

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 50-751

ADMINISTRATIVE DOCUMENTS

Dental Team Leader Memo - NDA 50, 751

Date: March 24, 1998
Drug: ATRIDOX™
Sponsor: Atrix Laboratories, Inc.
Re: 120 Day Safety Report

The 120 Day Safety Report for this NDA was due at a time when the sponsor had very little to report. This product is not yet marketed, and the sponsor was only a few weeks into new studies at that point. The sponsor asked to be allowed to report only serious adverse events at that time, and report all adverse events with the amendment to the NDA that was eventually submitted 12/31/97. The Division agreed, and all safety data from the four studies that were included in the amendment were reported and reviewed.

JSI

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

cc:

Original NDA 50-744
HFD-540/Div. Files
HFD-540/DD/Wilkin
HFD-540/Blay

JSI 9/24/98

Patent Information

As required by 21 CFR Part 314.53, information is included below on each patent related to New Drug Application 50-751, for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

Patent Information for the ATRIDOX™ Drug Product			
Patent Number / Country 21 CFR 314.53 (c) (i)	Expiration Date 21 CFR 314.53 (c) (i)	Type of Patent 21 CFR 314.53 (c) (ii)	Name of Patent Owner 21 CFR 314.53 (c) (iii)
5,324,519 / U.S.	6-28-2011	Drug Product	Atrix Laboratories, Inc.
4,938,763 / U.S.	10-3-2008	Method of Use	Atrix Laboratories, Inc.
5,278,201 / U.S.	1-11-2011	Drug Product	Atrix Laboratories, Inc.
AU 666676 / Australia	9-30-2012	Method of Use	Atrix Laboratories, Inc.
AU 644581 / Australia	9-27-2009	Drug Product	Atrix Laboratories, Inc.
IL 91850 / Israel	9-29-2009	Drug Product	Atrix Laboratories, Inc.
MX 173182 / Mexico	10-2-2009	Drug Product and Method of Use	Atrix Laboratories, Inc.
NZ 232107 / New Zealand	1-15-2010	Drug Product	Atrix Laboratories, Inc.
ZA 89/7511 / South Africa	10-3-2009	Drug Product	Atrix Laboratories, Inc.

As further required by 21 CFR Part 314.53 (c) (2), an original declaration for each formulation, composition, or method of use patent is included on the following pages.

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
U.S.A.



PHONE: (970) 482-5868
FAX: (970) 482-9735
EMAIL: atrixlab@frii.com
<http://www.atrixlabs.com>

Original Declaration

The undersigned declares that Patent No. 5,324,519 (U.S.) covers the formulation, composition, and/or method of use of the ATRIDOX™ drug product. This product is the subject of this application (NDA 50-751) for which approval is being sought:

Richard R. Dunn
Richard R. Dunn, Ph.D.,
Vice President of Drug Delivery

4/15/97
Date

2579 MIDPOINT DRIVE
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FAX: (970) 482-9735
EMAIL: atrixlab@frii.com
http://www.atridabs.com

Original Declaration

The undersigned declares that Patent No. 4,938,763 (U.S.) covers the formulation, composition, and/or method of use of the ATRIDOX™ drug product. This product is the subject of this application (NDA 50-751) for which approval is being sought:

Richard R. Dunn
Richard R. Dunn, Ph.D.,
Vice President of Drug Delivery

4/15/97
Date

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
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<http://www.atrxlabs.com>

Original Declaration

The undersigned declares that Patent No. 5,278,201 (U.S.) covers the formulation, composition, and/or method of use of the ATRIDOX™ drug product. This product is the subject of this application (NDA 50-751) for which approval is being sought:

Richard R. Dunn
Richard R. Dunn, Ph.D.,
Vice President of Drug Delivery

4/15/97
Date

2579 MIDPOINT DRIVE
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FAX: (970) 482-9735
EMAIL: atrixlab@frii.com
<http://www.atrxlabs.com>

Original Declaration

The undersigned declares that Patent No. AU 666676 (Australia) covers the formulation, composition, and/or method of use of the ATRIDOX™ drug product. This product is the subject of this application (NDA 50-751) for which approval is being sought:

Richard R. Dunn
Richard R. Dunn, Ph.D.,
Vice President of Drug Delivery

4/15/97
Date

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
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PHONE: (970) 482-5868
FAX: (970) 482-9735
EMAIL: atrixlab@frii.com
http://www.atridabs.com

Original Declaration

The undersigned declares that Patent No. AU 644581 (Australia) covers the formulation, composition, and/or method of use of the ATRIDOX™ drug product. This product is the subject of this application (NDA 50-751) for which approval is being sought:

Richard R. Dunn
Richard R. Dunn, Ph.D.,
Vice President of Drug Delivery

4/15/97
Date

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
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PHONE: (970) 482-5868
FAX: (970) 482-9735
EMAIL: atrixlab@frii.com
<http://www.atrxlabs.com>

Original Declaration

The undersigned declares that Patent No. IL 91850 (Israel) covers the formulation, composition, and/or method of use of the ATRIDOX™ drug product. This product is the subject of this application (NDA 50-751) for which approval is being sought:

Richard L. Dunn
Richard R. Dunn, Ph.D.,
Vice President of Drug Delivery

4/15/97
Date

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
U.S.A.



PHONE: (970) 482-5868
FAX: (970) 482-9735
EMAIL: atrixlab@frii.com
http://www.atrixlabs.com

Original Declaration

The undersigned declares that Patent No. MX 173182 (Mexico) covers the formulation, composition, and/or method of use of the ATRIDOX™ drug product. This product is the subject of this application (NDA 50-751) for which approval is being sought:

Richard R. Dunn
Richard R. Dunn, Ph.D.,
Vice President of Drug Delivery

4/15/97
Date

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
U.S.A.



PHONE: (970) 482-5868
FAX: (970) 482-9735
EMAIL: atrixlab@friti.com
<http://www.atrxlabs.com>

Original Declaration

The undersigned declares that Patent No. NZ 232107 (New Zealand) covers the formulation, composition, and/or method of use of the ATRIDOX™ drug product. This product is the subject of this application (NDA 50-751) for which approval is being sought:

Richard R. Dunn
Richard R. Dunn, Ph.D.,
Vice President of Drug Delivery

4/15/97
Date

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
U.S.A.



