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APPLICATION NUMBER:NDA 50-751

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

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NDA: 50-751/3S
Applicant: Atrix Laboratories, Inc., 2579 Midpoint Drive, Fort Collins, CO 80525-4417
Name of Drug: Atridox
Route of Administration: Topical
Documents Reviewed: NDA 50-751: Vol. 1.1, 1.21-1.74, 1.286, Vol. 8.1, 8.2-8.21
Indication: Chronic Adult Periodontitis
Related INDs: IND
Related NDAs: AADA 62-865
Dental Officer: J. Kelsey, D. D.S., M. B. A. (HFD-540)

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Introduction : The sponsor, Atrix Laboratories, Inc., has developed a flowable, bioabsorbable drug delivery system (ATRIGEL[®] Delivery System) which solidifies upon contact with the aqueous fluids in the periodontal pocket, resulting in a sustained release system for incorporated drug. For periodontal treatment, the delivery system has been paired with the antimicrobial drug, doxycycline hyclate. Doxycycline hyclate was chosen because it is an approved drug with known activity against periodontal pathogens. The safety profile of doxycycline hyclate is also well characterized. The product presentation has a two syringe configuration, with one syringe containing the drug substance and the other syringe containing the ATRIGEL[®] Delivery System. The product is constituted prior to use. The proposed trade name for the product is ATRIDOX[™] . The sponsor submitted three trials, ACS-34, ACS-35, and AGD9603 to support the efficacy and safety of ATRIDOX[™] .

Study Design : ACS-34 and ACS-35 were pivotal, randomized, single blind, parallel studies. They were designed as the primary Phase 3 clinical trials to demonstrate clinical efficacy of the two-phase dosage form (ATRIDOX[™]) to be marketed. The four-arm design of these studies was based upon recommendations of FDA. These arms included 1) ATRIDOX[™], 2) vehicle control (placebo), 3) scaling and root planning (active control), 4) oral hygiene (no treatment control). The clinical endpoint of these studies was gain in periodontal attachment level. Clinical efficacy was demonstrated by comparing the doxycycline (ATRIDOX[™]) group to the vehicle and oral hygiene groups with respect to gain in periodontal attachment. Additional objectives were to: 1) compare the ATRIDOX[™] group to the vehicle and oral hygiene groups with respect to reductions in periodontal probing depth and bleeding on probing scores, as well as safety measures. 2) compare the ATRIDOX[™] group with the scaling and root planning (SRP) group with respect to gain in periodontal attachment, reductions in probing depth and bleeding on probing, and measures of safety. In the single-blind design, the examiner who performed the clinical efficacy evaluations was blinded to treatment identification. The investigators who administered the treatment and the subjects were unblinded because of dissimilarity of treatment. In these two trials, ATRIDOX[™] drug product [VR-303-ABS: ATRIGEL[®] Delivery System with 10% doxycycline hyclate, equivalent to 8.5% doxycycline] was covered with Coe-Pak[™] dressing and removed at Day 7.

Study AGD9603 was a phase 3, randomized, single blind, three-arm, parallel group, multicenter study. A total of 605 subjects were enrolled at 14 investigational sites. Subjects were randomized to one of the three arms: 1) ATRIDOX™ drug product [VR-303-ABS: ATRIGEL® Delivery System with % doxycycline hyclate, equivalent to % doxycycline] retained with Octyldent™ adhesive and left to biodegrade or be expelled naturally (Doxy-Left In), 2) ATRIDOX™ drug product [VR-303-ABS: ATRIGEL® Delivery System with % doxycycline hyclate, equivalent to % doxycycline] covered with Coe-Pak™ dressing and removed at Day 7 (Doxy-Removed), or 3) vehicle control (placebo).

The primary objective for this study was 1) to show equivalence of the gains in attachment level between ATRIDOX™ left in place to bioabsorb or be naturally expelled when retained with Octyldent™ adhesive and ATRIDOX™ removed at Day 7 when covered with Coe-Pak™ dressing, and 2) to demonstrate the superiority of these two ATRIDOX™ regimens to the vehicle control retained with Octyldent™ adhesive.

The secondary objective was to examine the same treatment combinations for probing depth and bleeding on probing changes.

Clinical efficacy measurements obtained were attachment level (primary), probing depth (secondary), and bleeding on probing (secondary). The primary objective was to compare change from Baseline to Month 9 for attachment level between the two doxycycline groups for equivalence, and compare these results with that of the vehicle for superiority.

In the single-blind design, the examiner who performed the clinical efficacy evaluations was blinded to treatment identification. The investigators who administered the treatment and the subjects were unblinded because of dissimilarity of treatment.

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Table 1 Study design of ACS-34, ACS-35 and AGD9603

Protocol	Design	Treatment	Primary Efficacy variable	N	Age range (mean)	% B/W/O M/F	Duration/ Frequency of Drug treatment
ACS-34	Single blind, randomized, parallel, vehicle control 9 month duration	ATRIDOX™ with Coe-Pak™, product removed at 7 days Vehicle with Coe-Pak™, product removed at 7 days Oral hygiene SRP	Periodontal attachment level	101	(48.5)	55.5/44.5 13.9/73.7/12.4	7 days x2 applications (reapplication at month 4)
				104			
				102			
				104			
ACS-35	Single blind, randomized, parallel, vehicle control 9 month duration	ATRIDOX™ with Coe-Pak™, product removed at 7 days Vehicle with Coe-Pak™, product removed at 7 days Oral hygiene SRP	Periodontal attachment level	106	(47.3)	52.4/47.6 23.6/68.3/8.0	7 days x2 applications (reapplication at month 4)
				106			
				102			
				108			
AGD9603	Single blind, randomized, parallel, vehicle control 9 month duration	ATRIDOX™ with Coe-Pak™, product removed at 7 days ATRIDOX™ with Octyldent, product not removed at 7 days Vehicle with Octyldent, product not removed at 7 days	Periodontal attachment level	204	(48.8)	57.0/43.0 19.2/72.2/8.6	7 days x2 applications (reapplication at month 4)
				198			
				203			

Efficacy analyses:

Study ACS-34

Table 2 Patient disposition ACS-34

	Treatment				Total
	ATRIDOX™	Vehicle	Oral hygiene	SRP	
Enrolled	101	104	102	104	411
Male	51	59	56	62	228
Female	50	45	46	42	183
Completed study (month 9)	93	96	88	98	375
Efficacy evaluable	95	94	95	99	383

Primary efficacy variable: Periodontal attachment level.

Secondary efficacy variable: Probing depth, bleeding on probing scores.

The critical decision rules related to this study were that the doxycycline product be clinically and statistically superior to the vehicle and oral hygiene treatments, and 75% as good as or better than the scaling and root planning treatment in terms of the three clinical outcome variables, i.e., attachment level, probing depth, and bleeding on probing.

