGATOR:

OBJECTIVES: The primary purpose of the study was to determine at the steady-state for each treatment regimen whether mean Cmax exceeded a threshold level of 1.0 mcg/ml, which is believed to be the lowest serum concentration exerting a systemic antimicrobial effect. Additional purpose was to determine the relative bioavailability of 20 mg doxycycline capsules as compared to 50 mg Vibramycin capsules.

FORMULATION: 1) 20 mg capsules of doxycycline hyclate manufactured by
50 mg capsules (Vibramycin®) by

STUDY DESIGN: This is a randomized, multiple dose, three-period, three-treatment crossover study. The three treatments were as follows:

A	20 mg BID	One 20 mg capsule administered q12 hours in the morning and evening
B	40 mg QD	Two 20 mg capsules administered q24 hours in the morning
C	50 mg BID	One 50 mg capsule administered q12 hours in the morning and evening

were administered over seven days for each treatment.

A total of 15 normal male subjects were enrolled in the study. Subjects were randomly assigned to one of the six sequence groups (Table 8.0, appendix). Subjects, after undergoing an overnight fast, reported to the clinical research facility on the morning of the first day of dosing. Prior to

dosing a 10 ml blood sample was collected for each subject. At about 8 AM (±2.0 hours) the first doses of study drug (either Drug A, B or C according to the randomization schedule) were administered to the subjects with 8 oz. of water. Subjects were discharged after being provided remaining drug supplies for days 1-4 with instructions regarding its proper use. Subjects returned to the clinical research facility on the mornings of days 5 and 6 after fasting overnight. On each of these two mornings, additional 10 ml blood samples were collected prior to the morning doses for trough levels. The study drugs were then administered and remaining drug supplies for day 5 were given to the subjects. On day 6, the subjects returned to the clinical research facility in the evening, in time for their PM dose of study medication, and to be confined for approximately 36 hours.

On the morning of the day 7, after at least 10 hours overnight fasting, subjects administered appropriate doses of Drug A, B or C with 8 oz. of water. Subjects remained ambulatory in a fasted state for four hours following this dose. Ten ml blood samples were collected at 0 (predose), 1,-1.5, 2, 4, 6, 12, 13, 14, 16, 18 and 24 hours postdose for the determination of doxycycline levels. Standardized evening meal was provided 2.5 hours before the evening dose. The remaining two treatments for each subject (period 2 and 3) continued on day 8 until day 21 and conducted the same way as the first treatment. Since the objective of this study was to determine the steady-state concentration-time course, there was no wash out between treatments.

ASSAY:

DATA ANALYSIS: Non-compartmental method was used in data analysis. AUC, Cmax, Tmax, λ_z, and $t_{1/2}$ were calculated in PCNONLIN, summary statistics and ANOVA's for attainment of steady-state were calculated in EXCEL. For evaluation of within-day differences in drug absorption and relative bioavailability of doxycycline formulations, it was assumed that subjects were at steady-state.

RESULTS: A total of 15 normal male subjects (aged 28 ± 6 yrs (20-40), height of 70 ± 3 in. (64-77), weight of 173 ± 26 (120-233) lbs., 8 Caucasians, 6 Blacks, and 1 other) were enrolled in the study, but only 14 subjects received study drugs. Subject 9 dropped out of the study before taking any dose of doxycycline for personal reasons. Subject 3 did not take the 50 mg dose because of adverse events (nausea and pain in the upper right quadrant). No blood samples were collected from Subject analysis of the 50 mg BID treatment period. Therefore, pharmacokinetic analyses are based on 13 subjects (except determinations of steady-state for which all collected data is included). Individual plasma levels are listed in Table A in appendix.

1. Achievement of steady-state

The $t_{1/2}$ of doxycycline is between 18-22 hours based on literature. Therefore it is anticipated that subjects will have achieved steady-state by the fifth day of doxycycline exposure. In appendix, Tables 1.0, 1.1, and 1.2 show trough concentrations observed on days 5, 6, and 7 of doxycycline administration during treatments A, B and C, and ANOVA results. The mean values are also summarized below:

Doxycycline Trough Concentrations (mcg/ml) (SD)

Treatment	Day 5	Day 6	Day 7
A[1]	0.320 (0.248)	0.400 (0.256)	0.380 (0.213)
B[1]	0.228 (0.0919)	0.248 (0.0895)	0.276 (0.112)
C[1]	0.783 (0.333)	0.856 (0.408)	0.937 (0.398)

[1] Treatment A = 20 mg BID; Treatment B = 40 mg QD; Treatment C = 50 mg BID

Result of ANOVA shows that achievement of steady-state was not supported for treatments A or C (p=0.079, 0.052). Steady-state was indicated in Treatment B (p=0.147). However, it is observed that mean trough concentration is lower on Day 7 than on Day 6 for Treatment A. Inspection of individual data shows that for Treatment C, only 6 of 13 subjects experienced their highest trough concentrations on Day 7. Therefore, it is believed that steady-state was achieved at least on Day 7.

2. Evaluation of Cmax values of three Treatments regarding to the threshold level of 1.0 μg/ml

One of the objectives of this study is to determine at the steady-state for each treatment regimen whether mean Cmax exceeded a threshold level of 1.0 mcg/ml, which is believed to be the lowest serum concentration exerting a systemic antimicrobial effect. The means (standard errors) are 0.772 μg/ml (0.380) and 0.834 μg/ml (0.284) for Treatment A and B respectively, and least-square means are 0.723μg/ml (0.117) and 0.814 μg/ml (0.117). These mean values are below 1.0 μg/ml and their confidence intervals did not contain 1.0. The mean value for Treatment C is well above 1.0 μg/ml threshold.

Inspection of individual data indicated that of the 13 evaluable subjects, three reached a Cmax exceeding 1.0 μg/ml in 20 BID group and three exceeded this Cmax in the 40 mg QD group, while 12 of 13 subjects had a Cmax exceeding 1.0 μg/ml in the 50 mg BID group.

3. Within-Day Comparison of AUC, Cmax, and Tmax values for Treatment A and C

AUC values and ratios calculated for each dosing interval are displayed in Tables 2.0, 2.1, and 2.2 in appendix. Cmax values and ratios are presented for morning and evening doses in Tables 3.0, 3.1 and 3.2, and Tmax values in Tables 4.0, 4.1 and 4.2 in appendix. The mean of these values are also summarized below:

Mean pharmacokinetic parameters after morning and evening doses following Treatments A and C:

PK Parameters(SD)	Treatment	AM	PM	Ratio (PM/AM)
AUC (μg.hr/ml)	A[1]	6.13 (2.86)	4.83 (1.94)	0.84 (0.19)
	C[1]	14.32 (5.15)	12.46 (3.75)	0.89 (0.14)
Cmax (μg/ml)	A	0.77 (0.39)	0.48 (0.17)	0.69 (0.22)
	C	1.74 (0.60)	1.27 (0.36)	0.75 (0.14)
Tmax (hr)	A	1.46 (0.43)	5.85 (3.29)	N/A
	C	1.54 (0.85)	4.15 (1.86)	N/A

[1]Treatment A = 20 mg BID; Treatment C = 50 mg BID

The AUC ratios show a reduction of absorption after the evening dose (2.5 hrs after a meal) compared to the morning dose (in the fasted state). The reduction of Cmax is even larger than that of AUC. This result is consistent with that reported in the literature, in which a 20% decrease in absorption was observed when doxycycline was administered immediately after the intake of food. The increase of Tmax from 1.46 to 5.85 hours, and 1.54 to 4.15 for Treatment A and C, respectively, indicates that food delayed the absorption of doxycycline. From study design section, it is noticed that scheduled blood samples differed in the morning and evening by the presence of a sample 1.5 hours after the morning dose. Based on the observation of delayed peak plasma concentration, the absence of 1.5 hours sample after evening dose is unlikely to cause a large error in determining the AUC value following the evening dose.

4. Relative bioavailability of the 20 mg and 50 mg (Vibramycin®) formulations

The mean AUC(0-24) values on Day 7 are 10.954 ± 4.658 μg.hr/ml for Treatment A and 26.779 ± 8.735 μg.hr/ml for Treatment C. The ratio of dose-normalized AUC(0-24), calculated as C/(A*2.5), had a value of 1.065 ± 0.337 indicating that the 20 mg formulation exhibited relative bioavailability similar to 50 mg Vibramycin®. The ratio of dose-normalized Cmax also showed similar absorption with mean ratio of 1.046 ± 0.365 at AM and 1.128 ± 0.343 at PM. No statistical analysis had been done for the comparison of dose-normalized AUC and Cmax.

Due to the long terminal half-life of doxycycline (18-22 hrs), λ_z and $t_{1/2}$ could not be well estimated from either the 12 hour plasma data or the 24 hour plasma data.

CONCLUSION:

This study evaluated the absorption of 20 mg doxycycline capsules produced by after multiple dose administration, and relative bioavailability to 50 mg Vibramycin®. Following conclusions can be made from the data provided in this study report:

1. Steady-state was achieved at least on Day 7 after administration of 20 mg doxycycline capsule BID, 2x20 mg doxycycline capsule QD and 50 mg Vibramycin® BID for 7 days.

2. Mean maximum doxycycline plasma levels after administration of 20 mg doxycycline capsule BID and 2x20 mg doxycycline capsule QD were below 1.0 µg/ml while mean Cmax value of 50 mg Vibramycin® was well above 1.0 µg/ml.

3. The absorption of doxycycline after the evening dose of both 20 mg doxycycline capsule and 50 mg Vibramycin® were decreased by 11% to 16% compared to the morning dose based on AUC(0-24) values most likely because of food effect. The mean Cmax values were reduced by 25% to 31%. Food also delayed the absorption, which is indicated by the increase of Tmax values from 1.46 to 5.85 hours, and 1.54 to 4.15 for 20 mg treatment and 50 mg treatment, respectively.

4. After normalized for dose, the absorption of doxycycline from 20 mg doxycycline capsule BID was similar to that from 50 mg Vibramycin® based on both AUC(0-24) and Cmax values.

TITLE: A 12-month multi-center, double-blind, placebo-controlled trial with a 12 month open-label extension evaluating the effect of low dose doxycycline on attachment levels in patients with periodontitis (Doxycycline plasma concentrations in chronic periodontal disease patients)

STUDY NO: 5732.11E VOLUME: 2.17

INVESTIGATOR:

SUMMARY OF THE STUDY: As stated in the title, this is a safety and efficacy study rather than a pharmacokinetics study. Blood samples were collected from subjects during their baseline, six and twelve month clinic visits. There samples were intended to provide supportive evidence of patient compliance, and validate patient exposure to doxycycline or placebo. Therefore, precise dosing and sampling times were not recorded. The results of the study are presented below:

Doxycycline plasma concentrations in samples collected at clinic visits during study 5732.11E

Treatment	6 month visit Doxycycline, ng/ml	12 month visit Doxycycline, ng/ml
10 mg QD (n=28)	18.3 ± 14.4	35.0 ± 21.7
20 mg QD (n=26)	373.1 ± 83.8	475.0 ± 65.4
20 mg BID (n=25)	651.8 ± 70.7	725.9 ± 73.9

Average Cmax and C_{av}^{ss} following the 20 mg BID regimen in CI-95-102 were 790 and 482 ng/ml. The values following the 20 mg QD corresponded similarly with a Cmax of 516 ng/ml and a C_{av}^{ss} of 239 ng/ml. The applicant indicated that the similarity between the Cmax values

from CI -95-102 and the plasma concentrations determined in 5732.11E was consistent with the patients taking their study medication prior to visiting the clinic. The difference in doxycycline concentration between six and twelve month visit was most likely due to the concerted effort instituted by the sites following the six month visit to remind patients to take their study medicine as instructed. Nevertheless, there were still many samples from patients in each treatment group that were below the limit of detection (400 ng/ml) which explains the presence of mean values on above table that are lower than the assay quantitation limits.

