CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-744

ADMINISTRATIVE DOCUMENTS

NDA 50-744

DEC 31 1997

Collagenex Pharmaceuticals, Inc.
Attention: Christopher Powala
Director, Drug Development and Regulatory Affairs
301 South State Street
Newtown, PA 18940

Dear Mr. Powala:

Please refer to your new drug application dated August 30, 1996, received August 30, 1996, submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for Periostat (doxycycline hyclate USP) Capsules, 20 mg.

We also refer to our letter dated August 27, 1997, in which you were informed that this new drug application was not approvable.

Furthermore, we refer you to your meeting with the Agency held on November 17, 1997, in which the not approvable decision was discussed.

After further consideration of your application and of material presented at the above meeting, it remains the decision of the Agency that efficacy has not been demonstrated for this product. Specifically, we do not consider the change in attachment levels demonstrated in your studies to be clinically significant. Therefore, this new drug application remains not approvable.

This Division is willing to discuss your Study "H" and how the results of that study might be used to support a claim for your product as an adjunct to scaling and root planing.

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

Sincerely yours,

/S/ 12/31/97

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
NDA 50-744
NDA Archives
HFD-002\ORM
HFD-105\Office Director
HFD-540\Hyman\Kelsey\Gilkes\Kozma-Fornaro\Blay\DeCamp\Vidra\Jacobs\See
HFD-520\Sheldon\Marsik
HFD-725\Dixon\Srinivasan
HFD-880\Bashaw\Wang

12/8/97

Drafted by: rab\12.18.97\c:royblay\letters\nda\approval\50744.001
Initialed by:
final:

GENERAL CORRESPONDENCE (GC)

Blatt
540

SEP 16 1996

Memo

NDA Periostat (doxycycline hyclate) Caps 20 mg

DATE: 9-12-96

SUBJECT: Change in NDA Number

As per attached comments from Tom Hassall and Mary Ann Holovac, and discussions with Mary-Jean Kozma-Fornaro(Acting Supv. CSO, HFD-540), Jonathan Wilkin(Division Director, HFD-540), and Jim Bona (Supv. CSO, HFD-520) it has been decided that NDA should be changed to NDA 50-744.

The applicant will be informed of the numbering change and of their need to send a letter stating that they will now submit their NDA under section 507 of the Federal Food, Drug, and Cosmetic Act.

/S/

Harold Blatt, CSO/Proj. Mgr.

cc:
NDA
NDA 50-~~477~~ 744
DIV FILES
HFD-540/Wilkin
HFD-540/Kozma-Fornaro ejca 9/16/96
HFD-540/Blatt
HFD-005/Hassall
HFD-085/Holovac
HFD-520/Bona

n50477.912

NDA 20-642
Periostat™ (Doxycycline hyclate capsules USP)
Section 14

PATENT CERTIFICATION UNDER 21 C.F.R. 314.50(i)(1)(ii)

In the opinion and to the best knowledge of CollaGenex Pharmaceuticals, Inc., thereare no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

Respectfully submitted,

Christopher Powala
Director of Drug Development
and Regulatory Affairs
CollaGenex Pharmaceuticals, Inc.
301 South State Street
Newtown, PA 18940

Irving N. Feit
Attorney for Patent Owner
Hoffman & Baron
350 Jericho Turnpike
Jericho, New York 11753
(516) 822-3550

NDA 20-642
Periostat™ (Doxyclycline hyclate capsules USP)
Section 13

PATENT INFORMATION UNDER 21 C.F.R. 314.53 (c)

U.S. Patent: 5,223,248

Effective Filing Date: February 11, 1991

Effective Issue Date: June 29, 1993

Expiration Date: February 11, 2011

Type of Patent: Method of Use

Name of Patent Owner: The Research Foundation of State University of New York

DECLARATION

In accordance with 21 C.F.R. 314.53(c) the undersigned declares that Patent No. 5,223,248 covers the formulation, composition, and/or method of use of Periostat™. This product is the subject of this application for which approval is being sought.

Respectfully submitted,

Christopher Powala
Director of Drug Development
and Regulatory Affairs
CollaGenex Pharmaceuticals, Inc.
301 South State Street
Newton, PA 18940

Irving N. Feit
Attorney for Patent Owner
Hoffmann & Baron
350 Jericho Turnpike
Jericho, New York 11753
(516) 822-3550

NDA 20-642
Periostat™ (Doxyclycline hyclate capsules USP)
Section 13

PATENT INFORMATION UNDER 21 C.F.R. 314.53 (c)

U.S. Patent: 4,666,897

Effective Filing Date: December 29, 1983

Effective Issue Date: May 19, 1987

Expiration Date: May 19, 2004

Type of Patent: Method of Use

Name of Patent Owner: The Research Foundation of State University of New York

DECLARATION

In accordance with 21 C.F.R. 314.53(c) the undersigned declares that Patent No. 4,666,897 covers the formulation, composition, and/or method of use of Periostat™. This product is the subject of this application for which approval is being sought.

Respectfully submitted,

Christopher Powala
Director of Drug Development
and Regulatory Affairs
CollaGenex Pharmaceuticals, Inc.
301 South State Street
Newton, PA 18940

Irving N. Feit
Attorney for Patent Owner
Hoffmann & Baron
350 Jericho Turnpike
Jericho, New York 11753
(516) 822-3550

NDA 20-642
Periostat™ (Doxyclycline hyclate capsules USP)
Section 13

PATENT INFORMATION UNDER 21 C.F.R. 314.53 (c)

U.S. Patent: RE 34,656

Effective Filing Date: December 29, 1983

Effective Issue Date: May 15, 1990

Expiration Date: May 15, 2007

Type of Patent: Method of Use

Name of Patent Owner: The Research Foundation of State University of New York

DECLARATION

In accordance with 21 C.F.R. 314.53(c) the undersigned declares that Patent No. RE 34,656 covers the formulation, composition, and/or method of use of Periostat™. This product is the subject of this application for which approval is being sought.

Respectfully submitted,

Christopher Powala
Director of Drug Development
and Regulatory Affairs
CollaGenex Pharmaceuticals, Inc.
301 South State Street
Newton, PA 18940

Irving N. Feit
Attorney for Patent Owner
Hoffmann & Baron
350 Jericho Turnpike
Jericho, New York 11753
(516) 822-3550

Note:

Exclusivity is not granted with 50-7 submissions.

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.

NDA/BLA # 50 744 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade and generic names/dosage form: PERIOSTAT Action: AP AE NA

Applicant Collagenex Therapeutic Class 35

Indication(s) previously approved N/A

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

Proposed indication in this application Treatment of adult periodontitis

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) X 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) __Adolecents(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.

X 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.

9/9/98

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

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY. INDICATION IS FOR ADULT PERIODONTITIS

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

/S/

Signature of Preparer and Title

9/8/98

Date

9/10/98

cc: Orig NDA/BLA # 50-744
HFD-540 /Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

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

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # NDA 50-744 Supplement # — Circle one: SE1 SE2 SE3 SE4 SE5 SE6

IF_____ Trade (generic) name/dosage form: Periostat (Doxycycline hyclate) Capsules 20 mg Action: AP AE (NA)

Applicant Collagenex Pharmaceuticals Therapeutic Class 3S

Indication(s) previously approved N/A

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application Treatment of adult periodontitis

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** 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 subgroups. Further information is not required.

___ 2. **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 formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. 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, explain the status of discussions on the back of this form.

___ c. 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.

✓ 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

/S/ CSO 8-22-97

Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Orig NDA/~~PLA~~ # 50-744
HFD-540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

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.

3/95

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-744

Collagenex Pharmaceuticals, Inc.
Attention: Christopher Powala
Director, Drug Development and Regulatory Affairs
301 South State Street
Newtown, Pennsylvania 18940

AUG 27 1997

Dear Mr. Powala:

Please refer to your new drug application dated August 30, 1996, received August 30, 1996, submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for Periostat (doxycycline hyclate USP) Capsules, 20 mg.

We acknowledge receipt of your submissions dated September 17 and 30, October 15 and 21, November 19, and December 24 and 27, 1996; March 12 and 24, April 2 (2) and 14, May 13, June 17, and June 27, 1997. The User Fee goal date for this application is August 30, 1997.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 507 of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

Clinical

You did not demonstrate efficacy for your product in the clinical trials submitted in support of your application.