Table 3 lists the analysis of the change of attachment level at 9 months (adjusted for center, block, center*block interaction, center*treatment interaction, block*treatment interaction) for the ITT and efficacy population. The ATRIDOX™ group had the largest change (reduction) of attachment level from baseline. The difference between the ATRIDOX™ group and the scaling and root planning group was not statistically significant (ITT population: $p=0.6730$, efficacy population: $p=0.2941$), the differences between the ATRIDOX™ group and the vehicle group and the oral hygiene group were statistically significant ($p<0.02$).

Table 3 Change of attachment level at 9 months from Baseline (ACS-34)

	Treatment	N	Change from Baseline (least square mean)	p-values
ITT population		402		
	ATRIDOX™(A)	99	-0.68167884	
	Oral Hygiene (OH)	99	-0.38833416	A vs. OH: 0.0135
	Scaling/Root Planning (SR)	102	-0.63292341	A vs. SR: 0.6730
	Vehicle (V)	102	-0.38944253	A vs. V: 0.0125
Efficacy population		329		
	ATRIDOX™(A)	80	-0.77210845	
	Oral Hygiene (OH)	83	-0.30958542	A vs. OH: 0.0012
	Scaling/Root Planning (SR)	84	-0.62946779	A vs. SR: 0.2941
	Vehicle (V)	82	-0.13480844	A vs. V: 0.0001

Table 4 lists the analysis of the change of pocket depth at 9 months (adjusted for center, block, center*block interaction, center*treatment interaction, block*treatment interaction) for the ITT and efficacy population. The ATRIDOX™ group had the largest change (reduction) of pocket depth from baseline. The difference between the ATRIDOX™ group and the scaling and root planning group was not statistically significant (ITT population: $p=0.3002$, efficacy population: $p=0.0504$), the differences between the ATRIDOX™ group and the vehicle group and the oral hygiene group were statistically significant ($p<0.01$).

Table 4 Change of pocket depth at 9 months from Baseline (ACS-34)

	Treatment	N	Change from Baseline (least square mean)	p-values
ITT population		402		
	ATRIDOX™(A)	99	-1.05282964	
	Oral Hygiene (OH)	99	-0.58898181	A vs. OH: 0.0001
	Scaling/Root Planning (SR)	102	-0.96014142	A vs. SR: 0.3002
	Vehicle (V)	102	-0.76544375	A vs. V: 0.0016
Efficacy population		329		
	ATRIDOX™ (A)	80	-1.13011362	
	Oral Hygiene (OH)	83	-0.51227804	A vs. OH: 0.0001
	Scaling/Root Planning (SR)	84	-0.93388683	A vs. SR: 0.0504
	Vehicle (V)	82	-0.79674469	A vs. V: 0.0012

Table 5 lists the analysis of the change of bleeding on probing at 9 months (adjusted for center, block, center*block interaction, center*treatment interaction, block*treatment interaction) for the ITT and efficacy population. The ATRIDOX™ group had the largest change (reduction) of bleeding from baseline. The difference between the ATRIDOX™ group and the scaling/root planning group, was not statistically significant (ITT population and efficacy population: $p > 0.05$); the differences between the ATRIDOX™ group and the oral hygiene group ($p < 0.05$); and between the ATRIDOX™ group and the vehicle group were statistically significant ($p < 0.05$).

Table 5 Change of bleeding on probing at 9 months from Baseline (ACS-34)

	Treatment	N	Change from Baseline (least square mean)	p-values
ITT population		402		
	ATRIDOX™ (A)	99	-0.49869146	
	Oral Hygiene (OH)	99	-0.38426446	A vs. OH: 0.0260
	Scaling/Root Planning (SR)	102	-0.49728766	A vs. SR: 0.9776
	Vehicle (V)	102	-0.46318037	A vs. V: 0.4820
Efficacy population		329		
	ATRIDOX™(A)	80	-0.49983304	
	Oral Hygiene (OH)	83	-0.36069135	A vs. OH: 0.0231
	Scaling/Root Planning (SR)	84	-0.48118078	A vs. SR: 0.7504
	Vehicle (V)	82	-0.48238024	A vs. V: 0.7695

Reviewer's comment: Study ACS-34 showed that the ATRIDOX™ treatment group was statistically significantly superior to the oral hygiene group ($p < 0.02$) and the vehicle group ($p < 0.02$), and was numerically better than the scaling and root planing group in the primary efficacy variable, gain in attachment level. The ATRIDOX™ treatment group was statistically significantly superior to the oral hygiene group ($p = 0.0001$) and the vehicle group ($p < 0.002$), and was numerically better than the scaling and root planing group in the secondary efficacy variable pocket depth. The ATRIDOX™ treatment group was statistically significantly superior to the oral hygiene group ($p < 0.03$), and was numerically better than the scaling and root planing group and the vehicle group in the secondary efficacy variable bleeding upon probing.

Study ACS-35

Table 6 Patient disposition ACS-35

	Treatment				Total
	ATRIDOX™	Vehicle	Oral hygiene	SRP	
Enrolled	106	106	102	106	420
Male	53	48	57	62	220
Female	53	58	45	44	200
Completed study (month 9)	94	93	94	102	383
Efficacy evaluable	96	96	94	103	389

Primary efficacy variable: Periodontal attachment level.

Secondary efficacy variable: Probing depth, bleeding on probing scores.

The critical decision rules related to this study were that the doxycycline product be clinically and statistically superior to the vehicle and oral hygiene treatments, and 75% as good as or better than the scaling and root planning treatment in terms of the three clinical outcome variables, i.e., attachment level, probing depth, and bleeding on probing.

Table 7 lists the analysis of the change of attachment level at 9 months (adjusted for center, block, center*block interaction, center*treatment interaction, block*treatment interaction) for the ITT and efficacy population. The scaling and root planning group had the largest change (reduction) of attachment level from baseline. The difference between the ATRIDOX™ group and the scaling and root planning group was not statistically significant (ITT population: $p=0.4430$; efficacy population: $p=0.6647$), the differences between the ATRIDOX™ group and the vehicle group and the oral hygiene group were statistically significant ($p<0.02$).