IN VITRO DISSOLUTION

Dissolution method, study results and specifications are summarized in the following table.

Sample Times, min (n=12)	Percent Dissolved (% Coefficient of Variation)	
	Lot #94215A*	Lot #10561C
5	88.0 (28.5)	45.2 (40.8)
10	106.5 (9.9)	66.8 (27.6)
20	108.6 (7.8)	82.6 (9.7)
30(Q)	109.5 (6.8)	89.3 (3.8)
45 (∞)	111.5 (5.9)	98.0 (6.6)

Dosage Form	Capsules (Opaque White #2)
Strength	20 mg
Apparatus Type	Paddles
Medium	Water at 37°C
Volume	900 ml
Speed of Rotation	75 rpm
Description of Method	As per USP: UV absorbance determined at 276 nm. The percent dissolved is calculated using average absorbance values compared to the absorbance value of a standard reference solution.
USP Dissolution Specification	Q % Dissolved in min

* Contains 5% manufacturing overage.

The applicant used USP dissolution method for doxycycline for 20 mg Periostat capsules. This method is good for the product manufactured by However, it is not discriminating enough for the product manufactured by which is the manufacture site for the to be marketed product. Even considering the 5% manufacturing overage, 80% dissolution is achieved at least at 10 minutes. It is the reviewer's opinion that a tighter dissolution specification should be applied to the current product. It is suggested that speed of

rotation should be reduced to 50 rpm.

COMMENTS (need to be conveyed to the Medical Officer):

1. Gender analysis conducted for Study CI-95-101 indicated a significant difference on bioavailability between females and males. The AUC_∞ and Cmax values were 14% to 26% and 61% to 70% higher for females compared to males. While this increase in bioavailability may not require different dosing methods for males and females, it may provide valuable information to the Medical Office in evaluating efficacy and safety data of clinical trials.

COMMENTS (need to be sent to the applicant):

2. The dissolution method and specification proposed in this NDA submission are not discriminating enough for the to be marketed product. A new dissolution method and specification should be established for this product and submitted to the Agency. It is suggested that the rotation speed should be at least reduced to 50 rpm for paddle method. If the dissolution under this condition is still too fast, other dissolution method may also be investigated to establish a more discriminating method and a tighter dissolution specification.

3. Based on the literature search conducted by the applicant, doxycycline absorption is decreased when coadministered with food by approximately 20% as measured by Cmax and AUC. Peak concentrations are achieved somewhat later following administration of food. These results are based on the studies at 100 mg and 200 mg doxycycline dose levels. No study has been conducted at 20 mg dose level. The review of bioavailability study in this NDA submission indicated a possible stronger food effect at 20 mg dose level than those at antibacterial therapeutic dose levels. Although not a condition of approval, the applicant is requested to conduct a well designed food effect study as a phase IV trial.

LABELING COMMENTS

/S/ 5/14/97

Dan Wang
Division of Pharmaceutical Evaluation III

Final initialed by E. D. Bashaw EB 5/14/97

cc:
NDA 50-744(Original)
HFD-540(~~Blay~~)(BLATT)
HFD-880(Division File)
HFD-880(Bashaw, Wang)
HFD-205(FOI)
HFD-344(Viswanathan)
CDR: Attn: Barbara Murphy

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commercial

information

Study CI-95-101

Bioequivalence of Formulations

Study CI 95-101 Body Weight

Table 4a.

Subject No	Sub initials	Sex	Body Weight, lb	Seq	Period
		F	115	BA	2
		F	129	BA	2
		F	160	AB	1
		F	145	AB	1
		F	134	BA	2
		F	118	BA	2
		F	128	AB	1
		F	146	BA	2
		F	147	BA	2
		F	135	AB	1
		F	139	BA	2
		F	152	AB	1
		F	193	BA	2
		F	143	AB	1
		F	152	AB	1
		F	152	AB	1
		F	169	BA	2
		M	138	AB	1
		M	133	AB	1
		M	161	AB	1
		M	207	AB	1
		M	191	BA	2
		M	190	BA	2
		M	167	BA	2
		M	222	BA	2
		M	194	AB	1
		M	190	AB	1
		M	221	BA	2
		M	135	AB	1
		M	220	BA	2
		M	192	AB	1
		M	173	BA	2
		M	160	AB	1
		M	170	BA	2
		M	191	BA	2
		M	173	AB	1
		M	217	BA	2
		M	155	AB	1
		M	156	BA	2
		M	198	AB	1
		M	156	BA	2
		M	164	AB	1

A = Formulation
B = Formulation

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APPENDIX 8.2.1.0 (PAGE 1 OF 2)

INDIVIDUAL PLASMA DOXYCYCLINE CONCENTRATIONS (ng/mL)
SINGLE DOSE; TREATMENT A

		Scheduled Time Relative to Dosing (hours)															
Subject No.	Sequence	Pre-Dose	0.5	1	1.5	2	2.5	3	4	6	10	15	24	30	36	48	72
	BA																
	BA																
	AB																
	AB																
	BA																
	AB																
	BA																
	AB																
	BA																
	BA																
	AB																
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Treatment A (test): 20 mg doxycycline hyclate (Periostat™)
BQL = a value below the limit of quantitation of the assay (15 ng/mL).

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APPENDIX 8.2.1.0 (PAGE 2 OF 2)

INDIVIDUAL PLASMA DOXYCYCLINE CONCENTRATIONS (ng/mL)
SINGLE DOSE; TREATMENT A

		Scheduled Time Relative to Dosing (hours)															
Subject No.	Sequence	Pre-Dose	0.5	1	1.5	2	2.5	3	4	6	10	15	24	30	36	48	72
	BA																
	BA																
	AB																
	AB																
	BA																
	AB																
	BA																
	AB																
	BA																
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	AB																
	BA																
	AB																

Treatment A (test): 20 mg doxycycline hyclate (Periostat™)
BQL = a value below the limit of quantitation of the assay (15 ng/mL).
NS = No sample taken, as subject withdrew from study.

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APPENDIX 8.2.1.1 (PAGE 1 OF 2)

INDIVIDUAL PLASMA DOXYCYCLINE CONCENTRATIONS (ng/mL)
SINGLE DOSE; TREATMENT B

		Scheduled Time Relative to Dosing (hours)															
Subject No.	Sequence	Pre-Dose	0.5	1	1.5	2	2.5	3	4	6	10	15	24	30	36	48	72
	BA																
	BA																
	AB																
	AB																
	BA																
	AB																
	BA																
	AB																
	BA																
	BA																
	AB																
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	BA																
	BA																

Treatment B (reference): 20 mg doxycycline hyclate (Periostat™, AAI)

BQL = a value below the limit of quantitation of the assay (15 ng/mL).

* = limit of quantitation 20 ng/mL, due to a reduction in sample volume.

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APPENDIX 8.2.1.1 (PAGE 2 OF 2)

INDIVIDUAL PLASMA DOXYCYCLINE CONCENTRATIONS (ng/mL)
SINGLE DOSE; TREATMENT B

		Scheduled Time Relative to Dosing (hours)															
Subject No.	Sequence	Pre-Dose	0.5	1	1.5	2	2.5	3	4	6	10	15	24	30	36	48	72
	BA																
	BA																
	AB																
	AB																
	BA																
	AB																
	BA																
	AB																
	BA																
	AB																
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	AB																
	BA																
	AB																

Treatment B (reference): 20 mg doxycycline hyclate (Periostat™, AAI)
BQL = a value below the limit of quantitation of the assay (15 ng/mL).
* = limit of quantitation 20 ng/mL, due to a reduction in sample volume.

TABLE 3.0

SUMMARY STATISTICS FOR PLASMA DOXYCYCLINE CONCENTRATIONS (ng/mL)

SINGLE DOSE; TREATMENTS A AND B

		Scheduled Time Relative to Dosing (hours)															
	Statistic	Pre-Dose	0.5	1	1.5	2	2.5	3	4	6	10	15	24	30	36	48	72
Treatment A	n	42	42	42	42	42	42	42	42	42	42	42	42	42	42	41	41
	Mean	BQL	186	321	328	301	301	293	290	175	162	98.5	71.0	48.9	32.9	24.0	BQL
	Std. Dev.	-	121	139	134	123	119	138	110	44.4	36.6	20.3	21.3	17.0	10.8	10.1	-
	CV%	-	65.1	43.1	41.0	41.0	39.7	47.0	38.1	25.4	22.7	20.6	30.1	34.8	32.9	42.0	-
	Median	BQL	180	294	288	279	276	247	275	174	162	97.1	65.7	44.7	32.7	24.8	BQL
	Min.																
	Max.																
Treatment B	n	42	42	42	42	42	42	42	42	42	42	42	42	42	42	42	42
	Mean	BQL	186	323	372	331	322	306	289	186	163	98.8	71.1	49.2	36.0	26.2	BQL
	Std. Dev.	-	102	105	138	122	128	116	120	47.5	43.5	18.7	17.2	13.2	10.6	10.7	-
	CV%	-	54.9	32.4	37.0	36.7	39.9	37.9	41.3	25.5	26.6	18.9	24.2	26.8	29.4	40.9	-
	Median	BQL	178	308	342	303	295	260	247	176	157	97.4	67.9	48.0	34.7	26.7	BQL
	Min.																
	Max.																

Treatment A (test): 20 mg doxycycline hyclate (Periostat™,
Treatment B (reference): 20 mg doxycycline hyclate (Periostat™,

Std. Dev. = standard deviation; CV% = percent coefficient of variation
BQL = a value below the limit of quantitation of the assay (15 ng/mL).

