

Subjects that participated in the treatment, vehicle control or SRP arms of ACS-34 or ACS-35 were excluded from this study due to concern about carry-over effects. Several exclusions were narrowed somewhat at the suggestion of FDA. For example, only subjects with impaired renal function *requiring dialysis* were excluded, rather than all patients with impaired renal function as had been the case in ACS-34 & 35. FDA prefers that products are studied in "all comers," unless there is good justification for excluding a particular group. Other exclusions that were narrowed somewhat concerned patients with connective tissue disease and cancer. In addition, the sponsor was more specific about the exclusion criteria concerning steroid use, and added an exclusion for subjects receiving subgingival antimicrobials (e.g. Actisite®).

Reviewer's Comment: The changes in exclusion criteria were reasonable and responded to the request of the Division.

Study Procedures

The study procedures in AGD 9603 were very similar to those in ACS-34 & ACS-35. The primary difference was that the test article (or vehicle control) in the Octyldent™ arms were not removed at seven days. Any product that remained in the pocket at the 4 month visit or at the end of the study was removed. Another difference between this study and ACS 34 & 35 was the inclusion of the question on tooth sensitivity in the adverse events section.

Results

There were more men than women; the ratio was 57:43. Protocol deviations in this study consisted almost entirely of subjects taking prohibited medications and receiving treatments or examinations outside the windows in time prescribed in the protocol. The deviations appeared to be randomly distributed among the various arms of the study and do not cause undue concern about the validity of the data collected. Twelve subjects were excluded from analysis at all time points because they failed to meet the inclusion or exclusion criteria.

Primary Efficacy Variable

The primary efficacy variable was mean attachment level gain at 9 months relative to baseline. Table 7 shows Mean Attachment Level Gain from baseline for the various arms for AGD9603 at nine months for both the Intent to Treat (ITT) and Efficacy Evaluable datasets.

Study AGD 9603 demonstrated that mean attachment level gain achieved at nine months using the Octyldent™ method of retention was equivalent to that achieved using the Coe-Pak™ method of retention. In addition gains achieved using ATRIDOX™ with both the Octyldent™ and Coe-Pak™ methods of retention were superior to the vehicle control retained with Octyldent™. Therefore, the sponsor has met the requirements for demonstrating efficacy with respect to the primary efficacy endpoint, gain in attachment level at nine months. See Dr. Gao's Statistical Review.

Table 7: Mean Attachment Level Gain at Nine Months (AGD9603)

	Treatment	N	Gain (mm.)	p-values	95% CI diff in means
ITT Population					
	ATRIDOX™ with Ocyldent™ Doxy left (A)	193	.83	A-B: .6403 A-C: .0008*	A-B: (-0.18, 0.08)
	ATRIDOX™ with Coe-Pak™ Doxy removed (B)	198	.86	B-C: .0001*	
	Vehicle Left ©	199	.60		
Efficacy Population					
	ATRIDOX™ with Ocyldent™ Doxy left (A)	185	.84	A-B: .7681 A-C: .0017*	A-B: (-0.19 0.13)
	ATRIDOX™ with Coe-Pak™ Doxy removed (B)	194	.87	B-C: .0005*	
	Vehicle Left ©	193	.57		

Secondary Efficacy Variables

The sponsor used the same secondary efficacy variables, Probing Pocket Depth (PPD), and Bleeding on Probing (BOP) as were used in Studies ACS-34 & ACS-35.

Probing Pocket Depth (PPD)

In Study AGD 9603 the mean probing depth reduction achieved at nine months using the Ocyldent™ method of retention was statistically different than that achieved using the Coe-Pak™ method of retention, with the Coe-Pak™ method achieving better results numerically (1.22 mm v. 1.07 mm - ITT dataset). Pocket depth reduction achieved using ATRIDOX™ with the Ocyldent™ method of retention was superior to the vehicle control.

Because the sponsor "won" on the primary efficacy endpoint of gain in attachment level and because the Octyldent™ method "beat" the vehicle and achieved levels of pocket depth reduction comparable to those achieved for SRP in ACS-34 & 35, the sponsor has adequately demonstrated efficacy for the product for reduction in pocket depth when using the Octyldent™ method, even though the numerical reduction in pocket depth was slightly higher in the Coe-Pak™ group. Table 8 shows the Mean Pocket Depth Reduction from baseline for the various arms for AGD 9603 at nine months.

Table 8: Mean Pocket Depth Reduction at Nine Months (AGD 9603)

	Treatment	N	Reduction	p-values	95% CI diff in means
ITT Population			(mm.)		
	ATRIDOX™ with Octyldent™ Doxy left (A)	193	1.07	A-B: .0120* A-C: .0017*	A-B: (-0.04, 0.27)
	ATRIDOX™ with Coe-Pak™ Doxy removed (B)	198	1.22	B-C: .0001*	
	Vehicle Left ©	199	.89		
Efficacy Population					
	ATRIDOX™ with Octyldent™ Doxy left (A)	185	1.12	A-B: .0744 A-C: .0001*	A-B: (-0.01, 0.25)
	ATRIDOX™ with Coe-Pak™ Doxy removed (B)	194	1.23	B-C: .0001*	
	Vehicle Left ©	193	.86		

Bleeding on Probing (BOP)

Study AGD 9603 demonstrated that Mean Reduction in Bleeding on Probing from baseline at nine months using the Octyldent™ method of retention was equivalent to that achieved using the Coe-Pak™ method of retention. In addition gains achieved using ATRIDOX™ with both the Octyldent™ and Coe-Pak™ methods of retention were superior to those obtained using vehicle control retained with Octyldent™. Therefore, the sponsor has met the requirements for

demonstrating efficacy with respect to the secondary efficacy endpoint, reduction in bleeding on probing at nine months. See Dr. Gao's Statistical Review. Table 9 shows Mean Reduction in Bleeding on Probing from baseline for the various arms for AGD 9603 at nine months.

Table 9: Mean Reduction in Bleeding on Probing at Nine Months (AGD 9603)

	Treatment	N	Reduction	p-values	95% CI diff in means
ITT Population			Index		
	ATRIDOX™ with Ocydent™ Doxy left (A)	193	.60	A-B: .0902 A-C: .0656	A-B: (-0.02, 0.16)
	ATRIDOX™ with Coe-Pak™ Doxy removed (B)	198	.66	B-C: .0004*	
	Vehicle Left ©	199	.54		
Efficacy Population					
	ATRIDOX™ with Ocydent™ Doxy left (A)	185	.63	A-B: .2407 A-C: .0088*	A-B: (-0.01, 0.16)
	ATRIDOX™ with Coe-Pak™ Doxy removed (B)	194	.68	B-C: .0001*	
	Vehicle Left ©	193	.53		

The demographic characteristics of the subjects studied in AGD 9603 are presented in Table 10 below. These data are from the efficacy evaluable dataset. Study AGD 9603 included a total of 605 subjects. The overall percentage of males was 57% and ranged from

% by treatment group. The overall mean age was 48.8 years and the range of means across treatment groups was _____ years. The breakdown by race was as follows: 72% White, 19% Black and 9% Other. The range across treatment groups for these groups was as follows: _____ % for Whites, _____ % for Blacks and _____ % for Other. Subjects who smoked 10 or more cigarettes per day comprised 31%, 6% smoked fewer than 10 cigarettes per day and 63% were non-smokers. Across treatment groups the range of smokers who smoked more than 10 cigarettes per day was 26.5% - 38.4%. In all instances the demographic data for the ITT and the efficacy evaluable datasets were very

similar.

