ORAPHARMA, INC.

732 Louis Drive
Warminster, PA 18974
215/956-2200 Tel
215/443-9531 Fax

June 29, 2000

NDA ORIG AMENDMENT

Jonathan K. Wilkin, MD
Director, Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 50-781
Minocycline PTS
Amendment: FDA Requested CMC Documentation

Dear Dr. Wilkin:

Reference is made to a telephone conversation held on March 13, 2000 between Dr. M. Gautam-Basak and Ms. K. Bhatt from your Division and the undersigned during which Dr. Gautam-Basak identified the need for clarification and guidance for some CMC issues.

A point raised (point 3) during this telephone conversation was the fact that test 5008 did not include specifications. OraPharma herewith submits our response to address this deficiency.

As a reviewing aid, we also include a copy of the contact report from the telephone conversation which identifies point 3.

If you have any questions regarding this submission, please contact me at (215) 956-2207.

Sincerely,

Markus F. Herzig
Executive Director of Regulatory Affairs

Form FDA 356h
Submitted in duplicate

ORIGINAL

Correspondence from Applicant

6-1-00

[redacted]

[redacted]

[redacted]

ORAPHARMA, INC.

www.oraPharma.com

[redacted] Drive
Warminster PA 18974

215/956-2200 Tel
215-443-9531 Fax

June 19, 2000

Jonathan K. Wilkin, MD
Director, Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

AMENDMENT

BC

RE: NDA 50-781
Amendment: CMC Information

Dear Dr. Wilkin:

our continuous review and preparation for the pre-approval inspections from the local district offices, we found a few typographical errors in our original NDA documentation.

Attached is a table listing all errata identified. The corrections are in stability data results. We have included pages in which the corrected numbers are highlighted. These pages are contained in volume 1.5 pages 11 – 13 in the original submission. Also included are corrected figures in which the data appears. Corresponding corrections will be made in the stability reports as they are updated. The corrections do not affect proposed expiration dating of the drug product.

If you have any questions regarding this submission, please call me a (215) 956-2207.

Sincerely,

Markus F. Herzig
Executive Director, Regulatory Affairs

RECD
JUN 21 2000
MEGA DOC RM
EVALUATION AND RESEARCH

MFH:stk

Attachments

Form FDA 356h
Submitted in duplicate
Desk copies for: Ms. Bhatt
Dr. Gautam-Basak

ORIGINAL

Correspondence from Applicant

86-1600

ORAPHARMA, INC.

732 Louis Drive
Warminster, PA 18974

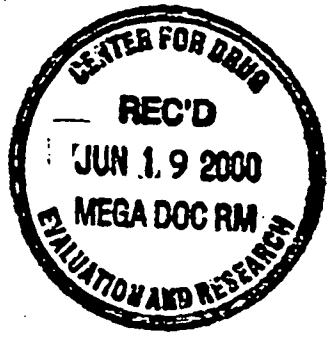
215/956-2200 Tel
215/443-9531 Fax

NDA ORIG AMENDMENT

June 16, 2000

Jonathan K. Wilkin, MD
Director, Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

SU



RE: NDA 50-781
Minocycline PTS
Amendment: 120 Day Safety Update

Dear Dr. Wilkin:

Pursuant to 21 CFR 314.50 (d)(5)(vi)(b), OraPharma, Inc. provides herewith the 4 months safety update after the initial submission. This up-date contains final information from our open-label study (OPI-104) for which 9 months data was included in the original submission. Since this study has now concluded, OraPharma, Inc. also includes the final report containing the 12 month observation data. We further included a revised draft package insert, the changes are on page 4 the italicized section OPI-104 and table 6.

If you have any questions regarding this submission, please contact me at (215) 956-2207.

Sincerely,

Markus F. Herzig
Executive Director of Regulatory Affairs

Form FDA 356h
Submitted in duplicate

ORIGINAL

Correspondence from Applicant
06-05-00

RAPHARMA, INC.
www.orapharma.com

[redacted] Lock Drive
[redacted] PA 18[redacted]
215/956-2200 Tel
215/443-9531 Fax

JUN 06 2000

June 5, 2000

NDA ORIG AMENDMENT

Jonathan K. Wilkin, MD
Director, Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

EC

RE: NDA 50-781
Amendment: FDA Requested Information

.ar Dr. Wilkin:

Reference is made to a telephone conversation held on April 7, 2000 between Dr. Gautam-Basak, Dr. Riley and Ms. Bhatt in your Division and the undersigned. Dr. Gautam-Basak requested OraPharma to submit a "mini-micro" CMC section to contain the bioburden testing of our product. Reference is also made to our submission to the IND (——') of this product of serial number 107 on November 8, 1999 and FDAs response via telefax on February 10, 2000.

Attached is the requested "mini-micro" CMC section addressing the issues raised by Dr. Riley. As requested, we included information submitted previously in our original NDA, and paginated the volume (3.1) in the b[redacted]tom center leaving the original NDA pagination in the lower right.

If you have any questions regarding this submission please contact me at (215) 956-2207.

Sincerely,

Markus F. Herzig
Executive Director, Regulatory Affairs

MFH:stk

ORIGINAL

Submission in Duplicate
Desk copies for Dr. Riley and Ms. Bhatt
Form FDA 356h

Attachment 1
Attachment 2
Attachment 3
Attachment 4

Correspondence from Applicant

05-18-00

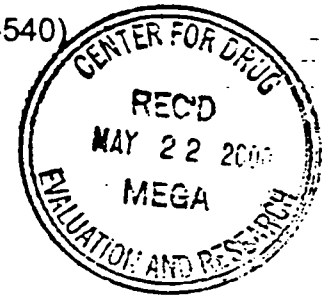
ORAPHARMA, INC.
www.orapharma.com

[illegible] Drive
Warminster PA 18974
215 956-2200 Tel
215 443-9531 Fax

AMENDMENT

May 18, 2000

Jonathan R. Wilkin, MD
Director, Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850



RE: NDA 50-781
Minocycline PTS
Amendment: Clinical Information Request

Dear Dr. Wilkin:

Reference is made to a telefax OraPharma, Inc. received on May 11, 2000 requesting clinical information.

Enclosed is OraPharma's response identifying the question posed and our answer. If the dental reviewer is interested in specific site information on pockets of 7-9 mm, OraPharma could make them available as well.

We hope this satisfactorily answers the dental officer's inquiry.

If you have any questions regarding this submission, please contact me at (215) 956-2207.

Sincerely,

Markus F. Herzig
Executive Director of Regulatory Affairs

Form FDA 356h
Submitted in duplicate

Correspondence from Agency to Applicant/Acknowlegement of NDA 4-28-00

HFD-540/KRhatt

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-781

APR 28 2000

OraPharma, Inc.
Attention: Mark F. Herzig
Executive Director, Regulatory Affairs
732 Louis Drive
Warminster, PA 18974

Dear Mr. Herzig:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Minocycline PTS (minocycline periodontal therapeutic system)

Therapeutic Classification: Standard (S)

Date of Application: February 16, 2000

Date of Receipt: February 17, 2000

Our Reference Number: NDA 50-781

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 16, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be December 17, 2000 and the secondary user fee goal date will be February 17, 20[redacted].

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with

the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call Kalyani Bhatt, Project Manager, at 301-827-2020.

Sincerely,

/S/ 4/28/00

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

cc:
Archival NDA 50-781
HFD-540/Div. Files
HFD-540/K.Bhatt

DISTRICT OFFICE

Drafted by: smc/April 28, 2000
filename: N58781.ACK

ACKNOWLEDGEMENT (AC)

ORAPHARMA, INC.
www.orapharma.com

732 Louis Drive
Warminster, PA 18974

215/956-2200 Tel
215/443-9531 Fax

April 19, 2000

Jonathan K. Wilkin, MD
Director, Division of Dermatological and Dental Drug Products (HFD-540)
Center for Drug Evaluation & Research
Food and Drug Administration
Document Control Room
9201 Corporate Boulevard
Rockville, MD 20850

RE: NDA 50-781
Minocycline PTS
Amendment: Requested Information

Dear Dr. Wilkin:

The enclosed information was faxed to Ms. K. Bhatt, project manager for the above referenced NDA on April 12 and 13, 2000 to provide the information as expeditiously as possible.

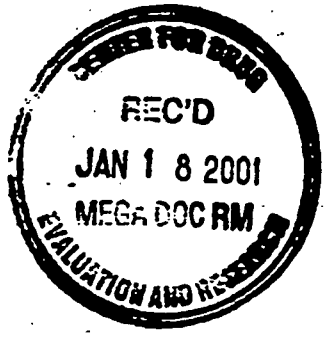
In order to have this information added to the NDA file, we are submitting the attached in duplicate.

