CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-751

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

AUG 27 1998

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA 50-751	**SUBMISSION DATE:** 7/24/98, 7/2/1998, 6/29/98, 6/24/98,
PRODUCT: Doxycycline hyclate	
BRAND NAME: ATRIDOX™ (ATRIGEL® delivery system with doxycycline hyclate)	**REVIEWER:** Dan Wang, Ph.D.
SPONSOR: ATRIX laboratories, Inc. 2579 Midpoint Dr. Fort Collins, CO 80525	**TYPE:** Original Amendment

The sponsor has submitted the proposed labeling for the ATRIDOX™ drug product which have been prepared as a follow up to their June 17, 1998 meeting with FDA. Among the issues discussed in the meeting, Agenda item #3a is a biopharmaceutics issue. The Agency requested that Atrix conduct an comparative *in vitro* drug release study for the method of product constitution used during Phase 3 clinical trials (i.e., 100 cycles / 15 minute wait / 10 cycles) and the proposed abbreviated method of product constitution (i.e., 100 cycles). The study report for this *in vitro* drug release study was submitted in this submission.

The *in vitro* release method used is

The amount of drug release was measured at 1, 3, 6, 12, 24 and 48 hours. The rate of drug release from the formulation was calculated according to the method recommended in FDA SUPAC Guidance Document for Nonsterile Semisolid Dosage Forms. For each drop of the product, the slope of the linear regression of the cumulative release of doxycycline per unit weight of product (μg/mg) vs. the square root of time ($min^{0.5}$) was calculated. This slope was defined as the release rate for the drop. The inspection of the data showed that the plot of the cumulative release of doxycycline per unit weight of product vs. the square root of time was a curve rather than a straight line. The slope calculated from a curve does not represent the release rate of the drop. Following comments were sent to the sponsor.

RECOMMENDATION

The sponsor has adequately studied the *in vitro* release of doxycycline from the two mixing methods. Similar release profiles were obtained. The proposed abbreviated method of product constitution is therefore acceptable.

/S/

Dan Wang, Ph.D. 8/20/98
Division of Pharmaceutical Evaluation III

FT initialed by E. Dennis Bashaw, Pharm.D. EDB 8/27/98

cc:
NDA 50-751(Original)
HFD-540(Blay)
HFD-880(Division File)
HFD-880(Bashaw, Wang)
HFD-205(FOI)
HFD-344(Viswanathan)
CDR: Attn: Barbara Murphy

APR 9 1998

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA 50-751	**SUBMISSION DATE:** 3/31/1997,
PRODUCT: Doxycycline hyclate	4/4/97, 5/20/97, 5/21/97, 12/31/97,
BRAND NAME: ATRIDOX™ (ATRIGEL® delivery system with doxycycline hyclate)	2/13/98, 2/18/98
	REVIEWER: Dan Wang, Ph.D.
SPONSOR: ATRIX laboratories, Inc. 2579 Midpoint Dr. Fort Collins, CO 80525	**TYPE:** Original

ADDENDUM

This is an addendum to the original review for NDA 50-751 to reflect additional findings and the comment from Clinpharm/Biopharm Briefing.

1. Further review of the submission indicated that the sponsor has not conducted a comparative *in vitro* release study for the new and existing mixing regimen. Instead, they compared the content of extraction obtained from the constituted product following the new and existing mixing regimen. This study did not provide any information about the characteristics of drug release. Therefore, the new mixing regimen can not be granted from the biopharmaceutics point of view.

2. The statistical analysis results reported by the sponsor for Study AGD9701 should be as follows.

   Pharmacokinetics parameters (SE) including AUC, Cmax and Tmax are summarized in the following table.

	Octyldent	No-dressing	Ratio of geometric mean	90% C.I.
AUC (μg-hr/mL)	126000 (14700)	80700 (12000)	1.65	0.927 - 2.12
Cmax (μg/mL)	2510 (362)	1910 (319)	1.40	1.12 - 2.42
Tmax (hr)	55.9 (13.3)	23.6 (7.24)	-	-

   The results (ratio of geometric mean and 90% C.I.) calculated by the sponsor appears to be incorrect relative to AUC and Cmax values. However, no further data analysis was conducted because of the invalidity of this study as a bioequivalence study.

3. *In vitro* release method and specification

b. Specification

Amount released should be between % at hour and % at hours.

/S/

4/8/98

Dan Wang, Ph.D.
Division of Pharmaceutical Evaluation III

FT initialed by E. Dennis Bashaw, Pharm.D. 6/9/98

cc:
NDA 50-751(Original)
HFD-540(Blay)
HFD-880(Division File)
HFD-880(Bashaw, Wang)
HFD-205(FOI)
HFD-344(Viswanathan)

MAR 23 1998

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA 50-751	**SUBMISSION DATE:** 3/31/1997,
PRODUCT: Doxycycline hyclate	4/4/97, 5/20/97, 5/21/97, 12/31/97,
BRAND NAME: ATRIDOX™ (ATRIGEL® delivery system with doxycycline hyclate)	2/13/98, 2/18/98
	REVIEWER: Dan Wang, Ph.D.
SPONSOR: ATRIX laboratories, Inc.	
2579 Midpoint Dr.	
Fort Collins, CO 80525	**TYPE:** Original

I. BACKGROUND

This NDA is submitted for ATRIDOX™ (doxycycline hyclate) drug product. ATRIDOX™ is a topical dosage form indicated for use in treating chronic adult periodontitis. As described in the proposed labeling, ATRIDOX™ is a subgingival sustained-release product composed of a two syringe mixing system. Syringe A contains 450 mg of the ATRIGEL® Delivery System, which is a bioabsorbable, flowable polymeric formulation composed of 36.7% poly(DL-lactide) (PLA) dissolved in 63.3% N-methyl-2-pyrrolidone (NMP). Syringe B contains doxycycline hyclate to give a potency equivalence of 42.5 mg doxycycline. The constituted product is a pale yellow to yellow viscous liquid with a concentration of 8.5% w/w of doxycycline. The administration method is to apply the constituted product into periodontal pocket until the formulation reaches the top of the gingival margin, then cover the pockets with an appropriate retentive material that will assure the material is retained in the periodontal pocket for up to seven days. The product coagulates in the periodontal pocket with the help of water. A repeat application is recommended approximately every four months.