Biostatistics

Based on the per-patient efficacy analyses performed by the biostatistical reviewer, the studies submitted failed to demonstrate statistical significance of Periostat 20 mg BID in at least two of the three primary studies for each of the three primary efficacy variables, change in attachment level from baseline at month 12, change in pocket depth from baseline at month 12, and the proportion of sites with bleeding-on-probing at month 12.

Chemistry

The following deficiencies were found in the Environmental assessment (EA):

1. You failed to include information on disposal sites and on the method of disposal for the drug

substance and drug product;

2. The drug substance manufacturer, , was not ascribed any emission permits or licenses (11/95 EA Guidelines, p. 13).

In addition, the application is not approvable, also under section 507 of the Act and 21 CFR 314.125, since usage of the established name of Periostat in the labeling is not in compliance with 21 CFR 201.10(g)(1).

We also have the following comments and requests for information that should be addressed:

Clinical

1. You will be required to conduct two new clinical trials to support claims of safety and efficacy for your product for the indication sought.

2. There should be different investigators and patients in each study.

3. The arms to be included in a trial for a 'stand-alone" periodontitis indication currently are:

a. Active
b. Scaling and root planing only
c. Placebo
d. Oral hygiene instruction

4. The Agency is willing to comment on your protocols before you initiate your new trials.

Chemistry

Please address the following three CMC informational requests:

1. You are requested to conduct a light protection study during the manufacture of both drug substance and drug product and during the development of your analytical methodologies.

2. Please explain why there are four positive stability slopes for all four primary stability batches (pp. 3-0314, 3-0315, 3-0316 and 3-0321).

3. In the labeling of the drug product, the chemical designation for doxycycline hyclate and the drug product storage conditions both require corrections.

Microbiology

1. The potential for the development of tetracycline resistant bacteria appearing in the gastrointestinal tract and/or genito-urinary tract in individuals taking Periostat needs to be addressed.

2. The potential for alterations in the microflora (e.g., overgrowth of yeast) or reduction in colonization resistance of the gastrointestinal tract and/or genito-urinary tract needs to be addressed.

Biopharmaceutics

1. The dissolution method and specification proposed in this NDA submission are not discriminating enough for the to-be-marketed product. A new dissolution method and specification should be established for this product and submitted to the Agency. It is suggested that the rotation speed should be reduced to at least rpm for the paddle method. If the dissolution under this condition is still too fast, other dissolution methods may also be investigated to establish a more discriminating method and a tighter dissolution specification.

2. Based on the literature search conducted by the applicant, doxycycline absorption is decreased when coadministered with food by approximately % as measured by Cmax and AUC. Peak concentrations are achieved somewhat later following administration of food. These results are based on the studies at 100 mg and 200 mg doxycycline dose levels. No study has been conducted at 20 mg dose level. The review of bioavailability study in this NDA submission indicated a possible stronger food effect at 20 mg dose level than at antibacterial therapeutic dose levels. Although not a condition of approval, the applicant is requested to conduct a well designed food effect study.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request a meeting or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

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

Sincerely yours,

/S/ 8/27/97

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

The reviewers of this application consisted of:

Clarence Gilkes, D.D.S., Dental Officer, HFD-540
James Vidra, Ph.D., Chemist, HFD-540
Norman See, Ph.D., Pharmacologist/Toxicologist, HFD-540
Fred Marsik, Ph.D., Microbiologist, HFD-520
Cheryl Dixon, Ph.D., Biostatistician, HFD-725
Dan Wang, Ph.D., Biopharmaceutist, HFD-880

cc:
Original NDA 50-744
HFD-540/Div. files
HFD-002/ORM
HFD-105/Office Director
HFD-101/L.Carter
HFD-830/ONDC Division Director
DISTRICT OFFICE
HFD-92/DDM-DIAB
HFD-540/Kozma-Fornaro 8/22/97
HFD-540/Blatt
HFD-540/Kelsey 8/21/97
HFD-540/Gilkes 8-20-97
HFD-540/DeCamp 8/14/97
HFD-540/Vidra 8/11/97
HFD-540/Jacobs 8/11/97
HFD-540/See 8/11/97
HFD-520/Sheldon 8/12/97
HFD-520/Marsik 8/11/97
HFD-725/Srinivasan 8/11/97
HFD-725/Dixon 8/8/97
HFD-880/Bashaw 8/11/97
HFD-880/Wang 8/8/97

Drafted by: hjb/June 19, 1997/n50744na.619
Initialed by:
final:

NOT APPROVABLE (NA)

MEMO

To: Roy Blay, Ph.D.

From: E. Dennis Bashaw, Pharm.D. 9/14/98

Date: Monday, September 14, 1998

Subject: NDA 50-744, Periostat (Doxycycline HCl 20mg)

Regarding the biopharmaceutics review of this NDA. The NDA is approvable from a biopharmaceutics standpoint. That being said there is a need for an in vivo study of the effect of food on the absorption of doxycycline from the Periostat dosage form. The study should be a standard two-way crossover study comparing Periostat administered in the fasted state to the fed state. The fed treatment leg should utilize the following diet:

The Official FDA High Fat Breakfast

2 Eggs (fried in butter)
2 Pieces of Bacon
2 Pieces of Toast w/Butter
2-4oz. of Hash Brown Potatoes
8oz of Whole Milk

This is the "standard" diet utilized for all NDA oral dosage forms. Given the long history of use of doxycycline at higher doses, this study can be deferred post-approval.

Consult #744 (HFD-540)

PERIOSTAT doxycycline hyclate capsules

The Committee noted many potential look-alike/sound-alike conflicts: PERIOMED, PERIOGUARD, PERIACTIN, etc. Additionally, "stat" is a common medical abbreviation for immediately. Since the product does not work immediately, it appears to be misleading.

The Committee finds the proposed proprietary name unacceptable.

/S/ 3/4/97, Chair
CDER Labeling and Nomenclature Committee

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-744

Collagenex Pharmaceuticals, Inc.
Attention: Christopher Powala
Director, Drug Development and Regulatory Affairs
301 South State Street
Newtown, Pennsylvania 18940

AUG 27 1997

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a. Active
b. Scaling and root planing only
c. Placebo
d. Oral hygiene instruction

4. The Agency is willing to comment on your protocols before you initiate your new trials.

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2. The potential for alterations in the microflora (e.g., overgrowth of yeast) or reduction in colonization resistance of the gastrointestinal tract and/or genito-urinary tract needs to be addressed.

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2. Based on the literature search conducted by the applicant, doxycycline absorption is decreased when coadministered with food by approximately 20% as measured by Cmax and AUC. Peak concentrations are achieved somewhat later following administration of food. These results are based on the studies at 100 mg and 200 mg doxycycline dose levels. No study has been conducted at 20 mg dose level. The review of bioavailability study in this NDA submission indicated a possible stronger food effect at 20 mg dose level than at antibacterial therapeutic dose levels. Although not a condition of approval, the applicant is requested to conduct a well designed food effect study.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request a meeting or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

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

Sincerely yours,

/S/

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

The reviewers of this application consisted of:

Clarence Gilkes, D.D.S., Dental Officer, HFD-540
James Vidra, Ph.D., Chemist, HFD-540
Norman See, Ph.D., Pharmacologist/Toxicologist, HFD-540
Fred Marsik, Ph.D., Microbiologist, HFD-520
Cheryl Dixon, Ph.D., Biostatistician, HFD-725
Dan Wang, Ph.D., Biopharmaceutist, HFD-880

Meeting I.D. 2116

Memorandum of Teleconference

Date: January 22, 1998, 10:00 AM

Sponsor: CollaGenex, Inc

Drug: Periostat, NDA 50-744

Subject: Discussion of NA and Use of Study H

FDA Attendees

Roy Blay, Ph.D., Project Manager RB 10/1/98
Jonathan K. Wilkin, M.D., Director, DDDDP
John V. Kelsey, D.D.S., M.B.A., Dental Team Leader

Sponsor Attendees

Mr. Robert Ashley, V.P., Commercial Development, CollaGenex
Dr. Brian Gallagher, President and CEO, CollaGenex
Mr. Christopher Powala, Director, Regulatory Affairs, CollaGenex

FDA stated that the NDA remained Not Approvable because the trials did not demonstrate clinical significance. FDA suggested that the sponsor might want to pursue an adjunctive indication since they felt their Study H was positive. If the results of Study H are positive and the sponsor is able to replicate the results in a second trial the product could be approved for the adjunctive indication. FDA said that the design of Study H submitted in the original protocol appears to be acceptable. The trial should have 2 arms: scaling and root planing (SRP) + placebo and SRP + active. The primary efficacy endpoint for a treatment of periodontitis claim would be change in attachment level at 9 months. Statistically significant superiority of the active arm over the placebo arm would constitute a "win." Positive results in these 2 trials would support the filing of a new NDA.