PHONE: (970) 482-5868
FAX: (970) 482-9735
EMAIL: atrixlab@frii.com
<http://www.atrxlabs.com>

Original Declaration

The undersigned declares that Patent No. ZA 89/7511 (South Africa) covers the formulation, composition, and/or method of use of the ATRIDOX™ drug product. This product is the subject of this application (NDA 50-751) for which approval is being sought:

Richard R. Dunn
Richard R. Dunn, Ph.D.,
Vice President of Drug Delivery

4/15/97
Date

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NOA/BLA # 50-751

Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

Trade and generic names/dosage form: ATLEX DOXYCYCLINE HYCLATE Action: AP AE NA
GEL 8.5%

Applicant ATLEX LABS, INC. Therapeutic Class ANTI-MICROBIAL - PEROXANOLIN

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate inadequate _____

Proposed indication in this application FOR USE IN PATIENTS WITH CHRONIC ADULT PEROXANOLIN

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? Yes (Continue with questions) No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

Neonates (Birth-1month) Infants (1month-2yrs) Children (2-12yrs) Adolescents (12-16yrs)

1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.
- a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- c. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing.
- (2) Protocols were submitted and approved.
- (3) Protocols were submitted and are under review.
- (4) If no protocol has been submitted, attach memo describing status of discussions.
- d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed. THE INDICATION FOR THIS PRODUCT IS IN ADULT (CHRONIC ADULT PEROXANOLIN). THIS WOULD BE EXTREMELY UNLIKELY TO BE USED IN PATIENTS UNDER 18.
5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? Yes No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from THE MEDICAL OFFICER (e.g., medical review, medical officer, team leader)

IS/
Signature of Preparer and Title

8/13/88

Date

cc: Orig NOA/BLA # 50-751
HFD-540/Div File
NOA/BLA Action Package
HFD-006/ KRoberts

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

(revised 10/20/97)

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

1
VBLA # 50-751

Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

ATRIDOX
HFD 540 Trade and generic names/dosage form: (DOXYCYCLINE HYCLATE) Action: AP (A) NA
GEL, 8.5%

Applicant ATREX LABS, INC Therapeutic Class ANTI-MICROBIAL - PEDIATRIC

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate inadequate _____

Proposed indication in this application FOR USE IN PATIENTS WITH CHRONIC ADULT - PEDIATRIC

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? _____ Yes (Continue with questions) No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

Neonates (Birth-1month) Infants (1month-2yrs) Children (2-12yrs) Adolescents(12-16yrs)

1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.
- a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- c. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing,
- (2) Protocols were submitted and approved.
- (3) Protocols were submitted and are under review.
- (4) If no protocol has been submitted, attach memo describing status of discussions.
- d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? _____ Yes No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from THE MEDICAL OFFICER (e.g., medical review, medical officer, team leader)

IS/
Signature of Preparer and Title

4/7/98
Date
C. Roberts 4/7/98

∴ Orig NDA/BLA # 50-751
HFD 540 /Div File
NDA/BLA Action Package
HFD-006/ KRoberts

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

(revised 10/20/97)

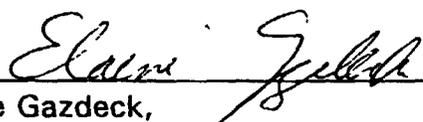
2579 MIDPOINT DRIVE
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U.S.A.



PHONE: (970) 482-5868
FAX: (970) 482-9735
EMAIL: atrixlab@frii.com
<http://www.atrxlabs.com>

Debarment Certification

Atrix Laboratories, Inc. hereby certifies that it did not and will not use in any capacity, the services of any person debarred under Section 306 of the Federal Food Drug and Cosmetic Act, in connection with this New Drug Application 50-751.



Elaine Gazdeck,
Vice President Regulatory Affairs/Quality Assurance

4-14-97
Date



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: September 1, 1998
To: NDA 50-751 file
From: Wilson H. DeCamp, Ph.D.
Chemistry Team Leader, HFD-540
Subject: Additional trade name issues for FPL

On further review of the July 2, 1998, submission of labels (in draft) and labeling, an additional technical point was identified in consultation with Dan Boring, Ph.D., of the Labeling and Nomenclature Committee.

The reference to the "Atrigel® Delivery System," even if removed from within the parentheses, is a proprietary name which must be accompanied by the established name [see 21 CFR 201.10(g)(1)]. This change may be accomplished on the label(s) either by placing the appropriate phrase immediately below the trade name, or by using an asterisk to refer the consumer to the appropriate information on the side panel. This change may be added to the package insert for consistency; however, there is adequate precedent (e.g., Ocuserit Pilo-20 and Ocuserit Pilo-40) for this change to be optional. ✓

Therefore, our recommendation (revised from the August 31, 1998, memo) is that the trade name should read as follows where it appears on the labels and (optionally) in the package insert:

If labels and/or labeling consistent with our previous letter have already been printed, the applicant should be advised that these labels may be used for six months or until exhausted, whichever comes first.

cc: ✓ HFD-540/Wilkin
HFD-540/Blay
HFD-540/Kozma-Fornaro
HFD-540/Kelsey
HFD-540/Pappas
HFD-540/DeCamp

egf 9/1/98

ISI



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: August 31, 1998
To: NDA 50-751 file
From: Wilson H. DeCamp, Ph.D.
Chemistry Team Leader, HFD-540
Subject: Trade name for FPL

Chemistry review #4 (March 4, 1998) found the labeling acceptable from a technical point of view. On review of the July 2, 1998, submission of labels (in draft) and labeling, certain additional minor modifications were found to be necessary.

Therefore, it is our recommendation that the trade name should read as follows where it appears on the labels and in the package insert:

As appropriate, within the running text of the package insert, _____ may be substituted for the longer phrase as long as the full phrase has already appeared on that page [see 21 CFR 201.10(g)(1)].

If labels and/or labeling consistent with our previous letter _____ have already been printed, the applicant should be advised that these labels may be used for six months or until exhausted, whichever comes first.

/S/

cc: ✓ HFD-540/Wilkin
HFD-540/Blay
HFD-540/Kozma-Fornaro
HFD-540/Kelsey
HFD-540/Pappas *Egl 8/31/98*
HFD-540/DeCamp

821

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Mr Dan Boring, Chair, (HFD-530)

From: Division of Dermatologic and Dental Drug Products
(HFD-540)
Attention Ernie Pappas Phone: 827-2066

WJ
6/2/97

Date: 6/2/97

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: ATRIDOX NDA# 50-751

Company Name: Atrix Laboratories, Inc.

Established name, including dosage form: doxycycline hyclate in Atrigel Delivery System

Other trademarks by the same firm for companion products: N.A.

Indications for Use (may be a summary if proposed statement is lengthy): Treatment of Periodontal disease

Initial comments from the submitter (concerns, observations, etc.):

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Consult #821 (HFD-540)

ATRIDOX doxycycline hyclate in Atrigel delivery system

The Committee noted one look-alike/sound-alike conflict with the proposed brand name: ATRIDINE. Since ATRIDINE is an OTC product, the Committee felt there was a low potential for mix-up. There were no misleading aspects found in the proposed brand name. The Committee recommends that the term "kit" or similar wording be used with the proprietary name to identify the multi-component nature of this product. Additionally, each syringe should be accurately labeled as to its particular contents, that is,

Syringe A - 450 mg of Atrigel delivery system and

Syringe B - 50 mg of doxycycline hyclate

The term ATRIDOX should be applied to the combination of the two syringes and should not appear on the individual syringes.

Overall, the Committee has no reason to find the proposed name unacceptable, however it should be used as recommended.