As part of this NDA, the applicant has submitted the results of two in vivo pharmacokinetic studies, study ACS-38 and study ACS-32. Study ACS-38 was to characterized the release profile of doxycycline in gingival crevicular fluid (GCF) following application of ATRIDOX™. Saliva and serum levels of doxycycline were also determined. This study compared the doxycycline release between subject groups receiving the drug product subsequently held in place by one of two different retentive materials and also the doxycycline release after oral administration. Study ACS-32 was a feasibility study conducted prior to ACS-38. The doxycycline release was compared for three treatment groups that had been treated with ATRIDOX™ and then: 1) covered with Coe-Pak periodontal dressing; 2) covered with Octyldent periodontal adhesive; 3) not covered with a retentive material.

On Dec. 31, 1997, the applicant submitted three additional PK studies to establish bioequivalence between 1) ATRIDOX treatments covered with Octyldent periodontal adhesive and not covered with a retentive material to obtain the labeling for not using retentive material in the treatment; 2)existing and new mixing regimen to obtain the labeling for a new mixing regimen; 3)aged and non-aged products.

In vitro dissolution section was submitted in Chemistry section and reviewed by the Chemist.

II. RECOMMENDATION

1. The applicant has adequately studied the pharmacokinetics/pharmacodynamics of doxycycline after topical application of ATRIDOX™. The results indicate much higher GCF doxycycline levels following topical application of ATRIDOX™ than those following 100 mg doxycycline oral dose. Systematic exposure of doxycycline after topical application of ATRIDOX™ is minimal compared to that after oral dose. See "**CONCLUSIONS**" section of the review for the results of these studies.

2. Bioequivalence is not established for 1) ATRIDOX treatments covered with Octyldent periodontal adhesive and not covered with a retentive material; 2)existing and new mixing regimen; 3)aged and non-aged products. Furthermore, the inconsistent sampling technique used for GCF sampling in all studies submitted caused high variability in doxycycline content determination. This method is considered only acceptable for the purpose of descriptive pharmacokinetics of doxycycline in GCF but not for the purpose of bioequivalence determination. Therefore, no labeling claim can be made based on bioequivalence studies.

3. The dissolution specification criteria proposed originally by the applicant is not acceptable. The applicant now agreed with the criteria proposed by the Agency.

4. Comment #1 needs to be conveyed to the applicant.

TABLE OF CONTENTS Page No.

III. Analytical Methods

Overall, the assay validation data are acceptable.

IV. SUMMARY OF *IN VIVO* PHARMACOKINETICS STUDIES

STUDY ACS-38 - A single-center pharmacokinetics study comparing drug release characteristics of VR-303-ABS (ATRIGEL® delivery system with doxycycline hyclate equivalent to 8.5% doxycycline) with Coe-Pak™ periodontal dressing, VR-303-ABS with Octyldent™ periodontal adhesive and oral doxycycline hyclate.

The objectives of this study was to characterize the release profile of doxycycline in the gingival crevicular fluid (GCF), saliva, and serum of subjects with chronic adult periodontitis following treatment with VR-303-ABS covered with Coe-Pak™ periodontal dressing, VR-303-ABS covered with Octyldent™ periodontal adhesive or oral doxycycline; to compare doxycycline levels of the three treatment groups; to compare the doxycycline levels in GCF from a different, but clinically comparable, periodontal site that has not been treated with VR-303-ABS with each of the VR-303-ABS-administered treatment GCF sites.

This was a single-center, single-blind (laboratory personnel who analyze samples were blinded), three-way parallel design. A total of 32 patients participated the study and 31 subjects completed the study (1 withdraw). These patients had chronic adult periodontitis characterized by at least two quadrants that contained at least four pockets which measured 5 mm or greater and bled on gentle probing. Thirteen subjects had VR-303-ABS applied to all qualifying sites in one half of the mouth (upper right and lower right or upper left and lower left) and Coe-Pak™ periodontal dressing applied over the treated sites. Thirteen subjects had VR-303-ABS applied to all qualifying sites in one half of the mouth and Octyldent™ periodontal adhesive applied over the treated sites. If the retentive material was lost between application at Day 1 and Day 7, the subject notified the investigator. At the investigator's discretion, the retentive material was reapplied. Six subjects were given oral doxycycline hyclate 100 mg dose at baseline and Hour 12, and daily thereafter for an additional 7 days (typical time period for use of oral doxycycline as an adjunct to periodontal treatment). Serum, GCF and saliva samples were obtained at Baseline and at Hours 2, 4, 6, 8, 12, 18 and 24 of Day 1 and at Days 2, 3, 5, 7, and 8. After the Day 7 samples were obtained, the VR-303-ABS and dressing were removed only from the Coe-Pak™ subjects. Retrieved VR-303-ABS was later returned to the sponsor. In the Octyldent™ group, product, if present, was not removed until three months (this design allowed observations on the safety and efficacy of leaving the product in place to bioabsorb or be expelled naturally). In addition, GCF and saliva samples were also obtained from all subjects at Days 10, 14, 21 and 28. After applying VR-303-ABS, subjects were instructed to refrain from eating for one hour and from having any solid food until after the Day 1 visit, and not to brush, floss, or use any mechanical oral hygiene procedures within the first 24 hours after VR-303-ABS application. Additional information about subjects and study design can be found in the summary sheet in appendix I.