Table 7 Change of attachment level at 9 months from Baseline (ACS-35)

	Treatment	N	Change from Baseline (least square mean)	p-values
ITT population		399		
	ATRIDOX™(A)	100	-0.78930163	
	Oral Hygiene (OH)	97	-0.52706640	A vs. OH: 0.0101
	Scaling/Root Planning (SR)	103	-0.86603159	A vs. SR: 0.4430
	Vehicle (V)	99	-0.47483870	A vs. V: 0.0021
Efficacy population		355		
	ATRIDOX™(A)	85	-0.81291932	
	Oral Hygiene (OH)	89	-0.53474871	A vs. OH: 0.0117
	Scaling/Root Planning (SR)	98	-0.85945115	A vs. SR: 0.6647
	Vehicle (V)	83	-0.46479918	A vs. V: 0.0022

Table 8 lists the analysis of the change of pocket depth at 9 months (adjusted for center, block, center*block interaction, center*treatment interaction, block*treatment interaction) for the ITT and efficacy population. The scaling and root planning group had the largest change (reduction) of pocket

depth from baseline. The difference between the ATRIDOX™ group and the scaling and root planning group was not statistically significant (ITT population: $p=0.7991$, efficacy population: $p=0.7649$), the differences between the ATRIDOX™ group and the vehicle group and the oral hygiene group were statistically significant ($p<0.01$).

Table 8 Change of pocket depth at 9 months from Baseline (ACS-35)

	Treatment	N	Change from Baseline (least square mean)	p-values
ITT population		399		
	ATRIDOX™(A)	100	-1.30281916	
	Oral Hygiene (OH)	97	-0.90724385	A vs. OH: 0.0001
	Scaling/Root Planning (SR)	103	-1.32589466	A vs. SR: 0.7991
	Vehicle (V)	99	-0.92151038	A vs. V: 0.0001
Efficacy population		355		
	ATRIDOX™(A)	85	-1.27880018	
	Oral Hygiene (OH)	89	-0.87422885	A vs. OH: 0.0001
	Scaling/Root Planning (SR)	98	-1.30631244	A vs. SR: 0.7649
	Vehicle (V)	83	-0.95203636	A vs. V: 0.0008

Table 9 lists the analysis of the change of bleeding on probing at 9 months (adjusted for center, block, center*block interaction, center*treatment interaction, block*treatment interaction) for the ITT and efficacy population. The ATRIDOX™ group had the largest change (reduction) of bleeding from baseline. The difference between the ATRIDOX™ group and the scaling and root planning group was not statistically significant (ITT population and efficacy population: $p>0.05$), the differences between the ATRIDOX™ group and the oral hygiene group and the vehicle group were statistically significant ($p<0.05$).

Table 9 Change of bleeding on probing at 9 months from Baseline (ACS-35)

	Treatment	N	Change from Baseline (least square mean)	p-values
ITT population		399		
	ATRIDOX™(A)	100	-0.62144165	
	Oral Hygiene (OH)	97	-0.44412573	A vs. OH: 0.0066
	Scaling/Root Planning (SR)	103	-0.58192822	A vs. SR: 0.5365
	Vehicle (V)	99	-0.44622298	A vs. V: 0.0071
Efficacy population		355		
	ATRIDOX™(A)	85	-0.61244176	
	Oral Hygiene (OH)	89	-0.42428306	A vs. OH: 0.0060
	Scaling/Root Planning (SR)	98	-0.57610888	A vs. SR: 0.5852
	Vehicle (V)	83	-0.44610581	A vs. V: 0.0177

Reviewer's comment: Study ACS-35 showed that the ATRIDOX™ treatment group was statistically significantly superior to the oral hygiene group ($p=0.01$) and the vehicle group ($p=0.002$), and was numerically better than the scaling and root planing group in the primary efficacy variable, gain in attachment level. The ATRIDOX™ treatment group was statistically significantly superior to the oral

hygiene group (pocket depth: $p < 0.001$, bleeding upon probing : $p < 0.007$) and the vehicle group (pocket depth: $p = 0.0001$, bleeding upon probing : $p < 0.02$), and was numerically better than the scaling and root planing group in the two secondary efficacy variables pocket depth and bleeding upon probing.

Study AGD9603

Table 10 Patient disposition AGD9603

	Treatment			Total
	ATRIDOX™ Coe-Pak™	ATRIDOX™ Octyldent™	Vehicle	
Enrolled	204	198	203	605
Male	108	121	116	345
Female	96	77	87	260
Completed study (month 9)	191	186	192	569
Efficacy evaluable	194	185	193	572

Primary efficacy variable: Periodontal attachment level.

Secondary efficacy variable: Probing depth, bleeding on probing scores.

The critical decision rules related to this study were that the two ATRIDOX™ treatment groups be clinically and statistically equivalent (clinically significant difference = 0.23mm, i.e., the 95% CI for the difference in means for the two groups lie in (-0.23, 0.23)), and that both be clinically and statistically superior to the vehicle treatment.

Table 11 lists the analysis of the change of attachment level at 9 months (adjusted for center, block, center*block interaction, center*treatment interaction, block*treatment interaction) for the ITT and efficacy population. The difference between the ATRIDOX™ with Octyldent™ group and the ATRIDOX™ with Coe-Pak™ group was not statistically significant (ITT population: $p = 0.6403$, 95% CI = (-0.18, 0.08); efficacy population: $p = 0.7681$, 95% CI for the difference in means for the two groups = (-0.19, 0.13)), the differences between the two ATRIDOX™ groups and the vehicle group were statistically significant ($p < 0.01$).

Table 11 Change of attachment level at 9 months from Baseline (AGD9603)

	Treatment	N	Change from Baseline (least square mean (s.d))	p-values	95% CI of difference in means
ITT population					
	ATRIDOX™ with Octyident™ (Doxy-left: A)	193	-0.8289 (0.050)	A vs. B: 0.6403 A vs. C: 0.0008	A-B: (-0.18, 0.08)
	ATRIDOX™ with Coe-Pak™ (Doxy-Removed: B)	198	-0.8616 (0.050)	B vs. C: 0.0001	
	Vehicle (C)	199	-0.5955 (0.050)		
Efficacy population					
	ATRIDOX™ with Octyident™ (Doxy-left: A)	185	-0.8420 (0.063)	A vs. B: 0.7681 A vs. C: 0.0017	A-B: (-0.19, 0.13)
	ATRIDOX™ with Coe-Pak™ (Doxy-Removed: B)	194	-0.8675 (0.062)	B vs. C: 0.0005	
	Vehicle (C)	193	-0.5720 (0.060)		

Table 12 lists the analysis of the change of pocket depth at 9 months (adjusted for center, block, center*block interaction, center*treatment interaction, block*treatment interaction) for the ITT and efficacy population. The difference between the ATRIDOX™ with Octyident™ group and the ATRIDOX™ with Coe-Pak™ group was statistically significant (ITT population: p=0.0120, 95% CI for the difference in means for the two groups =(-0.04,0.27); efficacy population: p=0.0744, 95% CI for the difference in means for the two groups =(-0.01,0.25)), favoring the ATRIDOX™ with Coe-Pak™ group; the differences between the two ATRIDOX™ groups and the vehicle group were statistically significant (p<0.01).