Table 10: Demographic Characteristics (AGD 9603)

Baseline Characteristic		Coe-Pak™		Octylident™		Vehicle	
		N	%	N	%	N	%
Sex	Male (345)	108	52.9	121	61.1	116	57.1
	Female (260)	96	47.1	77	38.8	87	42.9
N		185		194		193	
Age	Mean	48.37		49.48		48.65	
	S.D.	9.98		10.68		9.92	
	Range						
Race	White	149	75.3	145	71.1	143	70.4
	Black	33	16.7	42	20.6	41	20.2
	Other	16	8.0	17	8.4	18	8.9
Smoking Status	Non-smoker	111	56.1	139	68.1	133	65.5
	≥ 10 Cigs/day	76	38.4	54	26.5	58	28.6
	≤ 9 Cigs/day	11	5.6	11	5.4	12	5.9

ADVERSE EVENTS

Adverse events for all clinical studies will be reported together. Events are reported by body system and category based on the ICD-9 classification system. In reviewing AGD 9603, FDA was particularly interested in the impact of leaving the product in the pocket for an extended period. In AGD 9603 FDA also looked at the extent to which teeth treated with doxycycline developed temperature or pressure sensitivity.

In the all clinical trials, a total of 919 subjects received doxycycline, 472 vehicle, 226 oral hygiene and 210 SRP.

The ATRIDOX™ and vehicle groups had statistically significantly higher rates of adverse events in the digestive, endocrine, nutritional, metabolic, genitourinary, mental, musculoskeletal, and respiratory systems, and among ill-defined conditions. It seems unlikely that topically applied doxycycline or vehicle would have such broad ranging systemic effects, and it must be remembered that the subjects were not blinded to treatment. Subjects didn't know whether they

were getting ATRIDOX™ or the vehicle, but they were aware that they received some treatment as opposed to SRP or oral hygiene, where nothing was placed in the periodontal pocket. Table 12 lists the percentage of subjects reporting all-causalities adverse events for all clinical studies.

In the Circulatory System category 16 subjects in the ATRIDOX™ group were reported as having an adverse event coded as, "unspecified essential hypertension." Only 2 subjects in the vehicle group, and none in the SRP or oral hygiene groups were reported to have unspecified essential hypertension. The difference between the ATRIDOX™ group and the other groups was statistically highly significant. The sponsor was queried about this finding and said that they had no reason to believe that there was any association between essential hypertension and the topical use of doxycycline. They believe that these results were a chance occurrence.

Reviewer's Comment: Though there is no apparent association between topical use of doxycycline and essential hypertension, this finding should be mentioned in the ADVERSE EVENTS section of the label.

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Table 12: Percentage of Subjects Reporting All-Causalities Adverse Events for All Clinical Studies

BODY SYSTEM/ Adverse Event	Percentage of Subjects			
	Doxy N=919	Vehicle N=472	OHI N=226	SRP N=210
DIGESTIVE SYSTEM				
All Terms in Body System	53.0	60.6	42.5	52.4
Unspecified gingival and periodontal disease (pocket depth increase, pain from extraction, discomfort from treatment, attachment loss, and gingival soreness, pain and irritation)	16.9	24.8	18.1	21.0
Unspecified disorder of the teeth and supporting structures (Toothache and pressure tooth sensitivity)	14.1	16.3	9.3	18.1
Acute periodontitis (dental abscess and infection)	7.6	12.1	9.3	8.6
Other and unspecified diseases of the oral soft tissues (Generalized mouth pain, redness and soreness)	5.1	5.9	3.1	6.2
Dyspepsia and other specified disorders of function of stomach	4.6	5.3	3.5	5.2
Acute gingivitis (Gingival inflammation, gingival sensitivity, and abscess)	3.5	6.4	4.9	6.2
Other specified diseases of hard tissues of teeth (tooth sensitivity including temperature sensitivity)	17.6	18.6	4.0	6.7
ILL-DEFINED CONDITIONS				
All Terms in Body System	38.5	42.8	37.2	37.1
Headache	30.1	33.5	28.8	28.6
RESPIRATORY SYSTEM				
All Terms in Body System	39.1	46.6	33.6	38.1
Acute nasopharyngitis (Common Cold)	23.1	26.5	18.1	17.1
Other diseases of the cavity and sinuses	7.0	8.9	4.0	8.1
Influenza and other respiratory manifestations	5.0	9.5	4.0	6.7
Allergic rhinitis, cause unspecified	3.3	5.1	4.9	5.7
Acute pharyngitis	4.6	7.0	1.8	3.3
MUSCULOSKELETAL SYSTEM				
All Terms in Body System	19.9	23.1	19.9	22.9
Myalgia and myositis, unspecified	6.0	4.9	5.3	4.3
Backache, unspecified	4.5	6.8	3.1	6.2
INJURY AND POISONING				
All Terms in Body System	12.0	15.9	13.3	15.2
Open wound of tooth (broken), uncomplicated	4.4	4.0	4.9	5.7

Prolonged Retention

One concern that was raised by leaving the product in the pocket to bioabsorb or be expelled naturally was that there would be adverse events associated with prolonged retention of the

product. A total of 649 subjects had ATRIDOX™ left in place for varying lengths of time up to 9 months. In study ACS-38 the sponsor looked at safety out to 84 days post placement, in Study ACS-32 up to 28 days. Finally, in AGD 9603 adverse event data were collected for nine months and FDA asked that adverse events be reported by time of occurrence relative to the beginning of the study.

The data presented by the sponsor support the fact that adverse events are not associated with leaving the product in the pocket to bioabsorb or be naturally expelled. The actual number of adverse events was small for all categories of event. There was not a disproportionate number of events observed in any time period for the various ICD-9 categories with the exception of "unspecified gingival and periodontal disease." This is the area which was of concern prior to the study - would leaving the product in the pocket for a prolonged period result in gingival irritation or periodontal abscesses? In that case a disproportionate number of adverse events were observed in the first 8 days following placement of the product, rather than farther in time from placement of the product. This result demonstrated that leaving the product in the pocket does not result in a disproportionate number of adverse events.

