

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
50-783**

Administrative Documents

NDA 50-783
Periostat® (doxycycline hyclate tablets), 20 mg
Certifications and Commitments

PATENT INFORMATION AND CERTIFICATION

Please see approved NDA 50-744 for Periostat® (doxycycline hyclate capsules), 20 mg for patent information and certification (volume 2.1, page 1-0221).

**APPEARS THIS WAY
ON ORIGINAL**

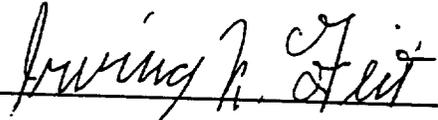
NDA 20-642
Periostat™ (Doxycycline hyclate capsules USP)
Section 14

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

In the opinion and to the best knowledge of CollaGenex Pharmaceuticals, Inc., there are 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™ (doxycycline hyclate capsules USP)
Section 13 - Patent Information

PATENT INFORMATION

A copy of the licencing agreements between CollaGenex Pharmaceuticals, Inc., Johnson and Johnson Consumer Products, Inc., and Research Foundation of State University of New York are attached. These documents provide CollaGenex Pharmaceuticals with rights to the patents.

This is followed by the Patent Information as required under 21CFR 314.53 (c).

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NDA 20-642
Periostat™ (Doxycycline 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

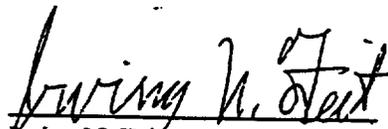
DECLARATION

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™ (Doxycycline 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

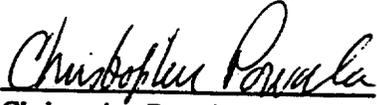
Type of Patent: Method of Use

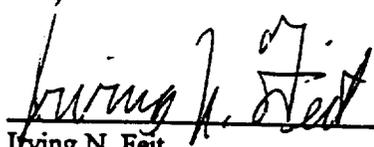
Name of Patent Owner: The Research Foundation of State University of New York

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

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

U.S. Patent: 4,704,383

Effective Filing Date: December 29, 1983

Effective Issue Date: November 3, 1987

Expiration Date: November 3, 2004

Type of Patent: Method of Use

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

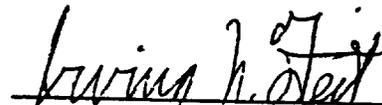
DECLARATION

In accordance with 21 C.F.R. 314.53(c) the undersigned declares that Patent No. 4,704,383 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
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NDA 20-642
Periostat™ (Doxycycline 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

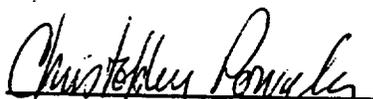
Type of Patent: Method of Use

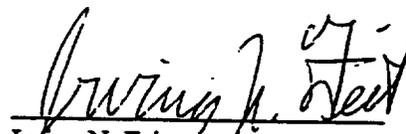
Name of Patent Owner: The Research Foundation of State University of New York

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

39

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EXCLUSIVITY SUMMARY for NDA # 50-783 SUPPL # _____
Trade Name: Periostat® 20 mg Generic Name: doxycycline hyclate tablets
Applicant Name Collagenex Pharmaceuticals, Inc. HFD- 540
Approval Date 2/2/01

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES / / NO / /

b) Is it an effectiveness supplement? YES / / NO / /

If yes, what type (SE1, SE2, etc.)? _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The Applicant submitted the referenced bioavailability /bioequivalence study in support of this NDA requesting approval for this formulation change.

d) Did the applicant request exclusivity?

YES / / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / / NO / /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 50-744, Periostat (doxycycline hyclate capsules) 20 mg

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /_X_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

- (c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- (a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")
- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?
- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

- (a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

- (b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?
- (c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / / NO / /

[*S. A.*]

Signature of Preparer
Title: Project Manager

1/29/01
Date

[*[Signature]*]
Signature of Office or Division Director

2/1/01
Date

cc:
Archival NDA
HFD-540/Division File HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi HFD-540/Cross

Form OGD-011347/Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

FDA Links Tracking Links Calendars Check Lists Searches Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements) [View Word Document](#)

NDA Number: 050783 **Trade Name:** PERIOSTAT (DOXYCYCLINE HYCLATE)20MG TABS
Supplement Number: 000 **Generic Name:** DOXYCLINE HYCLATE
Supplement Type: N **Dosage Form:**
Regulatory Action: OP **COMIS Indication:** TREATMENT OF ADULT PERIODONTITIS
Action Date: 4/3/00
Indication # 1 An adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis
Label Adequacy: Does Not Apply
Formulation Needed: NEW FORMULATION developed with this submission
Comments (if any):

	<u>Lower Range</u>	<u>Upper Range</u>	<u>Status</u>	<u>Date</u>
18 years	Adult	Completed	1/24/01	
0 years	17 years	Waived	1/24/01	

Comments: Adult periodontitis does not occur in children.