The sponsor stated that they did not share the Division's opinion that the results of their Studies E, F & G are not clinically significant. They also said that they did not understand the Division's criteria for determining clinical significance.

FDA said that further discussion of the non-approval decision should be taken up with the ODE V Office Director, the Deputy Center Director, or possibly the Ombudsman. The sponsor said that it did not understand the Division's reasoning for its decision regarding clinical significance; therefore, it would not know how to properly appeal the decision.

FDA explained its rationale. FDA first noted that the results did not reach the sponsor's own target for treatment effect of, "... at least .6 mm after 12 months of therapy." Because a supra gingival prophylaxis is not standard treatment for moderate to severe periodontitis, FDA was unable to find similar studies in the literature. So, FDA compared the change from baseline in the sponsor's studies to SRP, which is standard therapy in moderate to severe periodontitis. FDA used historical efficacy data for SRP from the proceedings of the *1996 World Workshop in Periodontics*, and applied the standard that is applied to "stand-alone" products to treat periodontal disease. That requirement is that the product must be 75% as good as SRP. The sponsor's results did not meet these criteria.

The sponsor said that the placebo effect may have confounded the data and noted that changes in attachment level from the prophy alone exceeded their expectations. The sponsor said that it did not intend its drug to be used as a stand-alone therapy and that the goal of treatment was maintenance to prevent periodontal attachment loss and that the analysis of the manual probe data supported this objective. FDA said that its analysis was based on those studies with statistically significant results as discussed at the November 17, 1997, meeting.

FDA asked if the patients in Studies E, F, and G received SRP prior to treatment. The sponsor said that the patients all had periodontal disease and had had treatment in the past and fit a variety of inclusion criteria but had not necessarily had SRP prior to study treatment. FDA noted that the study design did not distinguish between initial and maintenance treatment.

The sponsor asked if Studies E, F, and G, plus Study H would be adequate to support the maintenance claim; they would be willing to conduct as a Phase 4 commitment. FDA said that stand-alone and adjunctive treatment are different indications and would require separate studies. Study H appears appropriate for the adjunctive claim but would require replication.

After considerable discussion, FDA said that these issues could not be settled during the teleconference and suggested that the sponsor present its concerns to the Office level for consideration.

Concurrences: JKelsey, 1.29.98; JKWilkin, 10.1.98

cc:
NDA 50-744
Division Files
HFD-540\Blay\Kelsey

Meeting I.D. 2337

Memorandum of Meeting

Date: March 12, 1998, 9:30 AM

Sponsor: CollaGenex, Inc

Drug: Periostat, NDA 50-744

Subject: Discussion of NA Issues

FDA Attendees

Michael Weintraub, M.D., Director, ODE V
Clarence C. Gilkes, D.D.S., Dental Officer
John V. Kelsey, D.D.S., M.B.A., Dental Team Leader
Cheryl Dixon, Ph.D., Statistician
Rajagapolan Srinivasan, Ph.D., Biostatistics Team Leader
Fred Hyman, D.D.S., M.P.H., Dental Officer
Joanna Soffa, Office of General Counsel
Susan Kummerer, Project Manager

Sponsor Attendees

Mr. Robert Ashley, V.P, CollaGenex
Dr. Jack Caton, University of Rochester
Dr. Brian Gallagher, President and CEO, CollaGenex
Dr. Joe Massaro, Biostatistician, Quintiles Inc.
Mr. Christopher Powala, Director, Regulatory Affairs, CollaGenex
Dr. John Stamm, Dean, Dental School, UNC
Ms. Nancy L. Buc, Buc & Beardsley
Mark Bradshaw, V.P., Icon Consultant

The sponsor said that the indication for the product would be the framework for the discussion. The drug product would be used between courses of conventional periodontic therapy as part of a professional program for the mitigation of periodontal disease. The sponsor said that they had provided evidence of the clinical significance of the product under conditions of use. Furthermore, the sponsor said that the use of the product was appropriate in terms of cost, potential risk to the patient, and convenience of use.

The sponsor noted that a diagnosis of periodontitis was serious, indicating a progressive disease requiring appropriate clinical intervention over a period of time. Such intervention would include appropriate dental hygiene, supragingival scaling, scaling and root planing (SRP), and possibly, surgery. The sponsor said that this drug product would be an adjunct to these standard dental practices, not a replacement.

FDA and the sponsor then discussed the relative merits of increased periodontal ligament attachment level (PAL) and decreased probing pocket depth (PPD) as efficacy criteria and which, if either, would pose a more stringent criteria for efficacy. The sponsor presented a series of slides demonstrating the efficacy of their product in terms of maintaining and stabilizing PAL, and preventing PAL loss. The sponsor noted that reduction of PPD was easier to demonstrate than gain in PAL; in fact, some patients demonstrated a loss in PAL despite SRP. The sponsor felt that such cases would be a good indication for the use of the drug product.

FDA said that specific clinical trial results previously submitted for review lacked clinical significance; however, pooled data from several trials did demonstrate statistical significance. FDA said that it would review the data in Study H once submitted as an amendment to the NDA. This data would be analysed with respect to the drug product being claimed as an adjunct to SRP. This review would be completed within 6 months of the sponsor's complete reply to all outstanding questions (this would include any chemistry issues).

The sponsor said that they would not object to an "adjunct to SRP" claim and would discuss labelling with the FDA that would indicate the use of the product as a possible adjunct to other clinical procedures.

FDA said that the use of the drug product as an adjunct to standard therapy rather than a replacement would be more acceptable provided that Study H supports the efficacy of the product.

The sponsor will propose the precise wording of the indication that they wish to include in labelling.

UMMARY

FDA will review Study H once submitted as an amendment to the NDA. This data will be analysed with respect to the drug product being claimed as an adjunct to SRP.

This review will be completed within 6 months of the sponsor's complete reply to all outstanding questions, including any chemistry issues.

The sponsor will not object to an "adjunct to SRP" claim and will discuss appropriate labelling, including the indication, with the FDA.

oncurrences: SKummerer, 3.19.98; CGilkes, 3.17.98; JKelsey, 3.17.98; CDixon, 3.18.98; Srinivasan, 3.18.98; FHyman, 3.19.98; MWeintraub, 4.13.98

c:
DA 50-744
ivision Files
FD-540\Blay\Gilkes\Kelsey\Hyman\Wilkin
FD-725\Srinivasan\Dixon
FD\105\Walling\Weintraub

Meeting I.D. 1923

Memorandum of Meeting

Date: November 17, 1997, 1:00 PM

Sponsor: CollaGenex, Inc

Drug: Periostat, NDA 50-744

Subject: Discussion of NA Issues

FDA Attendees

Roy Blay, Ph.D., Project Manager 23 10/1/98
Jonathan K. Wilkin, M.D., Director, DDDDP
Michael Weintraub, M.D., Director, ODE V
Clarence C. Gilkes, D.D.S., Dental Officer
John V. Kelsey, D.D.S., M.B.A., Dental Team Leader
Cheryl Dixon, Ph.D., Statistician
Rajagapolan Srinivasan, Ph.D., Biostatistics Team Leader
Fred Hyman, D.D.S., M.P.H., Dental Officer
Kevin Darryl White, M.B.A.,Project Manager
Mary Jane Walling, Associate Director, ODE V
M.F. Huque, Ph.D., Acting Division Director, DOB IV
Mary Jean Kozma-Fornaro, R.N., Supervisory Project Manager

Sponsor Attendees

Dr. H. P. K. Agersborg, Chairman, CollaGenex
Mr. Robert Ashley, V.P., Commercial Development, CollaGenex
Dr. Timothy Blieden, Professor Eastman Dental Center
Dr. Mark Bradshaw, V.P., Biostatistics, ICON
Dr. Sebastian Ciancio, Professor, SUNY at Buffalo
Dr. Ralph D'Agostino, Professor, Boston University
Dr. Brian Gallagher, President and CEO, CollaGenex
Dr. Joe Massaro, Biostatistician, Quintiles Inc.
Mr. Christopher Powala, Director, Regulatory Affairs, CollaGenex
Dr. John Stamm, Dean, Dental School, UNC

Introductions were made. The sponsor noted that they had had a teleconference with the Division following receipt of the NA letter.