Table 12 Change of pocket depth at 9 months from Baseline (AGD9603)

	Treatment	N	Change from Baseline (least square mean (s.d))	p-values	95% CI of difference in means
ITT population					
	ATRIDOX™ with Octyident™ (Doxy-left: A)	193	-1.0721 (0.042)	A vs. B: 0.0120 A vs. C: 0.0017	A-B: (0.04, 0.27)
	ATRIDOX™ with Coe-Pak™ (Doxy-Removed: B)	198	-1.2212 (0.043)	B vs. C: 0.0001	
	Vehicle (C)	199	-0.8873 (0.042)		
Efficacy population					
	ATRIDOX™ with Octyident™ (Doxy-left: A)	185	-1.1167 (0.047)	A vs. B: 0.0744 A vs. C: 0.0001	A-B: (0.01, 0.25)
	ATRIDOX™ with Coe-Pak™ (Doxy-Removed: B)	194	-1.2318 (0.046)	B vs. C: 0.0001	
	Vehicle (C)	193	-0.8575 (0.045)		

Table 13 lists the analysis of the change of bleeding on probing at 9 months (adjusted for center, block, center*block interaction, center*treatment interaction, block*treatment interaction) for the ITT and efficacy population. The ATRIDOX™ group had the largest change (reduction) of bleeding from baseline. The difference between the ATRIDOX™ with Octyldent™ group and the ATRIDOX™ with Coe-Pak™ group was not statistically significant (ITT population: $p=0.0902$, 95% CI for the difference in means for the two groups = (0.02, 0.16); efficacy population: $p=0.2407$, 95% CI for the difference in means for the two groups = (0.01, 0.16)), the difference between the ATRIDOX™ with Octyldent™ group and the vehicle group was statistically significant ($p<0.01$) in the efficacy population but not in the ITT population ($p=0.0656$). The differences between the ATRIDOX™ with Coe-Pak™ group and the vehicle group was statistically significant ($p<0.01$).

Table 13 Change of bleeding on probing at 9 months from Baseline (AGD9603)

	Treatment	N	Change from Baseline (least square mean (s.d))	p-values	95% CI of difference in means
ITT population					
	ATRIDOX™ with Octyldent™ (Doxy-left: A)	193	-0.60084371	A vs. B: 0.0902 A vs. C: 0.0656	A-B: (0.02, 0.16)
	ATRIDOX™ with Coe-Pak™ (Doxy-Removed: B)	198	-0.66159248	B vs. C: 0.0004	
	Vehicle (C)	199	-0.53530585		
Efficacy population					
	ATRIDOX™ with Octyldent™ (Doxy-left: A)	185	-0.6318 (0.028)	A vs. B: 0.2407 A vs. C: 0.0088	A-B: (0.01, 0.16)
	ATRIDOX™ with Coe-Pak™ (Doxy-Removed: B)	194	-0.6771 (0.027)	B vs. C: 0.0001	
	Vehicle (C)	193	-0.5313 (0.027)		

Reviewer’s comment: Study AGD9603 showed that the two ATRIDOX™ treatment groups were statistically equivalent in terms of the primary efficacy endpoint, change of attachment level from baseline. Both ATRIDOX™ treatment groups were statistically significantly superior to the vehicle group in the primary efficacy variable, change in attachment level. The two ATRIDOX™ treatment groups were statistically significantly superior to the vehicle group in the two secondary efficacy variables pocket depth and bleeding on probing.

The influence of age, gender, race, smoking status, maintenance: Smoking status, maintenance information were not submitted in the electronic data base. The effect of age, gender, race were not statistically significant in studies ACS34, ACS35, and AGD9603 ($p>0.05$).

Integrated safety:

Table 14 lists the frequencies of reported adverse events by body system and treatment groups. The ATRIDOX™ groups had higher percentages of adverse events than other groups in the circulatory system ($p<0.001$), the ATRIDOX™ groups and the vehicle group had higher percentages of adverse events than other groups in the digestive system ($p=0.004$), endocrine, nutritional, metabolic systems ($p=0.021$),

genitourinary system (p=0.004), ill-defined conditions (p<0.001), mental system (p=0.009), musculoskeletal system (p= 0.019), and respiratory system (p<0.001).

Table 14 Number of Subjects Reporting All-Causalities Adverse Events Not Associated With Medical History Events (ACS34, ACS-35, AGD9603)

	Treatment group										p*
	ATRIDOX™/Coc-Pak™ (N=411)		ATRIDOX™/Octylident™ (N=198)		Vehicle (N=413)		Oral Hygiene (N=204)		Scaling/Root Planning (N=210)		
	N	%	N	%	N	%	N	%	N	%	
Body system											
Circulatory System	18	4.4	8	4.0	5	1.2	1	0.5	1	0.5	<0.001
Digestive System	239	58.2	123	62.1	252	61.0	91	44.6	106	50.5	0.004
Endocrine, Nutritional, Metabolic	15	3.6	6	3.0	13	3.1	2	1.0	2	1.0	0.021
External Causes of Injury and Poisoning	3	0.7	0	0.0	10	2.4	1	0.5	2	1.0	0.537
Genitourinary System	45	10.9	21	10.6	34	8.2	7	3.4	14	6.7	0.004
ill-defined Conditions	187	45.5	96	48.5	197	47.7	67	32.8	62	29.5	<0.001
Infectious and Parasitic	23	5.6	12	6.1	20	4.8	7	3.4	9	4.3	0.240
Injury & Poisoning	73	17.8	37	18.7	85	20.6	26	12.7	31	14.8	0.203
Mental	25	6.1	13	6.6	18	4.4	4	2.0	6	2.9	0.009
Musculoskeletal System	103	25.1	47	23.7	100	24.2	36	17.6	38	18.1	0.019
Neoplasms	2	0.5	1	0.5	1	0.2	1	0.5	1	0.5	0.919
Nervous System & Sense Organs	30	7.3	16	8.1	37	9.0	9	4.4	11	5.2	0.222
Pregnancy & Childbirth Complications	0	0.0	1	0.5	0	0.0	0	0.0	1	0.5	0.430
Respiratory System	208	50.6	102	51.5	209	50.6	61	29.9	70	33.3	<0.001
Skin & Subcutaneous Tissue	24	5.8	16	8.1	21	5.1	8	3.9	11	5.2	0.323

* Mantel-Haenszel chi-square test.

Table 15 lists the frequencies of reported treatment-related adverse events by body system and treatment groups. The ATRIDOX™ groups and the vehicle group had numerically higher percentages of adverse events than other groups in the digestive system (p=0.246), and ill-defined conditions (p=0.057).