IS/ 8/18/97, Chair
CDER Labeling and Nomenclature Committee



Blay 540

NDA 50-751

Food and Drug Administration
Rockville MD 20857

NOV 26 1997

Atrix Laboratories, Inc.
Attention: Elaine Gazdeck, Vice-President for Regulatory Affairs and Quality Assurance
2579 Midpoint Drive
Fort Collins, CO 80525

Dear Ms. Gazdeck:

Please refer to your pending March 31, 1997 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Atridox (doxycycline hyclate) Gel, 8.5%.

We also refer to your amendment dated May 20, 1997.

To complete our review of the chemistry, manufacturing and controls section of your submission, we request the following:

1. The regulatory specifications for Doxycycline Hyclate, USP should be expanded to include specification limits for the related impurities such as
2. We note that included more comprehensive testing than that done by The test results included both particle size and heavy metals specifications, which are not included in the Please consider this difference and revise the specifications to be consistent.
3. Please include a description of the material used to package the bulk drug substance as received from
4. Please include stability data derived from studies on the drug substance manufactured by These studies should be supported with a stability protocol used to assess the drug substance under stressed and accelerated conditions, as well as storage at specified long term storage conditions.
5. The should be submitted for these components, both as received from the supplier and as tested by Atrix.
6. Please submit a statement concerning reprocessing, if any, of lots of the finished product that fail specifications. If the product is reprocessed, please submit a protocol for recovering the raw materials and reprocessing the finished product.
7. The regulatory specifications do not include a viscosity test and limits for testing the polymeric components in Syringe A. Please submit such methods and specifications, or provide a commitment outlining your plans to do so.
8. We observed a discrepancy between the acceptance criteria for Test Method Validation Protocol and the regulatory specifications for the drug product.

- The specifications stated in the acceptance criteria are not consistent with regulatory specifications. Please clarify this discrepancy.
9. The regulatory specifications for the drug product indicate three test levels for release of the doxycycline. Please revise the specifications to reflect only one specification for the release of doxycycline from the product.
 10. The regulatory specifications for the drug product are too broad and should contain an upper limit. In this regard, these specifications should resemble the data obtained for the validation of test method (NDA Vol. 1.4, pg. 196). Therefore, a specification of % is recommended.
 11. We recommend that an alternate analytical method be considered which will be more appropriate as a measure of the *in vitro* release rate. Relying upon the USP principles (which were developed for solid oral dosage forms) may be an inappropriate model, since, in this test, the product releases the drug substance into a sink that approximates infinite volume. Your product releases the doxycycline into the very small volume of the periodontal pocket (less than mL). It is conceivable that a flow method will be a more appropriate model. Please submit your comments on this observation, including whether this can be satisfied with a post-approval (Phase 4) commitment.
 12. The container/closure system does not include letters of authorization (LOAs) for information regarding the container parts for
 13. The acceptance specifications for component parts do not include the USP required tests, i.e., light transmission, container-permeation, vapor transmission tests, compatibility tests. This compatibility test includes leaching and/or migration tests on the plastic and rubber components of the container/closure system as required by USP 23, pgs. 1783 and 1736, respectively.
 14. The primary stability studies do not include 12 months of real time data in support of the proposed 18 month expiration date. Please submit this data in accordance with your commitment (see NDA Vol. 1.4, pg. 353).
 15. Pertaining to microbial limits, even though the subject drug was shown to be a potent antimicrobial agent, acceptance criteria for microbial limits should be established as part of the product specification. Microbial limits should comply with that of USP for topical non-sterile drug product: total count of < 100 cfu/g or mL, yeast and mold count of < 10 cfu/g or mL, and the absence of *Pseudomonas aeruginosa*, *Escherichia coli*, and *Staphylococcus aureus*.
 16. The preservative effectiveness testing (PET) data provides justification for skip-lot microbial limits testing. Testing can be conducted annually or at a reasonable time interval.
 17. Pertaining to stability, PET should be part of the stability program. Please submit a commitment to perform PET (initially and at expiry) on stability samples from the first three production lots.

NDA 50-751
Page 3

In addition, please note that the FDA Modernization Act of 1997 provides for repeal of Section 507 of the FD&C Act. We expect that certain revisions to our regulations will be published in the near future. We recommend that you consult with our Division concerning the implications, if any, of these revisions for this application.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Roy Blay, Project Manager, at (301) 827-2020.

Sincerely yours,

11/26/97

Wilson H. DeCamp, Ph.D.
Chemistry Team Leader
Division of Dermatologic and Dental Drug
Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc: Original NDA 50-751
HFD-540/Div. Files
HFD-540/Wilkin
HFD-540/CSO/Blay
HFD-540/Pappas
HFD-540/DeCamp
HFD-830/Chen

Katlyn O'Connell 11/26/97
EGR 11/26/97 Tom Wilkin

Drafted by: whd/November 26, 1997/n50751.ir

INFORMATION REQUEST (IR)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
9200 Corporate Avenue

CONSULTATION REVIEW

Date: June 11, 1997

To: CDER/(HFD-540)

Thru: Acting Branch Chief,
Patricia Cricenti *ipc*
Division Director,
Timothy A. Ulatowski *TU 6/11/97*

From: Scientific Reviewer/HFZ-480

Document No: NDA 50-751

Company Name: Atrix Laboratories

Device: Atridox

Per discussions on June 11, 1997 with Harold Blatt (CDER/HFD-540), this consult is to confirm the status of two 510(k)s associated with the subject NDA:

- K820454 - Burrton Medical syringe cap
- K854547 - Sherwood Davis & Geck blunt needle

Both 510(k)s were cleared by CDRH; K820454 in March 8, 1982 and K854547 in February 4, 1986. A review of the CDRH database did not identify any issues or concerns associated with these two devices.

If you have further questions, please do not hesitate to call me at (301) 594-1287.

JS
Von Nakayama

MEMO

RE: NDA 50-751

From: Dan Wang, Ph.D.

To: Roy Blay

Subject: Comment to Agenda item # 3a in orig. Amendment subm. Hcd on July 2, 1998

The following comment needs to be sent to the sponsor:

The *in vitro* release data for two mixing procedures have been reviewed. By retrospectively looking at the data, the data analysis method used by the sponsor to compare the *in vitro* release characteristics of two mixing procedures is considered not appropriate for Atridox. To compare the similarity between the rate of release, it is recommended that the sponsor calculate f_2 (similarity factor) defined in "Guidance for Industry, Immediate Release Solid Oral Dosage Form, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In vitro Release Testing and In Vivo Bioequivalence Documentation", page 23. An f_2 value between 50 and 100 suggests the two dissolution profiles are similar, and would be acceptable as evidence of similarity of *in vitro* release by the Agency in this situation.

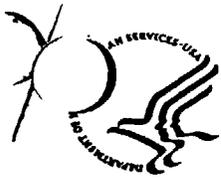
Dan Wang, Ph.D.