The sponsor noted that they had reviewed their Phase 3 statistical analysis plan and saw that their inclusion criteria were not met in certain cases resulting in incorrect recruitment. The sponsor dropped these subjects from the revised data analysis prepared for the meeting. FDA asked if the violators were identified prior to the breaking of the blind. The sponsor said that identification was made after the blind was broken.

The sponsor explained why they used the GEE method of data analysis in the NDA. They also presented a time line for development of their product.

The sponsor confirmed that the attachment level measured using the Florida probe was their primary efficacy endpoint. FDA noted that the sponsor had initially stated that a change of 0.6 mm in attachment level would be regarded as a "win." FDA said that actual clinical results were not impressive.

There was discussion about the indication. The sponsor said that their indication is as an adjunct to a supra gingival scaling and prophylaxis; it is not a "stand alone" treatment intended to replace other modalities. The treatment is designed to manage the patient between dental visits. FDA expressed concern that the treatment might be used in lieu of scaling and root planing (SRP). The sponsor felt that this issue could be addressed in labeling.

There was discussion about the fact that data from the studies indicated that the product prevented deterioration of attachment levels by more than 2 mm. FDA noted the distinction made between "promoting attachment gain" and "preventing attachment loss." The FDA also noted that it was necessary to combine all studies to achieve statistical significance for this parameter.

The sponsor said that they have completed an additional study (Study H) that looks at their product as an adjunct to SRP and presented preliminary results. FDA said that they would like to see the results of this study.

FDA said that it would discuss the new material internally and communicate its decision to the sponsor.

Concurrences: MJWalling, 11.19.97; CGilkes, 11.25.97; FHyman, 11.20.97; JKelsey, 12.18.97; CDixon, 11.21.97; RSrinivasan, 11.21.97; MWeintraub, 2.17.98; JKWilkin, 10.1.98

cc:
NDA 50-744
Division Files
HFD-540\Blay\Gilkes\Kelsey\Hyman
HFD-725\Srinivasan\Huque\Dixon
HFD\105\Walling\Weintraub

RECORD OF TELEPHONE CONVERSATION	DATE: September 16, 1998 4:20 PM
Drs. Bashaw, Srinivasan, Dixon, Kelsey, Wilkin, and DeCamp were in attendance. Dr. DeCamp said that upon review of the original submitted labeling that the relative prominence of the established name was not commensurate with the prominence of the tradename as provided for in 21 CFR 201.10(g)(2). Dr. DeCamp asked Mr. Powala of the status of their FPL. Mr. Powala replied that FPL had not yet been printed. Dr. DeCamp asked Mr. Powala to commit to revising the size of the established name commensurate with the regulations. Mr. Powala said that he would do so and provide that commitment in writing both by facsimile and hard copy. Regarding stability issues brought up by Mr. Powala, Dr. DeCamp said that the issues had been considered and suggested that the sponsor submit a supplement providing for a change in expiry dating immediately after receipt of the action letter. Mr. Powala agreed to do so. cc: NDA 50-744 NDA Arch. HFD-540\Blay\Kelsey\DeCamp\Vidra WD 9/16/98 9/16/98	NDA NUMBER 50-744 IND NUMBER xxxxxxxxx TELECON INITIATED BY: APPLICANT/ SPONSOR; (FDA) MADE: (BY TELEPHONE); IN PERSON PRODUCT NAME Periostat FIRM NAME Collagenex NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD Christopher Powala TELEPHONE: 215-579-7388 x16
SIGNATURE 9/16/98 Roy A. Blay	DIVISION HFD-540, DDDDP

Dental Team Leader Memo - NDA 50-744
Response to Meeting of 11/17/97

Date: December 15, 1997

Drug: Periostat™ (doxycycline hyclate capsules, USP)

Sponsor: Collagenex Pharmaceuticals, Inc.

Re: Clinical Significance of NDA Results

This memo is to comment on the issue of the clinical significance of the results of the studies submitted to support approval of Periostat™, NDA 50-744. This is in follow-up to a meeting with the sponsor on November 17, 1997, during which both the statistical significance and the clinical significance of the sponsor's study results were discussed. The Clinical Review of this NDA and the Team Leader's Memo of August 8, 1997 had opined that the results were not clinically significant. After further review, I continue to hold that opinion.

Use of this product as an "adjunct to a supra gingival scaling and prophylaxis (prophy)" which is the way the sponsor seeks to use this product, is an odd choice for this patient population, though the Agency did not object to this indication. Though it may improve the outcome slightly, prophylaxis is not standard therapy for moderate to severe periodontitis, characterized by 5-9 mm pockets. A prophy would be a weak positive control in a study of moderate to severe periodontitis.

Statistical issues aside, the mean difference in attachment levels of .32 mm. (p=.071) and .42 mm. (p=.012) in the two studies looking at the Florida probe data after 12 months of therapy seem very modest. In evaluating the clinical significance of these results the sponsor's own opinion about what they would view as clinically significant was considered first. In response to a question from FDA at a meeting on 9/28/92, the sponsor stated, "...our target is a treatment effect of at least .6 mm after 12 months of therapy."

Next the literature was consulted for guidance about what constitutes a clinically significant effect. Because supra gingival scaling and prophylaxis is not standard therapy for moderate to severe periodontitis, there are no studies that looked at this therapy in this group. This use is more like a "stand-alone" periodontitis indication (treatment in lieu of SRP) and the Division has said in the past that in studies for the "stand-alone" periodontitis indication, efficacy endpoints at least 75% as good as SRP would be required. This position is consistent with comments in the ***Proposed guidelines for American Dental Association acceptance of products for professional, non-surgical treatment of adult periodontitis,*** as developed by the Taskforce on Design and Analysis in Dental and Oral Research:

"To accept products, however, based solely on statistical superiority to a negative control was widely viewed as too permissive for evaluating an antiperiodontitis agent to be used in any setting. By acceptance of products with statistically significant but small effects compared to a negative control, the ADA would risk endorsing products which informed members of the periodontal community might disdain to recommend because of insufficient benefit."

In assessing the clinical significance of the results presented were compared to the historical results of SRP, which is the standard therapy for moderate to severe periodontal disease. From a summary of the literature presented in the proceedings of the ***1996 World Workshop in Periodontics***, SRP results in an average .55 mm. improvement in attachment levels in moderate sites (4-6 mm) and 1.29 mm. in severe sites (>7 mm) for an average of .92 mm. The patients in the group from which the sponsor has taken its pivotal results had initial pocket depths of 5-9 mm., so were somewhat more severe at baseline than the patients reported in the literature summary. Also, the sponsor's own Study H, in 140 patients, includes an SRP only arm. FDA has not reviewed the results of that study, but the sponsor presented preliminary results of a 1.2 mm. improvement in attachment level in patients with ≥7 mm. pockets, with SRP alone. This is consistent with results in the literature.

There is some beneficial effect to performing a prophy in this patient group as evidenced by the improvements in AL seen in the placebo groups in these studies (all patients got a prophy). In contrast, the AL improvements reported for SRP in the literature are simply pre- and post-values, so the differences reported are from baseline. To more accurately compare the groups, the absolute improvement in attachment levels from baseline were assessed. The differences from baseline in attachment levels were .56 mm. in both studies. These values are still short of 75% of the historical values for SRP (.69 mm.).