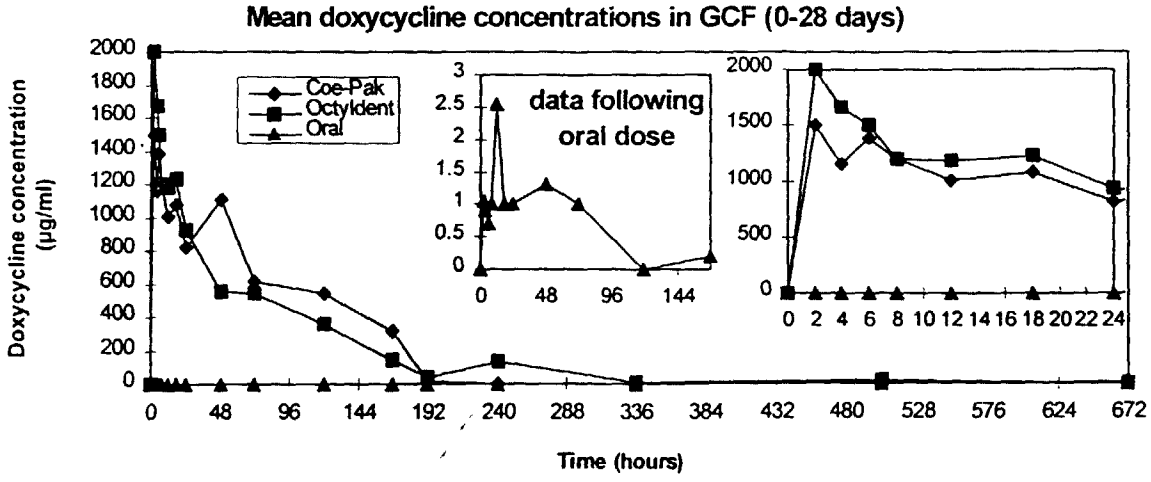
Sampling of GCF - Prior to administering the VR-303-ABS or oral doxycycline hyclate, one site per treated quadrant were selected for the GCF samples; thereby providing two GCF sample sites in the treated half of the mouth. The reported value at each time point was the mean of the two

samples. This site, in each quadrant, must be a buccal interproximal site. These sites was considered the Treated GCF sites, known as the "T" site. All subsequent "T" GCF samples were taken from these sites. A third qualifying site were selected in an untreated quadrant of the mouth. This site was considered the Control site, known as the "C" site. GCF samples form the "T" site and "C" site were obtained using two Periopaper® strips per site. The strip was held with needle holder and inserted to the maximum depth possible. If polymer is present, insert the strip between the polymer and the gingiva. The volume of GCF on each strip was assessed and recorded.

RESULTS:

Pharmacokinetics

1. Doxycycline release profiles in GCF - VR-303-ABS doxycycline release profiles in GCF were assessed by two methods: mean doxycycline concentration at each time point and the conventional Cmax, tmax method. The applicant indicated that assessment of the mean doxycycline concentration in GCF at each time point was considered to be the most meaningful parameter for determining peak doxycycline concentration. This is primarily due to an issue with sampling variability. The doxycycline concentration found in the periodontal pocket can vary depending on how close the GCF sampling strip is placed to the drug product in the pocket. It is believed that this is why some subjects have high concentrations at later time points. This sampling variation causes the Tmax calculation to be less meaningful than the mean concentrations at each individual time point when describing the release profiles of doxycycline in GCF in each of the respective treatment group. The reviewer agrees with the applicant's opinion. The mean doxycycline concentration data can be found in the appendix I. The release profile of the mean concentration of doxycycline in GCF are also plotted below.



Following treatment with VR-303-ABS, doxycycline levels in GCF peaked at 2 hours in both the Coe-Pak™ (mean =1500 µg/mL) and Octyldent™ (mean = 2000 µg/mL) groups. These levels

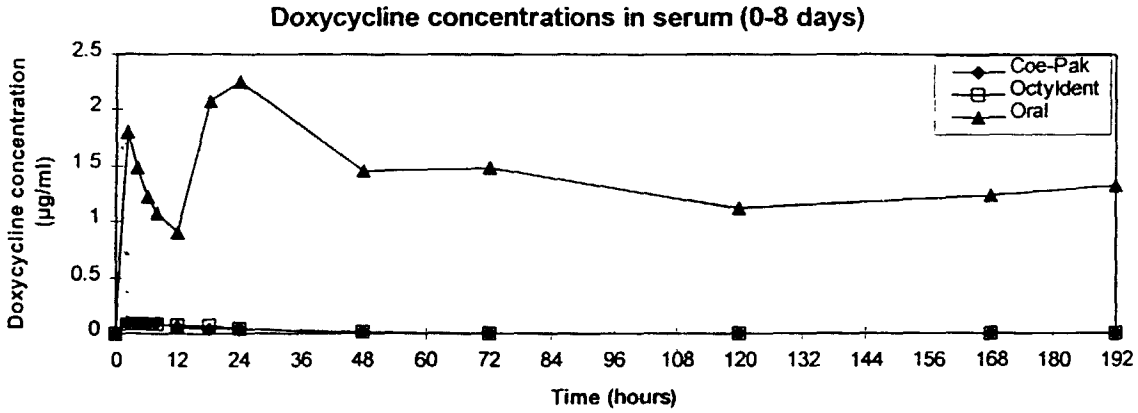
remained above 1000 µg/mL in both groups through 18 hours at which time the levels began to decline gradually. By Day 7, the mean levels in the Coe-Pak™ and Octyldent™ groups were 317 µg/mL and 148 µg/mL respectively. Subjects receiving oral doxycycline had peak GCF levels of 2.5 µg/mL at 12 hours following the initial oral dose, and generally at levels near 1.0 µg/mL or less through Day 10. The doxycycline GCF levels in untreated site from most samples were zero. In the samples that did have doxycycline levels (less than 10%), the doxycycline levels were normally less than 10 µg/mL.