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TABLE 4.2 (PAGE 1 OF 3)

INDIVIDUAL C_{max} (ng/mL) VALUES WITH SUMMARY AND COMPARATIVE STATISTICS

Subject No.	Sequence	A	B	A-B	A/B	Ln A/B
	BA	470	636	-166	0.739	-0.302
	BA	487	486	1.37	1.00	0.00282
	AB	403	371	31.2	1.08	0.0806
	AB	466	605	-140	0.769	-0.263
	BA	513	608	-94.3	0.845	-0.169
	AB	335	398	-62.7	0.842	-0.171
	BA	409	747	-338	0.547	-0.603
	AB	461	409	52.1	1.13	0.120
	BA	388	768	-381	0.505	-0.684
	BA	486	427	58.2	1.14	0.128
	AB	476	407	69.2	1.17	0.157
	BA	317	326	-8.24	0.975	-0.0256
	AB	416	494	-78.7	0.841	-0.173
	BA	530	359	172	1.48	0.391
	AB	469	406	63.4	1.16	0.145
	AB	400	453	-52.6	0.884	-0.123
	AB	311	415	-104	0.749	-0.289
	AB	342	303	39.2	1.13	0.122

Treatment A (test): 20 mg doxycycline hyclate (Periostat™,
Treatment B (reference): 20 mg doxycycline hyclate (Periostat™

TABLE 4.2 (PAGE 2 OF 3)

INDIVIDUAL C_{max} (ng/mL) VALUES WITH SUMMARY AND COMPARATIVE STATISTICS

Subject No.	Sequence	A	B	A-B	A/B	Ln A/B
	AB	281	282	-0.251	0.999	-0.000892
	BA	214	275	-60.1	0.781	-0.247
	BA	233	235	-1.89	0.992	-0.00810
	BA	310	331	-20.6	0.938	-0.0645
	BA	172	321	-148	0.538	-0.620
	AB	247	244	3.44	1.01	0.0140
	AB	232	221	10.5	1.05	0.0465
	BA	240	263	-22.6	0.914	-0.0900
	AB	293	342	-49.4	0.856	-0.156
	BA	251	299	-47.5	0.841	-0.173
	AB	149	244	-94.4	0.613	-0.490
	BA	308	418	-110	0.737	-0.306
	AB	331	388	-56.7	0.854	-0.158
	BA	310	358	-48.8	0.864	-0.146
	AB	760	638	122	1.19	0.175
	BA	264	281	-16.7	0.940	-0.0614
	AB	462	306	157	1.51	0.414
	BA	962	707	255	1.36	0.308

Treatment A (test) 20 mg doxycycline hyclate (Periostat™,
Treatment B (reference): 20 mg doxycycline hyclate (Periostat™

TABLE 4.2 (PAGE 3 OF 3)

INDIVIDUAL C_{max} (ng/mL) VALUES WITH SUMMARY AND COMPARATIVE STATISTICS

Subject No.	Sequence	A	B	A-B	A/B	Ln A/B
	BA	273	270	3.02	1.01	0.0111
	AB	306	327	-21.6	0.934	-0.0682
	BA	392	394	-1.66	0.996	-0.00423
	AB	334	287	47.1	1.16	0.152
	BA	329	354	-24.7	0.930	-0.0722
	AB	304	401	-97.7	0.757	-0.279
Statistic						
Geometric LS Mean		348.7	378.9			92%
95% CI (lower)						
95% CI (upper)						
90% CI (lower)						86%
90% CI (upper)						98%
n		42	42			42
Median		332				
Minimum						
Maximum			768	255	1.51	0.414
Mean		372	400			
Std Dev.		148	142			
CV%		39.9	35.6			
Geometric Mean		349	379			
Mean of logs		5.85	5.94			
Std Dev. of logs		0.359	0.325			
n		42	42	42	42	42

Treatment A (test): 20 mg doxycycline hyclate (Periostat™,
Treatment B (reference): 20 mg doxycycline hyclate (Periostat™,

LS Mean = least squares mean; CI = confidence interval for LS mean or LS mean ratio
Std Dev. = standard deviation; CV% = percent coefficient of variation

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TABLE 4.0 (PAGE 1 OF 3)
INDIVIDUAL AUC_∞ (ng.h/mL) VALUES WITH SUMMARY AND COMPARATIVE STATISTICS

Subject No.	Sequence	A	B	A-B	A/B	Ln A/B
	BA	6675	6864	-189	0.972	-0.0279
	BA	5630	5112	518	1.10	0.0966
	AB	6399	7051	-652	0.907	-0.0971
	AB	3867'@	3645'@	222	1.06	0.0591
	BA	5947	6471	-523	0.919	-0.0843
	AB	4322	4577	-255	0.944	-0.0574
	BA	6830'	8651'	-1821	0.790	-0.236
	AB	5085'	5318'	-234	0.956	-0.0449
	BA	5314'	7077'	-1764	0.751	-0.287
	BA	NC	5690'	-	-	-
	AB	5868	4890	978	1.20	0.182
	BA	3776'	3843	-67.0	0.983	-0.0176
	AB	4490	5162	-672	0.870	-0.139
	BA	7009	4999	2010	1.40	0.338
	AB	6336	6487'	-151	0.977	-0.0236
	AB	6620'@	6526'	94.2	1.01	0.0143
	AB	3981	4924	-943	0.808	-0.213
	AB	6246	6866	-619	0.910	-0.0945

Treatment A (test): 20 mg doxycycline hyclate (Periostat™,
Treatment B (reference): 20 mg doxycycline hyclate (Periostat™,

NC = value could not be determined, a terminal phase could not be identified
- = value could not be estimated.
Unreliable estimate due to:
' = the $t_{1/2}$ was greater than two fold the period over which it was determined.
@ = 3 data points used for extrapolation in the determination of λ_z

TABLE 4.0 (PAGE 2 OF 3)
INDIVIDUAL AUC_∞ (ng.h/mL) VALUES WITH SUMMARY AND COMPARATIVE STATISTICS

Subject No.	Sequence	A	B	A-B	A/B	Ln A/B
	AB	5523*#	5924*#	-401	0.932	-0.0701
	BA	3910	4057	-147	0.964	-0.0369
	BA	4736*#	5014*	-278	0.945	-0.0571
	BA	5363	6252	-889	0.858	-0.153
	BA	3853*	5002	-1149	0.770	-0.261
	AB	4327	4476	-149	0.967	-0.0339
	AB	4655*	4688*#	-32.8	0.993	-0.00703
	BA	4235*	3825*	410	1.11	0.102
	AB	5355*	6564	-1209	0.816	-0.204
	BA	3166	5295*	-2130	0.598	-0.514
	AB	2957	3032*#	-74.3	0.975	-0.0248
	BA	4814	6437	-1623	0.748	-0.291
	AB	5815*	5678*	137	1.02	0.0239
	BA	5324	5323*	0.125	1.00	0.000023
	AB	7487*@	6530*@	957	1.15	0.137
	BA	5684*#	5255*#	429	1.08	0.0785
	AB	4571	4821*	-249	0.948	-0.0531
	BA	7948	7109	839	1.12	0.112
	BA	4596	4283	313	1.07	0.0705
	AB	5279	6545	-1266	0.807	-0.215

Treatment A (test): 20 mg doxycycline hyclate (Periostat™)
Treatment B (reference): 20 mg doxycycline hyclate (Periostat™)

Unreliable estimate due to:
* = the $t_{\frac{1}{2}}$ was greater than two fold the period over which it was determined.
# = the extrapolated area was greater than 20% of the total.
@ = 3 data points used for extrapolation in the determination of λ_z

CollaGenex, Inc
Periostat™
Protocol C1-95-101

TABLE 4.0 (PAGE 3 OF 3)
INDIVIDUAL AUC_∞ (ng h/mL) VALUES WITH SUMMARY AND COMPARATIVE STATISTICS

Subject No	Sequence	A	B	A-B	A/B	Ln A/B
	BA	4651*	4609	42.5	1.01	0.00918
	AB	5097*@	6070*	-973	0.840	-0.175
	BA	5136	5046	89.7	1.02	0.0176
	AB	4202	5157*	-955	0.815	-0.205
Statistic						
Geometric LS Mean		5074.3	5377.9			94%
95% CI (lower)		4902.6	5195.9			
95% CI (upper)		5252.1	5566.2			
90% CI (lower)						91%
90% CI (upper)						98%
n		41	41			41
Median		5136	5275	-189	0.964	-0.0369
Minimum						
Maximum						
Mean		5197	5503			
Std Dev		1144	1148			
CV%		22.0	20.9			
Geometric Mean		5074	5385			
Mean of logs		8.53	8.59			
Std Dev. of logs		0.224	0.214			
n		41	42	41	41	41

Treatment A (test): 20 mg doxycycline hyclate (Periostat™,
Treatment B (reference): 20 mg doxycycline hyclate (Periostat™

LS Mean = least squares mean; CI = confidence interval for LS mean or LS mean ratio
Std. Dev. = standard deviation; CV% = percent coefficient of variation
Unreliable estimate due to:
* = the $t_{\frac{1}{2}}$ was greater than two fold the period over which it was determined.
# = the extrapolated area was greater than 20% of the total.
@ = 3 data points used for extrapolation in the determination of λ_z

Study 92-034

Comparison of Formulation and 50 mg Vibramycin

Table 8.0

Randomization Schedule

Subject	Sequence	Period 1	Period 2	Period 3
	1	C	A	B
	2	A	B	C
	3	B	C	A
	4	B	A	C
	5	C	B	A
	6	A	C	B
	2	A	B	C
	1	C	A	B
	3	B	C	A
	4	B	A	C
	6	A	C	B
	5	C	B	A
	3	B	C	A
	2	A	B	C
	1	C	A	B

Table A

PHARMAKINETICS LABORATORIES, INC.
DOXYCYCLINE PLASMA LEVELS (μg/ml)

SUBJECT	PHASE	TIME0	TIME1	TIME2	TIME3	TIME4	TIME5	TIME6	TIME7	TIME8	TIME9	TIME10	TIME11	TIME12	TIME13	TIME14
	1															
	2															
	3															
	1															
	2															
	3															
	1															
	2															
	3															
	1															
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	3															
	1															
	2															
	3															
	1															
	2															
	3															

Table 1.0

Doxycycline Trough Concentrations (µg/ml)
20 mg Doxycycline *bid* (Treatment A)

Subject Number	Day 5	Day 6	Day 7	Period
	0.293	0.250	0.284	2
	0.268	0.288	0.323	1
	0.343	0.477	0.648	3
	0.218	0.291	0.375	2
	0.468	0.290	0.310	3
	0.000	0.298	0.311	1
	0.217	0.522	0.444	1
	0.434	0.527	0.496	2
	0.200	0.176	0.134	2
	0.119	0.205	0.194	1
	0.379	0.317	0.322	3
	0.146	0.221	0.207	3
	1.060	1.170	0.966	1
	0.337	0.565	0.303	2

Anova: Two-Factor Without Replication

SUMMARY	*Count*	*Sum*	*Average*	*Variance*
Day 5	14	4.482	0.320143	0.061440
Day 6	14	5.597	0.399786	0.065664
Day 7	14	5.317	0.379786	0.045327

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Subject	2.018786	13	0.155291	18.12042	8.4E-10	2.119165
Day	0.048068	2	0.024034	2.804441	0.078911	3.36901
Error	0.222819	26	0.00857			
Total	2.289672	41				

Table 1.1

Doxycycline Trough Concentrations (µg/ml)
40 mg (2 x 20 mg) Doxycycline *qd* (Treatment B)

Subject Number	Day 5	Day 6	Day 7	Period
	0.173	0.131	0.143	3
	0.248	0.270	0.557	2
	0.270	0.264	0.334	1
	0.174	0.138	0.173	1
	0 278	0.236	0.264	2
	0.216	0.260	0.236	3
	0 278	0.394	0.342	2
	0 314	0.301	0.324	3
	0.185	0.207	0.216	1
	0.124	0.152	0.163	3
	0.266	0.224	0.340	2
	0.000	0.152	0.192	1
	0.328	0 405	0.375	2
	0.342	0.337	0.204	3

Anova: Two-Factor Without Replication

SUMMARY	*Count*	*Sum*	*Average*	*Variance*
Day 5	14	3.196	0.228286	0.008441
Day 6	14	3.471	0.247929	0.008015
Day 7	14	3.863	0.275929	0.012426

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Subject	0.274379	13	0.021106	5.428551	0.000125	2.119165
Day	0.016052	2	0.008026	2.064293	0.147207	3.36901
Error	0.101087	26	0.003888			
Total	0.391519	41				