Tooth Sensitivity

One concern that was raised by FDA was the possibility that the presence of doxycycline in the periodontal pocket might result in tooth sensitivity due to the fact that the hyclate salt of doxycycline has a low pH. To address this question, the sponsor added a question regarding tooth sensitivity in the bridging study (AGD 9603). This question had not been asked in studies ACS-34 & ACS-35. The second most commonly reported adverse event by ICD-9 code was "Other Specified Diseases of Hard Tissues of Teeth." This category included temperature sensitivity of teeth, and was experienced by 4% of subjects in the oral hygiene group, 7% of subjects receiving SRP, 18% receiving ATRIDOX™, and 19% of subjects receiving vehicle. It appears that asking the question regarding tooth sensitivity may have elicited a positive response in subjects who might not have mentioned it otherwise. SRP is known to cause tooth sensitivity, yet only 7% of SRP subjects reported events in this category, compared to 4% of oral hygiene subjects, who would not be expected to have treatment related tooth sensitivity. The tooth sensitivity question was not asked in the studies that included the OHI and SRP arms. On the other hand, 18% in the ATRIDOX™ group and 19% in the vehicle group reported tooth sensitivity. While it cannot be ruled out that the vehicle causes increased sensitivity, if the sensitivity was due to the low pH of doxycycline, one would expect to see more sensitivity in subjects in the ATRIDOX™ group than in subjects in the vehicle group. The doxycycline does not appear to increase tooth sensitivity.

Two subjects treated with vehicle experienced an apparent localized allergic response. This is a 0.14% incidence of occurrence of allergic response to this product.

Three subjects reported an adverse taste associated with the doxycycline hyclate product; this constituted 1.4% of the study subjects.

Sex, age, race and smoking status did not appear to be correlated with adverse events.

Study AGD 9701

This study was conducted to support labeling for the product that calls for no retentive material. This was a Phase 3, single-center, single-blind, randomized, parallel design, bioequivalence study comparing the drug release characteristic of ATRIDOX™ when retained with Octyldent™ and ATRIDOX™ when no retentive material is used. Twenty-four subjects aged with chronic adult periodontitis were randomized to two groups of twelve each. Study duration was seven days with all drug product removed at that time. The GCF samples collected were evaluated using and C_{max} , T_{max} , and AUC were calculated for each subject. Adverse events were collected by observing and interviewing the subjects.

Reviewer's Comment: In order for the sponsor to be able to label the product for use without retentive material, equivalence between doxycycline concentration in GCF, with and without retention had to be shown. Safety and efficacy of this product had been established by the pivotal trials.

The results of this study have been reviewed Biopharmaceutics and found to be unacceptable for making the bridge from the Octyldent™ retention method to no retention. The Division had agreed that, in principle a study demonstrating bioequivalence would be acceptable, but the data were too variable to be of use in this regard. See Dr. Wang's Biopharmaceutics review for a more detailed discussion.

Discussion

The subjects studied in the clinical trials ranged in age from , had chronic adult periodontal disease defined as moderate to severe disease characterized by at least two quadrants of the mouth, each containing at least four pockets which measured 5mm or greater and bled on gentle probing. Subjects also could not have substantial calculus, defined as no more than 20% of the tooth surfaces having detectable calculus. Subjects were stratified into three groups at baseline by pocket depth. The primary endpoint was gain in attachment level and the secondary endpoints were reduction in probing pocket depth and reduction in bleeding on probing. The studies were nine months in duration. The sponsor conducted three trials which are considered pivotal - one of these was the bridging study to the new method of retention and leaving the product in the pocket.

The conclusion of this review is that the sponsor met all the decision rules with respect to the primary efficacy variable, attachment level. The attachment level gains reported for ATRIDOX™ in the three pivotal trials were between .68 and .86 mm. at nine months for the ITT population. This was comparable to the gains achieved by SRP in these studies. The results with respect to the secondary endpoints, though lesser in magnitude, demonstrated that

the product is also efficacious in reducing pocket depths and bleeding on probing.

Bleeding on Probing (BOP)

The sponsor evaluated BOP in all three of the trials that are submitted as pivotal, ACS-34, ACS-35 and AGD 9603. In ACS-35 the decision rules for showing efficacy in reduction in bleeding on probing were met. In ACS-34 there was a statistically significant difference between ATRIDOX™ and oral hygiene (weak positive control) in this parameter, and reductions in BOP in the ATRIDOX™ and SRP arms were almost identical. However a statistically significant difference was not observed between ATRIDOX™ and vehicle with respect to reduction in BOP.

In the third pivotal study, AGD 9603, vehicle retained with Octyldent™ was compared to ATRIDOX™ with two different retention methods, Coe-Pak™ and Octyldent™. In this case, the comparison with respect to bleeding on probing between vehicle retained with Octyldent™ and ATRIDOX™ retained with Coe-Pak™ showed a marginally significant difference for the ITT population, and a statistically significant difference for the Efficacy Evaluable population. The comparison between vehicle retained with Octyldent™ and ATRIDOX™ retained with Octyldent™ showed a highly significant difference. In summary, ATRIDOX™ was better than oral hygiene with respect to reduction in BOP in all three studies, and was numerically better than SRP in the two studies that included an SRP arm. Even though a statistically significant difference was not observed in the active to vehicle comparison in ACS-34, a statistically significant difference was seen in ACS-35 and AGD 9603. Taken as a whole, this submission provides data demonstrating that ATRIDOX™ is efficacious in reducing BOP. The evidence includes the fact that ATRIDOX™ was better than oral hygiene and almost identical to SRP with respect to reduction in BOP in both ACS-34 and ACS-35. Though the results of ACS-34 did not demonstrate a statistically significant difference between ATRIDOX™ and vehicle, ATRIDOX™ was superior to vehicle in both ACS-35 and AGD 9603 with respect to reduction in BOP.

Comparison of Methods of Retention

In their original studies (ACS-34 & ACS-35), the ATRIDOX™ was retained by Coe-Pak™ periodontal dressing and product and dressing were removed after seven days. The sponsor then decided that they would prefer to market a product that could be left in the pocket until it bioabsorbed or was expelled by brushing and flossing. Also Octyldent™, a dental adhesive, was to be used for retention, rather than the Coe-Pak™, because the Octyldent™ could be brushed and flossed off, thereby obviating the need for a return visit to the dentist. The Division agreed that the sponsor could receive approval for that indication based on results of a single trial of nine months duration (AGD 9603) if the pivotal studies using Coe-Pak™, which at that time had not been completed, supported approval. This was a three arm trial as follows:

1. ATRIDOX™ with Coe-Pak™ removed after 7 days as in the pivotal trials

2. ATRIDOX™ with Octyldent™ left to biodegrade as in the proposed labeling
3. Vehicle control with Octyldent™ left to biodegrade as in the proposed labeling

The primary efficacy endpoint was change in attachment level at nine months. Secondary efficacy endpoints were change in pocket depth (PPD) and Bleeding on Probing (BOP). In order to "win," the Octyldent™ arm had to be equivalent to the Coe-Pak™ arm and both had to be superior to vehicle. In the case of the primary efficacy variable, gain in attachment level, the decision rules were met.