This page was last edited on 1/24/01

[Signature

1/24/01
Date

[S/] 1/24/01

[S/] 2/1/01

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Edit Pediatric Information for Submission N050783 - N/000

Indication

An adjunct to scaling and root planing to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis

Adequacy of Proposed label: Does Not Apply

Formulation Status: NEW FORMULATION developed with this submission

Decision Date: 2001-01-23 00:00

Comments & Recommendations (please date):

Related Applications:

Enter Pediatric Ranges Below

Application Range	Current Status/Due Date	Final Status/Action Date
Min. <input type="text" value="18"/> Max. <input type="text" value="Adult"/> <input type="checkbox"/> kg <input type="checkbox"/> mo. <input checked="" type="checkbox"/> yr. <input type="checkbox"/> kg <input type="checkbox"/> mo. <input type="checkbox"/> yr.	Status: <input type="text" value="Completed"/> Due Date: <input type="text" value="2001-01-24"/>	Status: <input type="text" value="Completed"/> Action Date: <input type="text" value="2001-01-24"/>
Reasons for Waivers and Deferrals/Comments:		
Min. <input type="text" value="0"/> Max. <input type="text" value="17"/> <input type="checkbox"/> kg <input type="checkbox"/> mo. <input checked="" type="checkbox"/> yr. <input type="checkbox"/> kg <input type="checkbox"/> mo. <input checked="" type="checkbox"/> yr.	Status: <input type="text" value="Waived"/> Due Date: <input type="text" value="2001-01-24"/>	Status: <input type="text" value="Waived"/> Action Date: <input type="text" value="2001-01-24"/>
Reasons for Waivers and Deferrals/Comments:		
Adult periodontitis does not occur in children.		

DEBARMENT CERTIFICATE

ICON Clinical Research certifies that to the knowledge of ICON, H. Wayne Hutman, M.D. is not debarred, and that it did not and will not use in any capacity the services of any individual, partnership, corporation or association debarred under subsections (a) or (b) of the Section 306 of the Federal Food, Drug and Cosmetic Act with respect to Clinical services in connection with the following:

5732.11K: A Randomized, Single-Dose, Three-Treatment, Three Period, Six-Sequence Crossover Study to Assess the Effects of Food on the Pharmacokinetics of Periostat® (doxycycline hyclate) 20mg Tablets and to Assess the Bioequivalence of Doxycycline Hyclate 20mg Capsules Compared to Doxycycline Hyclate 20mg Tablets.

By: *Diane Carter*

Title: *QA Auditor II*

Date: *16 Feb 2000*

By: *Joan L Sandberg*

Title: *Clinical Project Manager*

Date: *16 Feb 2000*



PHARMACEUTICAL MANUFACTURING RESEARCH SERVICES, INC.

Certification of Compliance with Generic Drug Enforcement Act of 1992

Pursuant to Section 306(k) of the Federal (U.S.) Food, Drug and Cosmetic Act, as amended by the Generic Drug Enforcement Act of 1992, Pharmaceutical Manufacturing Research Services, Inc. hereby certifies that it will not use, in any capacity, the services of any person debarred under subsections (a) and (b) of the Generic Drug Enforcement Act of 1992.

Pharmaceutical Manufacturing Research Services, Inc. further certifies that, during the previous five years, it has not sustained a conviction that is described under subsections (a) and (b) of the Generic Drug Enforcement Act of 1992. In addition, to the best of our knowledge, no person affiliated with Pharmaceutical Manufacturing Research Services, Inc. has been convicted of an offense described under subsections (a) and (b) of the Generic Drug Enforcement Act of 1992.