Table 1.2

Doxycycline Trough Concentrations (µg/ml)
50 mg Doxycycline (Vibramycin®) *bid* (Treatment C)

Subject Number	Day 5	Day 6	Day 7	Period
	0.757	0.762	0.707	1
	0.818	0.937	1.150	3
	0.548	0.574	1.010	3
	1.520	2.040	1.860	1
	0.763	0.989	0.797	2
	0.808	1.000	1.400	3
	0.926	0.996	1.100	1
	0.509	0.543	0.547	3
	0.564	0.678	0.635	2
	1.310	0.966	1.040	1
	0.371	0.488	0.443	2
	0 854	0.628	0.980	3
	0.430	0.523	0.512	1

Anova: Two-Factor Without Replication

SUMMARY	*Count*	*Sum*	*Average*	*Variance*
Day 5	13	10.178	0.782923	0.110161
Day 6	13	11.124	0.855692	0.166238
Day 7	13	12.181	0.937	0.158041

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Subject	4 658801	12	0.388233	16.80462	7.74E-09	2.183377
Day	0.154466	2	0.077233	3.343018	0.05239	3.402832
Error	0.554467	24	0.023103			
Total	5.367734	38				

Table 2.0

AUC (µg·hr/ml) for Individual Dosing Intervals with Summary Statistics
20 mg Doxycycline *bid* (Treatment A)

Subject	AUC, µg·hr/ml AM	AUC, µg·hr/ml PM	Total AUC, µg·hr/ml	Ratio PM/AM	Period
	4.146	3.425	7.571	0.826	2
	7.515	5.258	12.773	0.700	1
	4.911	3.398	8.308	0.692	2
	6.776	4.880	11.656	0.720	3
	5.514	4.681	10.195	0.849	1
	6.262	5.580	11.841	0.891	1
	6.645	5.991	12.636	0.902	2
	2.604	3.244	5.848	1.246	2
	2.950	3.185	6.135	1.079	1
	5.898	5.583	11.480	0.947	3
	3.837	2.942	6.779	0.767	3
	13.351	10.253	23.604	0.768	1
	9.250	4.323	13.573	0.467	2
Mean	6.128	4.826	10.954	0.835	
SD	2.860	1.940	4.658	0.193	
CV%	46.674	40.195	42.521	23.073	
Median	5.898	4.681	11.480	0.826	
Min					
Max					

Table 2.1

AUC (µg·hr/ml) 0-24 hr with Summary Statistics
40 mg (2 x 20 mg) Doxycycline *qd* (Treatment B)

Subject		Total AUC, µg·hr/ml	Period
		7.078	3
		14.973	2
		7.406	1
		12.527	2
		10.133	3
		12.669	2
		10.762	3
		6.895	1
		6.704	3
		13.953	2
		7.214	1
		10.736	2
		12.292	3
	Mean	10.257	
	SD	2.929	
	CV%	28.554	
	Median	10.736	
	Min		
	Max		

Table 2.2

AUC (µg·hr/ml) for Individual Dosing Intervals with Summary Statistics
50 mg Doxycycline (Vibramycin®) *bid* (Treatment C)

Subject	AUC, µg·hr/ml AM	AUC, µg·hr/ml PM	Total AUC, µg·hr/ml	Ratio PM/AM	Period
	12.815	10.685	23.499	0.834	1
	16.505	12.747	29.252	0.772	3
	14.541	12.818	27.359	0.882	3
	24.535	19.585	44.120	0.798	1
	12.838	12.039	24.876	0.938	2
	21.248	15.618	36.865	0.735	3
	15.469	14.500	29.968	0.937	1
	8.281	9.984	18.265	1.206	3
	10.383	10.768	21.151	1.037	2
	18.930	15.023	33.953	0.794	1
	9.606	8.009	17.615	0.834	2
	14.476	15.240	29.716	1.053	3
	6.576	4.908	11.483	0.746	1
Mean	14.323	12.456	26.779	0.890	
SD	5.151	3.748	8.735	0.140	
CV%	35.962	30.091	32.620	15.737	
Median	14.476	12.747	27.359	0.834	
Min					
Max					

Table 3.0

Cmax (µg/ml) for Individual Dosing Intervals with Summary Statistics
20 mg Doxycycline *bid* (Treatment A)

Subject		Cmax, µg/ml AM	Cmax, µg/ml PM	Ratio PM/AM	Period
		0.472	0.310	0.657	2
		0.739	0.502	0.679	1
		0.663	0.383	0.578	2
		1.060	0.553	0.522	3
		0.594	0.418	0.704	1
		0.696	0.527	0.757	1
		0.948	0.555	0.585	2
		0.300	0.353	1.177	2
		0.315	0.316	1.003	1
		0.687	0.581	0.846	3
		0.575	0.299	0.520	3
		1.670	0.948	0.568	1
		1.260	0.469	0.372	2
	Mean	0.768	0.478	0.690	
	SD	0.385	0.173	0.216	
	CV%	50.122	36.280	31.373	
	Median	0.687	0.469	0.657	
	Min				
	Max				

Table 3.1

Cmax (µg/ml) with Summary Statistics
40 mg (2 x 20 mg) Doxycycline *qd* (Treatment B)

Subject	Cmax, µg/ml	Period
	0.660	3
	1.080	2
	0.547	1
	1.190	2
	0.766	3
	0.960	2
	0.990	3
	0.465	1
	0.389	3
	1.340	2
	0.734	1
	0.756	2
	0.959	3
Mean	0.834	
SD	0.284	
CV%	34.050	
Median	0.766	
Min		
Max		

Table 3.2

Cmax (µg/ml) for Individual Dosing Intervals with Summary Statistics
50 mg Doxycycline (Vibramycin®) *bid* (Treatment C)

Subject	Cmax, µg/ml AM	Cmax, µg/ml PM	Ratio PM/AM	Period
	1.620	1.300	0.802	1
	1.930	1.190	0.617	3
	2.010	1.470	0.731	3
	3.050	1.970	0.646	1
	1.390	1.090	0.784	2
	2.330	1.520	0.652	3
	2.060	1.360	0.660	1
	1.000	1.070	1.070	3
	1.180	1.110	0.941	2
	2.090	1.500	0.718	1
	1.340	0.862	0.643	2
	1.780	1.560	0.876	3
	0.831	0.513	0.617	1
Mean	1.739	1.270	0.751	
SD	0.604	0.363	0.140	
CV%	34.751	28.585	18.659	
Median	1.780	1.300	0.718	
Min				
Max				

Table 4.0

Tmax (hr) for Individual Dosing Intervals with Summary Statistics
20 mg Doxycycline *bid* (Treatment A)

Subject	*Tmax, hr AM	*Tmax, hr PM	Period
	2	12	2
	2	4	1
	1	1	2
	1.5	6	3
	2	6	1
	2	6	1
	1	6	2
	1.5	1	2
	1.5	6	1
	1	4	3
	1	6	3
	1.5	6	1
	1	12	2
Mean	1.46	5.85	
SD	0.43	3.29	
CV%	29.50	56.23	
Median	1.5	6.0	
Min			
Max			

*Tmax is measured in hours from the most recent dose.

Table 4.1

Tmax (hr) with Summary Statistics
40 mg (2 x 20 mg) Doxycycline *qd* (Treatment B)

Subject	Tmax, hr	Period
	1	3
	2	2
	1	1
	1.5	2
	1.5	3
	2	2
	1	3
	1.5	1
	1.5	3
	1	2
	1	1
	1	2
	1.5	3
Mean	1.35	
SD	0.38	
CV%	27.90	
Median	1.5	
Min		
Max		

[a]Tmax is measured in hours from the most recent dose.

Table 4.2

Tmax (hr) for Individual Dosing Intervals with Summary Statistics
50 mg Doxycycline (Vibramycin®) *bid* (Treatment C)

Subject	*Tmax, hr AM	*Tmax, hr PM	Period
	1	2	1
	1.5	4	3
	2	6	3
	2	6	1
	1	1	2
	1	4	3
	1	6	1
	1	6	3
	2	1	2
	1	4	1
	1	4	2
	1.5	4	3
	4	6	1
Mean	1.54	4.15	
SD	0.85	1.86	
CV%	55.44	44.87	
Median	1.0	4.0	
Min			
Max			

*Tmax is measured in hours from the most recent dose.

Study CI-95-102

Comparison of Formulation and 50 mg Vibramycin

CollaGenex, Inc.
Periostat™
Protocol CI-95-102

APPENDIX 8.2.1.0 (PAGE 1 OF 2)

INDIVIDUAL PLASMA DOXYCYCLINE CONCENTRATIONS (ng/mL)

MULTIPLE DOSE (DAY 7); TREATMENT A

		Pre-AM Dose		Scheduled Time Relative to Dosing (hours)												
Subject No.	Sequence	Day 5	Day 6	Pre-Dose	0.25	0.5	1	1.5	2	2.5	3	4	6	9	12	16	24
	ACB																
	BCA																
	CBA																
	BAC																
	CAB																
	ABC																
	ABC																
	CBA																
	ACB																
	CAB																
	BAC																
	BCA																
	BAC																
	CBA																
	BCA																
	CAB																
	ABC																
	ACB																
	BAC																
	CAB																

Treatment A = 20 mg doxycycline hyclate (Periostat™) QD for 7 days

12-0443

CollaGenex, Inc.
Periostat™
Protocol CI-95-102

APPENDIX 8.2.1.0 (PAGE 2 OF 2)

INDIVIDUAL PLASMA DOXYCYCLINE CONCENTRATIONS (ng/mL)

MULTIPLE DOSE (DAY 7); TREATMENT A

		Pre-AM Dose		Scheduled Time Relative to Dosing (hours)													
Subject No.	Sequence	Day 5	Day 6	Pre-Dose	0.25	0.5	1	1.5	2	2.5	3	4	6	9	12	16	24
	CBA																
	BCA																
	ACB																
	ABC																
	ACB																
	CAB																
	CBA																
	BCA																
	BAC																
	ABC																

Treatment A = 20 mg doxycycline hyclate (Periostat™) QD for 7 days

CollaGenex, Inc.
Periostat™
Protocol CI-95-102

APPENDIX 8.2.1.1 (PAGE 1 OF 2)

INDIVIDUAL PLASMA DOXYCYCLINE CONCENTRATIONS (ng/mL)

MULTIPLE DOSE (DAY 7); TREATMENT B

		Pre-AM Dose		Scheduled Time Relative to Dosing (hours)													
Subject No.	Sequence	Day 5	Day 6	Pre-Dose	0.25	0.5	1	1.5	2	2.5	3	4	6	9	12	16	24
	ACB																
	BCA																
	CBA																
	BAC																
	CAB																
	ABC																
	ABC																
	CBA																
	ACB																
	CAB																
	BAC																
	BCA																
	BAC																
	CBA																
	BCA																
	CAB																
	ABC																
	ACB																
	BAC																
	CAB																

Treatment B = 20 mg doxycycline hyclate (Periostat™) BID for 7 days

CollaGenex, Inc.
Periostat™
Protocol CI-95-102

APPENDIX 8.2.1.1 (PAGE 2 OF 2)

INDIVIDUAL PLASMA DOXYCYCLINE CONCENTRATIONS (ng/mL)

MULTIPLE DOSE (DAY 7); TREATMENT B

		Pre-AM Dose		Scheduled Time Relative to Dosing (hours)													
Subject No.	Sequence	Day 5	Day 6	Pre-Dose	0.25	0.5	1	1.5	2	2.5	3	4	6	9	12	16	24
	CBA																
	BCA																
	ACB																
	ABC																
	ACB																
	CAB																
	CBA																
	BCA																
	BAC																
	ABC																

Treatment B = 20 mg doxycycline hyclate (Periostat™) BID for 7 days
NS = No sample taken.