There was an unexpected high mean value of 130 µg/mL on Day 10 in the Octyldent group caused by GCF concentration values in three subjects. It was indicated by the sponsor that the high variability in GCF levels was related to the GCF paper strip coming in contact with areas of retained product. Inspection in individual data revealed that overall GCF concentration data were acceptable. However, for some other studies reviewed later, the sampling technique for GCF doxycycline concentration caused inconsistent observations in GCF levels and were considered not acceptable.

2. Doxycycline levels in saliva and serum.

Following treatment with VR-303-ABS, doxycycline levels in saliva also peaked at 2 hours in both the Coe-Pak™ (mean = 4 µg/mL) and Octyldent™ (mean = 9 µg/mL) groups. These mean levels dropped below 2 µg/mL at 6 hours in the Coe-Pak™ group and at 24 hours in the Octyldent™ group. Minimal doxycycline was detected in the saliva of subjects administered oral doxycycline. The highest level in these subjects was 0.12 µg/mL at 18 and 24 hours. Doxycycline concentration profile in saliva can be found in appendix I.

Mean serum doxycycline levels are show below.



Low levels of doxycycline were detectable in the serum of both groups receiving VR-303-ABS at levels of 0.08 to 0.1 µg/mL from 2 to 8 hours post product application and dropped to 0.05 to 0.07 µg/mL from Hour 12 to Hour 24. After Day 2, serum levels of doxycycline were

undetectable (LOD=0.04 μg/mL). In contrast, much higher concentrations (about 100 times) were observed following oral administration.

Traditional pharmacokinetic parameters (AUC, Cmax and tmax) were also calculated as follows.

Body Fluid	Parameter	Coe-Pak™ mean	Octyldent™ mean	Oral doxycycline mean
GCF[1]	Cmax (μg/mL)	2,640	3,100	3.50
	AUC (μg-h/mL)	120,000	93,000	115
	Tmax (hours)	24.26	10.56	23.86
Serum[1]	Cmax (μg/mL)	0.12	0.10	2.60
	AUC (μg-h/mL)	2.32	2.10	264
	Tmax (hours)	5.14	5.08	15.85
Saliva[1]	Cmax (μg/mL)	4.15	8.41	0.12
	AUC (μg-h/mL)	92.8	148	10.5
	Tmax (hours)	3.68	2.30	18.03

Pharmacodynamics - Periodontal Measurements

According to the literature, suspected periodontal pathogens have a susceptibility to doxycycline ranging from μg/mL. The MIC level of suspected periodontal pathogens is ≤ 6 μg/mL. It is observed that GCF doxycycline levels after the treatment with VR-303-ABS were well above this range (100 to 700 times higher). GCF doxycycline levels following oral dose were also normally above this range. The results of clinical outcome are summarized in the following table.

Measurement	Time Point	VR-303-ABS with Coe-Pak™	VR-303-ABS with Octyldent™	Oral Doxycycline
Mean Probing Depth Reduction (mm) (S.E.)	Day 28	1.15 (0.15)	N/A	1.39 (0.51)
	Month 3	N/A	1.09 (0.17)	N/A
Bleeding on Probing Reduction (S.E.)	Day 28	0.91 (0.07)	N/A	0.97 (0.2)
	Month 3	N/A	0.93 (0.15)	N/A

The results were similar for the three treatment groups. No differences in clinical outcome were observed between the Coe-Pak™ group, where polymer product was removed at 7 days, and the Octyldent™ group, where the polymer product was not removed at Day 7. This indicates that not removing the residual product at Day 7 has no impact on clinical efficacy. No remaining product was noted at Month 3, the final evaluation point in the Octyldent™ group.

CONCLUSIONS:

Both VR-303-ABS treatment groups had high GCF doxycycline concentrations during the 7 day treatment period. The concentrations were times of the MIC level of suspected periodontal pathogens. The oral treatment group had much lower GCF levels (an average of 1.0

to 2.5 μg/mL). The saliva doxycycline levels were at the magnitude of 1 to 9 μg/mL for VR-303-ABS treatments and minimal after oral doxycycline administration (the highest being 0.12 μg/mL). After both VR-303-ABS treatments, serum doxycycline levels were low with Cmax of 0.12 μg/mL, while oral administered doxycycline produced much higher serum doxycycline levels (mean Cmax of 2.6 μg/mL).

The clinical outcome of the three treatment groups were similar. Both safety and efficacy data indicated that removal of the residual product at Day 7 was not necessary.

STUDY ACS-32 - A multicenter, parallel design study, comparing drug release characteristics of VR-303-ABS (ATRIGEL delivery system with doxycycline hyclate, equivalent to 8.5% doxycycline) with Coe-Pak™ periodontal dressing, VR-303-ABS with Octyldent™ periodontal adhesive and VR-303-ABS without a retentive material

As stated in the title, the objective of this study was to quantitate and determine whether the levels of doxycycline released in the GCF of subjects with chronic adult periodontitis were comparable in all three treatment groups. Secondary objectives were to evaluate the retention characteristics of the product in periodontal pockets with and without the use of Coe-Pak™ and Octyldent™ retentive materials and to assess overall safety.