With respect to the secondary endpoint of reduction in pocket depth, there was a statistically significant difference between the two methods of retention in the TTH dataset. The Coe-Pak™ method was favored with a mean reduction in pocket depth of 1.22 mm versus 1.07 mm for the Octyldent™ method. However, in the Efficacy Evaluable dataset the same comparison was not statistically significant. In the secondary endpoint of reduction in bleeding on probing, the decision rules were met.

The sponsor has met the decision rules for the comparison of the Coe-Pak™ and Octyldent™ methods with respect to gain in attachment level and reduction in bleeding on probing. In the case of the comparison of reduction in pocket depth, there was a statistically significant difference between the two methods with a .15 mean difference in pocket depth reduction favoring the Coe-Pak™ method. This could mean that the sponsor could label their product for use with the Octyldent™ method of retention, but not make the claim for reduction in pocket depths.

Because the sponsor has "won" on the primary endpoint of attachment level gain and on BOP and because the Octyldent™ arm wins in a comparison with vehicle with respect to pocket depth reduction, the sponsor has demonstrated that ATRIDOX™ retained with Octyldent™ with the product left in the pocket to biodegrade or be expelled naturally, is efficacious with respect to all three endpoints (attachment level, pocket depths and bleeding on probing).

No Retention Method

Study AGD 9701 was conducted to support labeling for the product that calls for no retentive material. This was a Phase 3, single-center, single-blind, randomized, parallel design, bioequivalence study comparing the doxycycline concentration in the GCF using ATRIDOX™ when retained with Octyldent™ and ATRIDOX™ when no retentive material was used. A third arm which was vehicle retained with Octyldent™ was also included. The results of this study have been reviewed by Biopharmaceutics and found to be unacceptable for making the bridge from the Octyldent™ retention method to no retention. The Division had agreed that, in principle a study demonstrating bioequivalence would be acceptable, but the data were too variable to be of use in this regard. See Dr. Wang's Biopharmaceutics review.

New Product Mixing Method

Study AGD 9607 was conducted to support a change in the way the product is mixed prior to placement. The to-be-marketed product is provided in two syringes, one of which contains the doxycycline powder and the other the polymer vehicle. The two syringes are joined and the contents are then pushed from one syringe to the other until thoroughly mixed. In the pivotal studies (ACS-34 & ACS-35) the product was mixed using 100 mixing cycles, followed by a 15 minute wait and then an additional 10 mixing cycles. In this study the product was mixed using only 100 mixing cycles and then used immediately. Octylident™ was used for retention in both cases. The sponsor had conducted an in vitro comparison of the two mixing methods and had shown them to be equivalent. AGD 9607 was conducted to confirm that the concentration of doxycycline in vivo, in the GCF, is equivalent using either of the mixing methods.

The Biopharmaceutics review concluded that the extreme variability of the data from this study precluded a showing of bioequivalence. Inspection of individual data showed high day to day variability which may be due to the sampling strip coming into contact with retained product. See Dr. Wang's Biopharmaceutics review.

Labeling

The following changes to the sponsor's proposed labeling include not only those recommended by clinical, but also those recommended by the other disciplines. Changes that resulted from the labeling day held on 3/11/98 have been incorporated into the attached label. An explanation of the changes recommended as a result of the clinical review follow.

Reviewer's Comment: The dataset analyzed by FDA to establish efficacy for the product was the ITT dataset. In the proposed labeling the sponsor uses data from the Efficacy Evaluable dataset. The results are very similar and the conclusions drawn from the trials are the same regardless of which method of analysis is used. The results cited in the tables regarding Attachment Level Gain and Probing Depth Reduction in the attached label are from the Efficacy Evaluable dataset.

In instances where the sponsor refers to "Placebo," this reviewer would prefer "Vehicle Control" because this arm includes the polymer and is lacking only the doxycycline. Especially when interpreting safety data, it is useful to be aware that the vehicle may have some effect.

The sponsor has proposed to use the following tables in the label for this product.

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pages of trade

secret and/or

confidential

commercial

information

Recommended Regulatory Action:

The sponsor has successfully demonstrated the safety and efficacy of ATRIDOX™ for the indication sought. With modifications to the labeling, the product may be approved for marketing.

JSI

4/3/98

John V. Kelsey, D.D.S., M.B.A.

cc: Original NDA

HFD-540/ Div File

HFD-540/DD/Wilkin

HFD-540/DO/Hyman/Gilkes

HFD-540/PM/Blay

4/3/98

AUG 12 1998

Dental Officer's Review of NDA 50-751
Response to Approvable Letter

Drug: ATRIDOX™ (ATRIGEL®
Delivery System with
doxycycline hyclate)

Submission date: July 6, 1998
Received date: July 8, 1998
Review date: August 11, 1998

Sponsor: Atrix Laboratories, Inc.

Project Manager: Roy Blay

Proposed indication:
Treatment of Chronic Adult
Periodontitis

Reviewer: J. Kelsey

Pharmacologic Category:
Antimicrobial - Periodontitis

Introduction:

This submission is in response to an AE letter issued to the sponsor on April 7, 1998. The Division had offered approval of the product at that point, but the sponsor declined, wishing to negotiate about the labeling of the product. The sponsor requested a meeting with the Division to discuss the proposed revisions to labeling, and this was held on June 17, 1998. The sponsor submitted their proposed labeling changes formally on July 6, 1998. Because the submission includes some new pharmacokinetic data, the submission was given a 6 month review clock, though the Division has told the sponsor that an action can be expected well ahead of the six month date. The user fee date for this submission is January 6, 1999.

There are four items that are being negotiated as follows:

- 1) In the CLINICAL STUDIES section the sponsor would like to delete reference to the decision rule of " " and replace with other language.
- 2) In the ADVERSE EVENTS section of the label the sponsor would like to modify the wording regarding the fact that a disproportionate number of subjects in the ATRIDOX™ group experienced essential hypertension. In addition, in response to a request by the Division, the sponsor provided a revised tabular summary of adverse events that included only data from subjects in the clinical trials.

3a) The sponsor is seeking a change in the mixing method to be used for constituting the product prior to use.

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- 3b) The sponsor is seeking to remove the requirement that a retentive material be used as was done in the pivotal trials.
- 4) The sponsor is seeking various minor wording changes.

These issues will be reviewed in order:

- 1) In the CLINICAL STUDIES section the sponsor would like to delete reference to the decision rule of and replace with other language.

In the labeling that the Division sent with the AE letter on April 7, 1998, under the CLINICAL STUDIES section it was stated that,

The sponsor would like to avoid using % anywhere in the label and would like to be able to say that results with ATRIDOX™ are "similar" to SRP. The results of the pivotal studies showed that ATRIDOX™ was clearly at least % as good as SRP, and in fact was numerically close to SRP, though not statistically equivalent.