CollaGenex, Inc.
Periostat™
Protocol CI-95-102

APPENDIX 8.2.1.2 (PAGE 1 OF 2)
INDIVIDUAL PLASMA DOXYCYCLINE CONCENTRATIONS (ng/mL)
MULTIPLE DOSE (DAY 7); TREATMENT C

		Pre-AM Dose		Scheduled Time Relative to Dosing (hours)													
Subject No	Sequence	Day 5	Day 6	Pre-Dose	0.25	0.5	1	1.5	2	2.5	3	4	6	9	12	16	24
	ACB																
	BCA																
	CBA																
	BAC																
	CAB																
	ABC																
	ABC																
	CBA																
	ACB																
	CAB																
	BAC																
	BCA																
	BAC																
	CBA																
	BCA																
	CAB																
	ABC																
	ACB																
	BAC																
	CAB																

Treatment C = 50 mg Vibramycin® QD for 7 days

CollaGenex, Inc.
Periostat™
Protocol CI-95-102

APPENDIX 8.2.1.2 (PAGE 2 OF 2)
INDIVIDUAL PLASMA DOXYCYCLINE CONCENTRATIONS (ng/mL)
MULTIPLE DOSE (DAY 7); TREATMENT C

		Pre-AM Dose		Scheduled Time Relative to Dosing (hours)													
Subject No.	Sequence	Day 5	Day 6	Pre-Dose	0.25	0.5	1	1.5	2	2.5	3	4	6	9	12	16	24
	CBA																
	BCA																
	ACB																
	ABC																
	ACB																
	CAB																
	CBA																
	BCA																
	BAC																
	ABC																

Treatment C = 50 mg Vibramycin® QD for 7 days

TABLE 3.0

SUMMARY STATISTICS FOR PLASMA DOXYCYCLINE CONCENTRATIONS (ng/mL)

MULTIPLE DOSE (DAY 7); ALL TREATMENTS

		Pre-AM Dose		Scheduled Time Relative to AM Dosing on Day 7 (hours)													
	Statistic	Day 5	Day6	Pre-Dose	0.25	0.5	1	1.5	2	2.5	3	4	6	9	12	16	24
Treatment A	n	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
	Mean	140	132	137	157	305	397	454	407	406	386	392	303	255	222	167	137
	Std Dev.	90.7	116	77.6	79 0	159	154	184	173	131	131	127	119	123	134	73.2	71.4
	CV%	65.0	88.2	56.8	50.2	52.2	38.9	40.5	42.6	32.3	34.0	32.3	39.2	48.4	60.1	43.9	52.0
	Median	118	105	112	139	298	356	397	343	364	355	385	276	220	195	158	124
	Min.																
	Max.																
Treatment B	n	30	30	30	30	30	30	29	30	30	30	30	30	30	30	30	30
	Mean	319	326	340	367	520	656	657	657	659	633	619	443	374	340	371	343
	Std. Dev.	124	147	138	124	233	242	220	263	286	223	208	146	133	188	162	119
	CV%	39.0	45.1	40.6	33.9	44.8	36.9	33.5	40.0	43.3	35.2	33.6	33.0	35.4	55.4	43.5	34.6
	Median	308	292	313	340	462	651	627	588	562	570	612	432	360	300	347	314
	Min.																
	Max.																
Treatment C	n	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
	Mean	251	251	305	339	615	796	902	873	783	809	761	573	441	390	310	268
	Std. Dev.	103	92.7	175	236	236	272	306	321	283	292	296	218	168	154	138	125
	CV%	41.1	37.0	57.2	69.5	38.4	34.2	33.9	36.7	36.1	36.1	38.9	38.1	38.2	39.5	44.7	46.8
	Median	235	240	274	281	679	800	899	825	749	765	765	531	449	392	298	277
	Min.																
	Max.																

Treatment A = 20 mg doxycycline hyclate (Periostat™) QD for 7 days; Treatment B = 20 mg doxycycline hyclate (Periostat™) BID for 7 days;
Treatment C = 50 mg Vibramycin® QD for 7 days.

Std. Dev. = standard deviation; CV% = percent coefficient of variation

CollaGenex, Inc.
Periostat™
Protocol CI-95-102

TABLE 3.1 (PAGE 1 OF 2)
INDIVIDUAL DOXYCYCLINE AUC_t (ng.h/mL) VALUES WITH SUMMARY STATISTICS

Subject No.	Sequence	Treatment		
		A	B	C
	ACB	4685	7101	12277
	BCA	6439	6040	13810
	CBA	8211	10825	21204
	BAC	6726	4687	11487
	CAB	3957	3634	10328
	ABC	3271	3431	8753
	ABC	4244	4727	2137
	CBA	3692	4306	7187
	ACB	5300	6323	11702
	CAB	6718	5002	12097
	BAC	11630	10333	13847
	BCA	6422	6669	11717
	BAC	5535	6644	14445
	CBA	12394	8082	11518
	BCA	4142	4472	7337
	CAB	3522	3546	7263
	ABC	4862	5058	11164
	ACB	6276	6854	14065
	BAC	4661	5770	3933
	CAB	3898	3502	7426

Treatment A = 20 mg doxycycline hyclate (Periostat™) QD for 7 days; Treatment B = 20 mg doxycycline hyclate (Periostat™) BID for 7 days;
Treatment C = 50 mg Vibramycin® QD for 7 days.

TABLE 3.1 (PAGE 2 OF 2)
INDIVIDUAL DOXYCYCLINE AUC, (ng.h/mL) VALUES WITH SUMMARY STATISTICS

Subject No.	Sequence	Treatment A	Treatment B	Treatment C
	CBA	5359	5632	11701
	BCA	5425	7300	14825
	ACB	5539	5297	10737
	ABC	4660	4624	10205
	ACB	2779	4495	6302
	CAB	8557	6039	15294
	CBA	4472	4955	11217
	BCA	4734	4725	9953
	BAC	6058	5442	13240
	ABC	7606	8045	7725
Staustic				
Median		5330	5370	11352
Min				
Max.				
Mean		5726	5785	10830
Std. Dev.		2216	1825	3745
CV%		38.7	31.5	34.6
n		30	30	30
Geometric Mean		5386	5539	10038
Mean of logs		8.59	8.62	9.21
Std. Dev. of logs		0.345	0.295	0.440

Treatment A = 20 mg doxycycline hyclate (Periostat™) QD for 7 days; Treatment B = 20 mg doxycycline hyclate (Periostat™) BID for 7 days; Treatment C = 50 mg Vibramycin® QD for 7 days.

Std. Dev. = standard deviation; CV% = percent coefficient of variation

TABLE 3.2 (PAGE 1 OF 2)
INDIVIDUAL DOXYCYCLINE C_{ss} (ng/mL) VALUES WITH SUMMARY STATISTICS

Subject No.	Sequence	Treatment		
		A	B	C
	ACB	195	592	512
	BCA	268	503	575
	CBA	342	902	884
	BAC	280	391	479
	CAB	165	303	430
	ABC	136	286	365
	ABC	177	394	89.1
	CBA	154	359	299
	ACB	221	527	488
	CAB	280	417	504
	BAC	485	861	577
	BCA	268	556	488
	BAC	231	554	602
	CBA	516	673	480
	BCA	173	373	306
	CAB	147	295	303
	ABC	203	421	465
	ACB	261	571	586
	BAC	194	481	164
	CAB	162	292	309

Treatment A = 20 mg doxycycline hyclate (Periostat™) QD for 7 days; Treatment B = 20 mg doxycycline hyclate (Periostat™) BID for 7 days;
Treatment C = 50 mg Vibramycin® QD for 7 days.

TABLE 3.2 (PAGE 2 OF 2)
INDIVIDUAL DOXYCYCLINE C_{ss}^{τ} (ng/mL) VALUES WITH SUMMARY STATISTICS

Subject No.	Sequence	Treatment A	Treatment B	Treatment C
	CBA	223	469	488
	BCA	226	608	618
	ACB	231	441	447
	ABC	194	385	425
	ACB	116	375	263
	CAB	357	503	637
	CBA	186	413	467
	BCA	197	394	415
	BAC	252	453	552
	ABC	317	670	322
Statistic				
Median		222	447	473
Min				
Max.				
Mean		239	482	451
Std Dev.		92.3	152	156
CV%		38.7	31.5	34.6
n		30	30	30
Geometric Mean		224	462	418
Mean of logs		5.41	6.13	6.04
Std. Dev. of logs		0.345	0.295	0.440

Treatment A = 20 mg doxycycline hyclate (Periostat™) QD for 7 days; Treatment B = 20 mg doxycycline hyclate (Periostat™) BID for 7 days; Treatment C = 50 mg Vibramycin® QD for 7 days.

Std. Dev. = standard deviation; CV% = percent coefficient of variation

TABLE 3.3 (PAGE 1 OF 2)
INDIVIDUAL DOXYCYCLINE C_{max} (ng/mL) VALUES WITH SUMMARY STATISTICS

Subject No.	Sequence	Treatment		
		A	B	C
	ACB	385	942	1218
	BCA	684	926	1454
	CBA	597	1541	1519
	BAC	618	903	1205
	CAB	353	417	1014
	ABC	273	395	751
	ABC	599	738	275
	CBA	349	642	717
	ACB	401	681	862
	CAB	572	627	786
	BAC	1144	1180	1307
	BCA	589	850	949
	BAC	621	786	1225
	CBA	720	992	974
	BCA	502	637	884
	CAB	428	493	1138
	ABC	455	516	915
	ACB	665	1054	1568
	BAC	320	690	328
	CAB	310	460	885

Treatment A = 20 mg doxycycline hyclate (Periostat™) QD for 7 days; Treatment B = 20 mg doxycycline hyclate (Periostat™) BID for 7 days;
Treatment C = 50 mg Vibramycin® QD for 7 days.

TABLE 3.3 (PAGE 2 OF 2)
INDIVIDUAL DOXYCYCLINE C_{max} (ng/mL) VALUES WITH SUMMARY STATISTICS

Subject No.	Sequence	Treatment A	Treatment B	Treatment C
	CBA	468	652	931
	BCA	458	1577	1512
	ACB	565	900	1298
	ABC	510	664	992
	ACB	287	755	569
	CAB	694	881	1511
	CBA	408	614	1168
	BCA	413	597	903
	BAC	394	622	1137
	ABC	702	966	798
Staustic				
Median		485	714	983
Min.				
Max.				
Mean		516	790	1026
Std. Dev.		179	285	330
CV%		34.7	36.1	32.1
n		30	30	30
Geometric Mean		490	746	961
Mean of logs		6.19	6.62	6.87
Std Dev. of logs		0.326	0.338	0.404

Treatment A = 20 mg doxycycline hyclate (Perlostat™) QD for 7 days; Treatment B = 20 mg doxycycline hyclate (Periostat™) BID for 7 days,
Treatment C = 50 mg Vibramycin® QD for 7 days.