Table 15 Number of Subjects Reporting Treatment-Related Adverse Events Not Associated With Medical History Events (ACS34, ACS-35, AGD9603)

	Treatment group										p*
	ATRIDOX™-Coc-Pak™ (N=411)		ATRIDOX™-Octylident™ (N=198)		Vehicle (N=413)		Oral Hygiene (N=204)		Scaling/Root Planning (N=210)		
	N	%	N	%	N	%	N	%	N	%	
Body system											
Digestive System	47	11.4	31	15.7	57	13.8	7	3.4	26	12.4	0.246
ill-defined Conditions	9	2.2	6	3.0	8	1.9	0	0.0	2	1.0	0.057
Injury & Poisoning	0	0.0	0	0.0	1	0.2	0	0.0	0	0.0	0.843
Mental	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	0.102
Respiratory System	0	0.0	1	0.5	0	0.0	0	0.0	0	0.0	0.602

• Mantel-Haenszel chi-square test.

Reviewer's Summary and Conclusion (which may be conveyed to the sponsor):

Studies ACS-34 and ACS-35 (pivotal studies) demonstrated that the ATRIDOX™ treatment was statistically more effective than oral hygiene and the vehicle in treating chronic adult periodontitis (Tables 3 and 7). There are no statistically significant differences between the ATRIDOX™ treatment and scaling and root planning treatment groups (Tables 3 and 7).

Study AGD9603 showed that the two ATRIDOX™ treatment groups (with Coe-Pak™ or with Octyldent™) were statistically and clinically equivalent in terms of the primary efficacy endpoint, change of attachment level from baseline (Table 11). Both ATRIDOX™ treatment groups were statistically significantly superior to the vehicle group in the primary efficacy variable attachment level (Table 11). The two ATRIDOX™ treatment groups were statistically significantly superior to the vehicle group in the secondary efficacy variable pocket depth (Table 12). The ATRIDOX™ with Coe-Pak™ treatment group was statistically significantly superior to the vehicle group in the secondary efficacy variable bleeding on probing (Table 13). The ATRIDOX™ with Octyldent™ treatment group was statistically significantly superior to the vehicle group in the secondary efficacy variable bleeding on probing in the efficacy populations, but not in the ITT population (Table 13). The ATRIDOX™ treatment had statistically significantly more reported adverse events in the circulatory system, digestive system, endocrine, nutritional, metabolic systems, ill-defined conditions, mental system, musculoskeletal system, and respiratory system than the oral hygiene group and the scaling /root planning group (Tables 14 and 15).

Thus, the studies ACS-34, ACS-35 and AGD9603 adequately demonstrated that the two ATRIDOX™ treatment groups were statistically and clinically equivalent, and also both were statistically more effective than oral hygiene and the vehicle in the treatment of chronic adult periodontitis.

/S/

02/17/98

Ping Gao, Ph.D.
Mathematical Statistician, DOB IV



Feb 17, '98

Concur: Rajagopalan Srinivasan, Ph.D.
Team Leader, DOB IV

HFD 540
NDA 50-751
HFD-540/Dr. Wilkin
HFD-540/Dr. Kelsey
HFD-540/Dr. Blay
HFD-725/Dr. Huque
HFD-725/Dr. Srinivasan

HFD-725/Dr. Gao
HFD-344/Dr. Carreras
Chron.

This review contains 13 pages.

MS word/d: \nda\50-751\50-751.doc\Feb. 17,'97; Ping Gao /(301)-827-2083

**APPEARS THIS WAY
ON ORIGINAL**

MAR 31 1998

STATISTICAL REVIEW AND EVALUATION
(addendum)

NDA: 50-751/3S
Applicant: Atrix Laboratories, Inc., 2579 Midpoint Drive, Fort Collins, CO 80525-4417
Name of Drug: Atridox
Route of Administration: Topical
Documents Reviewed: NDA 50-751: Vol. 1.1, 1.21-1.74, 1.286, Vol. 8.1, 8.2-8.21
Indication: Chronic Adult Periodontitis
Related INDs: IND
Related NDAs: AADA 62-865
Dental Officer: J. Kelsey, D. D.S., M. B. A. (HFD-540)

Introduction : According to the protocol of studies ACS-34, ACS-35, the change of attachment level at 9 months from baseline for the ATRIDOX™ group should be no less than 75% of the change for the scaling and root planning group. This means that both limits of the 95% confidence interval for the mean change of attachment level should be no less than 75% of the change for the scaling and root planning group.

In this addendum, the confidence intervals were calculated and presented in Table 1. The least squares means of the change of attachment level and standard deviation (these are the adjusted values of the raw means and raw standard deviations) were used for all the calculations.

Table 1 Confidence intervals for the Change of attachment level at 9 months from Baseline
(ACS-34 and ACS-35)

ACS34				
ITT population				
Treatment	Amount of Change from Baseline (least square mean)	Standard deviation (least square mean)	75% of change of SR group	95% CI for Atridox group
ATRIDOX™	0.68167884	0.082485		(0.67010, 0.69326)
Scaling/Root Planning (SR)	0.63292341	0.081713	0.47469	
Efficacy Population				
ATRIDOX™	0.77210845	0.097048		(0.75703, 0.78719)
Scaling/Root Planning (SR)	0.62946779	0.095999	0.47210	
ACS35				
ITT population				
ATRIDOX™	0.78930163	0.071889		(0.77956, 0.79904)
Scaling/Root Planning (SR)	0.86603159	0.069513	0.64952	
Efficacy Population				
ATRIDOX™	0.81291932	0.079072		(0.80171, 0.82413)
Scaling/Root Planning (SR)	0.85945115	0.072521	0.64459	

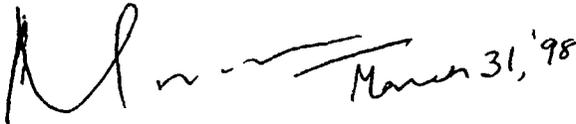
Table 1 shows that all the lower confidence interval limits were above the corresponding threshold of 75% of the change of the scaling and root planning group (ACS-34, ITT population: 0.67010 > 0.47469;

ACS-34 efficacy population: 0.75703>0.47210; ACS-35, ITT population: 0.77956>0.64952; ACS-35 efficacy population: 0.80171>0.64459). This demonstrates that the change of attachment level at 9 months from baseline for the ATRIDOX™ group was no less than 75% of the change for the scaling and root planning group.

Reviewer's Summary and Conclusion (which may be conveyed to the sponsor):

For studies ACS-34, ACS-35, the change of attachment level at 9 months from baseline for the ATRIDOX™ group was no less than 75% of the change for the scaling and root planning group.

IS/ U 03/31/98
Ping Gao, Ph.D.
Mathematical Statistician, DOB IV



Concur: Rajagopalan Srinivasan, Ph.D.
Team Leader, DOB IV

- HFD 540
- NDA 50-751
- HFD-540/Dr. Wilkin
- HFD-540/Dr. Kelsey
- HFD-540/Dr. Blay
- HFD-725/Dr. Huque
- HFD-725/Dr. Srinivasan
- HFD-725/Dr. Gao
- HFD-344/Dr. Carreras
- Chron.