Reviewer's Comment: Use of or any synonyms that indicate sameness between the clinical results using ATRIDOX™ and SRP are not supported by the data. The issue then is how to address the comparison between SRP and ATRIDOX™ in the label. The statement originally proposed is accurate, but doesn't reflect the fact that ATRIDOX™ was substantially better than % as good as SRP. During the 6/17/98 meeting there was discussion about adding a parenthetical statement indicating that the % as good as SRP standard was required of any sponsor seeking approval of a stand alone therapy for treatment of periodontitis. That would clarify that this is a standard and not the specific results of the studies. The sponsor has proposed additional language that would also be informative and should be included. This reviewer recommends that this section of the label be revised as follows:

than the way it was used in the pivotal trials. In the three pivotal trials either Coe-Pak™ periodontal dressing or Octylident™ dental adhesive were used to retain the ATRIDOX™ in the pocket. The sponsor sought to show bioequivalence between these methods in a trial involving 24 subjects, but the data were too variable to be useful.

In this submission the sponsor makes three arguments for the fact that use of a retentive agent should not be required:

First they argue that while they were unable to show bioequivalence, they have identified a therapeutic drug range based on concentration of doxycycline in the gingival crevicular fluid (GCF), and that this range falls above the minimum inhibitory concentration (MIC) of doxycycline required to inhibit periodontal pathogens. They go on to note that the doxycycline levels obtained with the no retention method were within this range.

They further looked at efficacy data collected from various of their studies in which the material was lost prior to seven days. These data show that the efficacy is similar to that achieved when the material is retained beyond 7 days.

Finally, they argue that the purpose for using the Coe-Pak™ periodontal dressing or Octylident™ dental adhesive was simply to assure that the residence time of the ATRIDOX™ in the pocket was the same for both active and vehicle. In similar situations the FDA has not required that labeling include mention of the retentive material.

Reviewer's Comment: While there is some merit to each of these arguments, this reviewer remains unconvinced. I am concerned about setting unfavorable precedent. We have not accepted antibiotic levels in the GCF at any concentration as a surrogate for treatment of periodontitis. Allowing the sponsor to make efficacy claims based on data cobbled together from various investigations post hoc invites data dredging. And while the issue of using the retentive material to assure a similar residence time was mentioned in the July 25, 1996 minutes that the sponsor references, this was not discussed in the study design of any of the trials.

4) The sponsor is seeking various minor wording changes.

In the pre-meeting package submitted by the sponsor, various minor wording changes were proposed. These were discussed at the June 17, 1998 meeting and subsequently one proposed change was withdrawn, while others were modified. Most changes were deemed acceptable by the Division. For clarity, the eight changes that were originally proposed in the pre-meeting package will be identified as Changes 1 - 8.

Reviewer's Comment: These changes were agreed to at the 6/17/98 meeting, and are acceptable.

Reviewer's Comment: Biopharmaceutics should review this change. This is different than what was discussed at the 6/17/98 meeting.

Reviewer's Comment: This change was agreed to at the 6/17/98 meeting and is acceptable.

Reviewer's Comment: This change was agreed to at the 6/17/98 meeting and is acceptable.

Reviewer's Comment: These changes were agreed to at the 6/17/98 meeting, and are acceptable.

Reviewer's Comment: This change was agreed to at the 6/17/98 meeting, and is acceptable.

Reviewer's Comment: These changes were agreed to at the 6/17/98 meeting, and are acceptable.

In addition to the original labeling issues that are discussed above, Atrix raised two new issues. One concerns the presentation of efficacy data. The Division had agreed to include two tables in the labeling that gave efficacy results with respect to attachment levels and pocket depths respectively. The sponsor now proposes to combine the results of the two studies (ACS-34 & ACS-35) and to present the results of all four treatment arms graphically.

Reviewer's Comment: Because the Division accepted the data that was presented in the tables, it is this reviewer's opinion that the Division should accept the data presented in a different format. It seems reasonable to combine the results of the two studies because they were of identical design. One concern though is the way in which statistical significance is noted. In the original tables, statistical significance is noted by superscripts adjacent to the data and keyed to descriptions at the end of the table. In the graphical presentation, the superscripts are associated with various time points on the x-axis and it is difficult to determine which efficacy data points are statistically significant. The sponsor should modify the table so that it is clear which data points are statistically significant. If an acceptable revision can be made, this reviewer would recommend acceptance of the graphical representation.

The second new issue is really a policy question that was submitted along with the proposed labeling changes. It is labeled "Arix Response to Statistical Criteria for Establishing Clinical Equivalence," and reiterates the sponsor's discussion about the fact that it would be very difficult to show bioequivalence using the standard equivalency methodology. They go on to note that Dr. Harkin negotiated an alternative methodology for demonstrating bioequivalence that was used in analysis of the data from Study AGD 9603. They ask whether this methodology will be acceptable to FDA for showing equivalency for the clinical endpoints used in AGD 9603 in the future.

Reviewer's Comment: The Division will respond to the sponsor on this question, but not as part of this labeling review.

These proposed changes will be discussed at the labeling day for this product scheduled for August 13, 1998.

JSI

8/12/98

John V. Kelsey, D.D.S., M.B.A.

- cc: Original NDA
- HFD-540/Div File
- HFD-540/DO/Hyman/Gilkes
- HFD-540/PM/Blay

8/12/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 50-751

CHEMISTRY REVIEW(S)

SEP 4 1998

**Division of Dermatologic and Dental Drug Products, HFD-540
Review of Chemistry, Manufacturing, and Controls**

NDA # 50-751 CHEM REVIEW # 5 REVIEW DATE: September 4, 1998

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	3/31/97	4/1/97	Chem Review #1
NC	4/16/97	4/18/97	Chem Review #1
NC	4/17/97	4/22/97	Chem Review #1
AZ	5/20/97	5/23/97	Chem Review #1
BC	7/21/97	12/8/97	Chem Review #1
BC	12/1/97	12/3/97	Chem Review #1
BC	12/3/97	12/4/97	Chem Review #1
BC	12/1/97	???	Chem Review #2
BC	12/8/97	12/9/97	Chem Review #2
BC	12/15/97	12/16/97	Chem Review #2
BC	1/6/98	1/8/98	Chem Review #2
BC (fax)	2/18/98	2/23/98	Chem Review #3
BC	2/13/98	2/17/98	Chem Review #4
BC	2/26/98	3/2/98	Chem Review #4
BC	3/2/98	3/4/98	Chem Review #4
AL	7/2/98	7/6/98	7/7/98
BZ	7/24/98	7/27/98	7/30/98

NAME & ADDRESS OF APPLICANT: Atrix Laboratories, Inc.
2579 Midpoint
Fort Collins, CO 80525-4417

DRUG PRODUCT NAME

Proprietary: Atridox
Nonproprietary/USAN: doxycycline hyclate
Code Name/#:
Chem. Type/Ther. Class: 3-S

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION: Chronic adult periodontitis

DOSAGE FORM: controlled release polymer

STRENGTH: 10% doxycycline hyclate (equivalent to 8.5% doxycycline)

ROUTE OF ADMINISTRATION: topical (subgingival)

HOW DISPENSED: XX Rx OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL.WT:**

See Chemist's Review #1

SUPPORTING DOCUMENTS:

1. AADA 62-585, doxycycline hyclate, Ranbaxy Laboratories
2. DMF
3. DMF
4. DMF
5. 510(k)
6. 510(k)
7. 510(k) K884652, Octyldent, Closure Medical, Inc.
8. 510(k)

RELATED DOCUMENTS (if applicable):

None

CONSULTS:

None

REMARKS/COMMENTS:

The July 2 AL (labeling amendment) contained the package insert, syringe labels, pouch label, and multiple unit carton label in draft form. Per the attached memoranda, revisions were proposed to the Applicant based on the requirements of 21 CFR 201.10(g)(1) and 201.15.