Std Dev. = standard deviation; CV% = percent coefficient of variation

TABLE 3.4 (PAGE 1 OF 2)
INDIVIDUAL DOXYCYCLINE t_{max} (h) VALUES WITH SUMMARY STATISTICS

Subject No.	Sequence	Treatment		
		A	B	C
	ACB	1.50	2.50	1.50
	BCA	1.00	1.00	2.00
	CBA	2.00	2.00	1.50
	BAC	3.00	2.50	1.50
	CAB	1.00	2.00	1.00
	ABC	1.50	3.00	4.00
	ABC	2.47	1.00	3.00
	CBA	1.50	4.00	1.00
	ACB	1.50	1.48	1.50
	CAB	9.00	1.50	1.50
	BAC	1.50	12.00	1.00
	BCA	1.50	1.00	2.00
	BAC	1.50	2.00	2.50
	CBA	4.00	1.98	0.25
	BCA	0.50	1.00	1.50
	CAB	4.00	1.50	1.50
	ABC	1.00	2.48	1.50
	ACB	1.50	3.00	1.50
	BAC	2.50	2.00	2.50
	CAB	1.50	1.50	1.00

Treatment A = 20 mg doxycycline hyclate (Periostat™) QD for 7 days; Treatment B = 20 mg doxycycline hyclate (Periostat™) BID for 7 days;
Treatment C = 50 mg Vibramycin® QD for 7 days.

TABLE 3.4 (PAGE 2 OF 2)
INDIVIDUAL DOXYCYCLINE t_{max} (h) VALUES WITH SUMMARY STATISTICS

Subject No.	Sequence	Treatment A	Treatment B	Treatment C
	CBA	1.50	4.02	2.00
	BCA	3.00	2.50	2.00
	ACB	4.00	3.00	3.02
	ABC	0.50	0.98	2.00
	ACB	2.00	4.00	1.50
	CAB	2.00	2.50	4.00
	CBA	0.50	4.02	1.00
	BCA	4.00	1.50	2.00
	BAC	1.50	1.00	2.00
	ABC	1.48	4.03	1.00
Statistic				
Median		1.50	2.00	1.50
Min				
Max.				
Mean		2.15	2.57	1.81
Std. Dev.		1.66	2.05	0.851
CV%		77.1	80.0	47.1
n		30	30	30

Treatment A = 20 mg doxycycline hyclate (Periostat™) QD for 7 days; Treatment B = 20 mg doxycycline hyclate (Periostat™) BID for 7 days; Treatment C = 50 mg Vibramycin® QD for 7 days.

Std. Dev. = standard deviation; CV% = percent coefficient of variation

TABLE 3.5 (PAGE 1 OF 2)
INDIVIDUAL DOXYCYCLINE DF (%) VALUES WITH SUMMARY STATISTICS

Subject No.	Sequence	Treatment		
		A	B	C
	ACB	152	114	187
	BCA	209	140	207
	CBA	108	96.0	95.7
	BAC	197	172	212
	CAB	163	64.9	192
	ABC	141	70.6	163
	ABC	294	134	251
	CBA	180	122	187
	ACB	124	65.8	116
	CAB	162	73.0	103
	BAC	188	84.5	183
	BCA	160	90.2	142
	BAC	234	94.5	161
	CBA	83.0	84.4	152
	BCA	245	114	249
	CAB	261	107	345
	ABC	164	50.2	139
	ACB	206	122	217
	BAC	115	77.3	149
	CAB	146	81.5	224

Treatment A = 20 mg doxycycline hyclate (Periostat™) QD for 7 days; Treatment B = 20 mg doxycycline hyclate (Periostat™) BID for 7 days; Treatment C = 50 mg Vibramycin® QD for 7 days.

DF (%) = Degree of fluctuation (calculated as $[(C_{max}^{ss} - C_{min}^{ss})/C_{av}^{ss}] * 100$, where C_{min}^{ss} is the minimum concentration during the dosing interval).

TABLE 3.5 (PAGE 2 OF 2)
INDIVIDUAL DOXYCYCLINE DF (%) VALUES WITH SUMMARY STATISTICS

Subject No.	Sequence	Treatment A	Treatment B	Treatment C
	CBA	157	68.7	132
	BCA	144	199	194
	ACB	209	154	252
	ABC	213	139	177
	ACB	199	160	168
	CAB	141	102	188
	CBA	172	81.9	203
	BCA	177	93.5	171
	BAC	102	80.7	148
	ABC	150	79.5	181
Statistic				
Median		164	94.0	182
Min				
Max.				
Mean		173	104	183
Std. Dev.		47.8	35.7	50.7
CV%		27.6	34.4	27.8
n		30	30	30
Geometric Mean		167	98.5	176
Mean of logs		5.12	4.59	5.17
Std Dev of logs		0.284	0.328	0.273

Treatment A = 20 mg doxycycline hyclate (Periostat™) QD for 7 days; Treatment B = 20 mg doxycycline hyclate (Periostat™) BID for 7 days; Treatment C = 50 mg Vibramycin® QD for 7 days.

DF (%) = Degree of fluctuation (calculated as $[(C_{max}^{ss}-C_{min}^{ss})/C_{av}^{ss}]*100$, where C_{min} is the minimum concentration during the dosing interval).
Std. Dev = standard deviation; CV% = percent coefficient of variation

TABLE 4.0 (PAGE 1 OF 2)
GEOMETRIC LEAST SQUARES MEANS, 95% CONFIDENCE INTERVALS (CI) ON THE MEANS, GEOMETRIC LEAST SQUARES MEAN RATIOS, AND 90% CONFIDENCE INTERVALS ON THE RATIOS FOR DOXYCYCLINE PHARMACOKINETIC PARAMETERS ON DAY 7

	Treatment			Overall Treatment P-Value	Pairwise Treatment Comparisons			
	A	B	C		B/A[2]	C/B[3]	C/A	C/A[4]
AUC_t (ng*h/mL)								
Geometric LS Mean or Mean Ratio	5386.2	5539.2	10037.9	<0.001	103%	91%	186%***	75%***
CI (Lower, Upper)[1]								
C_{max} (ng/mL)								
Geometric LS Mean or Mean Ratio	224.4	461.6	418.2	<0.001	103%	91%	186%***	
CI (Lower, Upper)[1]								
C_{min} (ng/mL)								
Geometric LS Mean or Mean Ratio	489.7	746.4	961.1	<0.001	152%***	129%***	196%***	79%***
CI (Lower, Upper)[1]	(445.1, 538.7)	(678.4, 821.2)	(873.6, 1057.4)		(136%, 171%)	(115%, 144%)	(175%, 220%)	(70%, 88%)

Treatment A = 20 mg doxycycline hyclate (Periostat ™)QD for 7 days, Treatment B = 20 mg doxycycline hyclate (Periostat ™)BID for 7 days, Treatment C = 50 mg Vibramycin® QD for 7 days
LS Mean = least squares mean
[1]95% confidence intervals on geometric LS means and 90% confidence intervals on geometric LS mean ratios
[2]Comparison for C_{max} based on 2 x Treatment A
[3]Comparison for AUC_t based on 2 x Treatment B
[4]Comparison based on 2.5 x Treatment A
*** Significant at the 0.001 level.

CollaGenex, Inc
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Protocol CI-95-102

TABLE 4.0 (PAGE 2 OF 2)
GEOMETRIC LEAST SQUARES MEANS, 95% CONFIDENCE INTERVALS (CI) ON THE MEANS, GEOMETRIC MEANS SQUARES RATIOS, AND 90% CONFIDENCE INTERVALS ON THE RATIOS FOR DOXYCYCLINE PHARMACOKINETIC PARAMETERS ON DAY 7

		Treatment			Overall Treatment P-Value	Pairwise Treatment Comparison			
		A	B	C		B/A	C/B	C/A	C/A[4]
DF (%)									
	Geometric LS Mean or Mean Ratio	166.8	101.2	187.3	<0.001	61%***	185%***	112%*	.
	CI (Lower, Upper)[3]								

Treatment A = 20 mg doxycycline hyclate (Periostat ™) QD for 7 days, Treatment B = 20 mg doxycycline hyclate (Periostat ™) BID for 7 days, Treatment C = 50 mg Vibramycin® QD for 7 days
LS Mean = least squares mean
DF (%) = Degree of fluctuation (calculated as $[(C_{max}'' - C_{min}'')/C_{ss}''] \times 100$, where C_{min}'' is the minimum concentration recorded during the dosing interval.)
[3]95% confidence intervals on geometric LS means and 90% confidence intervals on geometric LS mean ratios.
[4]Comparison based on 2.5 x Treatment A
* Significant at the 0.050 level; *** Significant at the 0.001 level.

12-0087

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Protocol CI-95-102

TABLE 4.1 (PAGE 1 OF 2)
LEAST SQUARES MEANS (UNTRANSFORMED DATA), LEAST SQUARES MEAN DIFFERENCES,
AND 90% CONFIDENCE INTERVALS (CI) ON THE DIFFERENCES FOR DOXYCYCLINE PHARMACOKINETIC PARAMETERS ON DAY 7

	Treatment			Overall Treatment P-Value	Pairwise Treatment Comparisons			
	A	B	C		B-A[3]	C-B[3]	C-A	C-A[4]
AUC, (ng*h/mL)								
LS Mean or Mean Difference	5725.8	5785.2	10829.9	<0.001	59.4	740.6	5104.0***	3484.7***
CI (Lower, Upper)[1]								
C_{max} (ng/mL)								
LS Mean or Mean Difference	238.6	482.1	451.2	<0.001	5.0	30.9	212.7***	
CI (Lower, Upper)[1]								
C_{min} (ng/mL)								
LS Mean or Mean Difference	516.1	790.0	1026.4	<0.001	273.9***	236.4***	510.3***	263.8***
CI (Lower, Upper)[1]								

Treatment A = 20 mg doxycycline hyclate (Periostat ™) QD for 7 days; Treatment B = 20 mg doxycycline hyclate (Periostat ™) BID for 7 days; Treatment C = 50 mg Vibramycin® QD for 7 days
LS Mean = least squares mean
[1]95% confidence intervals on LS means and 90% confidence intervals on mean differences.
[2]Comparison for C_{max} based on 2 x Treatment A
[3]Comparison for AUC, based on 2 x Treatment B
[4]Comparison based on 2.5 x Treatment A
*** Significant at the 0.001 level

12-0088

55

TABLE 4.1 (PAGE 2 OF 2)
LEAST SQUARES MEANS (UNTRANSFORMED DATA), LEAST SQUARES MEAN DIFFERENCES,
AND 90% CONFIDENCE INTERVALS (CI) ON THE DIFFERENCES FOR DOXYCYCLINE PHARMACOKINETIC PARAMETERS ON DAY 7

	Treatment			Overall Treatment P-Value	Pairwise Treatment Comparisons		
	A	B	C		B-A	C-B	C-A
DF (%)							
LS Mean or Mean Difference CI (Lower, Upper)[1]	173.2	107.4	190.6	<0.001	-65.8***	83.2***	17.4
t_{max} (h)[2]							
Median or Median Difference Min., Max. 90% CI (Lower, Upper)[3]	1.50 . .	2.00 . .	1.50 . .	.	0.24 . .	-0.25 . .	0.00 . .