Division of Pharmaceutical Evaluation III

FT initialed by E. Dennis Bashaw, Pharm.D. Edw 7/20/98

CCP - 201 7/20/98 to sponsor on 7/22/98

23



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-751

JUL 14 1998

Atrix Laboratories
Attention: Elaine Gazdeck
Vice President, Regulatory Affairs
2579 Midpoint Drive
Fort Collins, Colorado 80525-4417

Dear Ms. Gazdeck:

We acknowledge receipt on July 6, 1998 of your July 2, 1998 resubmission to your new drug application (NDA) for Atridox (8.5% doxycycline in the ATRIGEL Delivery System) for Controlled Release in Subgingival Application.

This resubmission contains additional information consisting of *in vitro* drug release experiment for the Atridox product.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is January 6, 1999.

If you have any questions, contact Mary Jean Kozma-Fornaro, Supervisor, Project Management, at (301) 827-2020.

Sincerely,

/S/

Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Blay

Memorandum of Teleconference

Date: April 6, 1998, 4:35 PM

Sponsor: Atrix Laboratories

Drug: Atridox, NDA 50-751

Subject: Discussion of Labelling Issues

FDA Attendees

Roy Blay, Ph.D., Project Manager RB 5/5/98
John Kelsey, D.D.S., M.B.A., Dental Team Leader

Sponsor Attendees

J. Steve Garrett, D.D.S., M.S., V.P., Dental Clinical Research
Amy Taylor, Reg. Affairs Project Leader

In response to the faxed comments from the sponsor regarding the Division's proposed labelling, Dr. Kelsey made the following responses:

1. The statement in the first paragraph of the ADVERSE REACTIONS section regarding the body systems for which a statistically significant number of adverse events were observed was taken from the FDA analysis of data from the three pivotal clinical studies. Dr. Kelsey said that after further discussion within FDA it was decided that this information added little to the label and that paragraph could be deleted.
2. It is Division policy to present all adverse events regardless of causality. The sponsor said that the table that presented adverse events that had been taken from their submission included adverse events associated with medical history. Dr. Kelsey agreed to change the table to reflect only adverse events that were not associated with medical history.
3. Unspecified hypertension was specifically mentioned in the labelling because it is a potentially serious adverse event and because the difference between the active treatment group and the other arms studied was highly significant. The sponsor pointed out that several of the subjects reported appear to have had preexisting hypertension and that a change in medication triggered the reporting. Dr. Kelsey said that he would consider dropping this section if appropriate.
4. Because of extreme variability in the findings, no claims can be made based on the studies of bioequivalence. The biopharmaceutists were unanimous regarding this point. The sponsor asked if additional information might sway FDA's opinion on this issue.

5. The sponsor said that they would like to be able to report the percentage comparison between active and SRP, rather than simply stating that the "% of SRP" rule had been met. The sponsor felt that the labelling underemphasized the accomplishments of the drug product as supported by their studies. Dr. Kelsey noted that the hypothesis that was tested was "% as good as SRP" and described the statistical test that had been applied to determine if this decision rule had been met. The sponsor asked if it would be possible to suggest alternative language with respect to the range of effectiveness of the drug. FDA said that this would be unlikely given the design and intent of their studies, but the sponsor could make a proposal.

Dr. Kelsey said that the sponsor could either accept the labelling as proposed and receive an approval letter or request an approvable letter after which revisions to labelling could be discussed.

The sponsor said that they would consider the options and respond shortly.

Concurrence: JKelsey, 4.16.98.

cc: -

NDA 50-751

Division Files

HFD-540\Blay\Kelsey

2/18/98

Memorandum of Teleconference

Date: March 18, 1997, 10:35 AM

Sponsor: Atrix Laboratories

Drug: Atridox, NDA 50-751

Subject: Discussion of Clinical Issues

FDA Attendees

Roy Blay, Ph.D., Project Manager 23 3/18/97

John Kelsey, D.D.S., M.B.A., Dental Team Leader

Sponsor Attendees (Atrix)

J. Steve Garrett, D.D.S., M.S., V.P., Dental Clinical Research

Amy Taylor, Reg. Affairs Project Leader

Wes Ortolano, Director, Clinical Studies

Elaine Gazdeck, V.P., Regulatory Affairs and Quality Assurance

Dr. Kelsey asked Dr. Garrett about the discrepancy in the baseline measurements for the 2 charts in the proposed labeling. Dr. Garrett said that the baselines were different since one chart was for attachment level gain and the other for pocket depth reduction. Dr. Garrett agreed that this might appear confusing since the same individuals were assessed for the data in the two charts. He will check the data and provide written comments about this question.

Dr. Kelsey asked Dr. Garrett to speculate on the cause of the striking number of cases of unspecified essential hypertension in the doxycycline group of the "All Causes" AE dataset. Dr. Garrett said that it was simply a chance occurrence. He said that he was unable to determine any relationship between the administration of their drug and the presence of essential hypertension.

On an unrelated matter, Dr. Kelsey said that as a result of internal discussion and for consistency, the sponsor would only need to do a single study to support a claim for their drug product as an adjunct to SRP.

The sponsor said that they would respond to the above issues by fax and hard copy.

Concurrence: JKelsey, 3.18.98

cc:

NDA 50-751

Division Files

HFD-540\Blay\Kelsey

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-751

CORRESPONDENCE

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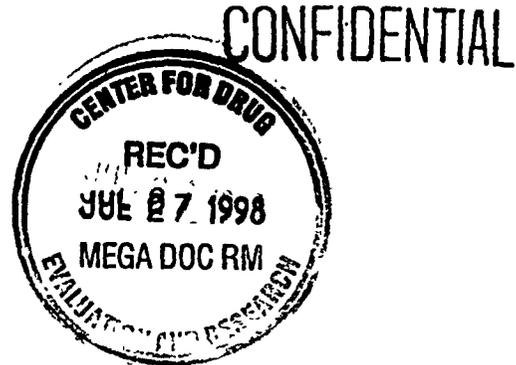


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July 24, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drugs
HFD-540
9201 Corporate Blvd.
Rockville, MD 20850



Attention: Roy Blay, Ph.D., Project Manager

Subject: NDA 50-751
ATRIDOX™ (ATRIGEL® Delivery System with Doxycycline Hyclate)

Enclosed is the statistical re-analysis of data requested by FDA Pharmacokinetic reviewer Dr. Dan Wang on July 22, 1998 via fax correspondence from your office (attached). The analysis output along with a hard copy of the SAS Program and SAS Program Log are included. The data utilized for this analysis can be found on pages 30-34 of our July 2, 1998 amendment to the NDA.

At our June 17, 1998 meeting with FDA, Dr. Dennis Bashaw and Dr. Dan Wang requested that Atrix perform an *in vitro* drug release experiment to support the proposed change to an abbreviated 100 cycle mixing method for product constitution. It was agreed that Atrix would utilize the analytical method for Extended Drug Release (T256) identified in the NDA, add additional time points to support rate of release, and consult SUPAC Guidance for Nonsterile Semisolid Dosage Forms, May 1997, for sample numbers and statistical evaluation.