This open-label study was conducted at two investigational centers, with 20 subjects enrolled at each center (6 subjects per treatment group and 2 supplemental subjects for training). The study design and inclusion criteria of this study were very similar to that of Study ACS-38, with VR-303-ABS without a retentive material in the place of oral administration treatment group. Subjects were randomized to one of three treatment groups. Following treatment, subjects returned to the study center for the collection of GCF samples at hours 2, 4, 6, 24, and Days 3,7, 14, and 28. Those subjects who received the Coe-Pak™ dressing had the dressing removed at Day 7. In all subjects, VR-303-ABS was not removed and remained in the periodontal pockets to be lost naturally or bioabsorbed. Periodontal examinations including pocket depth and bleeding on probing, were conducted at screening and Day 28.

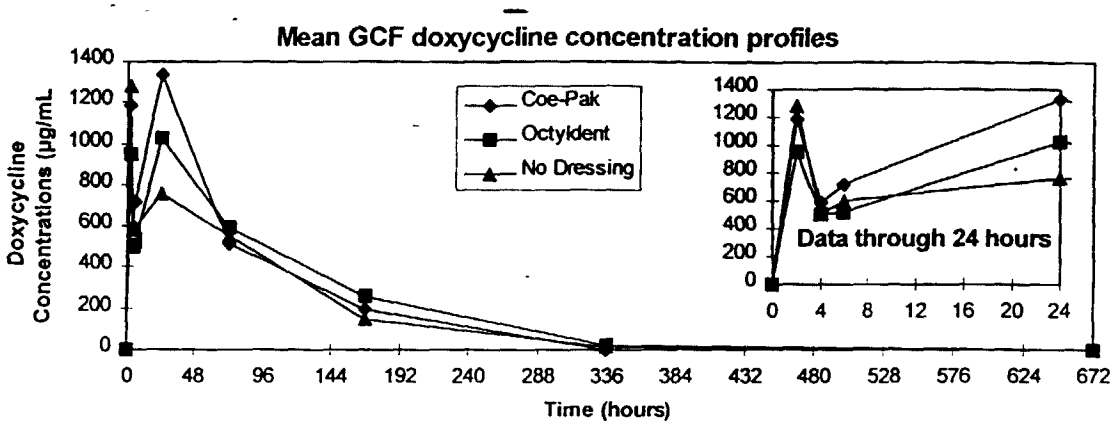
Pharmacokinetics was evaluated by doxycycline release into GCF. Comparison of the three treatment groups was conducted using analysis of variance for GCF concentrations at each time point, the percent of each subject's retained product and retentive material remaining at each time point and the subject's mean change-from-baseline values for clinical measurements (Day 28).

Results:

Pharmacokinetics

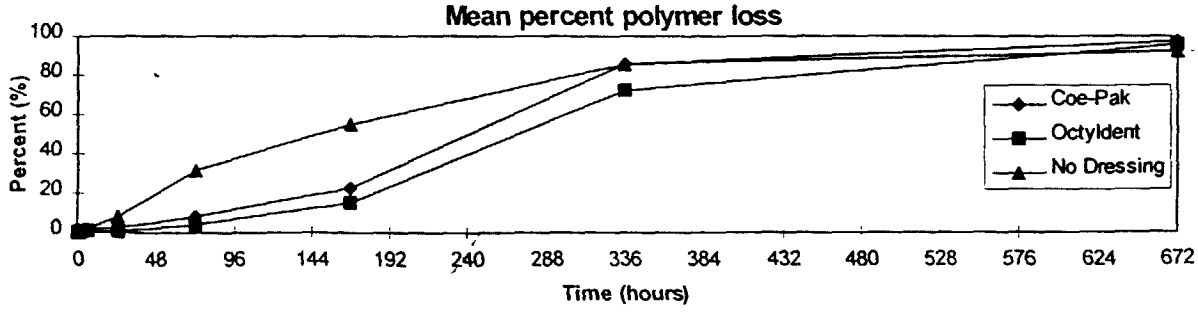
Mean GCF concentrations, standard error and statistical analysis results can be found in the

appendix I. Mean GCF concentrations after three treatment are also plotted below:



Similar to Study ACS-38, high variability was observed for GCF concentrations at each time point. ANOVA analysis showed no significant difference between treatment groups at all time points. In a later submission, the applicant sought for a labeling of no dressing treatment. Per reviewer's request, the applicant conducted a bioequivalence analysis for Octyldent treatment and no dressing treatment. The results showed that ratio of means (no dressing versus Octyldent treatments) and 90% confidence intervals for AUC and Cmax were 1.44 (C.I.=0.98, 2.12) and 0.83 (C.I. = 0.59, 1.15), respectively. The result of 40% higher AUC from no dressing treatment did not match the mean concentration plotted above and no reasonable explanation can be found.

No significant differences were noted in product retention between the Coe-Pak™ dressing and Octyldent™ adhesive groups. No polymer had been lost at Hour 2, however, one subject in the no-dressing group had lost polymer by Hour 4. No subjects in the two retentive material groups lost polymer until Day 3, when one subject in the Octyldent™ adhesive group lost polymer. By Day 7, two Coe-Pak™ dressing subjects, two Octyldent™ subjects and six no-dressing subjects had lost polymer from at least one of the two GCF sites. Mean percent polymer loss are plotted here.



It is observed that no-dressing group had a higher percentage loss of polymer than the other two groups.

Periodontal Measurements

Clinical parameters, including pocket depth reduction and bleeding on probing score reduction, were measured for three treatment groups. Mean values(standard errors) are summarized in the following table.