Treatment A = 20 mg doxycycline hyclate (Periostat ™) QD for 7 days; Treatment B = 20 mg doxycycline hyclate (Periostat ™) BID for 7 days; Treatment C = 50 mg Vibramycin® QD for 7 days
LS Mean = least square mean
[1]95% confidence intervals on geometric LS means and 90% confidence interval on geometric LS mean ratios.
DF (%) = Degree of fluctuation (calculated as $[(C_{max}'' - C_{min}'')/C_{ss}''] \times 100$, where C_{min}'' is the minimum concentration recorded during the dosing interval.)
[2]t_{max} analysed using non-parametric techniques
[3]Confidence interval for median difference in t_{max}
***Significant at the 0.001 level.

In Vitro Dissolution

registration number 10-49418. We operate our laboratory in compliance with Good Manufacturing Practices and maintain our records as confidential and the property of the contracting firm."

TEST RESULTS FOR DOXYCYCLINE HYCLATE CAPSULES FOR COLLAGENEX, INC.
10/3/95 PAGE: 2 OF 3

LOT#: 94215A STRENGTH: 20 mg PROJECT: JT77A
ACTIVE INGREDIENT: DOXYCYCLINE HYCLATE
PACKAGING: PLASTIC BOTTLE

TP#: 11372B - UV DISSOLUTION OF DOXYCYCLINE IN DOXYCYCLINE HYCLATE CAPSULES
LIMITS: Not less than % (Q) of the labeled amount of Doxycycline is dissolved in minutes
DATE TESTED: 9/27/95

RESULTS:

	% DISSOLVED				
SAMPLE	5 MINUTES	10 MINUTES	20 MINUTES	30 MINUTES	45 MINUTES
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
MEAN (12)	88.0	106.5	108.6	109.5	111.5
%RSD	28.5	9.9	7.8	6.8	5.9

Reviewed By: _____ Date: 10/3/95
Data Compilation

registration number 10-49418. We operate our laboratory in compliance with Good Manufacturing Practices and maintain our records as confidential and the property of the contracting firm."

TEST RESULTS FOR DOXYCYCLINE HYCLATE CAPSULES FOR COLLAGENEX, INC.
10/3/95 PAGE: 3 OF 3

LOT#: 10561C STRENGTH: 20 mg PROJECT: JT77A
ACTIVE INGREDIENT: DOXYCYCLINE HYCLATE
PACKAGING: PLASTIC BOTTLE

TP#: 11372B - UV DISSOLUTION OF DOXYCYCLINE IN DOXYCYCLINE HYCLATE CAPSULES
LIMITS: Not less than % (Q) of the labeled amount of Doxycycline is dissolved in minutes
DATE TESTED: 9/27/95

RESULTS:

	% DISSOLVED				
SAMPLE	5 MINUTES	10 MINUTES	20 MINUTES	30 MINUTES	45 MINUTES
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
MEAN (12)	45.2	66.8	82.6	89.3	98.0
%RSD	40.8	27.6	9.7	3.8	6.6

59

Reviewed By. _____ Date: 10/3/95
Data Compilation

DEC 7 1997

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA 50-744	**SUBMISSION DATE:** 12/1/1997
PRODUCT: Doxycycline hyclate	
BRAND NAME Periostat™	
SPONSOR: CollaGenex Pharmaceuticals, Inc. 301 South State Street Newtown, PA 18940	**REVIEWER:** Dan Wang, Ph.D.
letter	**TYPE:** Response to 8/27/1997 Action

In Dec. 1, 1997's fax, the applicant requested clarification on several comments the Agency made in the action letter dated Aug. 27, 1997. Among those, comment #2 was a biopharm comment. In the original NDA, the applicant proposed to use USP doxycycline hyclate dissolution method and specification for the currently applied product - 20 mg doxycycline hyclate. With this method, % dissolution is achieved in less than minutes (less than 5 minutes on average) for the to be marketed product. The reviewer thus asked the applicant to develop a more discriminating dissolution method for the purpose of quality control. The following is the applicant's response to this comment.

"Doxycycline hyclate capsules are a USP product. It is the sponsor's intent to manufacture and market USP product. The dissolution method and specifications contained in the NDA are identical to that identified in the U.S. Pharmacopeia. Therefore, it is the sponsor's position that revising the dissolution method and specification are not warranted in the situation. Does the Reviewer agree?"

The following comment needs to be conveyed to the applicant.

The Reviewer does not agree with the applicant. The USP method is appropriate for the currently marketed doxycycline hyclate products which have dose levels of 50 mg and above. However, the product of this NDA is at 20 mg dose level. The dissolution data submitted in the original NDA showed very fast dissolution of currently applied product under USP dissolution condition. The % dissolution is achieved in less than minutes (less than 5 minutes on average) for the to be marketed product. This method is not discriminating enough for product's quality control purpose and considered not appropriate for the to be marketed 20 mg doxycycline hyclate. The reviewer reinforces the comment in the original NDA review.

/S/ 12/4/97

Dan Wang

Division of Pharmaceutical Evaluation III

Final initialed by E. D. Bashaw 12/7/97

cc:
NDA 50-744(Original)
HFD-540(Blay)
HFD-880(Division File)
HFD-880(Bashaw, Wang)
HFD-205(FOI)
HFD-344(Viswanathan)
CDR: Attn: Barbara Murphy

JUL 30 1998

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA 50-744	**SUBMISSION DATE:** 3/31/98, 4/28/98
PRODUCT: Doxycycline hyclate	
BRAND NAME Periostat™	
SPONSOR: CollaGenex Pharmaceuticals, Inc. 301 South State Street Newtown, PA 18940	**REVIEWER:** Dan Wang, Ph.D. **TYPE:** Major Amendment

BACKGROUND

The sponsor responded to the Division's "Action Letters" of Aug. 27, 1997 and Dec. 31, 1997 which identified deficiencies in the NDA. Among these deficiencies, two are from Biopharmaceutics. The sponsor's response to these two deficiencies are reviewed in the following.

REVIEW OF THE RESPONSES

Comment #1:

"The dissolution method and specification proposed in this NDA submission are not discriminating enough for the to be marketed product. A new dissolution method and specification should be established for this product and submitted to the Agency. It is suggested that the rotation speed should be at least reduced to 50 rpm for paddle method. If the dissolution under this condition is still too fast, other dissolution method may also be investigated to establish a more discriminating method and a tighter dissolution specification."

Response:

The sponsor have undertaken an investigation in order to define a more discriminating method. Among the parameters explored were: 1) use of USP apparatus 1; 2) reduction of medium volume; 3) variation of medium pH (pH 4.5, 6.5 and 7.5 phosphate buffers); 4) reduction of paddles RPM and 5) combinations of these modifications. Overall, the sponsor have concluded from this investigation that simple reduction of paddle speed to 50 RPM has resulted in an appropriately discrimination method, namely:

Method:	USP Apparatus 2 (Paddles)/Water @ 37°C, 900 mL/50 RPM
Criteria:	NLT % (Q) Dissolved in minutes

The sponsor had applied the method to the five lots of Periostat™, 20 mg. The results of the dissolution studies were summarized in tables and figures attached. After reviewing the data, the following comment was conveyed to the sponsor:

"Preliminary evaluation of your data suggests that the proposed method and specification still

lack lot to lot of discrimination. It is our opinion that the use of the 50 rpm rotation speed with a Q value of % in minutes would provide the proper balance between the discrimination and release ability of lots. Should the sponsor elect to accept the specification method, such acceptance would constitute the full response to this issue. If, however, the sponsor still wishes to pursue the minute time point, then lower dissolution speeds (such as those used for suspensions), i.e. 25 rpm, must be investigated. The overall goal of the in vitro technology is to provide a test which is sufficiently rigorous to detect lots with different release performance and yet not incur an undo regulatory burden."

On April 28, 1998, the sponsor responded to the above comment in another amendment.

Response:

The sponsor will heed the advice of the reviewer and will revise the specification for the dissolution method. The new specification will be a Q values of % in minutes.

Comment #2:

Based on the literature search conducted by the applicant, doxycycline absorption is decreased when coadministered with food by approximately 20% as measured by Cmax and AUC. Peak concentrations are achieved somewhat later following administration of food. These results are based on the studies at 100 mg and 200 mg doxycycline dose levels. No study has been conducted at 20 mg dose level. The review of bioavailability study in this NDA submission indicated a possible stronger food effect at 20 mg dose level than those at antibacterial therapeutic dose levels. Although not a condition of approval, the applicant is requested to conduct a well designed food effect study as a phase IV trial.

Response:

The sponsor agrees to conduct a food effect study as a post-approval commitment. The sponsor will submit the study protocol for review and comment prior to conducting the study.

RECOMMENDATION

The sponsor's response to Biopharmaceutics comments are acceptable. The new dissolution method and specification are:

Method: USP Apparatus 2 (Paddles)/Water @ 37°C, 900 mL/50 RPM
Criteria: NLT % (Q) Dissolved in minutes

The food effect study will be conducted as a post-approval commitment.

/S/

6/24/98

Dan Wang
Division of Pharmaceutical Evaluation III

Final initialed by E. D. Bashaw 7/30/98

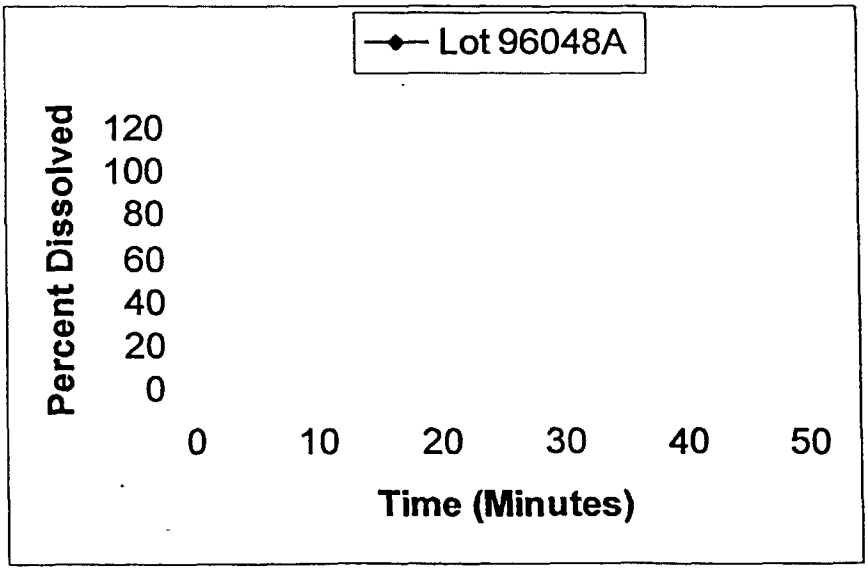
cc:
NDA 50-744(Original)
HFD-540(Blay)
HFD-880(Division File)
HFD-880(Bashaw, Wang)
HFD-205(FOI)
HFD-344(Viswanathan)
CDR: Attn: Barbara Murphy

Periostat™ (doxycycline hyclate capsules USP), 20 mg
Lot 96048A

Method: USP Apparatus 2 (Paddles)/Water @ 37°C, 900 mL/50 RPM
Criteria: NLT % (Q) Dissolved in Minutes

Sample/Time	5 min	10 min	20 min	30 min	45 min (1)
	Percent Dissolved				
1					
2					
3					
4					
5					
6					
Average	77	89	92	94	101
%RSD	20.9	4.6	2.8	2.5	4.3

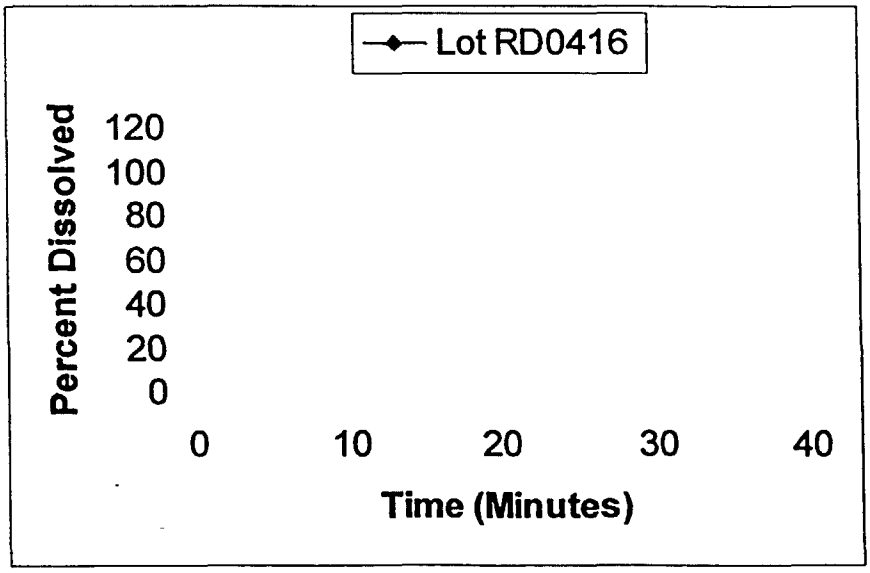
(1) RPM increased to after the minute time point.