This addendum contains 2 pages.

MS word/d: \nda\50-751\50-751b.doc\Mar. 31,'97; Ping Gao /(301)-827-2083

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-751

MICROBIOLOGY REVIEW(S)

REVIEW FOR HFD-540
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805

OCT 17 1997

Microbiologist's Review #1 of NDA 50-751
October 9, 1997

- A. 1. **APPLICATION NUMBER:** 50-751
- APPLICANT:** Atrix Laboratories
2579 Midpoint Drive
Fort Collins, CO 80525-4417
2. **PRODUCT NAMES:** Atridox, doxycycline hyclate
3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** Atridox consists of a two syringe mixing system. Syringe A contains 450 mg of the liquid Atrigel Delivery System. Syringe B contains 50 mg of doxycycline hyclate powder. The reconstituted product contains 8.5% w/w of doxycycline. Atridox is administered into the periodontal pocket.
4. **METHOD(S) OF STERILIZATION:** non-sterile
5. **PHARMACOLOGICAL CATEGORY:** Atridox is a topical dosage form indicated for use in treating chronic adult periodontitis.
- B. 1. **DATE OF INITIAL SUBMISSION:** March 31, 1997
2. **AMENDMENT:** none
3. **RELATED DOCUMENTS:** IND
4. **ASSIGNED FOR REVIEW:** September 25, 1997
5. **DATE OF CONSULT REQUEST:** September 19, 1997

C. **REMARKS:**

The active ingredient, doxycycline, is a broad-spectrum semisynthetic tetracycline which inhibits bacterial protein synthesis. The subject drug is to be manufactured by Atrix Laboratories in Fort Collins, Colorado.

D. CONCLUSIONS:

The submission is not recommended for approval as submitted. Specific comments are provided :

ISI

10/9/97

**Brenda Uratani, Ph.D.
Review Microbiologist**

BUC 10/17/97

cc:

NDA 50-751
HFD-540/ Div. File
HFD-805/ Uratani
HFD-540/CSO/H. Blatt
HFD-540/Chemist/E. Pappas
drafted by: Brenda Uratani, 10/9/97
R/D initialed by P. Cooney, 10/9/97

DENTAL CONSULT
DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

MAR 6 1998

NDA#: 50-751

REVIEW: #1

REVIEW DATE: 12/1/97

UBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL NDA	3/31/97	4/1/97	4/11/97

NAME & ADDRESS OF APPLICANT: ATRIX LABORATORIES, INC.
2579 MIDPOINT DRIVE
FORT COLLINS, CO

CONTACT PERSON: Elaine Gazdeck
Vice President Regulatory Affairs &
Quality Assurance
Phone Number: 907-482-5868
Fax Number: 907-482-9734

DRUG PRODUCT NAME:

Proprietary:	ATRIDOX™(ATRIGEL®Delivery System w/doxycycline hyclate)
Nonproprietary	None
Code Names/#s	None
Chemical Name:	Doxycycline Hyclate
Molecular Description:	See USP(1)
Therapeutic Class	3S

INDICATION(S): Chronic-Adult Periodontitis

DOSAGE FORM:	Gel
STRENGTH:	8.5% w/w
ROUTE OF ADMINISTRATION:	Topical
DISPENSED:	Rx

RELATED DOCUMENTS: IND

**DENTAL CONSULT
DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW**

NDA#: 50-751

REVIEW: #1

REVIEW DATE: 12/1/97

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DENTAL CONSULT
DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW

NDA#: 50-751

REVIEW: #1

REVIEW DATE: 12/1/97

REMARKS/COMMENTS:

This product is based on the use of a derivative of the class of tetracycline antibiotics to treat periodontal infections.

INTRODUCTION:

This review is of the application for the product "ATRIDOX™ (ATRIGEL® Delivery System with doxycycline hyclate)" which is a subgingival sustained-release product for the treatment of chronic-adult periodontitis. The ATRIDOX™ (ATRIGEL® Delivery System) consists of two components syringe A and syringe B. Syringe A contains 450mg of a bioabsorbable, flowable polymeric formulation composed of 36.7% poly (DL-lactide) (PLA) dissolved in 63.3% N-methyl-2-pyrrolidone. Syringe B contains 50mg of doxycycline hyclate equivalent to 42.5mg doxycycline per syringe. When components of both syringes are mixed and applied to the aqueous fluid in the periodontal pocket solidification takes place allowing for a sustained release of the doxycycline.

Chronic-adult periodontitis has been shown to be correlated with the presence of specific bacterial types. The bacteria most commonly associated with the disease are: *Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans*, *Bacteroides forsythus*, *Campylobacter rectus*, *Eikenella corrodens*, *Prevotella intermedia*, and *Fusobacterium nucleatum* (2). Doxycycline and/or tetracycline in concentrations of 1 to 6µg/mL has been shown to inhibit the growth of these organisms (3). The ATRIDOX™ (ATRIGEL® Delivery System) is intended to delivery for a period of seven (7) days an amount of doxycycline capable of inhibiting bacteria associated with chronic-adult periodontitis.

PRE-CLINICAL EFFICACY (IN VITRO)

SPECTRUM OF ACTIVITY AND MECHANISM(S) OF ACTION

The tetracycline* class of antibiotics have a broad spectrum of activity against microorganisms including facultative, aerobic and anaerobic bacteria (4). This class of antibiotics is bacteriostatic with their main mechanism of action being to inhibit protein synthesis (4). A relatively minimal stereochemical modification to the basic tetracycline ring structure resulted in the development of doxycycline in 1967. This modification conferred better lipophilic activity to the tetracycline molecule and

* The term tetracycline in this review will refer to tetracycline and its derivative unless otherwise noted

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created a tetracycline with unique pharmacodynamic and tissue penetration characteristics. It also significantly improved the antimicrobial activity of tetracycline against bacteria (5).

The applicant has submitted their own in-vitro susceptibility data to demonstrate the activity of doxycycline against the following organisms (number in parenthesis represents the number of organisms tested). These isolates represent stock organisms not fresh clinical isolates: *A. actinomycetemcomitans* (12), *C. rectus* (5), *F. nucleatum* (10), *P. gingivalis* (5), *P. intermedia* (8). The MIC₉₀ for the *A. actinomycetemcomitans* isolates was $\leq 4\mu\text{g/mL}$ while the MIC₉₀ for the other organisms were $\leq 0.5\mu\text{g/mL}$. It is noted that testing was not done on a full range of organisms associated with adult periodontitis. The applicant has referenced studies which demonstrated the activity of doxycycline against those they tested and those which were not tested. These papers have been reviewed and found to be appropriate.