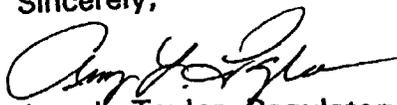
Per our conversation of July 23, 1998, it is our understanding that since the drug release profile submitted did not present a linear release profile, the statistical analysis from the SUPAC Nonsterile Semisolid Dosage Form Guidance was deemed inappropriate by FDA reviewers.

As requested in your fax correspondence, Atrix has re-analyzed the data using the similarity factor f_2 identified in SUPAC Immediate Release Solid Oral Dosage Form Guidance for comparison. Per our conversation of July 23, 1998, the mean % dissolved at each time point were incorporated for the reference (Rt) and test (Tt) groups respectively and the number of time points used to define the drug release profile was incorporated for the variable n in the equation. As a value of 79 was derived from this equation, it is our understanding per your fax correspondence of

July 22, 1998 that the Agency would consider this acceptable evidence of similarity for the two methods of product constitution and would therefore allow the use of the 100-cycle mixing method for commercial product constitution.

If there are any questions regarding the enclosed materials, please give me a call.

Sincerely,



Amy L. Taylor, Regulatory Affairs Manager

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July 2, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drugs
HFD-540
9201 Corporate Blvd.
Rockville, MD 20850



Attention: Roy Blay, Ph.D., Project Manager

Subject: NDA 50-751
ATRIDOX™ (ATRIGEL® Delivery System with Doxycycline Hyclate)

Enclosed are materials regarding proposed labeling for the ATRIDOX™ drug product which have been prepared as a follow up to our June 17, 1998 meeting with FDA. Along with the archive copy, reviewer copies for clinical, statistical, pharmacology, microbiology, and chemistry disciplines are included. A desk copy for Dr. Wilkin has also been forwarded with this packet.

Information regarding Agenda Item #'s 1, 2, 3b, 4, and Atrix's response to statistical requirements to measure clinical equivalence were previously forwarded to the agency in fax correspondence of June 24, 1998. Please note that per our telephone correspondence with Dr. Kelsey of July 1, 1998, Atrix has provided wording for Agenda Item # 1 that has been updated from the previous fax correspondence.

Information regarding Agenda Item # 3a was previously forwarded to the agency in fax correspondence of June 29, 1998.

Additionally, the product label included with our April 8, 1998 approvable letter has been modified to incorporate each of the proposed changes outlined by Agenda Items 1-4. Changes have been highlighted by redline/strikeout for ease of review.

Per Dr. Kelsey's request, an electronic copy of the labeling text has been included with the archive and clinical reviewer copies of the amendment. Please note that the graphs for the clinical studies and pharmacokinetics subsections of the label are included as separate electronic files.

Atrix appreciates FDA's timely response to each of the items outlined.

If there are any questions regarding the enclosed materials, please give me a call.

Sincerely,

Amy L. Taylor, Regulatory Affairs Manager

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May 11, 1998

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drugs
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Document Control Room, FDA, CDER, ODE V
5600 Fishers Lane
Rockville, MD 20857

Attention: Roy Blay, Ph.D., Project Manager

Subject: NDA 50-751
ATRIDOX™ (ATRIGEL® Delivery System with Doxycycline Hylcate)

6/16/98
This material is submitted as a pre-meeting package for a response meeting. Draft copies also provided
[Signature]

In accordance with 21 CFR 314.110(a)(1), on April 10, 1998, Atrix notified FDA that NDA 50-751 would be amended in response to the approvable letter issued by the agency on April 7, 1998.

Subsequent to this notification, Atrix requested a meeting with FDA to discuss issues surrounding the ATRIDOX™ product label. Meeting materials were forwarded via overnight courier to FDA on May 8, 1998. Enclosed is a copy of materials for the meeting, scheduled for June 17, 1998, which includes the proposed product labeling and associated supportive data. Additionally, the SAS data sets and associated statistical programming used to derive the data for Item # 3B4 (reference pages 48 and 49) is included with this amendment as Appendix E. Atrix felt it was not necessary to submit the information in Appendix E with the meeting package, but did want to provide the FDA statistical reviewer with a complete discussion on how the data for this specific point was derived.

After a teleconference on April 24, 1998 with Dr. Wilkin and Dr. Kelsey to discuss in general the issues surrounding the labeling, Atrix believes that the enclosed package will be sufficient to support the proposed product label and is therefore also submitting these materials as a formal amendment to the application.

If there are any questions regarding the enclosed materials, please do not hesitate to contact me.

Sincerely,

[Signature]
Amy L. Taylor,
Regulatory Affairs Manager

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April 10, 1998

Roy Blay, DDS
Project Manager, NDA 50-751
Food and Drug Administration
Center for Drug Evaluation Research
Division of Dermatologic and Dental Drug Products
HFD-540
9201 Corporate Boulevard
Rockville, MD 20850

NOTE
4/16/98
R3

Dear Dr. Blay,

This letter is in response to the April 7, 1998 correspondence Atrix received from the FDA informing us that the ATRIDOX™ product is approvable for the treatment of chronic adult periodontitis for a gain in clinical attachment level, reduction in probing depth and reduction in bleeding on probing. We want to inform you that Atrix intends to file an amendment to NDA 50-751 following a meeting to discuss labeling issues with the FDA that was requested on April 10, 1998.

If there are any questions regarding this information, please call me at (970) 482-5868.

Sincerely,

A handwritten signature in cursive script, appearing to read "Amy Taylor".

Amy Taylor
Regulatory Affairs Project Leader

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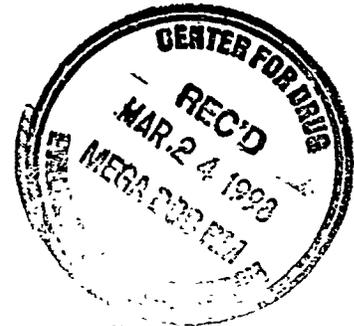
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March 19, 1998

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Attention: Dr. Roy Blay, Project Manager

Subject: NDA 50-751
ATRIDOX™ (ATRIGEL® Delivery System with Doxycycline Hyclate)

Enclosed is information requested by Dr. Kelsey in our teleconference of March 18, 1998. Responses to Dr. Kelsey's inquiry regarding baseline data included in the tabular summaries of the product labeling for attachment level gain and probing depth reduction and review of adverse event data for essential hypertension are included.

If there are any questions regarding the enclosed information, please give me a call.

Sincerely,

A handwritten signature in cursive script, appearing to read "Amy L. Taylor".

Amy L. Taylor,
Regulatory Affairs Project Leader

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March 9, 1998

Roy Blay, DDS
Project Manager, NDA 50-751
Food and Drug Administration
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Division of Dermatological and Dental Drug Products
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9201 Corporate Boulevard
Rockville, MD 20850

4/22/98 - response noted.
The sponsor has responded
appropriately to the
issues raised on
the 483.
[Signature]



Dear Dr. Blay,

We received notification of a 483 issued to Dr. Bogle, one of our clinical study site investigators. Enclosed is a copy of the Form FDA 483 issued to Dr. Bogle on February 20, 1998 during an inspection at his clinical study site for Atrix Clinical Study ACS-34 and Dr. Bogle's response to the Form FDA 483.