Periostat ™ (doxycycline hyclate capsules USP), 20 mg
Lot RD0416

Method: USP Apparatus 2 (Paddles)/Water @ 37°C, 900 mL/50 RPM
Criteria: NLT % (Q) Dissolved in Minutes

Sample/Time	5 min	10 min	20 min	30 min
	Percent Dissolved			
1				
2				
3				
4				
5				
6				
Average	65	89	93	103
%RSD	16.6	12.4	8.6	1.2

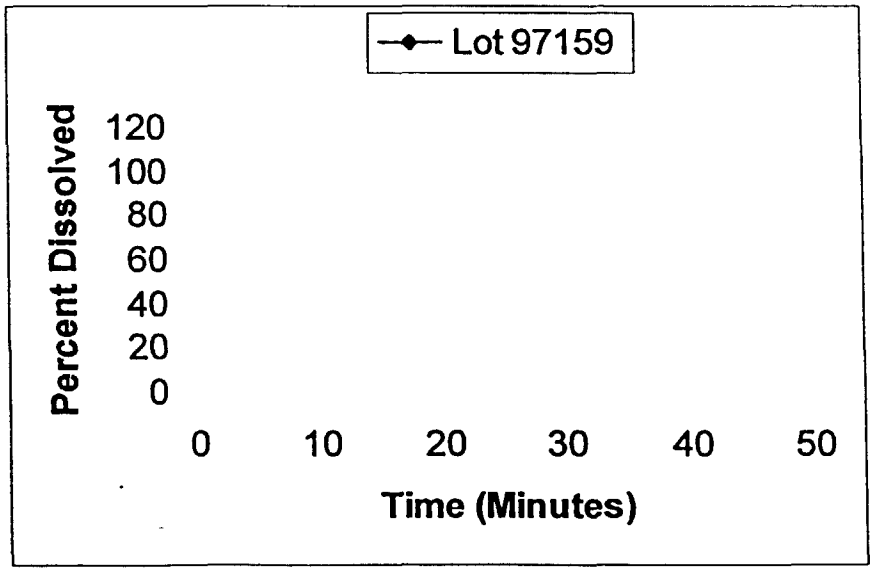


Periostat ™ (doxycycline hyclate capsules USP), 20 mg
Lot 97159

Method: USP Apparatus 2 (Paddles)/Water @ 37°C, 900 mL/50 RPM
Criteria: NLT % (Q) Dissolved in Minutes

Sample/Time	5 min	10 min	20 min	30 min	45 min (1)
	Percent Dissolved				
1					
2					
3					
4					
5					
6					
Average	44	82	94	97	105
%RSD	36.0	17.0	5.1	3.8	2.3

(1) RPM increased to after the minute time point.

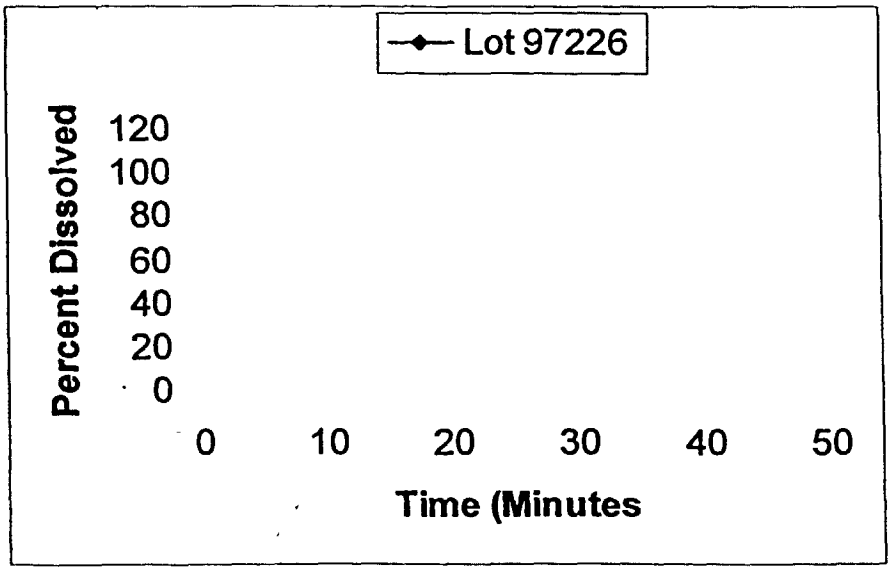


Periostat ™ (doxycycline hyclate capsules USP), 20 mg
Lot 97226

Method: USP Apparatus 2 (Paddles)/Water @ 37°C, 900 mL/50 RPM
Criteria: NLT % (Q) Dissolved in Minutes

Sample/Time	5 min	10 min	20 min	30 min	45 min (1)
	Percent Dissolved				
1					
2					
3					
4					
5					
6					
Average	58	77	88	91	98
%RSD	30.3	13.7	3.6	1.2	1.0

(1) RPM increased to after the minute time point.

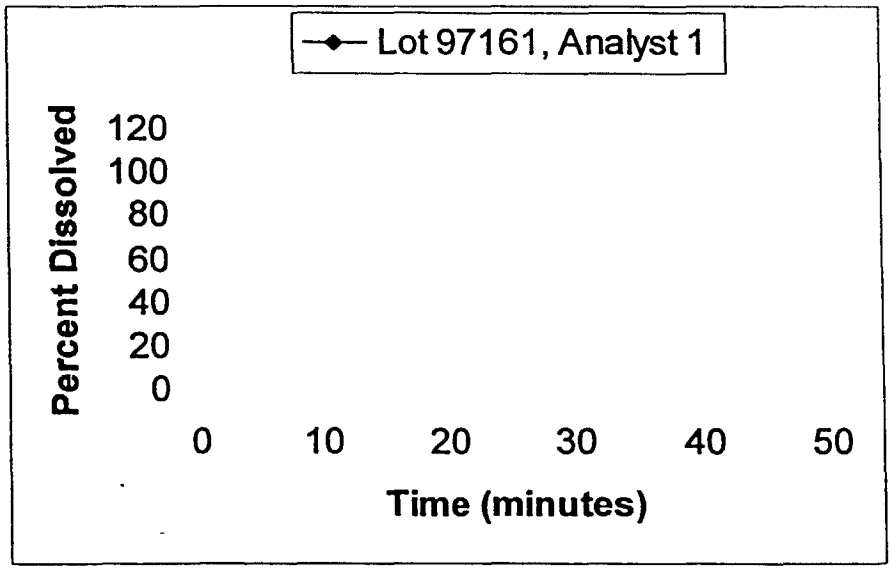


Periostat ™ (doxycycline hyclate capsules USP), 20 mg
Lot 97161
Analyst 1

Method: USP Apparatus 2 (Paddles)/Water @ 37°C, 900 mL/50 RPM
Criteria: NLT)% (Q) Dissolved in Minutes

Sample/Time	5 min	10 min	20 min	30 min	45 min (1)
	Percent Dissolved				
1					
2					
3					
4					
5					
6					
Average	69	81	95	97	101
%RSD	21.8	4.4	4.7	4.3	1.5

(1) RPM increased to after the minute time point.

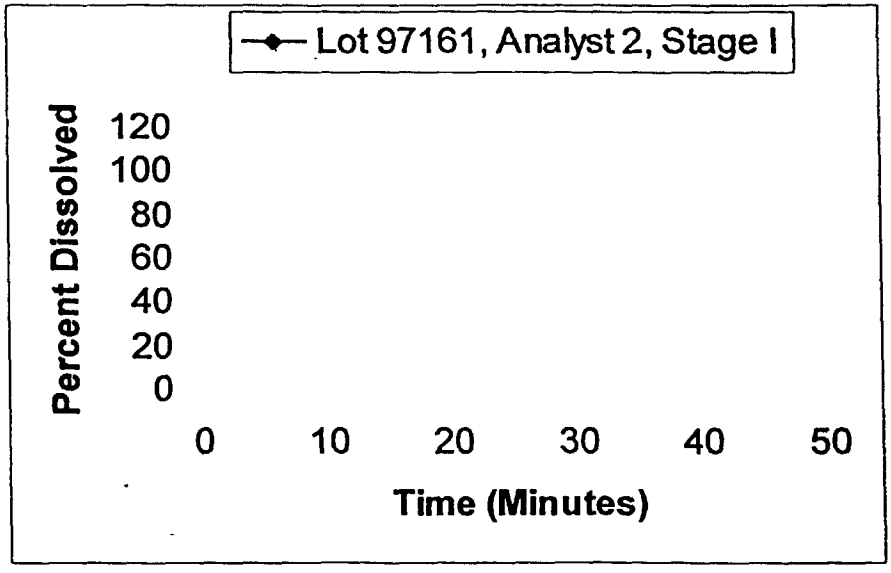


Periostat ™ (doxycycline hyclate capsules USP), 20 mg
Lot 97161
Analyst 2, Stage I

Method: USP Apparatus 2 (Paddles)/Water @ 37°C, 900 mL/50 RPM
Criteria: NLT % (Q) Dissolved in Minutes

Sample/Time	5 min	10 min	20 min	30 min	45 min (1)
	Percent Dissolved				
1					
2					
3					
4					
5					
6					
Average	48	80	90	93	104
%RSD	30.4	20.0	13.3	10.6	1.6

(1) RPM increased to after the minute time point.
(2) Fails Stage I



Periostat ™ (doxycycline hyclate capsules USP), 20 mg
Lot 97161
Analyst 2, Stage II

Method: USP Apparatus 2 (Paddles)/Water @ 37°C, 900 mL/50 RPM
Criteria: NLT % (Q) Dissolved in Minutes

Sample/Time	5 min	10 min	20 min	30 min	45 min (1)
	Percent Dissolved				
1					
2					
3					
4					
5					
6					
Average	66	90	97	99	105
%RSD	41.1	9.6	3.1	2.4	1.2

(1) RPM increased to after the minute time point.