MECHANISM(S) OF RESISTANCE:

Tetracycline resistance is widespread among bacteria (6). This resistance may be due to: 1) limiting access of tetracycline to the ribosomes, 2) altering the ribosome to prevent effective binding of tetracycline, or 3) producing tetracycline-inactivating enzymes (7). Combinations of these mechanisms of resistance have been described (7).

Fourteen determinants coding for tetracycline resistance in bacteria are currently known. Of these *tet(A-E)*, *tet(G)*, *tet(K)*, *tet(L)*, and *tet(P)* encode proteins that mediate an efflux mechanism for tetracycline and the *tet(M)*, *tet(O)*, and *tet(Q)* genes encode proteins that prevent tetracycline from attaching to the ribosomes. A third class of genes, including *tet(X)*, encode proteins mediating the breakdown of tetracycline. The mechanism of the *tet(F)* determinant has not been conclusively determined (8). All but classes C, D, K, and L confer resistance to minocycline (8). *Tet(M)* confers resistance to both tetracycline and minocycline as well as all second generation tetracycline analogs (9). Many of the tetracycline genes from gram-negative bacilli are located on plasmids and are readily transmissible within and between species (8). Other transmissible tetracycline-resistance genes particularly those found in gram-positive organisms are located on transposable chromosomal elements that can be transferred between organisms by conjugation (10). In general, resistance to one tetracycline indicates resistance to all tetracyclines. This resistance is primarily due to the acquisition of Tet determinants, rather than mutation (9).

EPIDEMIOLOGY

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DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
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REVIEW: #1

REVIEW DATE: 12/1/97

Development of resistance to tetracycline among organisms isolated from the periodontal pockets is frequently seen in patients with periodontal disease treated with tetracycline (11). The presence of tetracycline-resistant organisms in the oral microflora of individuals with no periodontitis and not receiving tetracycline has also been described. These tetracycline-resistant bacteria have been shown to constitute between 2 - 6% of the viable count in subgingival samples (12).

PRE-CLINICAL (IN-VIVO)

PHARMACOKINETICS:

The standard dose of approximately 4.25mg doxycycline delivered by the product is well below the usual dose of doxycycline (i.e. 200mg first day followed by 100mg for the next 7 to 10 days) given to eradicate bacteria at the site of infection (13). The applicant has provided data to demonstrate that doxycycline levels in the gingival crevicular fluid (GCF) peaked at ~1,500µg/mL 2 hours following treatment with ATRIDOX. These levels were shown to remain above 1000µg/mL for at least 18 hours, at which time the levels began to decline gradually. Local levels of doxycycline remained around µg/mL through day . These levels are above the minimum inhibitory concentration (MIC) for the majority of periodontal pathogens (1-6µg/mL) (3, 15).

Levels of µg/mL were detected in the serum of individuals hours post product application. Levels dropped to µg/mL from hour post application and were nondetectable after day 2 (limit of detection is µg/mL).

Levels of doxycycline in stool samples were not determined.

CLINICAL EFFICACY

CLINICAL MICROBIOLOGY:

The applicant undertook one (1) single-blind, single center clinical study (ACS 33) in which 45 subjects (23 treatment group and 22 control) between the ages of years old where enrolled to determine the effects of doxycycline treatment on the development of resistant bacteria. The secondary objective of the study was to observe the effects of doxycycline upon normal microbiota, periodontal pathogens, and possible overgrowth of opportunistic organisms such as enteric Gram-negative bacilli and yeast.

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NDA#: 50-751

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The study found that a number of the subjects enrolled had doxycycline resistant microorganisms in their oral cavity prior to the application of the doxycycline containing product. This finding is in agreement with the published literature (12). The portion of the study which dealt with the potential development of doxycycline-resistant bacteria during treatment with the product showed a transient increase in doxycycline-resistant bacteria in the saliva of the treated group compared to the control at days 7 and 21. While there was a difference in the doxycycline-resistant organisms in the subgingival plaque with the treated group appearing to have a higher incident of doxycycline-resistant bacteria than the control, this difference was not shown to be consistently statistically significant ($p \leq .05$) over the study period time. This transient increase in the resistant population of bacteria over the period of time after cessation of treatment is consistent with published data from similar studies (15, 16).

The study also showed that there was a decrease at specific times during a 21 day period in the subgingival-plaque counts of *P. gingivalis*, *P. intermedia*, *B. forsythus*, *F. nucleatum*, *E. corrodens*, and *C. rectus* organisms associated with periodontal disease compared to subjects in the control group which practiced a specific oral hygiene regimen but were not treated with doxycycline. The statistical significance of these results could not be adequately determined. It appeared, however, that the results were not consistently statistically significant for each organism ($p \leq .05$). The counts of *A. actinomycetemcomitans* were too low in both the treated and control subjects to allow any meaningful conclusions to be drawn about changes in the numbers of this organism between treated and control groups. Subjects were followed for a period of 6 months with the majority of changes in numbers of organisms occurring within the first 21 day period. There was also a decrease in the aerobic and anaerobic bacteria in the doxycycline treated group compared to the control group. The findings of reductions in organisms in the treated subjects compared to the control subjects in this study are not unexpected and are consistent with the published literature (15). There was no analysis done to correlate reductions in the numbers of these organisms and periodontal health.

The study did not demonstrate any significant overgrowth of opportunistic microorganisms in the doxycycline treated subjects or controls. This finding is consistent with the findings of other studies using tetracyclines to treat periodontal disease (17). This does not preclude the fact that such occurrences can happen particularly in the immunocompromised and thus a precautionary statement is appropriate for inclusion in the labeling (package insert).

No data were submitted addressing the issues of development of tetracycline-resistant bacteria in the gastrointestinal tract, genito-urinary tract or other body sites of individuals receiving doxycycline treatment.

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No data were submitted in relation to the gastrointestinal tract specifically addressing alterations in the microflora of the gastrointestinal tract such as: 1) overgrowth of already present microorganisms such as yeast and *Clostridium difficile*; or 2) reduction in colonization resistance.

CONCLUSIONS AND RECOMMENDATIONS:

The use of Doxycycline hyclate as it is proposed to be used should present no more of a potential of creating resistant populations of bacteria or altering the intestinal microflora of patients than tetracyclines used at the recommended doses for the treatment of bacterial infections.

The microbiology data submitted supports the request of the applicant to market this product for the treatment of chronic-adult periodontitis. The "Microbiology" portion of this NDA is approved contingent on the following changes being made to the "Microbiology", "Precautions", and "Clinical Studies" portion of the labeling (package insert).