The sponsor reported an analysis of subjects who had sites that deteriorated more than 2 mm. or more than 3 mm. A reduction in this parameter would be clinically relevant, though this reviewer could not find a study that evaluated this parameter in conjunction with SRP. In assessing the supportive value of these results in approving the NDA, it was noted that the sponsor achieved statistically significant results in the moderate and severe disease groups in only one study, even though a large number of sites were included - this was for the >2 mm. group. Interestingly, these results are from the one study (Study F) that did not support the efficacy findings for attachment levels around which the sponsor is trying to accumulate support for approval (Studies E & G). There were three identical studies done, but the results of the second (Study F) were quite different than the other two (Studies E & G). The fact that there was so much variability among the three identical studies does not lend comfort in accepting the limited support for efficacy that E & G provide.

The data on change in probing pocket depths were also reviewed. In the **World Workshop** proceedings, the literature review showed mean reductions in pocket depth of 1.29 mm. in the moderate group and 2.16 mm. in the severe group. Again, there was considerable variability. If the absolute improvement in the parameters from baseline is considered, the improvement was .71 mm. in the moderate group for all studies combined and 1.39 mm in the severe group for all

studies combined. These results were again short of the 75% of SRP threshold (.97 mm. & 1.62 mm.).

In conclusion, the data are hardly robust. If results from the study that were significant at p=.071 are accepted, the sponsor was able to show a modest difference in attachment levels in one stratum in two of three studies. Attachment level differences of .32 mm. and .42 mm. at one year are not considered to be clinically significant, especially in view of the sponsor's a priori estimate of a .6 mm. difference.

In an attempt to assess clinical significance, the results were compared to historical values for SRP (there was no concurrent SRP arm), and adjusted for the fact that a prophy was performed by assessing the change from baseline for the active arm. Sponsors of stand alone periodontics products have been told that their results have to be 75% as good as SRP and this level was not reached. Their data regarding deterioration of attachment levels beyond threshold limits was also reviewed, but the results were not statistically significant. Data on changes in pocket depth were considered and again, the changes did not reach the level of 75% of SRP. I continue to feel that the result are not clinically significant.

There are several options that can be offered to the sponsor:

1. Conduct two new studies for the "adjunct to prophylaxis" indication with the hope of achieving a .6 mm. attachment level difference.

2. Submit the results of their Study "H," which looks at their product as an adjunct to SRP, along with a confirmatory study. If both are positive, the sponsor could get a claim for their product as an adjunct to SRP. We would carefully consider what, if anything, could be put in the labeling based on the studies being reviewed now. This option would be easier than option 1. because it would require only 2 arms.

3. If the results of their Study "H" are not positive, the sponsor would have to do two new studies to get an "adjunct to SRP" claim.

The sponsor should be informed of the Division's decision that clinically significant results have not been achieved in two well-controlled studies and that the Not Approvable decision stands. The sponsor should also know that the Division will be happy to discuss the options available at this point.

/S/

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

cc:

Original NDA 50-744
HFD-540/Div. Files
HFD-105/Office Director

HFD-540/DD/Wilkin 12/30/97
HFD-540/Kozma-Fornaro
HFD-540/Blay
HFD-540/Gilkes
HFD-540/DeCamp
HFD-540/Vidra
HFD-540/Jacobs
HFD-540/See
HFD-520/Sheldon
HFD-520/Marsik
HFD-725/Srinivasan
HFD-725/Dixon
HFD-880/Bashaw
HFD-880/Wang

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 50-774 type Revised letter sent on 12/31/97

Food and Drug Administration
Rockville MD 20857

Collagenex Pharmaceuticals, Inc.
Attention: Christopher Powala
Director, Drug Development and Regulatory Affairs
301 South State Street
Newtown, PA 18940

DEC 30 1997

Dear Mr. Powala:

Please refer to your new drug application dated August 30, 1996, received August 30, 1996, submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for Periostat (doxycycline hyclate USP) Capsules, 20 mg.

We also refer to our letter dated August 27, 1997, in which you were informed that this new drug application was not approvable.

Furthermore, we refer you to your meeting with the Agency held on November 17, 1997, in which the not approvable decision was discussed.

After further consideration of your application and of material presented at the above meeting, it remains the decision of the Agency that efficacy has not been demonstrated for this product. Specifically, we do not consider the change in attachment levels demonstrated in your studies to be clinically significant. Therefore, this new drug application remains not approvable.

This Division is willing to discuss your Study "H" and how the results of that study might be used to support a claim for your product as an adjunct to scaling and root planing.

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

Sincerely yours,

/S/

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-744

CORRESPONDENCE

COLLAGENEX
pharmaceuticals

ORIGINAL

NEW CORRESP

September 25, 1998

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic & Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857

RE: NDA 50-744 - Periostat® (doxycycline hyclate) 20 mg Capsules
General Correspondence: Labeling

Dear Dr. Wilkin:

Please refer to NDA 50-744 for Periostat® (doxycycline hyclate) 20 mg capsules which is proposed for use as an adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

Additional reference is made to our submission dated September 22, 1998 which contained our response to the Division's proposed labeling for Periostat®. As part of that submission we proposed that the 3 and 6 month data on Gain in Attachment Level and Reduction in Pocket Depth from the SRP trial should also be included in the clinical section, in particular so that the clinician would not be misled into thinking that the patient had to be on the drug for 9 months to achieve statistically (and clinically) significant benefits.

Having carefully reviewed the approved labeling for Atridox™, the most recent comparable product to be approved for marketing by the Division, it appears that the preferred format for the presentation of clinical data in the PI is in graphical form. Hence we are providing four graphs representing the tabulated data in pockets with baseline pocket depth of $\geq$ 7mm and 4 - 6mm from the Periostat SRP study. These graphs were generated using the data which were included in tabular form in our submission dated September 22, 1998. As the graphs are easier for the clinician to assimilate that data tables, we propose that they be included in the labeling in a manner identical to that in the Atridox labeling, as a replacement for the tabular data they represent.

If you have any questions regarding this matter, please contact the undersigned at 215-579-7388, ext. 16 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala

Christopher Powala
Director, Drug Development
& Regulatory Affairs

CollaGenex Pharmaceuticals, Inc., 301 South State Street, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

COLLAGENEX
pharmaceuticals

ORIGINAL

NEW CORRESP

NC

September 24

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic & Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857

RE: NDA 50-744 - Periostat® (doxycycline hyclate) 20 mg Capsules
General Correspondence: Literature References

Dear Dr. Wilkin:

Please refer to NDA 50-744 for Periostat® (doxycycline hyclate) 20 mg capsules which is proposed for use as an adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

The purpose of this submission is to provide hard copy of literature references which provide evidence that doxycycline, at the recommended dose (20 mg BID), has no impact on human fertility (attached). This submission is in follow-up to the faxed copies sent to Dr. Roy Blay, Project Manager, HFD-540 on this date.

If you have any questions regarding this submission, please contact the undersigned at 215-579-7388, ext. 16 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Director, Drug Development
& Regulatory Affairs

CollaGenex Pharmaceuticals, Inc., 301 South State Street, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

COLLAGENEX
pharmaceuticals

September 24, 1998

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic & Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857

ORIGINAL

NEW CORRES

NC

RE: NDA 50-744 - Periostat® (doxycycline hyclate) 20 mg Capsules
General Correspondence

Dear Dr. Wilkin:

Please refer to NDA 50-744 for Periostat® (doxycycline hyclate) 20 mg capsules which is indicated for use as an adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

Additional reference is made to a September 21, 1998 conversation between Dr. Roy Blay and the undersigned regarding minor changes in the text of the bottle and shipper labels. During this conversation, Dr. Blay requested that CollaGenex write a formal submission to the NDA detailing the minor changes to the Periostat® bottle and shipper label.

As requested, please note the following changes to the bottle and shipper labels:

1. The company name will be revised to reflect it's true name, CollaGenex Pharmaceuticals. It will be re-positioned to bottom center.

2. While CollaGenex commits to revising the established name to be more prominent (submission dated 9/16/98), further revision is being made to remove the "USP" designation as it is not required.