The Form FDA 483 states: "The protocol was not always followed for concomitant medications in that two subjects received antibiotics during the study." As the sponsor, Atrix Laboratories, Inc. reviewed all case report forms from the study for any administration of medications excluded by the protocol and removed data from any corresponding timepoints in order to derive an appropriate efficacy evaluable dataset (reference NDA 50-751 sections: 2.3.1 Subjects Excluded From Efficacy Evaluable Analyses, Volume 44, Pages 47 and 50; 2.8.1 Concomitant Medications, Volume 47, Pages 328, 329, 347 and 348).

Specific exclusion information for the two subjects cited on the 483 is included on the following page.

If you have any questions or need additional information please contact me.

Sincerely,

Amy Taylor
Regulatory Affairs Project Leader

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March 2, 1998

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Attention: Dr. Roy Blay, Project Manager

Subject: NDA 50-751
ATRIDOX™ (Atrigel® Delivery System with Doxycycline Hyclate)

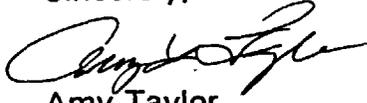
Enclosed is amended information for NDA 50-751 that was originally submitted on April 7, 1997.

This amendment includes a correction to the ATRIDOX™ Drug Product Regulatory Specification (Document number 08027.001) submitted on February 26, 1998. A typographical error in this regulatory specification has been detected and is corrected. Under Related Substances in section 3.0 of the revised specification, the percent of detected is change from Since there are no compendial limits in USP for related substances, the European Pharmacopeia (EP) compendium was consulted. A limit of % was established for bulk drug substance and drug substance filled in the B Syringe based on the EP monograph for bulk drug substance. A limit of % has been established for constituted product based on stability data (refer to pages 200-210 in the January 6, 1998 chemistry amendment).

An archive copy of this amendment is enclosed along with a copy for the Clinical Reviewer. As required by 21 CFR 314.60(c), a field copy of this amendment has been forwarded to the Denver District Office. A copy of the cover letter for this field copy is attached.

If there are any questions regarding this information, please call me at
(970) 482-5868.

Sincerely,



Amy Taylor
Regulatory Affairs Project Leader

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February 26, 1998

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CONFIDENTIAL

Attention: Dr. Roy Blay, Project Manager

Subject: NDA 50-751
ATRIDOX™ (Atrigel® Delivery System with Doxycycline
Hyclate)

Enclosed is amended information for NDA 50-751 that was originally submitted on April 7, 1997.

Included in this document is the response to the proposed Extended Drug Release limits discussed with the FDA during a February 20, 1998 teleconference. Please note that an update of the ATRIDOX™ finished product specification, incorporating new limits for drug release, is also included with the response. Also, please note that a copy of this chemistry response was faxed to Dr. Blay on February 25, 1998.

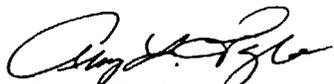
The responses to the four clinical issues raised by the FDA during the February 18, 1998 teleconference are also included in this document. These issues include 1) providing sub-analyses of the effects of smoking on efficacy outcome, 2) providing an evaluation of calculus at Baseline, Month 9, and a comparison of differences at these two time points, 3) providing a cross-reference in the application for evaluation of tooth sensitivity, and 4) providing a summary table that identifies all patients experiencing abscesses on the treated side of the mouth in clinical studies ACS-32, ACS-38 and AGD9603.

An archive copy of this amendment is enclosed. A copy of the chemistry response is included for the Chemistry Reviewer and a copy of the entire

amendment is included for the Clinical Reviewer. As required by 21 CFR 314.60(c), a field copy of chemistry section of this amendment has been forwarded to the Denver District Office. A copy of the cover letter for this field copy is attached.

If there are any questions regarding this information, please call me at (970) 482-5868.

Sincerely,



Amy Taylor, Regulatory Affairs Project Leader

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2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
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February 18, 1998

Food and Drug Administration
Center for Drug Evaluation
Division of Dermatologic and Dental Drugs
HFD-540
Document Control Room FDA CDER, ODE V
5600 Fishers Lane
Rockville, MD 20857

Attention: Dr. Roy Blay, Project Manager

Subject: NDA 50-751
ATRIDOX™ (Atrigel® Delivery System with Doxycycline
Hyclate)

Enclosed is amended information for NDA 50-751 that was originally submitted on April 7, 1997.

The amended information includes responses to issues discussed with the FDA during the February 6, 1998 teleconference. The first issue was a question posed by Dr. Wang, FDA Biopharmaceutist. She asked that Atrix conduct the standard bioequivalence test for the three bioequivalence studies, AGD9701, AGD9607, and AGD9705. The final reports for the three bioequivalence studies were submitted in volumes 19, 20, and 21 of the December 31, 1997 amendment to NDA 50-751. On February 11, 1998, Dr. Blay called to request that Atrix also conduct the standard bioequivalence test for clinical study ACS-32. The final study report for ACS-32 was submitted on April 7, 1997 in volumes 14 and 15 of the original NDA.

The standard bioequivalence test includes performing a two one-sided test on the log-transformed parameters (AUC and C-max) and determining the 90% confidence intervals around the difference of geometric mean values of test and reference treatment. The results of all of these analyses are written as amendments to each of the respective final study reports.

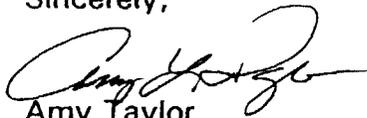
The second issue discussed with the FDA during the February 6, 1998 teleconference was regarding a change in the Extended Drug Release

specification. The FDA proposed eliminating the three tier testing of Extended Drug Release and instituting a single tier structure with limits for mean and individual assay time points. Enclosed is our response to this proposal. Please note that a draft of the proposed new Extended Drug Release specification is also included with the response. Also, please note that a copy of this chemistry response was faxed to Dr. Blay on February 17, 1998.

An archive copy of this amendment is enclosed. A copy of the chemistry response is included for the Chemistry Reviewer and a copy of the pharmacokinetic response is included for the Pharmacokinetics Reviewer and Statistics Reviewer. A copy of the entire amendment is also included for the Clinical Reviewer. As required by 21 CFR 314.60(c), a field copy of chemistry section of this amendment has been forwarded to the Denver District Office. A copy of the cover letter for this field copy is attached.

If there are any questions regarding this information, please call me at (970) 482-5868.

Sincerely,



Amy Taylor

Regulatory Affairs Project Leader

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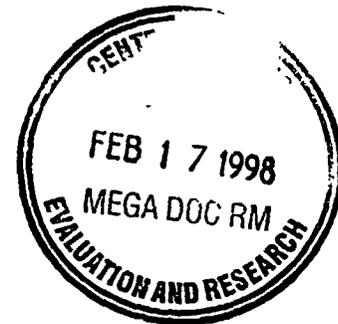
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February 13, 1998

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Rockville, MD 20857



Attention: Dr. Roy Blay, Project Manager

Subject: NDA 50-751
ATRIDOX™ (Atrigel® Delivery System with Doxycycline
Hyclate)

Enclosed is amended information for NDA 50-751 that was originally submitted on April 7, 1997.