REFERENCES

1. USP Dictionary of USAN and International Drug Names. 1996. Doxycycline hyclate. US Pharmacopeial Convention, Inc., Rockville, MD.
2. Okuda, K. 1994. Bacteriological diagnosis of periodontal disease. *The Bull Tokyo Dental College*; 35:107-119.
3. Slots, J, TE Rams. 1990. Antibiotics in periodontal therapy: advantages and disadvantages. *J Clin Periodontol*. 17:479-493.
4. Standiford, HC. 1995. Tetracycline and chloramphenicol, p. 306-310. *In* GL Mandell, JE Bennett, R Dolin(ed.), *Principles and Practice of Infectious Diseases*, 4th ed., Churchill Livingstone, NY.
5. Jonas, M, JB Comer, and BA Cunha, p. 219-234. *In* AM Ristuccia, BA Cunha (ed.), *Antimicrobial Therapy*, Raven Press, NY.
6. Levy, SB. 1988. Tetracycline resistance determinants are widespread. *Amer. Soc. Microbiol News* 54:418-421.
7. Speer, B, NB Shoemaker, and AA Salyers. 1992. Bacterial resistance to tetracycline; mechanism, transfer, and clinical significance. *Clin Microbiol Rev*. 5:387-399.
8. Olsvik, B, I Olsen, F Tenover. 1994. The tet(Q) gene in bacteria isolated from patients with refractory periodontal disease. *Oral Microbiol and Immunol*. 9:251-255.

**DENTAL CONSULT
DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW**

NDA#: 50-751

REVIEW: #1

REVIEW DATE: 12/1/97

9. LaCroix, J, and CB Walker. 1995. Detection and incidence of the tetracycline resistance determinant tet(M) in the microflora associated with adult periodontitis. *J Periodontol.* 66:102-108.
10. Clewell, DB, SE Flannagan, and DD Jaworski. 1995. Unconstrained bacterial promiscuity: The TN 916 - TN 1545 family of conjugative transposons. *Trends in Microbiol.* 3:229-236.
11. Magnusson, I, RG Mark, WB Clark, et al. 1991. Clinical, microbiologic and immunological characteristics of subjects with "refractory" periodontal disease. *J Clin Periodontol.* 61:686-691.
12. Fiehn, NE and J Westergard. 1990. Doxycycline-resistant bacteria in periodically diseased individuals after systemic doxycycline therapy and in healthy individuals. *Oral Microbiol and Immunol.* 5:219-222.
13. Vibramycin (doxycycline). 1996. Physician's Desk Reference. Medical Economic Data Production Co., Montvale, NJ.
14. Goodson, JM. 1994. Antimicrobial strategies for treatment of periodontal diseases. *Periodontol 2000* 5:142-168.
15. Greenstein, G. 1995. Bacterial resistance to tetracyclines. *J Periodontol* 66:925-932.
16. Crout, RJ, HM Lee, K Schroeder, et al. 1996. The "cyclic" regimen of low-dose doxycycline for adult periodontitis: A preliminary study. *J Periodontol.* 67:506-514.
17. Larsen, T. 1991. Occurrence of doxycycline resistant bacteria in the oral cavity after local administration of doxycycline in patients with periodontal disease. *Scand J Infect Dis.* 23:89-85.

PACKAGE INSERT DRAFT

**DENTAL CONSULT
DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW**

NDA#: 50-751

REVIEW: #1

REVIEW DATE: 12/1/97

1. Stratton CW, Lorian V. Mechanisms of action for antimicrobial agents: general principles and mechanisms for selected classes of antibiotics. *Antibiotics in Laboratory Medicine*, 4th edition, Williams and Wilkins, Baltimore, MD, 1996, pg. 579.
2. Ibid.
3. Slots J, Rams TE. 1990. Antibiotics in periodontal therapy: advantages and disadvantages. *J. Clin Periodontology* 17:479-493.

The following statements pertaining to microbiology which appear under "PRECAUTIONS" are appropriate as worded and should remain in the labeling:

The following statement pertaining to microbiology needs to be included under "CLINICAL STUDIES":

|S|
3/6/98

Frederic J. Marsik, Ph.D.
Review Microbiologist

cc: Original 50-751
HFD-540 Division File
HFD-540/MO/C. Gilkes
HFD-540/DO/J. Kelsey
HFD-540/Chem/J. Vidra
HFD-540/Pharm/Tox/N. See
HFD-540/Stat/S. Thomson
HFD-540/Biopharm/D. Bashaw

Concurrence Only
HFD-520/Dep/Dir/L. Gavrilovich
HFD-520/TLMicro/A.T. Sheldon

CD#1 init 2/25/98 AJP
Final Initialed 3/6/98 AJP
72 3/6/98
16 3/9/98

**DENTAL CONSULT
DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
CLINICAL MICROBIOLOGY REVIEW**

NDA#: 50-751

REVIEW: #1

REVIEW DATE: 12/1/97

HFD-540/CSO/R. Blay
HFD-520/Micro/F. Marsik

**APPEARS THIS WAY
ON ORIGINAL**

**REVIEW FOR HFD-540
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805**

JAN 30 1998

**Microbiologist's Review #2 of NDA 50-751
Response to Information Request Letter
January 22, 1998**

A. 1. **APPLICATION NUMBER:** 50-751

APPLICANT: Atrix Laboratories
2579 Midpoint Drive
Fort Collins, CO 80525-4417

2. **PRODUCT NAMES:** Atridox, doxycycline hyclate

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** Atridox consists of a two syringe mixing system. Syringe A contains 450 mg of the liquid Atrigel Delivery System. Syringe B contains 50 mg of doxycycline hyclate powder. The reconstituted product contains 8.5% w/w of doxycycline. Atridox is administered into the periodontal pocket.

4. **METHOD(S) OF STERILIZATION:** non-sterile

5. **PHARMACOLOGICAL CATEGORY:** Atridox is a topical dosage form indicated for use in treating chronic adult periodontitis.

B. 1. **DATE OF INITIAL SUBMISSION:** March 31, 1997

2. **AMENDMENT:**

3. **RELATED DOCUMENTS:**

4. **ASSIGNED FOR REVIEW:** January 21, 1998

5. **DATE OF CONSULT REQUEST:** January 12, 1998

C. **REMARKS:**

The submission responds to questions presented to the Applicant as a result of Microbiologist's Review #1.

D. CONCLUSIONS:

The submission is recommended for approval with respect to microbiology.

/S/

1/22/98

**Brenda Uratani, Ph.D.
Review Microbiologist**

File 1/20/98

cc:

**NDA 50-751
HFD-540/ Div. File
HFD-805/ Uratani
HFD-540/CSO/H. Blatt
HFD-540/Chemist/E. Pappas
drafted by: Brenda Uratani, 1/22/98
R/D initialed by P. Cooney, 1/22/98**