3. The shipper label will be revised to designate the correct number of bottles being shipped. The label now states that will be shipped.

For you review, I am providing you with a copy of the bottle and shipper labels CollaGenex intends to use.

If you have any questions regarding this matter, please contact the undersigned at 215-579-7388, ext 16. (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Director, Drug Development
& Regulatory Affairs

CollaGenex Pharmaceuticals, Inc., 301 South State Street, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

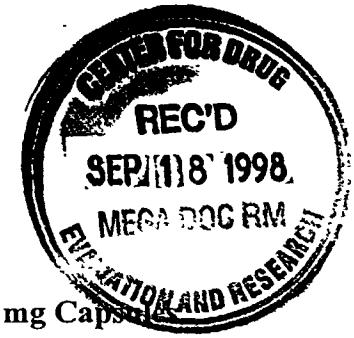
COLLAGENEX
pharmaceuticals

ORIGINAL

September 16, 1998

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic & Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857

NEW CORRESP.



RE: NDA 50-744 - Periostat® (doxycycline hyclate, USP) 20 mg Capsules
General Correspondence

Dear Dr. Wilkin:

Please refer to NDA 50-744 for Periostat® (doxycycline hyclate, USP) 20 mg capsules which is proposed for use as an adjunct to sub-gingival scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

Additional reference is made to the September 16, 1998 teleconference between representatives of the Division and Mr. Christopher Powala of CollaGenex. During this conversation, it was noted that the height of the established name in the examples of the bottle and shipper label submitted in the Periostat NDA was satisfactory relative to the trade name. However, the Division requested that the prominence of the established name (doxycycline hyclate, USP) be increased.

In response to this request, CollaGenex will maintain the relative height of the established name and increase its width to one half the width of the trade name on both the bottle and shipper label to increase its relative prominence.

I trust that this adequately responds to the Division's request. If you have any questions regarding this matter, please contact the undersigned at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Director, Drug Development
& Regulatory Affairs

CollaGenex Pharmaceuticals, Inc., 301 South State Street, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

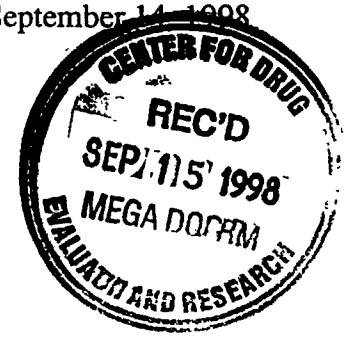
COLLAGENEX
pharmaceuticals

DUPLICATE

~~ORIG AMENDMENT~~

NEW CORRESP

September 14, 1998



Jonathan K. Wilkin, M.D., Director
Division of Dermatologic & Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857

RE: NDA 50-744 - Periostat® (doxycycline hyclate, USP) 20 mg Capsules
Minor Amendment: Response to FDA Request for Information

Dear Dr. Wilkin:

Please refer to our NDA 50-744 for Periostat® (doxycycline hyclate, USP) 20 mg capsules which is proposed for use as an adjunct to sub-gingival scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

Additional reference is made to the Division's facsimile of September 14, 1998 (attached) which requests that CollaGenex commit to conduct, study as outlined in the aforementioned fax.

In response to this facsimile, CollaGenex hereby commits to conduct this the food effect study post-approval.

I trust that this adequately responds to the Division's request. If you have any questions regarding this matter, please contact the undersigned at 215-5769-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Director, Drug Development
& Regulatory Affairs

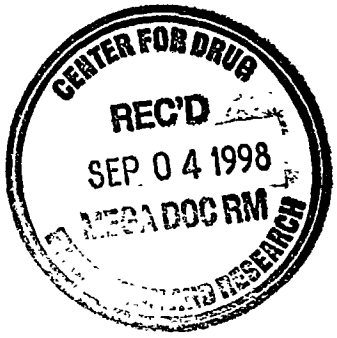
Desk Copy: Dr. Roy Blay, Project Manager, HFD-540

CollaGenex Pharmaceuticals, Inc., 301 South State Street, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

COLLAGENEX
pharmaceuticals

ORIG AMENDMENT
BL

September, 3, 1998



ORIGINAL

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic & Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857

RE: NDA 50-744 - Periostat® (doxycycline hyclate, USP) 20 mg Capsules
Minor Amendment: Response to Request for Information

Dear Dr. Wilkin:

Please refer to NDA 50-744 for Periostat® (doxycycline hyclate, USP) 20 mg capsules which is proposed for use as an adjunct to sub-gingival scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis.

Additional reference is made to the September 2, 1998 teleconference between the Division and CollaGenex. During this teleconference, Dr. Jake Kelsey, Dental Team Leader, HFD-540, requested that we provide the following information. For ease in review, each of Dr. Kelsey's requests are reiterated and are followed by our response. Be advised that we incorporated this information into the proposed labeling which is provided in Attachments 1 and 2.

Request #1:

"Regarding the mechanism of action, can the sponsor provide a reference showing the relationship between elevated collagenase in the GCF and periodontal destruction."

Response to Request #1:

Provided herewith is the requested reference:

Lee, W., Aitken, S., Sodek, J., McCulloch, C.: Evidence of a Direct Relationship Between Neutrophil Collagenase Activity and Periodontal Tissue Destruction *In Vivo*: Role of Active Enzyme in Human Periodontitis. J. Periodontal Res 1995, 30: 23-33.

BEST POSSIBLE COPY

CollaGenex Pharmaceuticals, Inc., 301 South State Street, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

Request #2:

Please provide a reference to support the statement that doxycycline pharmacokinetics have been referenced in numerous scientific publications.

Response to Request #2:

Provided herewith is the requested reference.

Saivain S., Houin G.: Clinical Pharmacokinetics of Doxycycline and Minocycline. Clin. Pharmacokinetics 1988; 15: 355-366.

Request #3:

Please provide the number of subjects who participated in the Steady-State Pharmacokinetic trial."

esponse to Request #3:

30 - randomized - in every arm of the study

xty ~~(60)~~ subjects participated in Study CI-95-102, Titled: "An open-label, multiple-dose, three-riod cross-over study evaluation pharmacokinetic dose-proportionality of the following drug rmulations in healthy volunteers: 20 mg doxycycline hyclate administered QD, 20 mg oxycycline hyclate administered BID, 50 mg Vibramycin® administered QD."

equest #4:

der the Special Populations: Gender section of the pharmacokinetic labeling, please lude a remark regarding the PK study which CollaGenex carried out.

sponse to Request #4:

vided herewith is text to be included in the Special Populations: Gender section of the ostat label:

tudy was conducted in 42 subjects where doxycycline pharmacokinetics were compared in n and women. It was observed that C_{max} was approximately 1.7-fold higher in women than in n. There were no apparent differences in other pharmacokinetic parameters.

uest #5:

se revise the Incidence (%) of Adverse Reactions table to include data from all studies dies E, F, G, and H) combined.

Response to Request #5:

We revised the Incidence of Adverse Reactions table to combine data from all studies. Please note that as in the previous table, we are providing listings for all adverse reactions with an incidence of 3% or greater.

Attachment 1 contains a hard copy and Attachment 2 contains a diskette (WordPerfect 6.1) of the latest version of the proposed labeling which incorporates these changes.

Trust that this adequately responds to your requests. If you have any questions regarding this matter, please contact the undersigned at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Director, Drug Development
Regulatory Affairs

Copy: Dr. Jake Kelsey, HFD-540

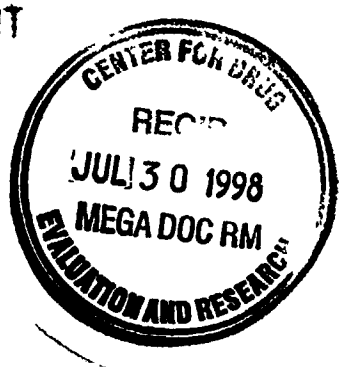
COLLAGENEX
pharmaceuticals

July 29, 1998

Dr. Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857

BC

ORIGINAL



RE: NDA 50-744 - Periostat™ (doxycycline hyclate, USP) 20 mg
Minor Amendment - Response to request for Information

Dear Dr. Wilkin:

Please refer to NDA 50-744 for Periostat™ (doxycycline hyclate, USP) 20 mg capsules which is proposed for use as an adjunct to supra- and sub-gingival scaling and root planing to promote and maintain attachment level gain and to reduce pocket depth and bleeding on probing in patients with adult periodontitis.