Centers time points	Mean Pocket Depth (mm) Changes			Mean Bleeding on Probing score changes		
	Coe-Pak™	Octyldent™	No Dressing	Coe-Pak™	Octyldent™	No Dressing
All Centers						
Baseline	5.33(0.27)	5.65(0.60)	5.67(0.47)	1.73 (0.42)	1.91(0.52)	1.80(0.42)
Day 28	-1.19(0.47)	-1.01(0.26)	-1.15(0.43)	-0.70(0.36)	-0.74(0.47)	-0.85(0.38)
Louisiana Sta. Univ.						
Baseline	5.18(0.20)	5.37(0.25)	5.61(0.51)	1.98(0.45)	2.22(0.54)	1.90(0.59)
Day 28	-1.21(0.25)	-1.02(0.34)	-1.11(0.21)	-0.57(0.44)	-0.65(0.55)	-1.02(0.46)
Univ. Of Colorado						
Baseline	5.48(0.26)	5.92(0.74)	5.73(0.47)	1.47(0.19)	1.60(0.27)	1.72(0.23)
Day 28	-1.18(0.66)	-1.00(0.20)	-1.18(0.58)	-0.83(0.23)	-0.83(0.39)	-0.72(0.28)

Plaque index changes were also measured and no significant difference was found between treatment groups. Positive clinical improvements were observed in all three treatments. Statistical analysis showed no significant difference between three treatment groups.

The applicant indicated that no serious adverse events were reported during the study. Treatment-related adverse events were typical of those seen in periodontal subjects and generally distributed evenly between treatment groups. There appeared to be no additional risk incurred by not removing the product at Day 7, thereby allowing it to be expelled naturally or bioabsorbed. Statistical meaningful efficacy and safety data were reported in two large multicenter trials and reviewed by the M.O.

Conclusions:

The results of this study indicate that mean GCF doxycycline levels were not significantly different between the treatment groups. High but similar variabilities in GCF doxycycline levels were observed for all three treatment groups. Longer retention time was observed for the two groups with retention materials. Clinical parameters, including pocket depth reduction and bleeding on probing score reduction, showed similar positive improvement for all three treatment groups. Safety data indicate there is no additional risk incurred by not removing the product at Day 7.

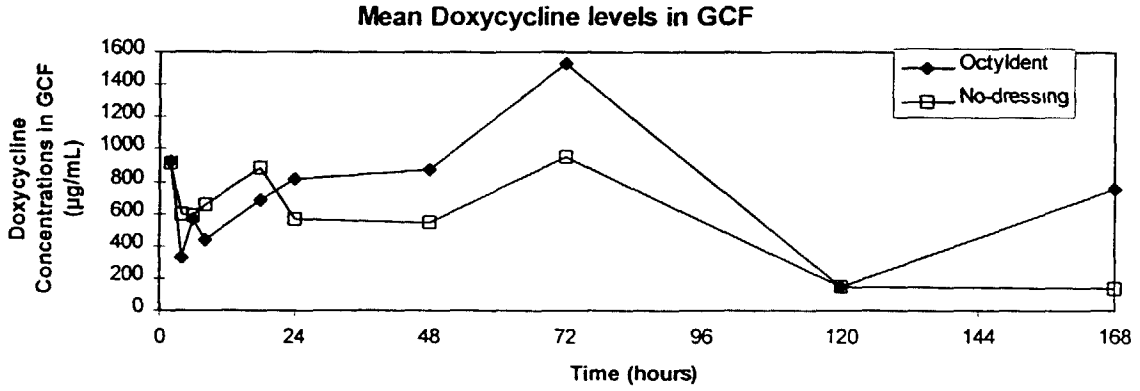
Study AGD9701 - A Single-Center, Single-Blind, Parallel Design, Bioequivalence Study Comparing Drug Release Characteristics of VR-303-ABS (ATRIGEL® Delivery System With Doxycycline Hyclate, Equivalent to 8.5% Doxycycline) Covered With Octyldent™ Periodontal

Adhesive Versus VR-303-ABS Used With No Retentive Material.

As stated in the title, the objective of this study was to determine whether the levels of doxycycline in the GCF of subjects with chronic adult periodontitis are comparable when treated with VR-303-ABS and covered with Octyldent™ periodontal adhesive versus being treated with VR-303-ABS and not covered with any retentive material. The design of this study was similar to those of Studies ACS-38 and ACS-32. Twenty-four patients were enrolled with 12 receiving VR-303-ABS covered with Octyldent™ and 12 receiving VR-303-ABS with no retentive material. GCF doxycycline levels were analyzed using method T280. No validation report was submitted for this study.

RESULTS:

The mean doxycycline levels in GCF are reproduced in the following plot.



Pharmacokinetics parameters (SE) including AUC, Cmax and Tmax are summarized in the following table.

	Octyldent	No-dressing	Ratio of geometric mean	90% C.I.
AUC (µg-hr/mL)	126000 (14700)	80700 (12000)	0.830	0.620 - 1.11
Cmax (µg/mL)	2510 (362)	1910 (319)	1.28	0.864 - 1.90
Tmax (hr)	55.9 (13.3)	23.6 (7.24)	-	-

The results show that bioequivalence is not demonstrated between the Octyldent group and No-dressing group. The mean AUC of No-dressing group is significantly lower than that of Octyldent group.

Another concern with this study is that the sampling technique is lack of consistency. Higher mean concentrations were observed at Day 3. Inspection of individual data showed high day to day variability. As indicated in study ACS-38, this might be related to the GCF paper strip coming in contact with areas of retained product. Along with this study (Study9701), same observation has been found for Study AGD9607 and Study AGD9705. Therefore, the three

studies submitted on Dec. 31, 1998 can not be used for bioequivalence purpose due to the inadequacy of sampling technique.