Signature: 
Title: Director, Quality Management
Date: 2/14/2000

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**CERTIFICATION: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

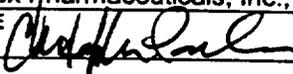
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purpose of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	H. Wayne Hutman, MD Medical Director South Florida Bioavailability Clinic, Inc.	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Christopher Powala	TITLE Senior Director, Drug Development & Regulatory Affairs
FIRM/ORGANIZATION CollaGenex Pharmaceuticals, Inc., 41 University Drive, Newton, PA 18940	
SIGNATURE 	DATE 3/22/00

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, Maryland 20857



March 31, 2000

User Fee Remittance
Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

Dear Sir/Madame:

Enclosed, please find a completed Form FDA 3397 and Check No. [redacted] in the amount of \$142,870.00 to support the review of NDA 50-783 (which does not require clinical data). Be advised that NDA 50-783 was filed with the Division of Dermatologic and Dental Drug Products (HFD-540) on this date. The User Fee I.D. Number is 3924.

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

Sincerely,

A handwritten signature in black ink, appearing to read "Christopher Powala".

Christopher Powala
Sr. Director, Drug Development
& Regulatory Affairs

Desk Copy: CDR. Frank Cross, Project Manager, HFD-540

Meeting Date: October 26, 1999
Meeting ID# 4819

Time: 1000

Location: N225

IND Periostat® (doxycycline hyclate USP) 20 mg, Capsules

Indication: Periodontitis

Sponsor: Collagenex Pharmaceuticals

Pre-IND/End of Phase 2 Meeting

Meeting Chair: Jonathan K. Wilkin, M.D.

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., CDR, Project Manager

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-830
Dennis Bashaw, Pharm.D., Biopharmaceutics Team Leader, DPEIII, HFD-880
Tapash Ghosh, Ph.D., Biopharmaceutist, DPEIII, HFD-880
John V. Kelsey, D.D.S., M.B.A., Dental Team Leader, DDDDP, HFD-540
Clarence Gilkes, D.D.S., Dental Reviewer, DDDDP, HFD-540
Fred Hyman, D.D.S., M.P.H., Dental Reviewer, DDDDP, HFD-540
R. Srinivasan, Ph.D., Biostatistics Team Leader, DOBIV, HFD-725
Shahla Farr, Ph.D., Biostatistician, DOBIV, HFD-725
Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

Christopher Powala, Director, Drug Development, Regulatory Affairs, CGPI
Christopher Phillips, Director of Manufacturing, CGPI

Patrick McNally, Director, Quality Management, Pharmaceutical Manufacturing Research Services, Inc.

Meeting Objectives:

Pre-IND/End of Phase 2 Meeting

With reference to the Meeting Request/Briefing Package, submitted August 26, 1999, the following discussion took place:

Divisional Comments:

1. The Sponsor is requested to submit the proposed Biopharmaceutic's study to a separate IND.
2. The Sponsor can submit this application as a 505(b)(1) application or submit a suitability petition for this application to be granted ANDA status. In addition, the Sponsor is advised that exclusivity may not be granted for the new Periostat formulation.

Sponsor: The Sponsor intends to submit this application as a 505(b)(1) application.

3. Does the Sponsor intend to co-market this new tablet formulation with the approved capsule formulation?

Sponsor: The Sponsor will withdraw NDA 50-744, Periostat (doxycycline hyclate USP) 20 mg, Capsules, upon approval of this new Periostat tablet formulation.

5. The Sponsor should request a Pediatric Waiver Request in accordance with 21CFR 314.55(c).

6. For applications submitted after February 2, 1999, per 21CFR 54.3 and 21CFR 54.4, an NDA applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests.

7. If the Sponsor has an Information for Patients leaflet/labeling, please submit it with the proposed NDA.

Chemistry, Manufacturing and Controls:

1. The Sponsor was advised that the proposed submission should be submitted as an original NDA.

2. Sponsor's Discussion Point #1 from the August 26, 1999, Meeting Briefing Package:

a. "Collagenex intends to market Periostat Tablets in the following container closure systems":

Agency:

The Sponsor should provide general container closure description, or if the same as the container closure system used in NDA 50-744, a reference to that NDA and a description of the [redacted]

b. Collagenex will be requesting — year expiration date based upon statistical projections. . .":

Agency:

A — year expiration date cannot be approved based upon three months stability data conducted at — and — on three commercial scale batches. If the three-month stability data were submitted, reviewed and found acceptable, the expiration date would only be — months.