The July 24 BZ amendment contained only biopharmaceutics data for review.

An approval letter for this application issued September 3, 1998.

CONCLUSIONS & RECOMMENDATIONS:

The attached memoranda, dated August 31, September 1 and September 3, constitute the substantive technical review of the labeling, and should be considered collectively to be chemistry review #5. Post-approval submission of FPL should be directed to the chemist for further technical review of the syringe labels, pouch label, and multiple unit carton label.

/S/

Chemistry Team Leader, HFD-540

9/4/98

cc: Original NDA 50-751
HFD-540/Division File
HFD-540/Wilkin
HFD-540/Kelsey
HFD-540/Kozma-Fornaro
HFD-540/See
HFD-540/Vincent
HFD-540/Wang
HFD-540/DeCamp
HFD-540/Pappas

Drafted by: **whd/9/4/98/n50751.rv5**

CHEMISTRY REVIEW

DIVISION OF DERMATOLOGIC and DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 50-751 CHEM.REVIEW-#: 4 REVIEW DATE: 3/2/98

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	3/31/97	4/1/97	Chem.Review #1
AMENDMENT/NC	4/16/97	4/18/97	" " "
AMENDMENT/NC	4/17/97	4/22/97	" " "
AMENDMENT/AZ	5/20/97	5/23/97	" " "
AMENDMENT/BC	7/21/97	12/8/97	" " "
AMENDMENT/BC	12/1/97	12/3/97	" " "
AMENDMENT/BC	12/3/97	12/4/97	" " "
AMENDMENT/BC	12/1/97 (Desk Copy)	Unknown	Chem.Review #2
AMENDMENT/BC	12/8/97	12/9/97	" " "
AMENDMENT/BC	12/15/97	12/16/97	" " "
AMENDMENT/BC	1/06/98	1/08/98	" " "
AMENDMENT/BC	2/18/98 (FAX)	2/23/98	Chem.Review #3
AMENDMENT/BC	2/13/98	2/17/98	2/23/98
AMENDMENT/BC	2/26/98 (desk copy)		
AMENDMENT/BC	3/02/98 (desk copy)		

NAME & ADDRESS OF APPLICANT: Atrix Laboratories, Inc.
2579 Midpoint
Fort Collins, CO 80525-4417

DRUG PRODUCT NAME
Proprietary: ATRIDOX
Nonproprietary/USAN: doxycycline hyclate
Code Names/#'s:
Chem.Type/Ther.Class: 3 S

ANDA Suitability Petition/DESI/Patent Status:
N/A [if applicable]

PHARMACOL.CATEGORY/INDICATION: Chronic Adult
Periodontitis

DOSAGE FORM: Topical

STRENGTHS: 8.5% (w/w of doxycycline)

ROUTE OF ADMINISTRATION: Atrigel Delivery System

DISPENSED: x Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL.WT: (Chemical Abstract Services, CAS, No. 24390-14-5)

(A) (See Chemist Review #1)

(B) ATRIGEL Delivery System: Consist of the following polymeric formulation:
N-methyl-2-pyrrolidone (NMP) & Poly (DL-lactide) (PLA)

SUPPORTING DOCUMENTS:

- (1) AADA 62-865 for Doxycycline Hyclate, USP (drug substance)
- (2) DMF
- (3) DMF
- (4) DMF

- (5) 510(k)

- (6) 510(k)
- (7) 510(k) (K884652) for Octylident Periodontal Adhesive
- (8)

Note: Letters of authorization were received from the manufacturers of the above products (Items 1-6).

RELATED DOCUMENTS (if applicable):

IND (Atrix
Laboratories, Inc.)

CONSULTS:

(1) Consult for Microbiology Review (#2) requested 1/12/98
Note: Not received by Division (HFD-540) as of this Chemist Review (#4).

REMARKS/COMMENTS:

Chemist review (#4) was drafted to address the draft labeling which was submitted with the applicant's amendment of 2/13/98. This draft labeling was reviewed under "Chemist Review

This chemist review also covers the applicant's amendments of 2/26/98 and 3/2/98. In this regard, the Applicant's submitted a commitment to restructure the specification for Extended Drug Release of the product. Therefore, new regulatory specifications which include limits for Extended Drug Release after 1 hour and 24 hours of % and % of label claim, respectively have been submitted. See attached Appendix for the revised ATRIDOX Drug Product Regulatory Specifications, which was submitted on 2/26/98 and further revised on 3/2/98 because of a typographical

error in reporting detected 4-epidoxycycline as % instead of %.

Note: Since the applicant did not agree to FDA's recommendation for the specification for Extended Drug Release of the product of %, the original stability specifications and the appropriate expiration date for the finished product could not be determined. However, since they have adjusted these specifications to % of label claim, the stability data therefore support an 18 month expiration date. The applicant may extend the expiration date to 24 months when more data are submitted, providing they are found to be within product specifications. The extension of the expiration date to 24 months may be extended in the annual report.

CONCLUSIONS & RECOMMENDATIONS:

The applicant's draft labeling of 2/13/98 was reviewed and found acceptable from a technical standpoint with the following exceptions

The applicant's has agreed to restructure the product release specifications with a specification for the constituted product of %, with no more than one sample assay time of % of label claim

Since the applicant has agreed to the % specifications for the constituted product, all of the CMC issues have been met. Therefore, the NDA may be approved from a CMC standpoint.

ISI

3/2/98

Review Chemist

cc: Orig. NDA 50-751
HFD-540/Division File
HFD-540/Pappas
HFD-540/Kelsey
HFD-540/See
HFD-540/Vincent
HFD-540/Blay
HFD-540/DeCamp
HFD-880/Wang

WD 3/4/98

JW 3/23/98

DIVISION OF DERMATOLOGIC and DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

FEB 19 1998

NDA #: 50-751 CHEM.REVIEW-#: 3 REVIEW DATE: 2/19/98

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	3/31/97	4/1/97	Chem.Review #1
AMENDMENT/NC	4/16/97	4/18/97	" " "
AMENDMENT/NC	4/17/97	4/22/97	" " "
AMENDMENT/AZ	5/20/97	5/23/97	" " "
AMENDMENT/BC	7/21/97	12/8/97	" " "
AMENDMENT/BC	12/1/97	12/3/97	" " "
AMENDMENT/BC	12/3/97	12/4/97	" " "
AMENDMENT/BC	12/1/97 (Desk Copy)	Unknown	Chem.Review #2
AMENDMENT/BC	12/8/97	12/9/97	" " "
AMENDMENT/BC	12/15/97	12/16/97	" " "
AMENDMENT/BC	1/06/98	1/08/98	" " "
AMENDMENT/BC	2/17/98 (FAX)	Unknown	2/19/98