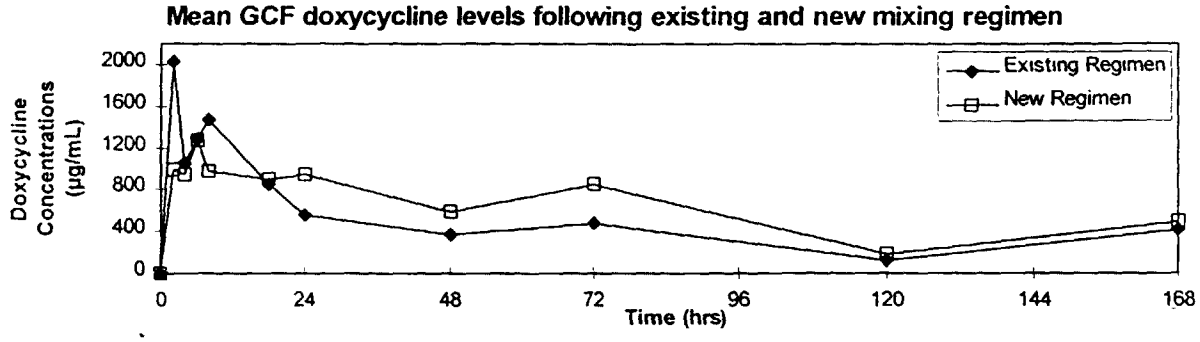
Study AGD9607 and AGD9705 are reviewed below for documentation purpose.

Study AGD9607 - A Single-Center, Single-Blind, Parallel Design, Bioequivalence Study Comparing Drug Release Characteristics of VR-303-ABS (ATRIGEL® Delivery System With Doxycycline Hyclate, Equivalent to 8.5% Doxycycline) Constituted with the Existing Mixing Regimen Versus VR-303-ABS Constituted with a New Mixing Regimen

As stated in the title, the objective of this study was to determine whether the levels of doxycycline in the GCF of subjects with chronic adult periodontitis were comparable when treated with VR-303-ABS using the existing mixing regimen versus a new mixing regimen. The design of this study was similar to those of Studies ACS-38 and ACS-32. Twenty-five patients were enrolled with 12 receiving VR-303-ABS constituted with the existing mixing regimen and 13 receiving the same product constituted with the new mixing regimen. All treated sites were covered with Octyldent™ periodontal adhesive. The existing mixing system includes a 15 minute wait after an initial 100 cycle mixing followed by 10 additional mixing cycles. The new regimen does not include the 15 minute wait or the additional 10 mixing cycles.

RESULTS:

Mean doxycycline levels in GCF are show in the following plot.



The results of statistical analysis for AUC and Cmax of these two treatments are shown below.

Ratio of AUC (new/existing)	90% C.I. of AUC (new/existing)	Ratio of Cmax (new/existing)	90% C.I. of Camx (new/existing)
0.830	0.620 - 1.11	1.28	0.864 - 1.90

Bioequivalence was not demonstrated for the existing and new mixing regimen. As with study AGD9701, inspection of individual data showed high day to day variability which may be related

to the GCF paper strip coming in contact with areas of retained product or other factors. Therefore, regardless of the result of bioequivalence analysis, the data from this study can not be used to support bioequivalence of the two treatments studied.

Study AGD9705 - A Single-Center, Open Label Study Assessing Drug Release Characteristics of VR-303-ABS (ATRIGEL® Delivery System With Doxycycline Hyclate, Equivalent to 8.5% Doxycycline)

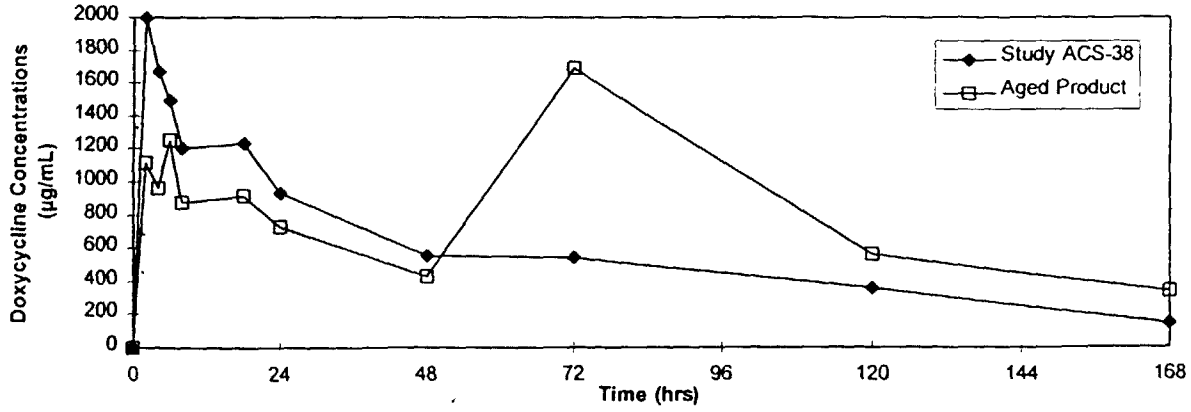
The primary objective of this study was to determine whether the doxycycline release profile of subjects treated with VR-303-ABS approaching the end of its proposed shelf-life was comparable to historical doxycycline GCF data collected in Atrix Study ACS-38 which used product that was not near the end of its shelf-life.

Formation: Lot number: 10J22A. To assure that the test article was approaching the end of its shelf-life, it was stored at an accelerated condition of 30°C at 60% relative humidity for approximately 11 months. Once the samples were packaged for use for the clinical study, they were stored at 5°C as would be consistent with clinical use.