This amendment includes changes made to the ATRIDOX™ product label since the December 31, 1997 amendment to NDA 50-751. The changes include typographical corrections, technical changes, and grammatical corrections. For ease of review, we are including both a red-line/strike-out and clean version of the label text as well as a tabular summary of all changes. Please note that the section numbers in the clean and red-line/strike-out versions of this label amendment correspond to the sections containing label information in the December 31, 1997 amendment.

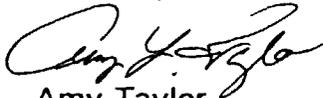
Also included in this amendment are updated regulatory specifications for the ATRIDOX™ Syringe A Label, ATRIDOX™ Syringe B Label, and the ATRIDOX™ Large Foil Pouch. The specifications for the syringe labels were last updated in Volume 1 of the January 6, 1998 amendment to NDA 50-751 (Pages 377 and 378). The current change in the syringe label specifications includes the type of black ink used for printing the syringe labels. The vendor initiated this change. The specification for the

large foil pouch was last submitted in Volume 3 of the original April 7, 1997 submission of NDA 50-751 (Page 126). In the changed specification, the reference to ink colors has been removed. The colors on the pouch are defined on the master artwork. A copy of the master artwork is also included in this submission.

In addition to the archival copy of this amendment, copies of this information are included for each of the following reviewing disciplines: Clinical, Microbiology, Chemistry/Manufacturing/Controls, and Pharmacology. As required by 21 CFR 314.60(c), a field copy of this amendment has been forwarded to the Denver District Office. A copy of the letter of certification for this field copy is attached.

If there are any questions regarding this information, please call me at (970) 482-5868.

Sincerely,



Amy Taylor

Regulatory Affairs Project Leader

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January 26, 1998

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Rockville, MD 20857



Attention: Dr. Roy Blay, Project Manager

Subject: NDA 50-751
ATRIDOX™ (Atrigel® Delivery System with Doxycycline
Hyclate)

Enclosed are two copies of the diskette containing the SAS Format Catalogue for Clinical Study AGD9603 that you requested during our January 22, 1998 telephone conversation. One of these diskettes is supplied for the Statistical Reviewer, Dr. Ping Gao, and the second diskette is provided as an archival copy.

Also included is a hard copy of the program used to generate the SAS Format Catalogue.

If there are any additional questions or comments, please contact me at (970) 482-5868.

Sincerely,

A handwritten signature in cursive script, appearing to read "Amy Taylor".

Amy Taylor, Regulatory Affairs Project Leader
Regulatory Affairs Associate

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December 1, 1997

CONFIDENTIAL

U.S. Food and Drug Administration
Denver District
Federal Center/Building 20
Denver, CO 80225-0087

Attention: Gary Dean, Director Denver District

In accordance with 21 CFR 314.60(c), a field copy of amended chemistry information is being submitted to the local FDA district office for Atrix Laboratories, Inc. This letter certifies that the amended information is a true copy of the portion of the NDA required to be submitted per 21 CFR 314.50(d)(1). It is identical to information submitted in the archival and chemistry review copies of the application.

Please contact me if you have any questions regarding the submitted information.

Sincerely,

Amy L. Taylor, Regulatory Affairs Project Leader

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FORT COLLINS, CO 80525-4417
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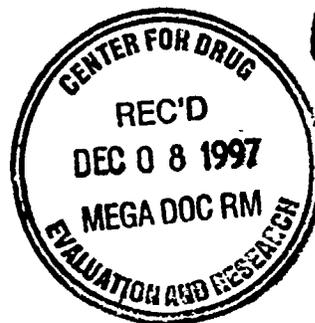
*Reviewed for
signature
date*

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ORIGINAL

July 21, 1997

Food and Drug Administration
Center for Drug Evaluation and Research
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Building 2, Second Floor, Room N-203
Rockville, MD 20850



CONFIDENTIAL

Ok'd. Atrix

BC

Attention: Dr. Hal Blatt, Consumer Safety Officer

Subject: NDA 50-751
Requested Information from CMC Teleconference of July 16, 1997

Attached is the information for Chemistry Reviewer Dr. Ernie Pappas that was requested in our teleconference of July 16, 1997. This information includes a summary results table of analysis conducted by Atrix for drug substance from _____ suppliers, along with the vendor Certificates of Analysis for each Batch. Please note that the summary table includes results from analysis for doxycycline assay and impurities by _____ which was used during product development, and for _____, which is being proposed as an improved method for commercial manufacturing. This summary table also includes a cross-reference to where each of the batches of drug substance were used in the course of product development. A tabular summary of all batches of drug substance used in nonclinical and clinical studies along with their impurity analysis was included in the original NDA submission, Volume 2, Page 226.

As was discussed during the teleconference, a third batch of doxycycline hyclate from _____ was received by Atrix last week. As soon as analysis results are completed, an updated summary will be forward to FDA and formally submitted to NDA 50-751.

If there are any questions regarding the enclosed information, please give me a call.

Sincerely,

Amy L. Taylor,
Regulatory Affairs Project Leader

ORIGINAL



ATRIX
LABORATORIES, INC

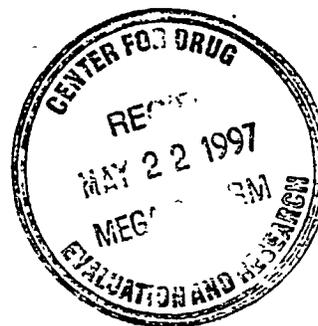
2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
U.S.A.

PHONE: (970) 482-5868
FAX: (970) 482-9735
EMAIL: atrixlab@frii.com
http://www.atrxlabs.com

May 21, 1997

NEW CORRESPONDENCE

Food & Drug Administration
Center for Drug Evaluation & Research
Division of Dermatologic & Dental Drug Products
HFD-540
9201 Corporate Blvd.
Building 2, Second Floor, Room N-203
Rockville, MD 20850



Attention: Dr. Hal Blatt, Consumer Safety Officer

Subject: NDA 50-751
ATRIDOX™ (ATRIGEL® Delivery System with Doxycycline Hyclate)

Enclosed are desk copies of new information submitted to NDA 50-751 on May 20, 1997. The new pharmacokinetics information included in this submission was requested by the reviewer in your fax of May 6, 1997. Additionally, as requested by the reviewer I have enclosed a desk copy of the Pharmacokinetic Technical Summary Section of the NDA in Word Perfect V6.1 Format. The new biostatistics information incorporated into the submission was requested by the reviewer during a teleconference held with Atrix on May 7, 1997 in which Robin Anderson was the coordinating CSO. Ms. Anderson requested that desk copies of this information also be forwarded to your attention. This information also includes example SAS programs in electronic format.