Additional reference is made to Dr. Roy Blay's July 28, 1998 telephone call at which time he requested that CollaGenex submit Periostat labeling on WordPerfect 6.1 diskette which does not contain annotations and coding restraints.

In response to this request, we are providing Periostat labeling on WordPerfect 6.1 diskette which has been revised accordingly.

If you have any questions regarding this matter, please contact the undersigned at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

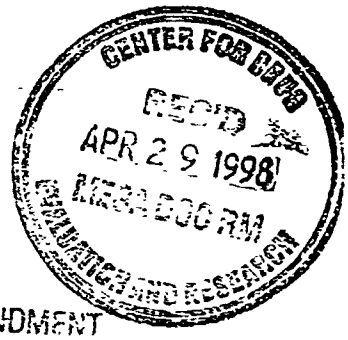
Christopher Powala
Director, Drug Development
& Regulatory Affairs

Desk Copy: Dr. Roy Blay, Project Manager, HFD-540

CollaGenex Pharmaceuticals, Inc., 301 South State Street, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

COLLAGENEX pharmaceuticals

ORIGINAL



April 28, 1998

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857

ORIG AMENDMENT
BZ

RE: NDA 50-744 - Periostat™ (doxycycline hyclate, USP) 20 mg Capsules
Minor Amendment: Response to Dental and Biopharmaceutical Reviewers Request for Information

Dear Dr. Wilkin:

Please refer to our NDA 50-744 for Periostat™ (doxycycline hyclate, USP) 20 mg capsules which is proposed for use as an adjunct to supra- and sub-gingival scaling and root planing to promote and maintain attachment level gain and to reduce pocket depth in patients with adult periodontitis.

Additional reference is made to the Division's facsimile of April 13, 1998 which requested information pertaining to the clinical and biopharmaceutical sections of the above-mentioned NDA. Each of the reviewers comments have been reiterated and are followed by our response.

Clinical Comments:

Please submit the following:

1. **All Causalities AE's not associated with medical history for all dosages together and all studies including all treatment groups.**

2. **All Causalities AE's not associated with medical history for 20 mg doxycycline and placebo in all studies.**

3. **All causalities AE's not associated with medical history for all dosages together in studies E,F,G & H, including all treatment groups.**

4. **All causalities AE's not associated with medical history for 20 mg doxycycline and placebo in studies E,F,G & H.**

CollaGenex Pharmaceuticals, Inc., 301 South State Street, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

Sponsor's Response:

On April 14, 1998 a teleconference was held between Dr. John Kelsey, Dental Team Leader, Dr. Roy Blay, Project Manager and Mr. Robert Ashley, CollaGenex to clarify the clinical comments. It was determined that no additional safety analysis was needed at this time and the Sponsor need not respond to these comments.

Biopharmaceutics Comments:

Preliminary evaluation of your data suggest that the proposed method and specification still lack lot to lot discrimination. It is our opinion that the use of the 50 rpm rotation speed with a Q value of % in minutes would provide the proper balance between the discrimination and release ability of lots. Should you elect to accept the specification method, such acceptance would constitute an acceptable response to this issue. If, however, you wish to pursue the minute time point, then lower dissolution speeds (such as those used for suspensions), i.e., 25 rpm, must be investigated. The overall goal of the in vitro technology is to provide a test which is sufficiently rigorous to detect lots with different release performance and yet not incur an undue regulatory burden.

Sponsor's Response:

The Sponsor will heed the advise of the reviewer and will revise the specification for the dissolution method. The new specification will be a Q value of % in minutes. We have revised the following test methods and have included them for review:

Attachment #2 contains the revised method for single point UV dissolution for doxycycline in doxycycline hyclate capsules (20 mg).

Attachment #3 contains the revised method the UV dissolution profile for doxycycline in doxycycline hyclate capsules.

Attachment #4 contains the revised bulk product specifications.

We trust that this adequately responds to the requests for information. If you have any questions regarding this submission, please contact the undersigned at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Director, Drug Development
& Regulatory Affairs

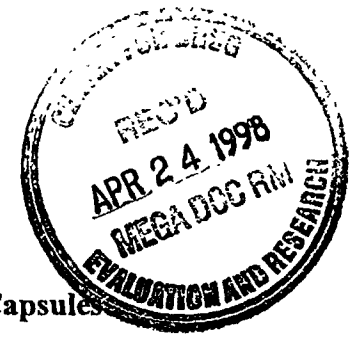
COLLAGENEX
pharmaceuticals

BS

Archive Copy ORIG AMENDMEN

April 23, 1998 ORIGIN

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857



RE: NDA 50-744 - Periostat™ (doxycycline hyclate, USP) 20 mg Capsules
Response to Request for Information - Minor Amendment

Dear Dr. Wilkin:

Please refer to NDA 50-744 for Periostat™ (doxycycline hyclate, USP) 20 mg capsules which is proposed for use as an adjunct to supra- and sub-gingival scaling and root planing to promote and maintain attachment level gain and to reduce pocket depth in patients with adult periodontitis.

Additional reference is made to the Division's facsimile of April 15, 1998 which requested an analysis of attachment level, pocket depth and bleeding on probing from the Study H data.

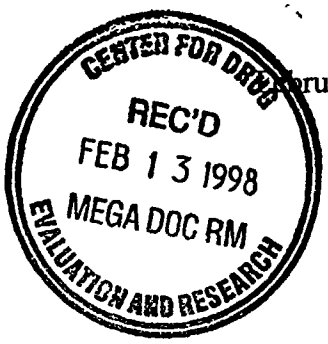
Submitted herewith is the response to this request. Attachment #1 contains the summary tables of the analysis of attachment level, pocket depth, and bleeding on probing. Attachment #2 contains the Proc. Contents of the data file, and Attachment #3 contains the diskette (review copy only). The diskette contains a zipped file. Instructions for unzipping are on the diskette under the file name of "zipfile.zip." To unzip the file, type "pkunzip zipfile" at the DOS prompt.

I trust that this adequately responds to the biostatistician's request. If you have any questions regarding this matter, please contact the undersigned at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Director, Drug Development
& Regulatory Affairs

COLLAGENEX
pharmaceuticals



February 10, 1998

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic & Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857

ORIGINAL

RE: NDA 50-744 - Periostat® (doxycycline hyclate, USP) 20 mg Capsules
Submission of Study 5732.11H Abbreviated Report

Dear Dr. Wilkin:

Please refer to NDA 50-744 for Periostat® (doxycycline hyclate, USP) 20 mg capsules which is proposed for use as part of a professional oral health program to promote clinical attachment level gain and reduce pocket depth and bleeding on probing in patients with adult periodontitis.

Submitted herewith, in triplicate, is an abbreviated report for Study 5732.11H titled: "A 9-Month, Multicenter, Double-Blind, Placebo-Controlled Trial Evaluating the Effect of Periostat® (20 mg doxycycline hyclate, capsules) BID in Conjunction with Scaling and Root Planing Versus Placebo BID in Conjunction with Scaling and Root Planing on Attachment Level and Pocket Depth in Patients with Adult Periodontitis."

We request that this report be incorporated as a portion of the above-referenced new drug application. If you have any questions regarding this submission, please contact the undersigned at 215-579-7388, ext. 16 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala
Director, Drug Development
& Regulatory Affairs

CollaGenex Pharmaceuticals, Inc., 301 South State Street, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

COLLAGENEX
pharmaceuticals

NC

ORIGINAL

December 8, 1997

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857

Re: NDA 50-744 - Periostat® (doxycycline hyclate, USP) 20 mg Capsules
Copies of Presentation made at FDA 11/17/97

Dear Dr. Wilkin,

Please refer to our NDA 50-744 for Periostat® (doxycycline hyclate, U.S.P.) 20 mg capsules which is proposed for use as part of a professional oral health program to promote periodontal attachment level gain and reduce pocket depth and bleeding on probing in patients with adult periodontitis.