Addendum:

The proposal to submit — months of data from one pilot batch of the Periostat Tablets and — months data from three commercial scale validation batches falls short of what was submitted with NDA 50-744. If this limited amount of data is deemed acceptable for filing, and if it is then updated with the — and — month results during review (i.e., at approximately — and — months post-submission), then the maximum expiry dating that could be accepted would be — months.

The filing and review standards will be the same for the proposed application as for the approved application.

c. "Does the reviewer agree with the proposed stability protocol?"

Agency:

Both long-term () and accelerated () proposed conditions appear to be acceptable, however, additional product quality tests for a tablet formulation should be added. The additional tests should include: hardness testing, color, odor and friability/brittleness.

2. Additional Comments:

The components and composition of the new drug product, the PERIOSTAT Tablet, should be provided.

Specifications for the new drug product should be provided.

3. Sponsor's Discussion Point #2 from the August 26, 1999, Meeting Briefing Package:

"Does the reviewer have any comments regarding the table of contents/format of the supplement?"

Yes, in general the table of contents deals exclusively with the drug product. The following are several suggestions for additional data:

- a. Section 3.1 ??, Add a drug substance section here which references the original approved NDA 50-744 and updated Letters of Authorization from your bulk drug supplier(s).
- b. Section 3.2.4.1, A copy of the active ingredient's Certificate of Analysis (COA) should be included here.
- c. Section 3.2.4.2, Identify those inactive ingredients, or excipients, as either compendial (USP, NF, etc.) or non-compendial. If non-compendial, then the COA or a detailed description of each non-compendial excipient specification should be submitted.
- d. Section 3.2.7, Add Sampling Procedures to this section.
- e. Section 3.3.5, To include those analytical methods that pertain to the Identity and Assay of the drug substance (DS), and its impurities, and for the assay procedure for the drug product and its impurities.

Pharmacology/Toxicology:

The proposed NDA submission should include a risk-benefit assessment of the proposed use of each excipient, including discussion, supported by data as appropriate, of the toxicology of each excipient. Published articles, compliance with official compendia, and marketing history may be adequate to qualify the excipients.

Biopharmaceutics:

The protocol as designed will address the impact of food on the Periostat dosage form and thus fulfill the Agency Biopharmaceutic's Phase 4 request for NDA 50-744. As for the new tablet dosage form, the protocol, as designed will address the degree of bioequivalency between the tablet and capsule dosage form. In regards to this new dosage form, the need for an in vivo food effect study will be dependent upon the results of this current study and the products in vitro performance (see pages 2-3 of the DRAFT Food-Effect Bioavailability and Bioequivalence Studies Guidance (Issued October 1997)).

Provided that the new Periostat tablet will replace the capsule on the marketplace and not be a co-marketing of products (except during a changeover period), then the Sponsor should re-design their study to investigate the food-fed performance of the tablet dosage form. In this situation the FDA would release the Sponsor from their previous phase IV commitment related to the capsule as the capsule would no longer be in the marketplace.

Clinical:

The proposed labeling for the new tablet formulation should be identical to the approved labeling, except for the description of the dosage form.

Biostatistics:

No comments.

Decisions (agreements) reached:

Unresolved issues or issues requiring further discussion:

None.

Signature, minutes preparer: [Signature]

Concurrence Chair (or designated signatory): [Signature]

Handout: Briefing Package, dated August 26, 1999

cc:

- IND [redacted] Division File
- HFD-105/OFFICE DIR/DeLap
- HFD-540 HFD-540/DIV DIR/Wilkin
- HFD-540/CHEM TL/DeCamp/10.26.99
- HFD-540/CHEM/Vidra
- HFD-540/PHARM TOX TL/Jacobs/10.26.99
- HFD-540/PHARM TOX/See/10.26.99
- HFD-880/BIOPHARM TL/Bashaw/10.26.99
- HFD-880/BIOPHARM/Ghosh/10.26.99
- HFD-540/DENTAL TL/Kelsey/10.26.99
- HFD-540/DO/Gilkes/10.26.99
- HFD-540/DO/Hyman
- HFD-725/BIOSTAT TL/Srinivasan/10.26.99
- HFD-725/BIOSTAT/Farr/10.26.99
- HFD-540/PM/Cross
- Drafted by: fhc/October 26, 1999
- c: \word\dental\ind [redacted] op2mina.doc
- Initialed by:
- final:

MEMORANDUM OF MEETING