If you have any questions regarding this submission, please contact me at (215) 956-2207.

Sincerely,

Markus F. Herzig
Executive Director of Regulatory Affairs

Form 356h
Submitted in Duplicate



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
OraPharma, Inc.	April 19, 2000
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** (Include Area Code)
215-956-2200	215-443-9531
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE
732 Louis Drive Warminster, PA 18974	Markus F. Herzig 732 Louis Drive Warminster, PA 18974

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 50-781

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)	PROPRIETARY NAME (trade name) IF ANY
Minocycline PTS (Minocycline Periodontal Therapeutic System)	—

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)	CODE NAME (If any)
7 - dimethylamine - 6 - demethyl - 6 - deoxytetracycline hydrochloride	—

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
topical	1 mg	Subgingival

(PROPOSED) INDICATION(S) FOR USE: Adjunctive therapy to scaling and root planing procedures in patients with adult periodontitis

...ICATION INFORMATION

APPLICATION TYPE *(check one)*
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)*
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☒ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION Requested Information

PROPOSED MARKETING STATUS *(check one)* ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

NA

...s References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current ...lication)

NA

This application contains the following items: *(Check all that apply)*

☐	1. Index	
☐	2. Labeling *(check one)*	☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50(c))	
☐	4. Chemistry section	
☒	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50(d) (1), 21 CFR 601.2)	
☐	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
☐	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)	
☐	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)	
☐	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)	
☐	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))	
☒	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)	
☐	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)	
☐	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)	
☐	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)	
☐	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)	
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))	
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355 (b) (2) or (j) (2) (A)	
☐	15. Establishment description (21 CFR Part 600, if applicable)	
☐	16. Debarment certification (FD&C Act 306 (k) (1))	
☐	17. Field copy certification (21 CFR 314.50(k) (3))	
☐	18. User Fee Cover Sheet (Form FDA 3397)	
☒	19. OTHER (Specify)	

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Markus F Herzig	Markus F. Herzig, Executive Director Regulatory Affairs	4/19/00

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
732 Louis Drive Warminster, PA 18974	215-956-2200

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
bert H. Humphrey Building, Room 531-H
) Independence Avenue, S.W.
ashington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.

CMC – Information

Dr. Gautam-Basak requested detailed composition information on the batches of minocycline PTS produced at AAI. The batch numbers for these clinical batches are 98155 and 98214.

The following is the batch information for these two batches:

Table 3.4.2.1-B Composition of Minocycline PTS microspheres

Component	Quality (%)	Quantity per Batch (grams)*
Minocycline Hydrochloride USP	[redacted]	[redacted]
Poly(glycolide-co-dl-lactide) G.A. Initiated	[redacted]	[redacted]
[redacted]	***	[redacted]
[redacted]	***	[redacted]
[redacted]	***	[redacted]

* Batch size: [redacted]
** As is basis (added in this manner to keep volume ratio of drug to polymer constant).
*** No present in final product

The composition of all batches manufactured at AAI are identical. These batches were used for all the clinical trials and also the NDA stability studies.

The detailed composition can be found in the original NDA Vol. 1.1 page 102 and Vol. 1.2 page 59.

BIOPHARMACEUTICS REVIEWER COMMENT

Comment 1: Full sponsor report for these studies should be submitted if available. The sponsor only submitted the summary for Lederle Study 15-16-1, 15-18-1 and 15-20-2.

Reply: The clinical Pharmacology section (8.3) in volume 1.20 does provide summaries of the Lederle Laboratories, Inc. conducted Phase 1 and 2 studies.

The completed (full) reports of these studies as received from Wyeth-Ayerst Research (who acquired Lederle Laboratories, Inc.) did not contain some appendix items. In the clinical data section in volume 1.21 on Page 1, a summary listing of the missing items is provided. Pages 2 through 6 contain correspondences from OraPharma, Inc. and Wyeth-Ayerst Research highlighting our efforts in getting complete documentation for these reports.

The full reports as they were made available to OraPharma, Inc. are included in the NDA. The study report for15-16-1 can be found in volume 1.21; the study report for 15-18-1 is contained in volumes 1.23 – 1.25; and the study report for 15-20-2 is located in volumes 1.32 and 1.33.

I hope this clarifies the comment 1 in the FDA telefax dated April 11, 2000. A reply for comment 2 will be provided under separate cover.