This is a seven-day, single-center, single-arm study. Twelve patients participated the study. The study design and method are similar to Study ACS-38. Octyldent adhesive was applied to the treated areas at the Hour 8 visit.

Results:

Mean GCF doxycycline concentrations following administration of aged product are compared with those obtained from Study ACS-38 in the following plot.



An unexpected high concentration was observed on Day 3. As indicated in previous study reviews, this might related to the inconsistent sampling technique.

Mean pharmacokinetic parameters obtained from this study and Study ACS-38 are summarized below.

	Study AGD9705 (n=12)			ACS-38 (Octyldent) (n=12)		
	Mean	S.E.	95% C.I.	Mean	S.E.	95% C.I.
Cmax	2290	371	1480 - 3110	3110	436	2150 - 4070
AUC	128000	31900	58000 - 198000	93000	12400	65600 - 120000
Tmax	31.1	11.5	5.79 - 56.4	10.56	7.90	-6.84 - 28

The result of bioequivalence analysis are listed below.

Ratio of AUC (aged/non-aged)	90% C.I. of AUC (aged/non-aged)	Ratio of Cmax (aged/non-aged)	90% C.I. of Camx (aged/non-aged)
1.10	0.675 - 1.78	0.720	0.439 - 1.18

Bioequivalence was not demonstrated for the two treatments studied. High variability among samples due to poor sampling skill was also observed in this study along with other studies. Therefore, the data from this study can not be used to support bioequivalence of aged product to non-aged product.

V. *IN VITRO* RELEASE STUDY

In original NDA submission, no *in vitro* drug release test method or specification were submitted under Human Pharmacokinetics and Bioavailability. The information was submitted under Chemistry section of the NDA. After the reviewer's request following 45-day filing meeting, the applicant submitted partial *in vitro* release data to the PK reviewer. A complete review of *in vitro* release studies has been conducted by the review chemist. Several meetings have been held between the PK reviewer, PK team leader, review chemist, and chemistry team. It was agreed that the *in vitro* release specification proposed by the applicant was not acceptable.

VI. CONCLUSIONS

Based on *in vivo* pharmacokinetic/pharmacodynamic studies, the following conclusion can be made:

1. Much higher GCF doxycycline concentrations (an average of more than 700 times) were observed after topical application of ATRIDOX™ than those after 100 mg oral doxycycline dose, while doxycycline concentrations were much lower in serum (about 20 times) following topical use of ATRIDOX™ than those after 100 mg oral doxycycline dose.

2. Following ATRIDOX™ treatments, mean GCF doxycycline levels were similar when two different retentive materials were used (Coe-Pak periodontal dressing and Octyldent periodontal adhesive). These levels were also similar to those when no retentive material was used.

3. High variability was observed for GCF doxycycline concentration determination following topical ATRIDOX™ treatments. The applicant indicated that this was related to the GCF paper strip coming in contact with areas of retained product when sampling. This sampling technique is considered not acceptable for the purpose of bioequivalence determination. Therefore, no labeling claim can be made based on bioequivalence studies.

4. A valid bioequivalence study has not been carried out for ATRIDOX™ treatments with and without retentive material. There is also no other supporting evidence for the no-dressing treatment indication. Therefore, the no-dressing treatment can not be granted from the biopharmaceutics point of view.

5. A valid bioequivalence evaluation trail has not been carried out for the new and existing mixing regimen. However, the in vitro release test showed that the release of doxycycline following the new mixing regimen met the *in vitro* release specification for the product. Therefore, the new mixing regimen are considered acceptable.

6. Removal of the residual product at Day 7 was not necessary. The residual product can be left in place to bioabsorb or be expelled naturally.

7. Clinical parameters, including pocket depth reduction and bleeding on probing score reduction, showed similar positive improvement for all treatment groups including topical ATRIDOX™ treatments with or without retentive materials, and 100 mg doxycycline oral dose. However, it should be noted that these clinical parameters are not the primary efficacy end points for the indication of this NDA.

VII. COMMENT(need to be sent to the applicant)

1. The sampling technique used for GCF sampling caused high variability in doxycycline GCF content determination. This method is considered only acceptable for the purpose of descriptive pharmacokinetics of doxycycline in GCF but not for the purpose of bioequivalence determination. Therefore, no labeling claim can be made based on bioequivalence studies.

VIII. LABELING COMMENTS

In the Pharmacokinetics section of the labeling, the applicant described the results of Study ACS-38. In this study, two different retentive materials were used (Coe-Pak periodontal dressing and

Octyldent periodontal adhesive, referred as Coe-Pak and Octyldent in the following). However, only the results of treatment using Coe-Pak were reported in the labeling.

In Product Administration section of the labeling, the applicant does not specify the retentive material to be used to retain the material in the periodontal pocket. Since the no-retentive material indication will not be approved (the method the applicant intends to use), it is very likely that Octyldent rather than Coe-Pak will be used as retentive material. If this is the case, pharmacokinetic study results should be reported for the treatment using Octyldent. If both retentive materials may be used in the future, the results from both treatments should be included in the labeling. Therefore, the Pharmacokinetics section of the labeling should be revised as following:

Pharmacokinetics

/S/ 3/23/98

Dan Wang, Ph.D.
Division of Pharmaceutical Evaluation III

FT initialed by E. Dennis Bashaw, Pharm.D. 3/13/98

cc:
NDA 50-751(Original)
HFD-540(Blay)
HFD-880(Division File)
HFD-880(Bashaw, Wang)
HFD-205(FOI)
HFD-344(Viswanathan)
CDR: Attn: Barbara Murphy