If you have any questions regarding the submitted information, please give me a call.

Sincerely,

Amy L. Taylor,
Regulatory Affairs Project Leader

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
GSO INITIALS	DATE

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U.S.A.



ORIGINAL

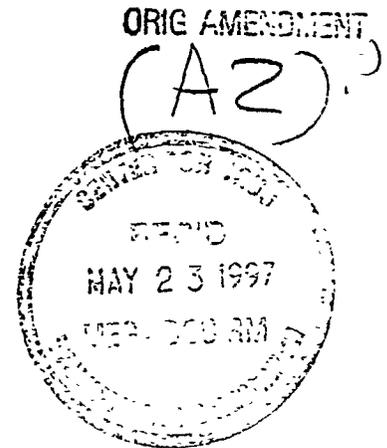
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May 20, 1997

Food and Drug Administration
Center for Drug Evaluation
Division of Dermatologic and Dental Drugs
HFD-540
Document Control Room FDA CDER, ODE V
5600 Fishers Lane
Rockville, MD 20857

Attention: Dr. Hal Blatt, Consumer Safety Officer

Subject: NDA 50-751
ATRIDOX™ (ATRIGEL® Delivery System with Doxycycline
Hyclate)



Enclosed is amended pharmacokinetic, chemistry, and biostatistical review information along with an updated User Fee cover sheet identifying that Atrix has been granted a small business exception for NDA 50-751. The new pharmacokinetics information included in this submission was requested by the reviewer in your fax of May 6, 1997. The new biostatistics information incorporated here was requested by the reviewer during a teleconference held with Atrix on May 7, 1997 in which Robin Anderson was the coordinating CSO. The new chemistry information is being submitted in support of the request by the pharmacokinetics reviewer, as the test methods requested for in vitro release of drug have been updated for clarity since the original submission of the NDA. The additional updated test method included with the new chemistry information has only been modified to eliminate redundant information.

An archive copy and corresponding review copies of amended technical information for the pharmacokinetics, chemistry, and biostatistical reviewers are included. Additional copies of the updated User Fee Cover Sheet are included for the Clinical, Pharmacology/Toxicology, and Microbiology reviewers. As the new chemistry information submitted includes updated test methods that were previously included in the methods validation section of the application (originally submitted as volume 5), three additional

copies of that information are also being forwarded for the chemistry reviewer. As required by 21 CFR 314.60(c), a field copy of this amended information has been forwarded to the Denver District office. A copy of the letter of certification for this field copy is attached.

Please contact me if you have any questions regarding the submitted information.

Sincerely,

A handwritten signature in black ink, appearing to read "Amy L. Taylor". The signature is fluid and cursive, with the first name "Amy" being the most prominent part.

Amy L. Taylor, Regulatory Affairs Project Leader

ORIGINAL



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May 12, 1997

LET CORRESPONDENCE

Food and Drug Administration
Center for Drug Evaluation
Division of Dermatologic and Dental Drugs, HFD-540
9201 Corporate Boulevard
Building 2, Second Floor, Room N-203
Rockville, MD 20850



Attention: Dr. Jonathan K. Wilken
Division Director

Subject: NDA 50-751
Policy on Clinical Study Design for Periodontal Drug Products

Recently at the annual meeting of the International Association of Dental Research (IADR), Atrix, as well as several other sponsors of drug products in development for the treatment of periodontal disease, presented data on the conduct and results of clinical studies. Based on these presentations, as well as other information that is publicly available, it appears that clinical studies conducted to provide substantial evidence of efficacy and safety in support of an NDA for the treatment of periodontitis may vary significantly in design.

Atrix's understanding of the requirements for protocol design have been derived from discussions with FDA and from the proceedings of the 1996 Joint Symposium on Clinical Trial Design and Analysis in Periodontics. With respect to stand alone therapy to treat adult periodontitis, it is our understanding that the clinical study design must include a comparison to placebo control, scaling and root planing (i.e. active control), and a negative control. To the best of our knowledge, based on the information that is publicly available, it would appear that studies to support a stand alone therapy in support of an NDA sponsored by do not meet these criteria. This is of concern to Atrix, as it would seem reasonable that products seeking approval for the same intended use and indication would be held to a level playing field with regard to clinical study design requirements. In addition, it is also our understanding that two well controlled studies are required to support product approval. Nothing publicly available indicates that a second study has been conducted by

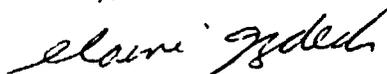
Atrix is seeking clarification on the FDA policy/recommendations for clinical study design for drug products intended as stand alone therapy to treat adult periodontitis, and would like the opportunity to discuss with you the nature of this policy and how it is interpreted. We were advised by FDA previously that all sponsors seeking approval of a therapy for periodontitis would need to conduct two studies of the 4 arm design described above, yet, at least in the public domain, we have not seen evidence that this is the case. We are striving to better understand this situation, and are seeking your guidance and insight.

Dr. Jonathan Wilken
May 12, 1997
Page 2

Dr. Steve Garrett, VP of Periodontal Research, and I would like to discuss this issue with you via telephone, at a mutually convenient time. We realize your schedule is very busy, but we would really appreciate having a better understanding of the scientific basis for the recommendations associated with clinical study design for stand alone periodontal therapy.

We look forward to speaking with you in the near future.

Sincerely,



Elaine M. Gazdeck, RAC
Vice President
Regulatory Affairs/Quality



Dr. Steven Garrett
Vice President
Periodontal Research

EMG:blh

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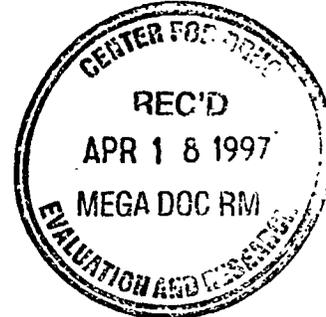
DUPLICATE

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NC
NEW CORRESP

April 16, 1997

Food and Drug Administration
Center for Drug Evaluation
Division of Dermatologic and Dental Drugs
HFD-540
Document Control Room FDA CDER, ODE V
5600 Fishers Lane
Rockville, MD 20857



Attention: Dr. Hal Blatt, Consumer Safety Officer

Subject: NDA 50-751
ATRIDOX™ (ATRIGEL® Delivery System with Doxycycline Hyclate)

Enclosed is amended patent information, debarment certification, and User Fee cover sheet for NDA 50-751. Atrix has been assigned User Fee ID Number 3247 as noted on the User Fee cover sheet. An archive copy and six additional copies for each technical section review copy are included. As required by 21 CFR 314.60(c), a field copy of this amended information has been forwarded to the Denver District office. A copy of the letter of certification for this field copy is attached.

Please contact me if you have any questions regarding the submitted information.

Sincerely,

A handwritten signature in cursive script, appearing to read "Amy L. Taylor".

Amy L. Taylor, Regulatory Affairs Project Leader

REVIEWS COMPLETED	
DISPOSITION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
INITIALS	DATE