NAME & ADDRESS OF APPLICANT: Atrix Laboratories, Inc.
2579 Midpoint
Fort Collins, CO 80525-4417

DRUG PRODUCT NAME

Proprietary: ATRIDOX
Nonproprietary/USAN: doxycycline hyclate
Code Names/#'s:
Chem.Type/Ther.Class: 3 S

ANDA Suitability Petition/DESI/Patent Status:

N/A [if applicable]

PHARMACOL.CATEGORY/INDICATION: Chronic Adult
Periodontitis

DOSAGE FORM: Topical

STRENGTHS: 8.5% (w/w of doxycycline)

ROUTE OF ADMINISTRATION: Atrigel Delivery System

DISPENSED: x Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL.WT: (Chemical Abstract Services, CAS, No. 24390-14-5)

(A)

(B) ATRIGEL Delivery System: Consist of the following polymeric formulation:
N-methyl-2-pyrrolidone (NMP) & Poly (DL-lactide) (PLA)

SUPPORTING DOCUMENTS:

- (1) AADA 62-865 for Doxycycline Hyclate, USP (drug substance)
- (2) DMF
- (3) DMF
- (4) DMF

- (5) 510(k)

- (6) 510(k)
- (7) 510(k) (K884652) for Octyldent Periodontal Adhesive
- (8)

Note: Letters of authorization were received from the manufacturers of the above products (Items 1-6).

RELATED DOCUMENTS (if applicable):

IND (Atrix
Laboratories, Inc.)

CONSULTS:

- (1) Consult for Microbiology Review (#2) requested 1/12/98

REMARKS/COMMENTS:

The original New Drug Application for the ATRIDOX drug product was found deficient in several of the CMC areas (see Chemist Review #1). These CMC issues were addressed by the Applicant with their amendment on 1/6/98. They were reviewed and found to be in approvable state providing the Applicant agreed to the recommendation of single specification for the constituted product of % (see Chemist Review # 2; . This single specification was conveyed to the applicant via telecon on 2/6/98.

Therefore, the Applicant responded to FDA's telecon of 2/6/98, whereby they agreed to a single specification but disagreed to the % specifications
They countered with the shelf life specifications of % of label claim for 1 hour and % of label claim for 24 hours. In this regard, the applicant counter proposal is not acceptable.

EER: Found acceptable on 2/19/98 per EES from the Office of Compliance.

CONCLUSIONS & RECOMMENDATIONS:

The NDA was approved from a CMC standpoint (see Chemist Review (#2) dated 2/9/98). However, the condition for approving the NDA was based on the Applicant's commitment to a single specification for the constituted product of % . In this regard, the applicant committed to a single specification but not to the % limits. **UNACCEPTABLE**

EER was found acceptable by the Office Compliance.

Therefore, the NDA is not approvable from a CMC standpoint for failure to include release specifications for the constituted product of % limits.

Note: It is this reviewer opinion that lowering our standards because the Applicant can not meet the product specifications is UNACCEPTABLE. Instead of lowering the specifications as they proposed, the Applicant should concentrate on correcting the moisture problem.

ISI *2/19/98*

Review Chemist

- cc: Orig. NDA 50-751
- HFD-540/Division File
- HFD-540/Pappas
- HFD-540/Kelsey
- HFD-540/See
- HFD-540/Vincent
- HFD-540/Blay
- HFD-540/DeCamp *WJ 2/19/98*
- HFD-880/Wang

gw 1/24/98 L J. Hill

FEB 19 1998

DIVISION OF DERMATOLOGIC and DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 50-751 CHEM.REVIEW #: 2 REVIEW DATE: 2/9/98

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	3/31/97	4/1/97	Chem.Review #1
AMENDMENT/NC	4/16/97	4/18/97	" " "
AMENDMENT/NC	4/17/97	4/22/97	" " "
AMENDMENT/AZ	5/20/97	5/23/97	" " "
AMENDMENT/BC	7/21/97	12/8/97	" " "
AMENDMENT/BC	12/1/97	12/3/97	" " "
AMENDMENT/BC	12/3/97	12/4/97	" " "
AMENDMENT/BC	12/1/97 (Desk Copy)	Unknown	Unknown
AMENDMENT/BC	12/8/97	12/9/97	12/16/97
AMENDMENT/BC	12/15/97	12/16/97	1/5/98
AMENDMENT/BC	1/06/98	1/08/98	1/09/98

NAME & ADDRESS OF APPLICANT: Atrix Laboratories, Inc.
2579 Midpoint
Fort Collins, CO 80525-4417

DRUG PRODUCT NAME
Proprietary: ATRIDOX
Nonproprietary/USAN: doxycycline hyclate
Code Names/#'s:
Chem.Type/Ther.Class: 3 S

ANDA Suitability Petition/DESI/Patent Status:
N/A [if applicable]

PHARMACOL.CATEGORY/INDICATION: Chronic Adult
Periodontitis

DOSAGE FORM: Topical

STRENGTHS: 8.5% (w/w of doxycycline)

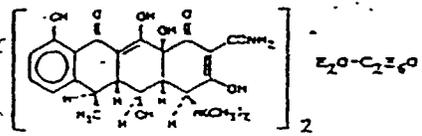
ROUTE OF ADMINISTRATION: Atrigel Delivery System

DISPENSED: X Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL.WT: (Chemical Abstract Services, CAS, No. 24390-14-5)

(A)
4-(Dimethylamino) - 1,4,4a,5,5a,6,11,12a-octahydro-1,4-benzoxepin-2-one hydrochloride.
(C₂₂H₂₂N₂O₄ · HCl)₂ · C₂H₄O · H₂O Mol wt 1025.89

CAS 24390-14-5



(B) ATRIGEL Delivery System: Consist of the following polymeric formulation:
N-methyl-2-pyrrolidone (NMP) & Poly (DL-lactide) (PLA)

SUPPORTING DOCUMENTS:

- (1) AADA 62-865 for Doxycycline Hyclate, USP (drug substance)
- (2) DMF
- (3) DMF
- (4) DMF

- (5) 510(k)

- (6) 510(k)
- (7) 510(k) (K884652) for Octylident Periodontal Adhesive
- (8)

Note: Letters of authorization were received from the manufacturers of the above products (Items 1-6).

RELATED DOCUMENTS (if applicable):

IND (Atrix
Laboratories, Inc.)

CONSULTS:

- (1) Consult for Microbiology Review (#2) requested 1/12/98

REMARKS/COMMENTS:

The original New Drug Application for the ATRIDOX drug product was found deficient in several of the CMC areas; i.e., Manufacturing and Packaging, Drug Product Specifications and Methods, and Stability. These CMC deficiencies were communicated to the applicant on 11/26/97 with our IR letter. Therefore, in accordance with 21 CFR 314.60, the applicant amended their NDA on 1/6/98 whereby they corrected these manufacturing and control deficiencies

The labeling remains acceptable from a technical standpoint. Tradename consult was received from the Labeling and Nomenclature Committee and found acceptable the tradename "ATRIDOX"

Methods validation has not been implemented to date because of the CMC deficiencies. Therefore, these deficiencies have

been corrected. Methods validation is pending; to be requested.

EER was requested 5/14/97; status is pending from the Office of Compliance.

Amendment dated 12/5/97 refers to FDA's results of GLP inspection of 12/2/97.

Environmental Assessment: NA

The applicant was granted a categorical exclusion on 11/22/97 per 21 CFR 25.31 (b) [62 FR 40570, July 29, 1997] for the environmental assessment for manufacture of the Atridox drug product. This categorical exclusion was based on the applicant data which calculated the EIC of drug substance into the aquatic environment. Therefore, the applicant's calculation of the concentration of the drug substance into the aquatic environment was found to be less than 1 part per billion. The basis for this claim was calculated using the "FDA Guidance to Industry" on the Expected Introduction Concentration (EIC).

**APPEARS THIS WAY
ON ORIGINAL**

CONCLUSIONS & RECOMMENDATIONS:

The applicant responded to the CMC deficiencies with their amendment of 1/6/98. The CMC issues were reviewed and found acceptable for Manufacturing and Packaging, Drug Product Specifications and Methods, and Stability. The labeling was found acceptable from a technical standpoint; however, the labeling should be revised to include labels of component contents in Syringe A and B. The tradename for the product was found acceptable

Microbiology review is pending per Micro consult dated 1/12/98.

EER was requested via EES on 5/14/97. To date of this EER is pending from the Office Compliance.

Therefore, the NDA is approvable from a manufacturing standpoint.

ISI

Review Chemist

2/9/98

cc: Orig. NDA 50-751
HFD-540/Division File
HFD-540/Pappas
HFD-540/Kelsey
HFD-540/See
HFD-540/Vincent
HFD-540/Blay
HFD-540/DeCamp
HFD-880/Wang

UA 2/19/98

*gw 1/26/98
R.J. Walker*

FEB 18 1998

DIVISION OF DERMATOLOGIC and DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 50-751 CHEM.REVIEW #: 1 REVIEW DATE: 12/10/97

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	3/31/97	4/1/97	4/14/97
AMENDMENT/NC	4/16/97	4/18/97	4/23/97
AMENDMENT/NC	4/17/97	4/22/97	4/29/97
AMENDMENT/AZ	5/20/97	5/23/97	5/29/97
AMENDMENT/BC	7/21/97	12/8/97	12/12/97
AMENDMENT/BC	12/3/97	12/4/97	12/12/97

NAME & ADDRESS OF APPLICANT: Atrix Laboratories, Inc.
2579 Midpoint
Fort Collins, CO 80525-4417

DRUG PRODUCT NAME

Proprietary: ATRIDOX
Nonproprietary/USAN: doxycycline hyclate
Code Names/#'s:
Chem.Type/Ther.Class: 3 S

ANDA Suitability Petition/DESI/Patent Status:
N/A [if applicable]

PHARMACOL.CATEGORY/INDICATION: Chronic Adult
Periodontitis

DOSAGE FORM: Topical

STRENGTHS: 8.5% (w/w of doxycycline)

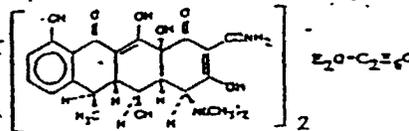
ROUTE OF ADMINISTRATION: .Atrigel Delivery System

DISPENSED: X Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL.WT: (Chemical Abstract Services, CAS, No.-24390-14-5)

(A) 4-(Dimethylamino) - 1,4,4a,5,5a,6,11,12a-octadecahydro-1,4-benzoxepin-10(2H)-one hydrochloride.
(C₂₂H₂₄N₂O₈ · HCl)₂ · C₂H₆O · H₂O Mol wt 1025.89

CAS 24390-14-5



(B) ATRIGEL Delivery System: Consist of the following
polymeric formulation
N-methyl-2-pyrrolidone (NMP) & Poly (DL-lactide) (PLA)

SUPPORTING DOCUMENTS:

- (1) AADA 62-865 for Doxycycline Hyclate, USP (drug substance)
- (2) DMF
- (3) DMF
- (4) DMF

- (5) 510(k)

- (6) 510(k)
- (7) 510(k) (K884652) for Octylident Periodontal Adhesive
- (8)

Note: Letters of authorization were received from the manufacturers of the above products (Items 1-6).

RELATED DOCUMENTS (if applicable):

IND (Atrix
Laboratories, Inc.)

CONSULTS:

- (1) Consults for Items 5, 6, 7, and 8 (above) requested on 6/3/97 from (CDRH)
- (2) Consult for Trade Name requested 6/2/97

REMARKS/COMMENTS:

The applicant has submitted a New Drug Application for the ATRIDOX drug product . This drug product contains doxycycline hyclate as the active ingredient. It is suspended in an Atrigel delivery system, a polymeric gel for the treatment of chronic adult periodontitis. In support of this NDA, the applicant has provided comprehensive information on the chemistry, manufacturing and controls of this drug product. The application also contains draft labeling.

Doxycycline Hyclate, USP is a non-sterile bulk drug substance and is the subject of an approved marketed antibiotic (AADA 62-865). Doxycycline Hyclate was originally proposed in IND for use in the ATRIDOX Delivery System.

However, even though the CMC information was very comprehensive, deficiencies still remain in the areas of Manufacturing and Packaging, Drug Product Specifications and Methods, and Stability.

The labeling was reviewed and found acceptable from a technical standpoint with one exception. In this regard, the Labeling and Nomenclature recommended that the labeling be revised to include labels of component contents in Syringe A and B

CONCLUSIONS & RECOMMENDATIONS:

The NDA was reviewed and found deficient in several of the CMC areas as follows: Manufacturing and Packaging, Drug Product Specifications and Methods, Stability and Microbiology. The labeling was found acceptable from a technical standpoint; however, the labeling should be revised to include labels of component contents in Syringe A and B. The tradename for the product was found acceptable.

EER was requested via EES on 5/14/97. To date of this EER is pending from the Office Compliance.

Therefore, it is recommended that CMC deficiencies be conveyed to Applicant with an information request letter; In this regard, the IR letter was sent to the applicant on 11/26/97.

In addition, the applicant should be informed that the correction of the CMC deficiencies be submitted to the Agency prior to the 90 day window from the USER fee date of 4/4/97.

Review Chemist

IS/

12/10/97

- cc: Orig. NDA 50-751
- HFD-540/Division File
- HFD-540/Pappas
- HFD-540/Kelsey
- HFD-540/See
- HFD-540/Vincent
- HFD-540/Blay
- HFD-540/DeCamp
- HFD-880/Wang

WA 2/12/98

QW 2/20/98