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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: November 23, 1999 Number of Pages (including cover sheet) - 5

TO: Christopher Powala, Director, Drug Development, Regulatory Affairs
COMPANY: Collagenex Pharmaceuticals, Inc.
FAX #: 215-579-1062

MESSAGE: Please find attached to this facsimile transmission, minutes of our October 26, 1999, pre-IND/End of Phase 2 Meeting concerning IND []

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
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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