Additional reference is made to our meeting of November 17, 1997 at which time, Dr. Roy Blay, CSO, requested that we provide a copy of the overheads used in the sponsor's presentation. Provided herewith are copies of the above-mentioned overheads.

If you have any questions regarding this matter, please do not hesitate to contact me at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala

Christopher Powala
Director Drug Development
& Regulatory Affairs

CollaGenex Pharmaceuticals, Inc., 301 South State Street, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

COLLAGENEX
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ORIGINAL

March 24, 1997

Dr. Joseph Vidra, Chemistry Reviewer
Division of Dematologic and
Dental Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857

BC
ORIG AMENDMENT

RE: NDA 50-744 - Periostat® (doxycycline hyclate, USP) 20 mg Capsules
Environmental Assessment - SBA Preparation

Dear Dr. Vidra:

Per your request, I am providing you with a redacted copy of the Environmental Assessment for Periostat® (NDA 50-744) for inclusion in the Summary Basis for Approval. Material contained in the Assessment which CollaGenex considers confidential has been covered by black ink or stamped "Confidential."

If you have any questions regarding this matter, please contact the undersigned at 215-579-7619 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala

Christopher Powala
Director, Drug Development
& Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

REC'D
MAR 2 5 1997
HFD-
EVALUATION AND RESEARCH

Desk Copy (cover letter only): Dr. Hal Blatt, CSO, HFD-540

CollaGenex Pharmaceuticals, Inc., 301 South State Street, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

COLLAGENEX
pharmaceuticals

November 19, 1996

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental
Drug Products (HFD-540)
Food and Drug Administration
9201 Corporate Drive
Rockville, MD 20857

RE: NDA 50-744
Periostat™ (doxycycline hyclate, USP) 20 mg Capsules
Minor Amendment

Dear Dr. Wilkin:

Please refer to our NDA 50-744 for Periostat™ (doxycycline hyclate, USP) 20 mg Capsules which is proposed for use as part of a professional oral health program to promote periodontal attachment level gain and reduce bone loss, pocket depth and bleeding on probing in patients with adult periodontal disease.

Further reference is made to an October 31, 1996 telephone conversation between Dr. Hal Blatt, Project Manager, HFD-540 and Christopher Powala, CollaGenex. During this conversation, CollaGenex was asked to submit the safety and laboratory analysis files in either SAS 6.8 or 6.11. In response to Dr. Blatt's request, we are providing herewith, 5 diskettes containing the safety and laboratory analysis files. We are also providing a table of contents for each file which describes each variable.

If you have any questions regarding this submission, please contact the undersigned at 215-579-7619 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala

Christopher Powala
Director, Drug Development
& Regulatory Affairs

desk copy: Dr. Hal Blatt, HFD-540 (letter only)
Mr. Kevin Daryl White, HFD-540 (letter only)

CollaGenex Pharmaceuticals, Inc., 301 South State Street, Newtown, PA 18940 USA
215-579-7388 215-579-8577

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

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

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: March 31, 1990.
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314).

NAME OF APPLICANT
CollaGenex Pharmaceuticals, Inc.

DATE OF SUBMISSION
11/19/96

TELEPHONE NO. (Include Area Code)
(215) 579-7619

ADDRESS (Number, Street, City, State and Zip Code)
301 South State Street
Newtown, PA 18940

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
50-744

DRUG PRODUCT

ESTABLISHED NAME (e.g., USP/USAN)	PROPRIETARY NAME (If any)
doxycycline hyclate capsules USP	**Periostat™**

CODE NAME (If any)	CHEMICAL NAME
	4-(Dimethlamino)-1,4,4a,5,5a,6,11,12a-octahydo-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
capsule	**oral**	**20mg**

PROPOSED INDICATIONS FOR USE

Treatment of adult periodontitis

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21CFR 314.420) REFERRED TO IN THIS APPLICATION:

IND
IND
AADA 62-374
AADA 62-839

INFORMATION ON APPLICATION

TYPE OF APPLICATION (Check one)

☒ THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION (Check one)

☐ PRESUBMISSION ORIGINAL APPLICATION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ SUPPLEMENTAL APPLICATION

PROPOSED MARKETING STATUS (Check one)

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx) ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

CONTENTS OF APPLICATION

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

	1. Index
	2. Summary (21 CFR 314.50 (c))
	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
▨	c. Labeling (21 CFR 314.50 (e) (2) (ii))
	i. draft labeling *(4 copies)*
	ii. final printed labeling (12 copies)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
	12. Case reports forms (21 CFR 314.50 (f) (1))
	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))
X	15. OTHER *(Specify)* Minor Amendment: Safety Analysis File on Diskette

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81
6. 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.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Christopher V. Powala Director, Drug Development & Regulatory Affairs	Christopher V. Powala	11/19/96

ADDRESS *(Street, City, State, Zip Code)*	TELEPHONE NO *(Include Area Code)*
CollaGenex Pharmaceuticals, Inc. 301 S. State Street, Newtown, PA 18940	(215) 579-7619

(WARNING: A willfully false statement is a criminal offense U.S.C. Title 18, Sec. 1001.)

COLLAGENEX
pharmaceuticals

June 6, 1996

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and
Dental Drug Products (HFD-540)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Wilkin:

The United States Federal Food, Drug and Cosmetic Act contains a requirement that sponsors of new drugs report to the U.S. Food and Drug Administration (FDA) whether they utilized the services of any person or firm in connection with the development or submission of an abbreviated new drug application or antibiotic application that has itself been debarred by FDA or whose employees involved with the application have been debarred by FDA or convicted of certain acts. CollaGenex, Inc. is providing the following information:

1. CollaGenex is not currently, nor has it ever been, debarred by FDA.

2 CollaGenex is not currently, nor has it ever been, involved in a debarment proceeding with FDA.

3. CollaGenex has not within the past five years, nor has it ever, been convicted of a felony under U.S. federal law for conduct relating to the development or approval, including the process for development or approval, of any abbreviated antibiotic drug applications (ANDA) or abbreviated antibiotic drug applications (AADA) or convicted of a conspiracy or accessory to do the same.

4. CollaGenex has not within the past five years, nor has it ever, been convicted of a misdemeanor under U.S. federal law or a felony under state law for conduct relating to development or approval, of any ANDA or AADA or convicted of a conspiracy or accessory to do same.

5. No employee of CollaGenex who worked on NDA . or data to support any premarket approval application is currently, or ever been, debarred by FDA.

6. No employee of CollaGenex who worked on an application or data to support NDA is currently, or ever has been, involved in a debarment proceeding with FDA.

CollaGenex Pharmaceuticals, Inc., 301 South State Street, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

7. No employee of CollaGenex who worked on an application or data to support NDA has in the past five years, or ever, been convicted of any of the following acts:

(I) a felony relating to the development or approval, including the process for development or approval, of any drug product or to any act relating to the regulation of any drug product under the U.S. Federal Food, Drug and Cosmetic Act, or a conspiracy to commit or an accessory in such a felony;

(II) a misdemeanor under U.S. federal law or a felony under U.S. state law relating to the development or approval, of any drug product or to any act relating to the regulation of drug products under the Food, Drug and Cosmetic Act, or a conspiracy or accessory to commit the forgoing or a felony under U.S. federal law relating to the same;

(III) a felony under either federal or state law (U.S.) which involved: bribery, payment of illegal gratuities, fraud, perjury, false statement, racketeering, blackmail, extortion, falsification or destruction of records, or interference with, obstruction of an investigation into, or prosecution of, any criminal offense or a conspiracy or accessory to do the same.

Certified and attested to this 6th Day of June, 1996, by:

Christopher Powala

Mr. Christopher Powala
Director, Drug Development
& Regulatory Affairs

NDA 20-642
Periostat™ (doxycycline hyclate)
Debarment Statement

CollaGenex, Inc. hereby certifies that at no time did it utilize the services of any person or firm that has been debarred under subsections (a) or (b) [section 306 (a) or (b)] of the Federal Food, Drug and Cosmetic Act, in connection with this new drug application

The following contract research organizations were employed by CollaGenex during the development of Periostat™ and are accompanied by a letter of certification reporting their position of good standing: