CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-805

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PATENT INFORMATION UNDER 21 CFR 314.53(c)

US Patent:	5,789,395
Effective Filing Date	August 30, 1996
Effective Issue Date:	August 4, 1998
Expiration Date:	August 30, 2016
Type of Patent:	Method of Use
Patent Owner:	The Research Foundation of State University of New York

DECLARATION

In accordance with 21 CFR 314.53© the undersigned declares that Patent No. 5,789,395 covers the formulation, composition, and/or method of use of Oracea™. This product is the subject of this application for which approval is being sought.

Respectfully submitted,

Christopher Powala
Vice President, Drug Development
And Regulatory Affairs
CollaGenex Pharmaceuticals, Inc.
41 University Drive
Newtown, PA 18940

Irving N. Feit
Attorney for Patent Owner
Hoffmann & Baron
6900 Jericho Turnpike
Syoffet, NY 11791

PATENT INFORMATION

Patents Issued:

NDA 50-805 contains three (3) method of use patents for which the Sponsor certifies. These patents are:

Patent No. 5,789,395: Method of using tetracycline compounds for inhibition of endogenous nitric oxide production.

Patent No. 5,919,775: Method of inhibiting inducible nitric oxide synthase with tetracyclines.

Patent No. 6,015,804: Method of using tetracycline compounds to enhance interleukin-10 production.

A copy of the licensing agreement between CollaGenex Pharmaceuticals, Inc. and the Research Foundation of the State University of New York is attached. This document provides CollaGenex Pharmaceuticals with rights to the above referenced patents. This Agreement immediately follows this summary.

Patents Pending:

During the review period of NDA 50-805, the Sponsor anticipates that the following patents will be issued by the U.S. Patent and Trademark Office that will cover further the formulation and methods of use for Oracea™. The Sponsor will submit these patents as a minor amendment to this NDA within 30 days of the date of issuance as required by 21 CFR 314.53(d)(1). Those patents expected to issue during the NDA review period are:

Application Serial No. 10/117,709: Method of treating acne wherein the said acne is acne rosacea.

Application Serial No. 10/414,808: Method of simultaneously treating ocular rosacea and acne rosacea.

Application Serial No. 10/272,499: Use of tetracyclines and tetracycline derivatives to treat acne and telangiectasia.

Application Serial No. 10/474,240: Controlled delivery of tetracyclines and tetracycline derivatives.

Application Serial No. 10/819,620: Once daily formulations of doxycycline.

1.3.2 Patent Certification

The Sponsor certifies Patent Numbers 5,789,395; 5,919,775, and 6,015,804. Copies of the certifications follow.

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 50 - 805 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

HFD-540 **Trade and generic names/dosage form:** _____

Applicant: CollaGenex Pharmaceuticals, Inc. **Therapeutic Class:** 3S

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: **For the topical treatment of psoriasis vulgaris in adults aged 18 years and above**

Is there a full waiver for this indication (check one)?

X Yes: **Please proceed to Section A.**

No: **Please check all that apply:** ____**Partial Waiver** ___**Deferred** ___**Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☑ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	**kg**_____	**mo.** 0	**yr.** __	**Tanner Stage**_____
Max_____	**kg**_____	**mo.** 0	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- **Too few children with disease to study**
- **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other: Sponsor specified exact population to study.**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
  There are safety concerns
  Adult studies ready for approval
- ☐ **Formulation needed**

Other:
Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____ kg____ mo. 0 yr. 18 Tanner Stage____
Max____ kg____ mo. 0 yr. 90 Tanner Stage____

Comments: 18 years and above

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Shalini Jain, PA-C
Regulatory Project Manager

cc: NDA
HFD-960/Grace Carmouze
(revised 12-22-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

COLLAGENEX
pharmaceuticals

September 8, 2005

Jonathan K. Wilkin, M.D., Director
Division of Dermatological & Dental Drug Products
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 50-805
Oracea™ (doxycycline [redacted] Capsules) 40mg
Minor Amendment: Addendum to Debarment Statement

Dear Dr. Wilkin:

Please refer to NDA 50-805 for Oracea™ (doxycycline [redacted] capsules) 40mg which is proposed for use as a treatment [redacted] inflammatory lesions in patients with rosacea.

Additional reference is made to the debarment statement contained in Module 1, Volume 1.1, Section 1.3.3. CollaGenex is providing herewith an addendum to the debarment statement:

Debarment Statement: Addendum:

In accord with the Food, Drug and Cosmetic Act, section 306(k)(1) CollaGenex Pharmaceuticals, Inc. further certifies, by signature below, that it did not and will not use in any capacity, the services of any person debarred under section 306 of the Food, Drug and Cosmetic Act in connection with the above-referenced new drug application.

Certified and attested to this 8th Day of September, 2005, by:

Christopher Powala
Vice President, Drug Development
& Regulatory Affairs

Desk Copy: Shalini Jain, PA-C, HFD-540

CollaGenex Pharmaceuticals, Inc., 41 University Drive, Suite 200, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

COLLAGENEX
pharmaceuticals

June 30, 2005

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

RE: NDA 50-805
Oracea™ (doxycycline [redacted] capsules) 40mg

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 utilize 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 Pharmaceuticals, 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 5 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 5 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 accessory to do the same;

5. No employee of CollaGenex who worked on NDA 50-805 or data to support any pre-market approval application is currently, or ever been, debarred by FDA;

CollaGenex Pharmaceuticals, Inc., 41 University Drive, Suite 200, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

6. No employee of CollaGenex who worked on an application or data to support NDA 50-805 is currently, or was ever involved in a debarment proceeding with FDA.

7. No employee of CollaGenex who worked the application or data to support NDA 50-805 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 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 30 Day of June, 2005, by:

Christopher Powala
Vice President, Drug Development
& Regulatory Affairs

Jonathan K. Wilkin, M.D
NDA 50-805
Debarment Statement

June 30, 2005

CollaGenex Pharmaceuticals, Inc. hereby certifies, to the best of its knowledge, that at no time did it utilize the services of any person, clinical investigator, or firm that has been debarred under the Federal Food, Drug and Cosmetic Act, in connection with this new drug application (NDA 50-805).

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

1. [redacted]

   [redacted] provided the following services: clinical monitoring, safety surveillance and AE reporting, statistical development, report writing, quality assurance and GCP auditing. A letter of certification is provided in Attachment 1.

2. [redacted]

   [redacted] provided clinical laboratory services used to generate lab data in the pharmacokinetic and clinical trials provided in NDA 50-805. A letter of certification is provided in Attachment 2.

3. [redacted]

   [redacted] provided the drug substance. [redacted] will be the supplier of doxycycline monohydrate to be used in the manufacture of the commercial batches. A letter of certification is provided in Attachment 3.

4. **Cardinal Health, 1100 Enterprise Drive, Winchester, KY 40391;** [redacted]

   Cardinal Winchester manufactures and release bulk drug product. Cardinal [redacted]

   A letter of certification from each facility is provided in Attachment 4.

5. [redacted]

   [redacted] provides packaging services for the final drug product. A letter of certification is provided in Attachment 5.

6. [redacted]

[redacted] prepared the environmental assessment/exclusion for the drug product. A letter of certification is provided in Attachment 6.

7. [redacted]

[redacted] assisted in the writing and assembly of the new drug application. A letter of certification is provided in Attachment 7.

Debarment Certification

This Certification Statement is provided for New Drug Application (NDA) 50-805, and is provided in compliance with the Generic Drug Enforcement Act of 1992.

[redacted] hereby certifies that we did not use in any capacity the services of any person debarred under section (a) or (b) of Section 306 of the federal Food, Drug and Cosmetic Act in connection with this application.

[redacted]

3 June 2005
Date

Debarment Certification

This Certification Statement is provided for the New Drug Application (NDA) of Oracea (COL 101).

[redacted] . hereby certifies that services of any person debarred under subsection (a) or (b) of Section 306 of the Federal Food, Drug and Cosmetic Act [21 U.S.C. Section 335 a(a)(b)] were not and will not be used in any capacity in connection with activities performed.

[redacted]

12 May 2005
Date

DEBARMENT STATMENT

We hereby declare that no ——— employee appears on the FDA Debarment List, furthermore ——— did not and will not use in capacity the services of any person debarred under subsections (a) or (b) [section 306 (a) or (b)] of the Generic Drug Enforcement Act of 1992.

Cardinal Health
1100 Enterprise Drive
Winchester, KY 40391
859.745.2200 tel
859.745.6636 fax

www.cardinal.com/pts

CardinalHealth

DEBARMENT CERTIFICATION AND CONVICTION STATEMENT

March 2, 2005

Philip Freidenreich, PhD
Director of Q A & Compliance
CollaGenex Pharmaceuticals, Inc.
41 University Drive, Suite 200
Newtown, PA 18940

Attn: Philip Freidenreich

This is to certify that Cardinal Health (formerly known as International Processing Corporation) has not used, and will not use in any capacity, the services of any person or firm debarred under sections 306(a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.

To the best of our knowledge there have been no convictions, for which a person could be debarred under sections 306(a) or (b) of the Act, within the previous 5 years of the applicant.

Sincerely,

G. Keith Arvin
Director, Quality Assurance
Cardinal Health

Cheryl L. Flack
Notary
State-at-Large
My commission Expires: November 21, 2006

[ ] [ ]

May 13, 2005

Philip Freidenreich
CollaGenex Pharmaceuticals, Inc.
41 University Drive
Suite 200
Newtown, PA 18940

Dear Phil,

This letter is in response to your request for information relative to FDA debarment. [redacted] does not employ individuals that have been debarred by the FDA under Sections 306 (a) or (b) of the Generic Enforcement Act of 1992.

Prior to employment, potential employees are required to complete a certification that states they have not been debarred under Sections 306 (a) or (b) of the Generic Enforcement Act of 1992.

Therefore, no one who has been debarred by the FDA under Sections 306 (a) or (b) of the Generic Enforcement Act of 1992 will be associated with any client project within [redacted].

If you need any additional information, please do not hesitate to contact me.

Sincerely,

[ ]

[redacted] [redacted]

CollaGenex
41 University Drive
Suite 200
Newtown, PA 18940

Subject: FDA Debarment List

March 2, 2005

Dear Philip Freidenreich, PhD, Director-Quality Assurance &Compliance,

There are no employees of
that appear on the FDA Debarment List.

Best Regards,

[redacted]

[ ]

March 2, 2005

Mr. Phillip Freidenreich
Director of Quality Assurance and Compliance
Collagenex Pharmaceuticals, Inc
41 University Drive, Suite 200
Newtown, PA 18940

Dear Mr. Freidenreich

RE: Debarment Certification

This is to certify that _____ does not employ any individual that is debarred. This certification is pursuant to sections 306(a) and (b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 335(a) and (b) as published in the Federal Register.

If there are any questions, or additional information required, please contact me at

Regards,

[ ]

June 23, 2005

Dr. Phil Freidenreich
CollaGenex Pharmaceuticals, Inc.
41 University Dr.
Suite 200
Newtown, PA 18940

Dear Dr. Freidenreich:

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 use the services of any company in connection with the development or submission of a new drug 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. To assist you in complying with this requirement, _____ is providing the following information:

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

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

3. _____ has not within the last 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 new drug applications (NDA) or abbreviated new drug applications (ANDA), or convicted of a conspiracy or accessory to do the same.

4. _____ has not within the last 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, or the process of the development or approval, of any NDA or ANDA or convicted of a conspiracy or accessory to do the same.

5. No employee of _____ who worked on the application or data to support any application for Collagenex Pharmaceutical, Inc. is currently, or ever been, debarred by FDA.

6. No employee of [redacted] who worked on an application or data to support an application for Collagenex Pharmaceutical, Inc. is currently, or ever been, involved in a debarment proceeding with FDA.

7. No employee of [redacted] who worked on an application or data to support an application for Collagenex Pharmaceutical, Inc. has in the past five years, or ever, been convicted of any of the following acts:

(1) 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 (FDCA), or a conspiracy to commit or an accessory in such a felony;

(2) 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 FDCA, or a conspiracy or accessory to commit the foregoing or a felony under U.S. federal law relating to the same;

(3) 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 23rd day of June, 2005, by:

[redacted]

June 15, 2005

Christopher Powala
Vice President
Drug Development & Regulatory Affairs
CollaGenex Pharmaceuticals, Inc.
41 University Drive, Suite 200
Newtown, PA 18940

Dear Mr. Powala:

On behalf of _____ . I hereby certify that the company itself, no employee of the company, and no subcontractor for the company has ever been debarred or involved in a debarment proceeding with the FDA.

Sincerely,

INDEPENDENT
INVESTIGATIONAL
REVIEW BOARD INC.
r Advocate for Clinical Research Participants

DATE: May 25, 2005

TO: Phil Freidenreich, Director
CollaGenex Pharmaceuticals, Inc.

FROM: Kim Lerner, Chairman
Independent Investigational Review Board, Inc.

SUBJECT: Confirmation of Principal Investigator Status

PROTOCOL: COL-101-ROSE-302

This memorandum is intended to provide verification that no Board Member or Administrative Staff of the Independent Investigational Review Board, Inc. has ever been listed on the FDA Debarment List. In addition, this verification, confirms that the IIRB reviewed and approved the following sites related to the above noted study.

Principal Investigator	Approval Date
Robert Martin, MD	6/10/04
Leonard Swinyer, MD	6/10/04
Michael Gold, MD	6/10/04
Peter Cooperrider, MD	6/10/04
Mitchel P. Goldman, MD	6/10/04
Richard White, MD	6/10/04
Helen Torok, MD	6/10/04
Mark Jackson, MD	6/10/04
Leslie Capin, MD	6/10/04
James Turner, MD	6/10/04
Harry Sharata, MD	6/10/04
Robert Skrokov, MD	7/13/04
Jame Q. Del Rosso, DO	8/17/04
Jo Lynne Herzog, M	8/17/04
Frank Dunlap, MD	8/17/04

If additional clarification is required, please let me know.

Thank you.

phone 954-327-0778 • fax 954-327-5778 • 6738 West Sunrise Blvd., Suite 102 • Plantation, FL 33313 • info@iirb.com (email) • www.iirb.com

17 May 2005

Philip Freidenreich, PhD
Senior Director, Quality Assurance and Compliance
CollaGenex Pharmaceuticals, Inc.
41 University Drive, Suite 200
Newtown, PA 18940

Re: Disbarment certification

Dear Philip:

To the best of our knowledge, _____ does not employ any individual who is debarred, pursuant to sections 306(a) and (b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 3335(a) and (b). Every employee must confirm during New Hire Orientation that they have not been debarred from the FDA.

If you have further questions, please contact us at one of the telephone numbers listed below.

Regards,

Copy:

COLLAGENEX
pharmaceuticals

May 25, 2006

Stanka Kukich, M.D., Director
Division of Dermatology & Dental
Drug Products
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: **NDA 50-905**
General Correspondence: Phase 4 Commitment

Dear Dr. Kukich:

In reference to our teleconference on this date, the Sponsor is providing a response to the Division's request for a Phase 4 commitment. The Division's request is reiterated and is followed by the Sponsor's response.

FDA Request:

A post-approval Medication Error Monitoring Program for the proprietary name, Oracea™. This program should consist of:

- **15-Day Reporting of all Medication Errors;**
- **Root Cause Analysis; and**
- **Trigger requiring a proprietary name change.**

Sponsor's Response:

CollaGenex Pharmaceuticals agrees to a Medication Error Monitoring Program for the proprietary name, Oracea™, consisting of the above three components. Specifically, the sponsor will report as if it were a "15 day report" any actual medication error, regardless of patient outcome. The sponsor will conduct a root cause analysis of any actual medication error and submit the analysis as a "follow-up" to the 15 day report.

CollaGenex Pharmaceuticals, Inc., 41 University Drive, Suite 200, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

Stanka Kukich, M.D., Director May 25, 2006
NDA 50-805
General Correspondence: Response to Request for Phase 4 Commitment

CollaGenex will promptly meet with the Division (a meeting request will be submitted asking for a Type A or earlier meeting within two business days of receipt of the approval letter) to discuss the circumstances that would trigger a name change. CollaGenex will propose its Phase IV commitment for the circumstances in which a name change will be triggered within two weeks of the meeting.

If there are any questions regarding this document, please contact the undersigned at 215-579-7388 (telephone) or 215-402-8577 (fax).

Sincerely,

Christopher Powala
Vice President, Drug Development
& Regulatory Affairs

DUPLICATE

COLLAGENEX
pharmaceuticals

May 23, 2006

Stanka Kukich, M.D., Director
Division of Dermatology and Dental
Drug Products
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 50-805
General Correspondence: Product and Dosage Form Name

Dear Dr. Kukich:

In preparation for our call on May 24, I thought it would be useful to explain our thinking about how the Oracea dosage form might be described in the label.

As we have discussed, our doxycycline product, tentatively named Oracea, is composed of 75% immediate release doxycycline beads and 25% [redacted] Because a portion of the product is [redacted], Oracea does not fit FDA's definitions of an immediate release product. The SUPAC-MR: Modified Release Solid Oral Dosage Forms guidance, for example, defines an immediate release product as one that "allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug." ORA's Laboratory Manual provides that immediate release capsules release the active ingredient "within a small period of time, typically less than 30-minutes." Oracea fits neither definition. In these circumstances, we believe that it would be misleading to state that Oracea is an immediate release product. If the drug description is silent as to the release characteristics, users will assume incorrectly that it is an immediate release product, inasmuch as it is FDA's usual practice to say nothing in the drug description when a product is immediate release. For this reason, silence also seems an inappropriate solution.

The best existing category for Oracea appears to be the "delayed release" category into which [redacted] products are generally placed. The term "Capsule: [redacted]" is generally described as [redacted] have been applied enclosed within a soluble container. (CDER Data Standards Manual attached). This is technically a correct description of Oracea.

Stanka Kukich, M.D., Director **May 23, 2006**
NDA 50-805
General Correspondence: Product and Dosage Form Name

If the delayed release terminology is not acceptable, we propose that a new term be identified to cover products that are partially immediate release and partially delayed release. In thinking about possibilities, we believe that " would be the most descriptive, but have also considered " or "

As we have discussed, this question is not just a technical labeling issue, but also a safety issue. Oracea was formulated to include a delayed release feature solely to ensure that it would not reach levels in the bloodstream that produces an antibiotic effect. At higher dosages, doxycycline is an antibiotic used to fight a variety of infections, including anthrax. Chronic use of doxycycline at antibiotic levels could contribute to antibiotic resistance. Physicians and pharmacists need to be informed of the delayed release feature and its purpose so that they do not assume that any non-bioequivalent immediate release dosage form can be used to treat rosacea. For this reason, we believe it important that the " feature be included in the name of the product and dosage form so it will be readily available to and seen by prescribers, dispensers, and patients alike.

We appreciate your consideration of this issue and look forward to discussing this further tomorrow.

Sincerely,

Christopher Powala
Vice President, Drug Development
& Regulatory Affairs

COLLAGENEX
pharmaceuticals

May 22, 2006

Stanka Kukich, M.D., Director
Division of Dermatology & Dental
Drug Products
Food and drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 50-805
Response to Request for Phase 4 Commitments

Dear Dr. Kukich:

Submitted herewith is the Sponsor's response to the Division's request for Phase 4 commitments. Each of the Division's requests is reiterated and is followed by the Sponsor's response.

FDA Request #1:

Submission of carcinogenicity study protocol and dose finding data: June 2007 Carcinogenicity study start date: August 2007 Submission of final carcinogenicity study report: February 2010.

Sponsor's Response:

The Sponsor agrees to this Phase 4 commitment.

FDA Request #2:

Conduct a properly designed human sperm motility and morphology study to evaluate the effects of long-term use of TRADENAME (doxycycline) 40mg on human sperm in male patients with rosacea. Study report submission within 2 years from date of approval.

Sponsor's Response:

The Sponsor agrees to this Phase 4 commitment.

FDA Request #3:

A study to examine longer term safety in at least 300 rosacea patients treated with TRADENAME (doxycycline) 40mg for at least 1 year. Study report submission within 2 years from date of approval.

Stanka Kukich, M.D.
NDA 50-805
Response to FDA Requested Phase 4 Commitments

May 22, 2006

Sponsor's Response:

Long-term exposure data has been collected in double-blinded, placebo-controlled studies on the 40mg doxycycline controlled release product as well as with a similar drug product with slightly higher plasma concentrations based on AUC_{0-24}.
This long-term safety data was provided to FDA in NDA 50-805. Though these data were collected in patients with adult periodontitis, this population, like those with rosacea, is relatively healthy and is of the same age range (≥ 30 years of age). The list below identifies the long-term data that currently resides with the Division:

Study No.	# Patients exposed to doxycycline only	Duration of Exposure	Reference
5732.11 E, F & G	119	12-18 months	NDA 50,744
5732.11 H	96	9 months	NDA 50,744
5732.11 J	107	9 months	NDA 50-783
DOXYMR-301	133	9 months	NDA 50-805
Total Patient Exposures	**455**	**9-18 months**	

Based on the 9-18 month exposure of 455 patients to doxycycline at the proposed dose, the Sponsor believes that it has satisfied the ICH recommendation for long-term safety. In addition, the outcome from these long-term, double-blinded, placebo-controlled trials demonstrated an adverse event profile similar to placebo and the current proposed product label more than represents the warnings, precautions and adverse event profile of the drug product.

Lastly, the Sponsor provided in the NDA, all post-marketing surveillance data captured from its marketed product, Periostat, which has similar, albeit slightly higher, drug exposure based on AUC. These spontaneously reported data were captured from a population prescribed more than 4 million prescriptions for long-term use. These data, like the data from the long-term, double-blinded, placebo-controlled clinical trials show that the product is safe for long term use as indicated. The Sponsor feels that long-term safety has been adequately demonstrated and more than meets the ICH recommendations. Therefore the Sponsor can not agree to this Phase 4 commitment.

If there are any questions regarding this document, please contact the undersigned at 215-579-7388 (telephone) or 215-402-1044 (fax).

Sincerely,

Christopher Powala
Vice President, Drug Development
& Regulatory Affairs

COLLAGENEX
pharmaceuticals

May 22, 2006

RECEIVED

DUPLICATE

MAY 23 2006

CDER CDR

Stanka Kukich, M.D., Director
Division of Dermatology & Dental
Drug Products
Food and drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 50-805
Response to Request for Phase 4 Commitments

NEW CORRESPONDENCE

N(C)

Dear Dr. Kukich:

Submitted herewith is the Sponsor's response to the Division's request for Phase 4 commitments. Each of the Division's requests is reiterated and is followed by the Sponsor's response.

FDA Request #1:

Submission of carcinogenicity study protocol and dose finding data: June 2007 Carcinogenicity study start date: August 2007 Submission of final carcinogenicity study report: February 2010.

Sponsor's Response:

The Sponsor agrees to this Phase 4 commitment.

FDA Request #2:

Conduct a properly designed human sperm motility and morphology study to evaluate the effects of long-term use of TRADENAME (doxycycline) 40mg on human sperm in male patients with rosacea. Study report submission within 2 years from date of approval.

Sponsor's Response:

The Sponsor agrees to this Phase 4 commitment.

FDA Request #3:

A study to examine longer term safety in at least 300 rosacea patients treated with TRADENAME (doxycycline) 40mg for at least 1 year. Study report submission within 2 years from date of approval.

Stanka Kukich, M.D.
NDA 50-805
Response to FDA Requested Phase 4 Commitments

May 22, 2006

Sponsor's Response:

Long-term exposure data has been collected in double-blinded, placebo-controlled studies on the 40mg doxycycline controlled release product as well as with a similar drug product with slightly higher plasma concentrations based on AUC_{0-24}.
This long-term safety data was provided to FDA in NDA 50-805. Though these data were collected in patients with adult periodontitis, this population, like those with rosacea, is relatively healthy and is of the same age range (≥ 30 years of age). The list below identifies the long-term data that currently resides with the Division:

Study No.	# Patients exposed to doxycycline only	Duration of Exposure	Reference
5732.11 E, F & G	119	12-18 months	NDA 50,744
5732.11 H	96	9 months	NDA 50,744
5732.11 J	107	9 months	NDA 50-783
DOXYMR-301	133	9 months	NDA 50-805
Total Patient Exposures	**455**	**9-18 months**	

Based on the 9-18 month exposure of 455 patients to doxycycline at the proposed dose, the Sponsor believes that it has satisfied the ICH recommendation for long-term safety. In addition, the outcome from these long-term, double-blinded, placebo-controlled trials demonstrated an adverse event profile similar to placebo and the current proposed product label more than represents the warnings, precautions and adverse event profile of the drug product.

Lastly, the Sponsor provided in the NDA, all post-marketing surveillance data captured from its marketed product, Periostat, which has similar, albeit slightly higher, drug exposure based on AUC. These spontaneously reported data were captured from a population prescribed more than 4 million prescriptions for long-term use. These data, like the data from the long-term, double-blinded, placebo-controlled clinical trials show that the product is safe for long term use as indicated. The Sponsor feels that long-term safety has been adequately demonstrated and more than meets the ICH recommendations. Therefore the Sponsor can not agree to this Phase 4 commitment.

If there are any questions regarding this document, please contact the undersigned at 215-579-7388 (telephone) or 215-402-1044 (fax).

Sincerely,

Christopher Powala
Vice President, Drug Development
& Regulatory Affairs

DUPLICATE

COLLAGENEX
pharmaceuticals

May 23, 2006

Stanka Kukich, M.D.
Director, Division of Dermatological & Dental Drug Products
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705

NEW CORRESPONDENCE
N000 C

Re: NDA 50-805
General Correspondence - ORACEA Trademark

Dear Dr. Kukich:

Reference is made to the May 22, 2006, 12:00 noon teleconference between the FDA and CollaGenex Pharmaceuticals, Inc. ("the Sponsor"). The FDA referred to the following trademarks which had been surfaced by DMETS as having potential for medication errors with ORACEA capsules, if the ORACEA trademark is approved.

- OMACOR (omega-3-acid ethyl esters) capsules
- ORASONE (prednisone) tablets
- ARAVA (leflunimide) tablets
- OVACE (sodium sulfacetamide 10%) foam and wash

The Sponsor continues to believe that the trademark ORACEA is appropriate and safe for use as proposed. Although the four trademarks cited by DMETS and the proposed trademark ORACEA may have some visual similarity, this is unlikely to result in confusion resulting in medication errors because of differences in indication, strength, dosage form, and appearance.

Please reference the General Correspondence: Oracea Trademark filed with the Division on April 17, 2006 in which the Sponsor described a review of three large data bases for actual medication errors resulting from confusion between OMACOR, ORASONE, ARAVA and OVACE. No such medication errors where discovered. The lack of any confusion and reported medication errors among the four products strongly suggests that due to differences in indication, strength, dosage form, appearance, and other reasons, the confusion on which DMETS speculates has not in fact occurred and would not occur with ORACEA capsules and any of the other four products.

This is a depiction of the Sponsor's product:

ORACEA capsules vs. OMACOR capsules

The Sponsor maintains the position that medication errors are not likely to occur due to confusion between ORACEA and OMACOR because:

- ORACEA would be available as a 40-mg hard gelatin capsule only; OMACOR is available as a 1-g transparent soft gelatin capsule.
- The daily dose of ORACEA is one 40-mg hard capsule. The daily dose of OMACOR is 4-g, taken as a single dose of 4 soft capsules or as two 1-g capsules twice a day.
- Though ORACEA and OMACOR both have only one strength, it is not likely that the prescriber will omit information about the dosing from the prescription. The prescriber of OMACOR would have to indicate on the prescription that four capsules should be taken each day, whether a single dose of 4 capsules or two 1-g capsules twice a day.
- ORACEA would be sold to the pharmacy in bottles of 30 capsules. OMACOR is sold to the pharmacy in bottles of 120 capsules.
- One month supply of ORACEA is 30 capsules; one month supply of OMACOR is 120 capsules.
- ORACEA capsules would be supplied as beige opaque hard gelatin capsules printed with "CGPI 40". OMACOR capsules are supplied as transparent soft gelatin capsules filled with light-yellow oil printed with "OMACOR".
- ORACEA and OMACOR are quite dissimilar phonetically.
- Patients receiving prescriptions for ORACEA would be likely to have received a sample of the product from the prescribing physician along with the prescription and therefore be able to recognize a difference.

ORACEA capsules vs. ORASONE tablets

No picture of ORASONE available.

The Sponsor maintains the position that medication errors are not likely to occur due to confusion between ORACEA and ORASONE because:

- According to the FDA website, ORASONE has been discontinued.
- According to Thomson & Thomson's SAEGIS database of products in use, ORASONE was discontinued in 2003.
- According to the IMS, the supplier of syndicated pharmacy data that is the industry standard:
    - Solvay Pharmaceuticals discontinued marketing ORASONE in 1998.
    - Sales of ORASONE were extremely low in 1998.
- The FDA approved an ANDA for ORASONE on 1/29/74 with three years dating. It is virtually impossible that any unexpired product remains in the pharmacy channel.
- ORACEA is available as a 40-mg capsule. ORASONE was supplied as 1-mg, 5-mg, 10-mg, 20-mg, and 50-mg tablets.
- Though the availability of a generic equivalent product, prednisone, allows for a pharmacist to dispense a prescription written for ORASONE, it is extremely unlikely that a prescriber would write ORASONE in 2006, as the product has not been marketed for eight years.
- Other versions of prednisone are available as 1-mg, 2.5-mg, 5-mg, 10-mg, 20-mg, 25-mg, and 50-mg tablets. There are no versions of prednisone available in a 40-mg

The Sponsor maintains the position that medication errors are not likely to occur due to confusion between ORACEA and OMACOR because:

- ORACEA would be available as a 40-mg hard gelatin capsule only; OMACOR is available as a 1-g transparent soft gelatin capsule.
- The daily dose of ORACEA is one 40-mg hard capsule. The daily dose of OMACOR is 4-g, taken as a single dose of 4 soft capsules or as two 1-g capsules twice a day.
- Though ORACEA and OMACOR both have only one strength, it is not likely that the prescriber will omit information about the dosing from the prescription. The prescriber of OMACOR would have to indicate on the prescription that four capsules should be taken each day, whether a single dose of 4 capsules or two 1-g capsules twice a day.
- ORACEA would be sold to the pharmacy in bottles of 30 capsules. OMACOR is sold to the pharmacy in bottles of 120 capsules.
- One month supply of ORACEA is 30 capsules; one month supply of OMACOR is 120 capsules.
- ORACEA capsules would be supplied as beige opaque hard gelatin capsules printed with "CGPI 40". OMACOR capsules are supplied as transparent soft gelatin capsules filled with light-yellow oil printed with "OMACOR".
- ORACEA and OMACOR are quite dissimilar phonetically.
- Patients receiving prescriptions for ORACEA would be likely to have received a sample of the product from the prescribing physician along with the prescription and therefore be able to recognize a difference.

ORACEA capsules vs. ORASONE tablets

No picture of ORASONE available.

The Sponsor maintains the position that medication errors are not likely to occur due to confusion between ORACEA and ORASONE because:

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- According to Thomson & Thomson's SAEGIS database of products in use, ORASONE was discontinued in 2003.
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    - Sales of ORASONE were extremely low in 1998.
- The FDA approved an ANDA for ORASONE on 1/29/74 with three years dating. It is virtually impossible that any unexpired product remains in the pharmacy channel.
- ORACEA is available as a 40-mg capsule. ORASONE was supplied as 1-mg, 5-mg, 10-mg, 20-mg, and 50-mg tablets.
- Though the availability of a generic equivalent product, prednisone, allows for a pharmacist to dispense a prescription written for ORASONE, it is extremely unlikely that a prescriber would write ORASONE in 2006, as the product has not been marketed for eight years.
- Other versions of prednisone are available as 1-mg, 2.5-mg, 5-mg, 10-mg, 20-mg, 25-mg, and 50-mg tablets. There are no versions of prednisone available in a 40-mg

strength. If a prescriber wished to write a prescription for 40 mg of ORASONE, the prescription would have to be written 2 x 20 mg tablets.
- ORACEA has six letters; ORASONE has seven letters. This contributes to a visual dissimilarity between the drug names.
- Patients receiving prescriptions for ORACEA would be likely to have received a sample of the product from the prescribing physician, along with the prescription and therefore be able to recognize a difference.

ORACEA capsules vs. ARAVA tablets

(actual size)

The Sponsor maintains the position that medication errors are not likely to occur due to confusion between ORACEA and ARAVA because:

- ORACEA would be available as a 40-mg capsule; ARAVA is available as 10 mg, 20 mg and 100 mg tablets.
- ARAVA requires a loading dose of one 100 mg per day for 3 days. The maintenance dose of ARAVA is 10 mg or 20 mg.
- ORACEA capsules would be printed with "CGPI 40"; ARAVA tablets are embossed with ZBN, ZBO, or ZBP.
- ORACEA and ARAVA are quite dissimilar phonetically.
- ORACEA has six letters; ARAVA has five letters. This contributes to a visual dissimilarity between the drug names.
- Patients receiving prescriptions for ORACEA would be likely to have received a sample of the product from the prescribing physician, along with the prescription and therefore be able to recognize a difference.

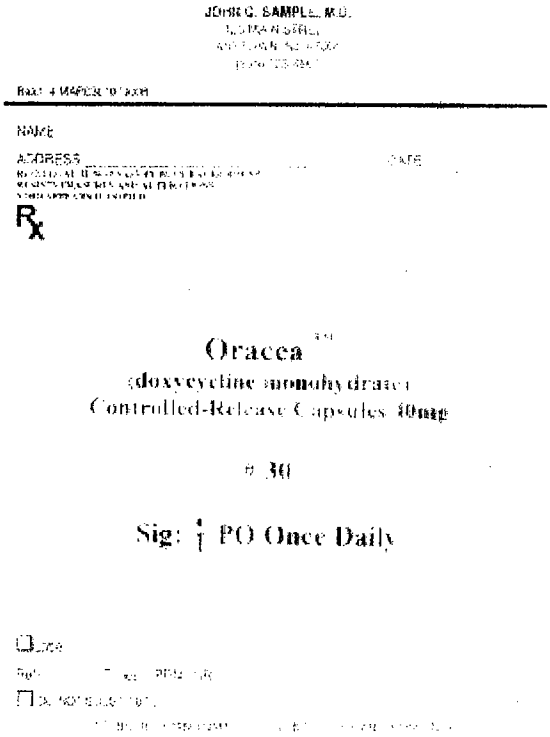
ORACEA capsules vs. OVACE foam or wash

The Sponsor maintains the position that medication errors are not likely to occur due to confusion between ORACEA and OVACE because:

- ORACEA would be available as a 40-mg capsule; OVACE is available as a topical wash in a bottle or a topical aerosol foam in a canister.
- ORACEA and OVACE are quite dissimilar phonetically.
- ORACEA has six letters; OVACE has five letters. This contributes to a visual dissimilarity between the trade names.
- Patients receiving prescriptions for ORACEA would be likely to have received a sample of the product from the prescribing physician, along with the prescription and therefore be able to recognize a difference.

The Sponsor will offer physicians the opportunity to receive pre-printed prescription pads for its product. When a physician requests pre-printed prescription pads, he or she will provide a voided prescription blank and complete an order form. The program is in compliance with all state and federal pharmacy regulations and is void in New York and South Dakota.

The pre-printed prescription pad program will further reduce the chance for medication errors. The product name is printed, rather than handwritten, reducing any potential problem related to legibility. A sample of a pre-printed prescription is attached here. The final version will reflect the FDA-approved nomenclature for the product, as well as the shaded background mandated by most states.


JOHN Q. SAMPLE, M.D.

NAME

ADDRESS DATE

℞

Oracea™

(doxycycline monohydrate)

Controlled-Release Capsules 40mg

30

Sig: 1 PO Once Daily

If there are any questions regarding this document, please contact the undersigned at 215-579-7388 (telephone) or 215-402-1044 (fax)

Sincerely

Christopher Powala
Vice President, Drug Development
& Regulatory Affairs

MEMORANDUM	Division of Medication Errors and Technical Support Office of Drug Safety WO 22, Mailstop 4447, HFD-420 Center for Drug Evaluation and Research

To: Stanka Kukich, MD
Director, Division of Dermatology and Dental Products
HFD-540

From: Kristina C. Arnwine, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Through: Linda Kim-Jung, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

Date: May 15, 2006

Subject: ODS Consult 06-0046-1, Oracea (Doxycycline [redacted] apsules) 40 mg, NDA 50-805

This memorandum is in response to a May 11, 2006 request from the Division of Dermatology and Dental Products (HFD-540) to reconsider the acceptability of the proprietary name Oracea based on the sponsor's rebuttal submission dated April 17, 2006. DMETS initially reviewed the proposed proprietary name, Oracea [redacted] in ODS Consult 05-0079 dated October 7, 2005 (attached to IND 65,733). DMETS did not recommend use of the name, Oracea [redacted] due to potential confusion with the use of the modifier [redacted] along with potential for sound-alike and/or look-alike confusion between the root name, "Oracea" and the currently marketed drug products: Arava, Omacor, Ovace, and Orasone. Subsequently, the sponsor submitted the root name, Oracea, without the modifier as the proposed proprietary name for this extended-release formulation. In ODS Consult 06-0046 dated March 28, 2006, DMETS did not recommend the used of the name, Oracea, due to the same safety concerns described in our previous consult (ODS Consult 05-0079) in regards to the root name, Oracea,.

A. Comment A – Look-alike and Sound-alike Concerns:

Although the four names and the proposed name might look alike, they are unlikely to result in confusion resulting in medical error because of differences in indication, strength, dosage form, and appearance.

If there were potential for Oracea to be confused with Arava, Omacor, Ovace, or Orasone, then that same potential would exist amongst the existing approved names. Stated another way, if Arava, Omacor, Ovace, and Orasone are all susceptible to confusion with Oracea, then logically they are also susceptible to confusion with each other. But in checking three large databases, Institute for Safe Medical Practices, FDA's MedWatch site, and the USP Quality Review, we found no evidence that any of the four has ever been confused with any of the other three, nor that any such confusion has led to any medical error. Our findings are set out in Attachment #1.

DMETS Response: DMETS recognizes that Oracea does not overlap with regard to ***all*** product characteristic categories with any one particular product. When examining postmarketing reports we note that not all product characteristics categories have to overlap in order for a medication error to occur. However, Oracea does overlap with regard to multiple product characteristics when compared to each of the aforementioned products. Additionally, the product characteristic differences listed above by the sponsor (i.e. indication, strength, dosage form, and appearance) are often not included in prescription orders, thus negating any differentiation those characteristics may impart.

- For example, indication of use is rarely included on prescription orders, and thus can not provide any differentiation if it is not included. Furthermore, product appearance is almost never included on prescription orders, and may only help in the prevention of the administration of an incorrect drug product *if* the patient had received the correct drug product previously and was able to recognize that the drug product was different from what was previously administered. However, at that point, an error was still committed and the wrong drug had already been dispensed to the patient.

- Product strength and dosage form are often not included in prescription orders when available in only one strength and one dosage form, as is the case with Oracea and Omacor. It is not unlikely for prescribing practitioners to omit the strength and dosage form on prescription orders, and in this case the drug product can still be dispensed without further clarification from the prescriber. Even when products have multiple strengths, only the desired dose, and not the product strength, may be included on a prescription, as is possible with Orasone. Although Orasone is available in 1 mg, 5 mg, 10 mg, 20 mg, and 50 mg tablets, a prescriber can order Orasone 40 mg, and the drug product can be dispensed without further verification from the prescriber because the pharmacist will fill the order with the strength that will achieve the desired dose. In this case a patient would be told to take two tablets of the 20 mg strength in order to achieve the 40 mg dose. This scenario applies to the other drug names as well.

- With regard to multiple dosage forms, Ovace is available in more than one dosage form (i.e. topical foam and topical wash); however, since the actual dispensed dosage form may be of no clinical consequence to the patient, the prescriber may omit the dosage form on the order and leave it up to the prerogative of the pharmacist to dispense the available dosage form or what is preferred by the patient.

Thus, there are in fact overlapping product characteristics which may allow for confusion between Oracea, Arava, Omacor, Orasone, and/or Ovace.

With regard to confusion among the existing names of Arava, Omacor, Orasone, and Ovace, it is not possible to compare the potential for confusion between Oracea and these products with the potential for confusion amongst these four products themselves. In fact, many cases of name confusion do not support this hypothesis. For example, name confusion exists between Celebrex and Cerebyx and between Celebrex and Celexa. If this hypothesis were true then we should also see confusion between Celexa and Cerebyx, but we have not. Each product has unique characteristics that may help differentiate it from the other products in question. The product characteristics that help prevent confusion between Arava, Omacor, Orasone, and Ovace, may in fact cause confusion when compared with Oracea. Additionally, due to the fact that medication errors are routinely under-reported, it is possible that medication errors have in fact occurred amongst these four products that were not reported to the Agency.

B. Comment B – Nomenclature Concerns

1.1 *Modifier Concerns:*

CollaGenex will not use the — modifier.

DMETS Response: DMETS concurs with the sponsor's decision to not use the modifier —.

1.2 *Modifier Concerns:*

CollaGenex believes that the use of any modifier has the potential to cause confusion because it implies that Oracea is modified formulation of an existing product. This is not the case as Oracea is a new drug. At the same time CollaGenex acknowledges DMETS' concern that practitioners know that Oracea is a controlled-release product, and proposed that this be made clear in the product's established name.

DMETS Response: In a discussion with the Review Division on May 19, 2006, DMETS learned that this product will not be considered extended-release or delayed-release, therefore the use of a modifier is not justified. However, if this conclusion changes, DMETS has the following concern:

DMETS acknowledges that the established name will denote that Oracea is an extended-release product and that there is not currently an immediate release product with the proprietary name Oracea. However, the possibility still exists that the sponsor may decide to market an immediate-release doxycycline, and desire to use the name Oracea. Without the use of the modifier for the extended-release product, it would be necessary to use a modifier to denote the immediate-release product, which is contradictory to current naming practices. If the sponsor is willing to commit to not introducing an immediate-release dosage form of doxycycline, DMETS concurs with the sponsor's decision to not to include a modifier. If not, DMETS recommends that the sponsor include a modifier.

2.1 *Established Name Concerns:*

There are many recent examples of approved products containing doxycycline which prominently bear the name of the salt in the established name. While CollaGenex does not agree with DMETS' position, it is willing to remove the ——— from the establishment name.

DMETS Response: DMETS concurs with the sponsor's decision to remove the ——— from the established name. Additionally, DMETS would like to note that ———————, and not a salt, which is the reasoning behind the recommendation for the removal of the term in the established name. This nomenclature is consistent with USP's recommendation on " ——— ' Furthermore, if product strength is based on an active moiety rather than a salt, DMETS routinely recommends the removal of the salt from the established name as well.

2.2 *Established Name Concerns (continued):*

The USP nomenclature is intended to establish a guideline for proprietary drug products that will ultimately be the subject of an ANDA. The drug product, Oracea, is not a generic product; it is the subject of a New Drug Application because it is a unique strength and dosage form and contains clinical data to support a new indication. Approval for this new use would be pursuant to section 501(b)(1) of the Food, Drug and Cosmetic Act, and is within the purview of the FDA's decision making authority. The conventions of the USP should therefore not control a new strength, dosage form and indication.

We note that FDA has recently exercised its authority in this context and acknowledged that ——— an appropriate nomenclature when supported by the release characteristics of the drug product. We refer you to the name Paxil® controlled-release capsules. Following the same reasoning, we propose that the establishment name of Oracea be "Oracea (Doxycycline ——— Capsules) 40 mg".

DMETS Response: In a discussion with the Review Division on May 19, 2006, DMETS learned that this product will not be considered extended-release or delayed-release, therefore the use of the term "extended-release" or "delayed-release" in the established name is not justified. However, if this conclusion changes, DMETS has the following concern:

DMETS acknowledges that Oracea is not a generic product, but rather the subject of a New Drug Application. However as the sponsor stated, the USP nomenclature is intended to establish guidelines for **proprietary** drug products that will **ultimately** be the subject of an ANDA. Oracea is an NDA product, which will likely be the subject of an ANDA in the future. Thus, the USP guidelines are in fact written for products such as Oracea. Furthermore, the term " ' does not speak to

how the release of the product is controlled. It does not denote whether the active ingredient is released at a steady rate over an extended period of time (i.e. extended-release) or if the release of any or all of the active ingredient is delayed after a specified period of time (i.e. delayed-release). DMETS reiterates that ' ——— is not an approved dosage form recognized by the USP. Currently there are only two modified release names, delayed-release and extended-release. We defer this decision to the CDER Labeling and Nomenclature Committee.

DMETS also acknowledges that Paxil CR (Paroxetine Controlled-release Capsules) was approved by the FDA. However, Paxil CR was approved February 16, 1999, before the existence of the Division of Mediation Errors and Technical Support and thus not subject to review and comment by DMETS. Since our inception, DMETS has routinely not recommended the use of the term ' ——— in established names, and continues to do so with this product.

In summary, DMETS does not recommend the use of the proprietary name Oracea. The sponsor has not provided a persuasive argument that Oracea will not cause medication errors as a result of name confusion between Orasone, Ovace, Omacor, and Arava. Moreover, we recommend implementation of the label and labeling comments communicated in ODS Consult 06-0046. The Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the name Oracea acceptable from a promotional perspective. We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Diane Smith at 301-796-0538.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kristina Arnwine
5/22/2006 10:57:24 AM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
5/22/2006 11:11:20 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
5/22/2006 12:43:26 PM
DRUG SAFETY OFFICE REVIEWER
Also signing for Carol Holquist, Director, DMETS in her absence

COLLAGENEX
pharmaceuticals

DUPLICATE May 16, 2006

Stanka Kukich, M.D., Director
Division of Dermatological & Dental
Drug Products
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

ORIG AMENDMENT
N-000-BC

CDER/CDR RECEIVED
MAY 18 2006
MAY 22 2006
RECEIVED CDER White Oak DI

RE: NDA 50-805
Oracea (doxycycline ___ USP) ___ Capsules 40 mg
Request for Information: Chemistry, Manufacturing & Controls

Dear Dr. Kukich:

Provided herewith is a response to the Division's request for information received on May 16, 2006. For ease in review, each of the Division's requests is being reiterated and is followed by our response.

FDA Request #1:

Please update the appearance specification for the drug product to include the printing on the capsule body with "CGPI 40."

Response:

The Sponsor has done so. Attachment #1 contains a revised drug product specification.

FDA Request #2:

Based on the current stability data, 24 months expiration time is granted for drug products packaged in bottle, 18 month expiration date is granted for the drug product packaged in blister.

Response:

The Sponsor acknowledges that the product packaged in bottles will be labeled with 24 month expiration dating and product packaged in blister cards will labeled with 18 month expiration dating.

CollaGenex Pharmaceuticals, Inc., 41 University Drive, Suite 200, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

Stanka Kukich, M.D. **May 16, 2006**
NDA 50-805
Request for Information - CMC

FDA Request #3:

Please make the inactive ingredients for the drug product in the package inert consistent with that on the package labels. Please display the inactive ingredients in the alphabetic order on the package labels.

Response:

Each of the inactive ingredients will be listed, in an identical and alphabetical order, on each package label and in the package insert. Attachment 2 contains a revised bottle and blister label as well as a revised package insert.

Should you have any questions regarding this document, please contact the undersigned at 215-579-7388 (telephone) or 215-402-1044 (fax).

Sincerely,

Christopher Powala
Vice President, Drug Development
& Regulatory Affairs

Division of Dermatology and Dental Products

Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Facsimile Transmission Cover Sheet

Date: 5/9/06 *Pages (including cover)* 16 + 1 = 17 total

To: Christopher Powala 215-579-7388 x3114

Company: Collabonex

Fax Phone#: 215-402-1044 *Our Fax # (301) 796-9895*
Voice # (301) 796-2110

Message: Hi Chris, I've attached the Oracea label (draft version) for your review. If we could receive your comments by Monday, May 15 by noon that would be great. Thanks!

From: Shalini Jain

Title: Reg. Project Mgr

Telephone: 301-796-0692

23 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 1a

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 4, 2006

TO: Stanka Kukich, MD, Acting Director
Division of Dermatology and Dental Products

VIA: Shalini Jain, Regulatory Project Manager
Division of Dermatology and Dental Products

FROM: Catherine Miller, MT(ASCP)
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, PharmD, Acting Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCS Review #2 of Patient Labeling for doxycycline capsules, NDA 50-805

The attached patient labeling (PPI) represents our revisions to the draft PPI submitted with the New Drug Application for doxycycline capsules, NDA 50-805 and revised by the review division. We have put this PPI in the in the patient-friendly format that we are recommending for all patient information, although, this format is not required for voluntary PPIs. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

Comments and Recommendations

1. We have simplified the wording in the PPI. The draft PPI submitted by the sponsor and revised by the review division has a Flesch Kinkaid reading level of 9.1, which is equivalent to a ninth grade first month reading level, and a Flesch Reading Ease score of 49.7. For optimal comprehension, patient materials should be written at a 6th to 8th grade reading level, with a reading ease score of at least 60 which corresponds with an 8th grade reading level. Our revised PPI has a Flesch Kinkaid reading level of 7.0 and a Flesch Reading Ease score of 65.1.

2. The PI states "See Patient Package Insert for additional information to give patients" in the Information for Patients subsection. According to the Federal Register notice titled "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" dated January 24, 2006, this PPI is not required to be appended to or accompany the PI until June 30, 2009. If the statement is to remain in the PI, the PPI

needs to be appended to or accompany the PI so the doctor will have access to it. We also recommend the statement in the PI provide the location of the PPI, such as "See Patient Package Insert at the end of [or that accompanies] this PI for additional information to give patients."

3. These revisions are based on draft labeling submitted on July 29, 2005 and revised by the review division on May 1, 2006. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

4. Comments to the review division are bolded, underlined and italicized. We will provide a marked-up and clean copy of the revised document in Word to the review division. Please call us if you have any questions.

5 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 16

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/s/

Catherine Miller
5/4/2006 12:24:58 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
5/4/2006 12:51:41 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 20, 2006

TO: Stanka Kukich, MD, Acting Director
Division of Dermatology and Dental Products

VIA: Shalini Jain, Regulatory Project Manager
Division of Dermatology and Dental Products

FROM: Catherine Miller, MT(ASCP)
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, PharmD, Acting Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCS Review of Patient Labeling for ORACEA (doxycycline capsules), NDA 50-805

The attached patient labeling (PPI) represents our revisions to the draft PPI submitted with the New Drug Application for ORACEA (doxycycline capsules), NDA 50-805. We have put this PPI in the in the patient-friendly format that we are recommending for all patient information, although, this format is not required for voluntary PPIs. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

Comments and Recommendations

1. We have simplified the wording in the PPI. The draft PPI submitted by the sponsor has a Flesch Kinkaid reading level of 11.9, which is equivalent to an eleventh grade ninth month reading level, and a Flesch Reading Ease score of 37. For optimal comprehension, patient materials should be written at a 6th to 8th grade reading level, with a reading ease score of at least 60 which corresponds with an 8th grade reading level. Our revised PPI has a Flesch Kinkaid reading level of 7.6 and a Flesch Reading Ease score of = 61.

2. The Information for Patients subsection of the PRECAUTIONS section is missing from the draft Prescribing Information (PI). The Information for Patients subsection should include information for prescribers to tell patients for safe and effective use of the drug [21 CFR 201.57(f)(2)]. Some examples include avoidance of excessive sunlight or artificial sunlight, the effect of bismuth subsalicylate, antacids and some

nutritional supplements on ORACEA, and the need to drink fluids with ORACEA to prevent irritation of the esophagus. The patient will rely on the prescriber for this information, given that the PPI for ORACEA is voluntary and the patient may not receive it.

3. These revisions are based on draft labeling submitted on July 29, 2005. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

4. Comments to the review division are bolded, underlined and italicized. We will provide a marked-up and clean copy of the revised document in Word to the review division. Please call us if you have any questions.

3 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 1c

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/s/

Catherine Miller
4/20/2006 01:39:50 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
4/20/2006 03:00:40 PM
DRUG SAFETY OFFICE REVIEWER

ORIGINAL

COLLAGENEX
pharmaceuticals

April 17, 2006

Stanka Kukich, M.D., Director
Division of Dermatological & Dental
Drug Products
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705

RECEIVED
APR 18 2006
CDER/CDR

APR 18 2006

NEW CORRESP
N-000-(C)

RE: NDA 50-805
General Correspondence: Oracea Trademark

Dear Dr. Kukich:

Reference is made to the April 7, 2006 facsimile containing the Division of Drug Safety's review of the trademark, Oracea™. While we respect the basis for these comments, CollaGenex maintains that the trademark Oracea can be safely used and is taking this opportunity to provide additional information to support that use. For ease in review, each of the Division of Drug Safety's comments is paraphrased in boldfaced font and is followed by a response.

DMETS COMMENT A – Look-alike and Sound-alike Concerns:

DMETS does not recommend the use of the proprietary name Oracea due to its potential, when written in a cursive style, to look similar to Arava, Omacor, Ovace and Orasone.

CollaGenex Response:

Although the four names and the proposed name might look alike, they are unlikely to result in confusion resulting in medical error because of differences in indication, strength, dosage form, and appearance.

If there were potential for Oracea to be confused with Arava, Omacor, Ovace or Orasone, then that same potential would exist amongst the existing approved names. Stated another way, if Arava, Omacor, Ovace, and Orasone are all susceptible to confusion with Oracea, then logically they are also susceptible to confusion with each other. But in checking three large databases, Institute for Safe Medical Practices, FDA's MedWatch site, and the USP Quality Review, we found no evidence that any of the four has ever been confused with any of the other three, nor that any such confusion has led to any medical error. Our findings are set out in Attachment #1.

CollaGenex Pharmaceuticals, Inc., 41 University Drive, Suite 200, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

The lack of any confusion among the four strongly suggests that, due to the differences in indication, strength, dosage form, appearance, and other reasons, the confusion on which ODS speculates has not in fact occurred, and would not occur with Oracea and any of the four.

DMETS COMMENT B – Nomenclature Concerns:

1.1 Modifier Concerns:

DMETS does not recommend use of the modifier — because of potential for confusion with — a common medical abbreviation.

CollaGenex Response:

CollaGenex will not use the — modifier.

1.2 Modifier Concerns:

DMETS recommends that the name include both a root and a suitable modifier to enable practitioners to discern that Oracea is an extended release product

CollaGenex Response:

CollaGenex believes that the use of any modifier has the potential to cause confusion because it implies that Oracea is a modified formulation of an existing product. This is not the case as Oracea is a new drug. At the same time CollaGenex acknowledges DMETS' concern that practitioners know that Oracea is a controlled release product, and proposes that this be made clear in the product's established name (see below).

2.1 Established Name Concerns:

DMETS notes that — are not included in the establishment names of USP monographed products and requests that — be removed from the established name.

CollaGenex Response:

There are many recent examples of approved products containing doxycycline which prominently bear the name of the salt in the established name (see Attachment # 2 for examples). While CollaGenex does not agree with DMETS' position, it is willing to remove the ——— from the establishment name.

2.2 Established Name Concerns (continued):

DMETS notes that the only two USP approved modified release names are delayed release and extended release and recommends them over the proposed

CollaGenex Response:

The USP nomenclature is intended to establish a guideline for proprietary drug products that will ultimately be the subject of an ANDA. The drug product, Oracea, is not a generic product; it is the subject of a New Drug Application because it is a unique strength and dosage form and contains clinical data to support a new indication. Approval for this new use would be pursuant to section 501 (b)(1) of the Food, Drug and Cosmetic Act, and is within the purview of the FDA's decision making authority. The conventions of the USP should therefore not control a new strength, dosage form and indication.

We note that FDA has recently exercised its authority in this context and acknowledged that controlled-release is an appropriate nomenclature when supported by the release characteristics of the drug product. We refer you to the name of Paxil® controlled-release capsules (see Attachment # 3). Following the same reasoning, we propose that the establishment name of Oracea be "Oracea (Doxycycline ———) 40mg".

In order not to duplicate efforts, the issues surrounding the container label, package insert and patient information will be discussed with the Division of Dermatological Drug Products as they become necessary.

We are available to discuss this with a representative of the Office of Drug Safety. If there are any questions regarding this document, please contact the undersigned at 215-579-7388 (telephone) or 215-402-1044 (fax).

Sincerely,

Christopher Powala
Vice President, Drug Development
& Regulatory Affairs

Desk Copy: Ms. Shalini Jain, Regulatory Health Project Manager, HFD-540

NDA 50-805

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

Date: April 7, 2006

To: Christopher Powala
Vice President, Drug Development and Regulatory Affairs
CollaGenex Pharmaceuticals, Inc.
Phone: (215) 579-7388
Fax: (215) 402-1044

From: Shalini Jain, PA-C, Regulatory Project Manager
Phone: (301) 796-0692
Fax: (301) 796-9894/9895

This transmission includes 9 pages (including this page)

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED BY APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is ***unauthorized and strictly prohibited.*** If you have received this facsimile in error, please notify Shalini Jain by telephone at 301-796-0692 immediately and return it to 10903 New Hampshire Ave., WO22, Room 5183, Silver Spring, MD 20993 by US Mail.

FDA Facsimile Memorandum

Date: April 7, 2006

To: Christopher Powala, V.P., Drug Development and Regulatory Affairs

From: Margo Owens, Project Manager

Subject: NDA 50-805, Oracea™

Dear Mr. Powala:

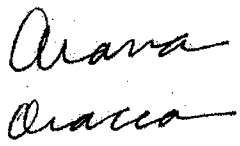
The Office of Drug Safety Reviewer has completed her review of your NDA 50-805 Oracea™, and has asked that the following comments be conveyed to you.

ODS Reviewer Comments:

DMETS does not recommend the use of the proprietary name Oracea — due to its potential to look similar to Arava, Omacor, Ovace, and Orasone.

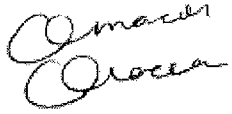
A. Look-Alike and Sound-Alike Concerns

1. Arava and Oracea — may look-alike when scripted, if the modifer — is omitted from the name. Arava (leflunamide) is an immunomodulatory agent indicated for the treatment of active rheumatoid arthritis. Arava is available as 10 mg, 20 mg, and 100 mg tablets and the usual dose is 20 mg daily. Arava and Oracea have two overlapping letters in the same position (ARAVA vs. ORACEA) that contributes to the look-alike characteristics of the two names. Additionally, the "CE" in Oracea can look like a "V" if written close together and without curvature (see writing sample below). In addition to the look-alike similarities, the two products have overlapping product characteristics, such as route of administration (oral) and frequency of administration (once daily). Both products are available in only one dosage form (tablet vs. capsule), and thus the dosage form may be omitted from a prescription. Although there is no direct overlap in strength, a 40 mg dose of Arava may be achieved with the available dosage strength. Arava is available in 20 mg tablets; therefore, a prescription for Oracea 40 mg QD may be misinterpreted as Arava 40 mg QD. A pharmacist may dispense two 20 mg tablets to achieve the total dose of 40 mg. In this scenario, a patient or healthcare provider may not recognize the wrong medication and dose was dispensed. This may result in inadequate rosacea treatment, allergic reactions, hepatic injury, and potentially fatal outcomes in patients with an existing infection. Thus, the look-alike similarities with the two product names coupled with overlapping product characteristics increase the potential for name confusion resulting in medication errors involving Arava and Oracea ——



2. Omacor and Oracea — may look similar when scripted, if the modifer — ' is omitted from a prescription. Omacor (omega-3-acid ethyl esters) is an anti-hyperlipidemic agent for the treatment of hypertriglyceridemia and secondary prevention of myocardial infarction. Omacor is available as

1 gram capsules and is dosed 2 to 4 grams daily for hypertriglyeridemia and 1 gram daily for the secondary prevention of myocardial infarction. Omacor and Oracea have the same number of letters (six) and contain three overlapping letters in the same positions (OMACOR vs. ORACEA), which contributes to the look-alike characteristics of the two names. Moreover, the endings ("-OR" vs. "-EA") may look similar when scripted (see sample below).



In addition to the look-alike similarities, Omacor and Oracea have the same frequency of administration (once daily), dosage form (capsule), and route of administration (oral). Although Omacor and Oracea have different strengths (1 gram vs. 40 mg); they are only available in the one strength, thus prescribers do not need to write this information on a prescription. A prescriber may write a prescription for "Omacor 1 PO QD, #30" vs. "Oracea 1 PO QD, #30". If the wrong medication is dispensed, adverse consequences may occur, such as untreated rosacea, untreated hypertriglyceridemia, drug interaction complications, and anaphylaxis in patients contraindicated to take either medication. The look-alike similarities combined with the overlapping product characteristics and directions for use increase the potential for confusion and error between Omacor and Oracea.—

3. Ovace and Oracea — were found to have look-alike similarities when scripted, if the modifer ' — is omitted from the name. Ovace (sulfacetamide) is topical sulfonamide used for the treatment of acne vulgaris. Ovace is available as a 10% topical wash in 6 ounce and 12 ounce bottles and 10% topical foam in 50 gram and 100 gram cans. Ovace is to be applied to the affected area twice daily for 8 – 10 days. The two drug names contain four overlapping letters in similar positions (OVACE vs. ORACEA), which contribute to the look-alike characteristics. Additionally the letters "V" and "R" may look-alike when scripted (see sample below). Moreover, one respondent in the inpatient prescription study interpreted the proposed name as "Ovacen" — and another interpreted the proposed name "Ovacea — both of which looks similar to Ovace, if the modifier — is omitted. Although the products have some differing product characteristics such as dosage form (wash, foam vs. capsule), route of administration (oral or topical), and dosing

frequency (twice daily vs. once daily), an erroneously written prescription may cause confusion and error. For example, although Ovace is available in two different dosage forms (foam vs. wash); prescribers may not indicate the specific dosage form and allow the pharmacist to dispense the dosage form in stock. Additionally, it is not unlikely to see prescriptions for both topical and maintenance medications written with (UD) as the directions for use. Both Ovace and Oracea are available in only one strength and thus the strength may be omitted on a prescription. The overwhelming visual similarities and the positive prescription study results combined with the overlapping directions for use increases the potential for confusion and error between Ovace and Oracea —

Oracea
Ovace

4. Orasone was found to have look-alike potential with Oracea — if the modifer — s omitted from the name. Orasone (prednisone) is a synthetic corticosteroid and is used as replacement therapy for secondary adrenocortical insufficiency and congenital adrenal hyperplasia. In addition, due to its anti-inflammatory effects, prednisone is used for a variety of conditions, such as rheumatoid arthritis, thrombotic thrombocytopenic purpura, asthma, sarcoidosis, membranous nephropathy, lupus nephritis, and in transplant recipients. Orasone is available as 1 mg, 5 mg, 10 mg, 20 mg, and 50 mg tablets and the typical dosage range is 5 mg – 60 mg per day in single or divided doses. Orasone and Oracea — ave the same three initial letters (ORA-). Additionally, when scripted, neither name requires any up- nor downstrokes, which contributes to their orthographic similarities (see sample, page 13). However, the endings (-SONE vs. -CEA) provide visual distinctions between the two names. Both products share characteristics such as dosage form (tablet, capsule), route of administration (oral), and possible dosing frequency (once daily). Although there is no direct overlap in strength, a 40 mg dose of Orasone may be achieved with the available dosage strengths. A prescription for Oracea 40 mg QD may be misinterpreted as Orasone 40 mg QD. A pharmacist may dispense two 20 mg tablets to achieve the total dose of 40 mg. In this scenario, a patient or healthcare provider may not recognize the wrong medication was dispensed. This may result in inadequate rosacea treatment, allergic reactions, mucocutaneous fungal infections, and potentially life threatening metabolic consequences. Thus, the look-alike similarities with the two product names coupled with overlapping product characteristics increase the potential for name confusion resulting in medication errors involving Orasone and Oracea —

Oracea
Orasone

B. NOMENCLATURE CONCERNS

1. Modifier Concerns

With respect to the proprietary name, Oracea, DMETS is concerned with the introduction of a proprietary name for an extended-release formulation without the use of a modifier. This naming convention may cause confusion as it does not follow traditional naming practices. Historically, extended-release formulations contain a modifier in conjunction with the root name to distinguish it from immediate-release formulations. By looking at the proposed proprietary name, it will be difficult for practitioners to discern that Oracea is an extended-release product, rather than immediate-release. We acknowledge the sponsor does not currently market an immediate-release formulation of doxycycline monohydrate, however, DMETS envisions errors and confusion if and when the sponsor decides to market an immediate-release formulation with a proprietary name. Additionally, there are many immediate-release doxycycline products available from other manufacturers with proprietary names without modifiers. DMETS recommends that the extended-release formulation contain a suitable modifier in conjunction with the root name (i.e. XL, ER, etc).

DMETS is aware that the sponsor previously submitted the proposed proprietary name, Oracea [redacted] However, DMETS is concerned with the potential for confusion with the proposed modifier [redacted] is a common medical abbreviation for the following: [redacted]

Furthermore, the use of the modifier [redacted] may cause confusion in the hospital setting where [redacted] night be interpreted as [redacted] n an inpatient prescription order resulting in the administration of an additional dose of the medication. For the aforementioned reasons, DMETS does not recommend use of the modifier [redacted]

2. Established Name Concerns

DMETS notes the sponsor proposes to use "Doxycycline [redacted] Capsules" as their established name. [redacted] i.e. [redacted] are not included in the established names of USP monographed products since they do not alter the interchangeability of the drug. The current monograph title for immediate-release doxycycline [redacted] is doxycycline capsules. Therefore, we would anticipate a similar naming convention for any modified release dosage form. Thus, we request [redacted] be removed from the established name. Additionally, we recommend consulting Guirag Poochikian, Acting Chair of the CDER Labeling and Nomenclature Committee (LNC), for guidance on the established name with respect to [redacted] is not an approved dosage form recognized by the USP. Currently the only two modified release names are delayed-release and extended-release.

C. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels, carton and insert labeling of Oracea, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

1. GENERAL COMMENTS

   a. The term ' [redacted] ' is not a recognized dosage form by the USP. DMETS recommends consulting Guiarag Poochikian, Acting Chair of the CDER Labeling and Nomenclature Committee (LNC), for the proper designation of the established name.

   b. The ninety-count bottle and the four-count patient sample appear to be unit-of-use containers. Ensure that these containers utilize child-resistant closures to be in accordance with the Poison Prevention Act.

   c. Increase the prominence of the established name so that is at least ½ the size of the proprietary name, per 21 CFR 201.10(g) (2).

   d. We note that [redacted] are not included in the established names of USP monographed products. Although this is not a monograph, we suggest revising the labels and labeling to follow existing USP nomenclature standards. For example:

(Doxycycline $\frac{\text{Oracea}}{\text{40 mg}}$ Capsules)

2. CONTAINER LABEL – 90 Count Bottle

   a. See General Comments A-1 through A-4.

   b. In order to minimize confusion, relocate the net quantity so that it is not presented in close proximity to the product strength.

   c. Include the "Usual Dosage" statement per 21 CFR 201.55.

   d. Some discrepancy exists regarding who Oracea is marketed by. The package insert states that Oracea is marketed by CollaGenex and manufactured by Cardinal Health. However the container label states that Oracea is manufactured by [redacted] nd Cardinal Health. Revise this statement

as necessary to correctly reflect who markets, manufactures, or distributes Oracea, per 21 CFR 201.1(h) (5).

3. CONTAINER LABEL – Patient Sample Folder

   a. See General Comments A-1 through A-4.

   b. In order to minimize confusion, revise the net quantity to read, "4 capsules" instead of ' 40 mg each."

   c. Revise the product strength to read, "40 mg/capsule," in order to ensure that healthcare practitioners and patients are aware that each capsule, not the entire contents of the sample pack, contains 40 mg. Additionally, ensure that the product strength is not presented in close proximity to the net quantity.

   d. Increase the prominence of the "Patient Sample…" statement. Additionally, revise it to read "Professional Sample – NOT FOR SALE."

   e. Revise the statement, " ," to read, "Take Oracea exactly as directed " so that it is presented in a manner that is easy for patients to understand. Additionally, the statement, as it is currently presented, is also contained in the prescribing information and is not necessary for patients to read in order to take the medication correctly.

   f. Revise the statements, "Oracea should be taken once daily in the morning… (See package insert for full prescribing information)," to read, "Oracea should be taken once daily in the morning on an empty stomach (at least one hour before or two hours after meals). so that the statement is comprehensive enough to ensure correct administration of the product, reduce the incidence of esophageal irritation, and present the information in a manner that is easy for patients to understand.

4. CARTON LABELING – Patient Sample Carton

   a. See General Comments A-1 through A-4 and comments C-3 through C-6.

   b. Revise the net quantity to read, "16 units each containing 4 capsules."

5. PACKAGE INSERT

   a. See General Comments A-1 and comment C-6.

   b. How Supplied Section

The first sentence states that Oracea contains 40 mg of doxycycline [redacted] ather than 40 mg of doxycycline as is stated throughout the labels and labeling. Revise accordingly.

6. PATIENT INFORMATION LABELING

   a. Submit the Patient Package Insert Labeling to the Division of Surveillance, Research, and Communication Support (DSRCS) for review and comment.

   b. Revise the "How should I take Oracea?" section as stated in comment C-6.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Shalini Jain
4/7/2006 03:11:47 PM
CSO

COLLAGENEX pharmaceuticals

ORIGINAL

April 7, 2006

Stanka Kukich, M.D., Director
Division of Dermatological & Dental
Drug Products
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

RECEIVED
APR 12 2006
CDER White Oak DR1

RECEIVED
APR 11 2006
CDR / CDER

RE: 50-805
Response to FDA Request for Information

N-000(82)
ORIG AMENDMENT

Dear Dr. Kukich:

Reference is made to our NDA 50-805 for Oracea™ (doxycycline ——— ——— capsules) 40mg which is proposed as a treatment ——— inflammatory lesions in patients with rosacea.

The purpose of this filing is to formally provide information that was previously filed with the Agency via e-mail dated February 27, 2006 to the attention of Ms. Shalini Jain, Regulatory Health Project Manager., HFD-540.

Submitted herewith, is a hard copy of the February 27th response. For ease in review, each of the Division's requests is reiterated and is followed by the Sponsor's response.

Request #1:

In Module 2, Volume 1.1, on page 28, the applicant provided a table outlining the proposed dissolution test conditions and, on page 40 the applicant included the average release data for three registration batches (two Phase 3 clinical trial batches and one PK study batch). The data used to generate this proposed dissolution method and the individual data used to generate the average release data cannot be located in the NDA.

Please direct us to where the dissolution method development report and, the individual release data for the three batches are located in the NDA. If none of this information was included in the NDA then we need the Sponsor to provide it in their response.

Response:

The individual dissolution release data for the two Phase 3 clinical trial lots and the one PK study lot can be found in Attachment #1. Please note that the dissolution methods development report can be found in Module 3, Volume 1.6 under tab titled: TR-03-26.

CollaGenex Pharmaceuticals, Inc., 41 University Drive, Suite 200, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

Stanka Kukich, M.D. **April 7, 2006**
NDA 50-805
Response to FDA Request for Information

Request # 2:

Please provide a table that gives the incidence of severe AE's (both numbers and %'s) classified by MedDRA system Organ Class and Preferred Term, safety population combined pivotal studies (COL101-ROSE-301 and 302).

Response:

The table containing the number of patients with severe adverse events in the combined Phase 3 studies can be found in Attachment 2.

We trust that this adequately responds to the Division's request for information. Should you have any questions regarding this document, please contact the undersigned at 215-579-7388 (telephone) or 215-402-1044 (fax).

Sincerely,

Christopher Powala
Vice President, Drug Development
& Regulatory Affairs

COLLAGENEX
pharmaceuticals

N-000 SY

ORIG AMENDMENT

ORIGINAL

March 17, 2006

RECEIVED
MAR 17 2006
CDER/CDF

NDA SAFETY UPDATE

RECEIVED
MAR 20 2006
CDER White Oak DR1

Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attention: Stanka Kukich, MD
Director, Division of Dermatologic and Dental Drug products (HFD-540)

Re: NDA 50-805 Safety Update Report
Oracea™ (doxycycline [redacted] capsules) 40 mg

Dear Dr. Kukich:

The original NDA for Oracea™ (doxycycline [redacted] apsules) 40 mg to [redacted] was submitted on July 29, 2005. This safety update report includes the following two items:

- Data from clinical study PERIO-DOXYMR-301, which was ongoing when the original NDA was submitted (described in Module 2, Section 2.7.4.1.1, Overall Safety Evaluation Plan and Narratives of Safety Studies), that provides relevant 9-month safety experience.
- Postmarketing safety data for the related approved product Periostat® (doxycycline hyclate) 20 mg that have become available since the original NDA submission.

No new clinical concerns have been identified. These new safety data do not affect the contraindications, warning, precautions, or adverse reactions sections of the product labeling as proposed in the original NDA.

If there are any questions regarding this application, please contact the undersigned at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala

Christopher Powala
Vice President, Drug Development
& Regulatory Affairs

CollaGenex Pharmaceuticals, Inc., 41 University Drive, Suite 200, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

MEMORANDUM	Division of Medication Errors and Technical Support Office of Drug Safety WO 22, Mailstop 4447, HFD-420 Center for Drug Evaluation and Research

To: Stanka Kukich, MD
Acting Director, Division of Dermatology and Dental Products
HFD-540

Through: Linda Kim-Jung, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

From: Kristina C. Arnwine, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Date: March 7, 2006

Subject: ODS Consult 06-0046, Oracea (Doxycycline [redacted] Capsules) 40 mg
NDA 50-805 (IND 67, 833)

This memorandum is in response to a February 6, 2006 request from your Division for a re-review of the proprietary name, Oracea. The container label, carton, insert, and patient information labeling were provided for review and comment. DMETS previously reviewed the proprietary name Oracea MR in a consult dated October 7, 2005 (See ODS Consult 05-0079, attached to IND 65,733). DMETS did not recommend use of the name Oracea [redacted] due to potential confusion with regard to the modifier [redacted] along with sound-alike and/or look-alike confusion potential between the root name, Oracea, and the currently marketed products Arava, Omacor, Ovace, and Orasone. Since the current request from your Division is for a review of the root name, Oracea, without the modifier, DMETS continues to have the same concerns as mentioned in our previous consult (ODS Consult 05-0079). DMETS has not identified any additional names that have the potential for sound-alike and/or look-alike confusion with Oracea since that initial review.

DMETS notes the sponsor proposes to use "Doxycycline [redacted] Capsules" as their established name. [redacted] are not included in the established names of USP monographed products since they do not alter the interchangeability of the drug. The current monograph title for immediate-release doxycycline monohydrate is doxycycline capsules. Therefore, we would anticipate a similar naming convention for any modified release dosage form. Thus, we request [redacted] be removed from the established name. Additionally, we recommend consulting Guirag Poochikian, Acting Chair of the CDER Labeling and Nomenclature Committee (LNC), for guidance on the established name with respect to [redacted] is not an approved dosage form recognized by the USP. Currently the only two modified release names are delayed-release and extended-release.

With respect to the proprietary name, Oracea, DMETS is concerned with the introduction of a proprietary name for an extended-release formulation without the use of a modifier. This naming convention may cause confusion as it does not follow traditional naming practices. Historically, extended-release formulations contain a modifier in conjunction with the root name to distinguish it from immediate-release formulations. By looking at the proposed proprietary name, it will be difficult for practitioners to discern that Oracea is an extended-release product, rather than immediate-release. We acknowledge the sponsor does not currently market an immediate-release formulation of doxycycline monohydrate, however, DMETS envisions errors and confusion if and when the sponsor decides to market an immediate-release formulation with a proprietary name. Additionally, there are many immediate-release doxycycline products available from other manufacturers with proprietary names without modifiers. DMETS recommends that the extended-release formulation contain a suitable modifier in

conjunction with the root name (i.e. XL, ER, etc).

In the review of the container labels, carton and insert labeling of Oracea, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

1. The term ' [redacted] is not a recognized dosage form by the USP. DMETS recommends consulting Guiarag Poochikian, Acting Chair of the CDER Labeling and Nomenclature Committee (LNC), for the proper designation of the established name.

2. The ninety-count bottle and the four-count patient sample appear to be unit-of-use containers. Ensure that these containers utilize child-resistant closures to be in accordance with the Poison Prevention Act.

3. Increase the prominence of the established name so that is at least ½ the size of the proprietary name, per 21 CFR 201.10(g)(2).

4. We note that [redacted] are not included in the established names of USP monographed products. Although this is not a monograph, we suggest revising the labels and labeling to follow existing USP nomenclature standards. For example:

(Doxycycline [redacted] Oracea Capsules)
40 mg

B. CONTAINER LABEL – 90 Count Bottle

1. See General Comments A-1 through A-4.

2. In order to minimize confusion, relocate the net quantity so that it is not presented in close proximity to the product strength.

3. Include the "Usual Dosage" statement per 21 CFR 201.55.

4. Some discrepancy exists regarding who Oracea is marketed by. The package insert states that Oracea is marketed by CollaGenex and manufactured by Cardinal Health. However the container label states that Oracea is manufactured by [redacted] Cardinal Health. Revise this statement as necessary to correctly reflect who markets, manufactures, or distributes Oracea, per 21 CFR 201.1(h)(5).

C. CONTAINER LABEL – Patient Sample Folder

1. See General Comments A-1 through A-4.

2. In order to minimize confusion, revise the net quantity to read, "4 capsules" instead of "4 controlled release capsules 40 mg each."

3. Revise the product strength to read, "40 mg/capsule," in order to ensure that healthcare practitioners and patients are aware that each capsule, not the entire contents of the sample pack, contains 40 mg. Additionally, ensure that the product strength is not presented in close proximity to the net quantity.

4. Increase the prominence of the "Patient Sample..." statement. Additionally, revise it to read "Professional Sample – NOT FOR SALE."

5. Revise the statement, '[redacted] to read, "Take Oracea exactly as directed [redacted];" so that it is presented in a manner that is easy for patients to understand. Additionally, the statement, as it is currently presented, is also contained in the prescribing information and is not necessary for patients to read in order to take the medication correctly.

6. Revise the statements, "Oracea should be taken once daily in the morning... (See package insert for full prescribing information)," to read, "Oracea should be taken once daily in the morning on an empty stomach (at least one hour before or two hours after meals). [redacted] so that the statement is comprehensive enough to ensure correct administration of the product, reduce the incidence of esophageal irritation, and present the information in a manner that is easy for patients to understand.

D. CARTON LABELING – Patient Sample Carton

1. See General Comments A-1 through A-4 and comments C-3 through C-6.

2. Revise the net quantity to read, "16 units each containing 4 capsules."

E. PACKAGE INSERT

1. See General Comments A-1 and comment C-6.

2. How Supplied Section

   The first sentence states that Oracea contains 40 mg of doxycycline [redacted] rather than 40 mg of doxycycline as is stated throughout the labels and labeling. Revise accordingly.

F. PATIENT INFORMATION LABELING

1. Submit the Patient Package Insert Labeling to the Division of Surveillance, Research, and Communication Support (DSRCS) for review and comment.

2. Revise the "How should I take Oracea?" section as stated in comment C-6.

In summary, DMETS continues to not recommend the use of the proprietary name, Oracea. Additionally, the Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the name Oracea acceptable from a promotional perspective. We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Diane Smith at 301-796-0538.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kristina Arnwine
3/24/2006 06:10:30 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
3/27/2006 10:34:46 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
3/28/2006 11:05:27 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/28/2006 11:20:24 AM
DRUG SAFETY OFFICE REVIEWER

N-000 SU

ORIG AMENDMENT

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March 17, 2006

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CDER/CDS

NDA SAFETY UPDATE

RECEIVED
MAR 20 2006
CDER White Oak DFI

Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Attention: Stanka Kukich, MD
Director, Division of Dermatologic and Dental Drug products (HFD-540)

Re: NDA 50-805 Safety Update Report
Oracea™ (doxycycline [redacted] capsules) 40 mg

Dear Dr. Kukich:

The original NDA for Oracea™ (doxycycline [redacted] capsules) 40 mg to [redacted] inflammatory lesions in patients with rosacea was submitted on July 29, 2005. This safety update report includes the following two items:

- Data from clinical study PERIO-DOXYMR-301, which was ongoing when the original NDA was submitted (described in Module 2, Section 2.7.4.1.1, Overall Safety Evaluation Plan and Narratives of Safety Studies), that provides relevant 9-month safety experience.

- Postmarketing safety data for the related approved product Periostat® (doxycycline hyclate) 20 mg that have become available since the original NDA submission.

No new clinical concerns have been identified. These new safety data do not affect the contraindications, warning, precautions, or adverse reactions sections of the product labeling as proposed in the original NDA.

If there are any questions regarding this application, please contact the undersigned at 215-579-7388 (telephone) or 215-579-8577 (fax).

Sincerely,

Christopher Powala

Christopher Powala
Vice President, Drug Development
& Regulatory Affairs

CollaGenex Pharmaceuticals, Inc., 41 University Drive, Suite 200, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

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FEB 14 2006

CDER White Oak DR1

ORIG AMENDMENT

N-000(BC)

February 10, 2006

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FEB 13 2006

CDR/CDER

Stanka Kukich, MD, Deputy Director
Division of Dermatology & Dental Drug Products, CDER
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1233

Re: NDA 50-805 - Oracea™ (doxycycline capsules) 40 mg
Minor Amendment: Updated Product Stability Data

Dear Dr. Kukich,

Please refer to NDA 50-805 for Oracea™ (doxycycline capsules) 40 mg.

Provided herewith are updated stability data on three individual batches of Oracea. Each of the three batches was packaged as bottles of 30, bottles of 100, and blister cards of four capsules per card. Detailed results from these ongoing stability studies may be found in Attachment #1.

Batch No.	Type of Batch	Bulk Batch Size (Capsules)	Packaging Configuration	Months at 30°C/60 %RH	Months at 40°C/75 %RH
0400289	NDA		Bottles of 30	18	6
0400289			Bottles of 100	18	6
0400289B			Blisters of 4	9	6
0401533	NDA		Bottles of 30	18	6
0401533			Bottles of 100	18	6
0401533B			Blisters of 4	9	6
0401534	NDA		Bottles of 30	18	6
0401534			Bottles of 100	18	6
0401534B			Blister of 4	9	6

It should be noted that all assay and related substance values remain well within specification, after 18 months at 30°C/60 %RH and 6 months at 40°C/75 %RH for bottles and after 9 months at 30°C/60 %RH and 6 months at 40°C/75 %RH for blisters.

ORIGINAL

These data have also been subjected to statistical analysis using STAB, an SAS® program for conducting stability analysis and expiration dating estimation. The results of these analyses may be found in Attachment #2. The results indicate that the projected shelf life extends long past the proposed expiration dating of 24 months.

Should you have any questions concerning this submission, please contact the undersigned or Dr. Philip Freidenreich at 215-579-7388 (telephone) or 215-402-1044 (facsimile).

Sincerely,

Christopher Powala, Vice President
Drug Development and Regulatory Affairs

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October 28, 2005

Stanka Kukich, M.D., Deputy Director
Division of Dermatology & Dental Products
Food & Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 50-805
Oracea™ (doxycycline [redacted] capsules) 40mg
Response to 74-Day Letter

Dear Dr. Kukich:

Please refer to the Division's 74-Day Letter dated October 14, 2005. Provided herewith is the Sponsor's response to this letter. Each of the Division's comments has been reiterated and is followed by a response.

Clinical/Biostatistics:

Comment #1:

"Provide a clear copy of the bar graph, p. 196 Module 2, Vol. 1.1."

Response:

Attachment 1 contains a copy of the bar graph found on page 196 of Module 2, Volume 1.1.

Comment #2:

"Provide either a safety assessment based on all current world-wide knowledge regarding this product or clarify where such world-wide knowledge is utilized for safety assessment in the current submission."

Response:

The safety assessment for Oracea™ (doxycycline [redacted] capsules) 40 mg that was filed in the NDA is up to date as of May, 2005 and can be found in the integrated summary of safety located in Module 2, Volume 1.1, Section 2.5.5.

To further clarify the contents of the safety assessment, please note that the two Phase 3 trials were conduct in the United States only. The Sponsor also provided copies of all quarterly reports of adverse events for its marketed product, Periostat® (doxycycline

CollaGenex Pharmaceuticals, Inc., 41 University Drive, Suite 200, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

Following ICH guidelines ICH E-9, section 2.2.2 the Sponsor chose the primary endpoint that most closely measures the intended label claim, i.e., ——— which is the most objective and clinically relevant efficacy parameter. In this situation, the IGA is not warranted, a position supported by leading dermatologists (see Attachment 2). The IGA also introduces a systematic bias in weighting the outcome of patients with lesser baseline symptomatology much more heavily than outcomes of patients with greater baseline symptom scores. Hence the statistical results from this analysis are not generalizable to the population referenced in the desired label claim (see Attachment 3). However, in consideration of the Agency's request, change in IGA and an analysis of the static, dichotomized IGA have been incorporated as secondary endpoints.

Despite the above position of the Sponsor, the Phase 3 trials were adequately powered for both lesion count and dichotomized static IGA parameters, and the data from the IGA was captured and analyzed as requested by the Division. Power calculations for the dichotomized IGA were conducted and filed with the Division as part of IND No. 67,833, Serial No. 016 dated January 31, 2005. The analysis and results of the dichotomized static IGA parameters are a part of the NDA and follow the mutually-agreed analysis methodology described in each of the protocols and the Statistical Analysis Plan.

In summary, the static dichotomized IGA data were analyzed per FDA's request, and the results for both studies are statistically significant. Hence for purposes of this submission the status regarding primary versus secondary endpoint of the IGA has become moot and efficacy of the product has been unambiguously demonstrated.

Comment #4:

"Your IGA appears to have been based on lesion counts rather than qualitative assessment of global disease severity. Please address what data you may have to qualitatively assess subjects for global disease severity in your clinical trials, i.e., composite evaluation of disease.:

Response:

The structure of the IGA was discussed in depth with the Division and the IGA that was used in the pivotal studies was approved in advance by the Division to be adequate to support the indication. Since the sponsor was seeking a claim of " ——— " in patients with rosacea, the IGA should only reflect the indication that is being sought. Please refer to the minutes from the Pre-IND/End of Phase 2 Meeting (See Attachment 4). For ease in review, the pertinent section of the Division's issued minutes is reiterated:

"Erythema may be evaluated separately as a secondary variable and not included in the Clinician's Global Severity Scale as proposed by the Sponsor. Erythema will be addressed as a secondary variable for labeling and erythema should not get worse."

The indication being sought is the primary determinant of the design of the IGA. Given the subjective nature of an assessment score, quality of lesions is part of the assessment, however, was not demonstrated separately.

In addition to the global assessment of inflammatory lesions, the Sponsor has provided results from the global assessment of erythema which can be found in Modules 5, Volume 1.9, Table 9, Page 37 for Study COL101-ROSE-301 and Module 5, Volume 1.32, Table 9, Page 43 for Study COL101-ROSE-302.

Pharmacology/Toxicology:

Comment #1:

"Submit a timeline, including protocol submission, study initiation and completion and final report submission, for the murine carcinogenicity assay."

Response:

To date, the Sponsor has no toxicology data in mice. The Sponsor intends to conduct a 7-day dose range finding study in July 2006. This study will encompass the development of bioanalytical assays to quantify plasma concentrations of doxycycline. Upon completion of the 7-Day study, the Sponsor will conduct a 4-week toxicology study in September 2006. The 4-week study will be followed by a 13-week toxicology study to determine appropriate doses for the carcinogenicity study. We anticipate the 13-week study to begin in January 2007. During June 2007, the Sponsor will file the proposed doses for use in the 104-week carcinogenicity study with the Agency for review by the Assessment Committee. The 104-week carcinogenicity study will begin in August of 2007. It is anticipated that the final report for the 104-week carcinogenicity study will be available in February 2010.

The protocols for the 4-week, 13 week and 104-week studies were provided in the NDA. The protocols can be found in Module 4, Volume 1.1, Section 4.2.

I trust that this adequately responds to the Division's comments. Should you require additional information, please contact the undersigned at 215-579-7388 (telephone) or 215-402-1044 (fax)

Sincerely,

Christopher Powala
Vice President, Drug Development
& Regulatory Affairs

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March 24, 2006

Stanka Kukich, M.D., Director
Division of Dermatological and Dental
Drug Products
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705

RECEIVED
MAR 29 2006
CDER White Oak DR1

RECEIVED
MAR 28 2006
CDER CDR

RE: NDA 50-805
Minor Amendment: Updated Product Stability Data

N 000 (BC)
ORIG AMENDMENT

Dear Dr. Kukich:

Please refer to NDA 50-805 for Oracea™ (doxycycline [redacted] capsules) 40 mg which is proposed for use as a treatment [redacted] inflammatory lesions in patients with rosacea.

Provided herewith are updated stability on three individual batches of Oracea. The batch numbers are identified below. Each of the three batches was packaged as blister cards of four capsules per card. Detailed results from these ongoing stability studies may be found in Attachment #1.

Batch No.	Batch Size	Packaging Component	New Stability Time point
0400289B	[redacted]	Blister card of 4 capsules	12 Months
0401533B		Blister card of 4 capsules	12 Months
0401534B		Blister card of 4 capsules	12 Months

All assay and related substances values remain well within specifications after 12 months 30°C/60% RH.

These data have also been subjected to statistical analysis using STAB, a SAS program for conducting stability analysis and expiration dating estimation. The results of these analyses may be found in Attachment #2. The results indicate that the projected shelf life extends beyond the proposed expiration date of 24 months.

Should you have questions regarding this document, please contact the undersigned at 215-579-7388 (telephone) or 215-402-1044 (fax).

Sincerely,

Christopher Powala
Vice President, Drug Development
& Regulatory Affairs

Desk Copy: Shalini Jain, Regulatory Health Project Manager, WO22, Room 5183

CollaGenex Pharmaceuticals, Inc., 41 University Drive, Suite 200, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 50-805

Collagenex Pharmaceuticals
Attention: Christopher Powala
Vice President, Drug Development and Regulatory Affairs
41 University Drive
Newtown, PA 18940

Dear Mr. Powala:

Please refer to your August 1, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oracea (doxycycline capsules, 40 mg), for the treatment of inflammatory lesions in patients with rosacea .

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on September 30, 2005 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues, and are requesting the following information:

Clinical/Biostatistics:

1. Provide a clear copy of the bar graph, p. 196 Module 2, vol. 1.1.

2. Provide either a safety assessment based on all current world-wide knowledge regarding this product or clarify where such world-wide knowledge is utilized for safety assessment in the current submission.

3. Phase 3 trials were designed with change in inflammatory lesions as the primary endpoint for efficacy, however, the Division had stated, at the End-of-Phase 2 Meeting May 3, 2004 as well as in the comments on the protocol conveyed to the sponsor Sept 27, 2004, that Phase 3 trials should be planned and powered for the two co-primary endpoints:
   a. success in IGA
   b. change in inflammatory lesion count

   Provide analysis results using success in IGA, in addition to the change in inflammatory analysis results already submitted.

4. Your IGA appears to have been based on lesion counts rather than a qualitative assessment of global disease severity.
   Please address what data you may have to qualitatively assess subjects for global disease severity in your clinical trials, i.e. composite evaluation of disease.

Pharmacology/Toxicology:

Submit a timeline, including protocol submission, study initiation and completion and final report submission; for the murine carcinogenicity assay.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Shalini Jain, Regulatory Project Manager, at (301) 796-0629.

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Deputy Director
Division of Dermatology and Dental Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Stanka Kukich
10/14/2005 03:00:09 PM

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Stability Commitment

for

Oracea™ (doxycycline [redacted] capsules) 40 mg

NDA 50-805

1. Post-approval stability analyses will be performed on the first three (3) marketable production batches and one (1) lot annually, thereafter, according to the approved stability protocol.

2. The results of the stability studies will be provided in the periodic reports as specified by the Agency.

3. CollaGenex Pharmaceuticals, Inc. will withdraw from the market any lots found to fall outside the approved specifications for Oracea™ (doxycycline [redacted] capsules) 40 mg. If there is evidence that the deviation is a single occurrence that does not affect the safety and efficacy of the product, CollaGenex will immediately discuss it with the appropriate chemistry team and provide justification for the continued distribution of that batch. Any change or deterioration in the distributed drug product will be reported as required under 21 CFR 314.81(b)(1)(ii).

Christopher Powala
Vice President
Drug Development & Regulatory Affairs

7/27/05
Date

CollaGenex Pharmaceuticals, Inc., 41 University Drive, Suite 200, Newtown, PA 18940 USA
215-579-7388 voice 215-579-8577 fax

Meeting Date: May 3, 2004 Time: 1:00 p.m. Location: S200A
Meeting ID# 12856

COL-101 (doxycycline [redacted] 40 mg [redacted] Capsules

Indication: Rosacea

Sponsor: Collagenex Pharmaceuticals, Inc.

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

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Shaw Chen, Associate Director for Special Product Review, Botanicals, ODEV, HFD-105
Norman Schmuff, Ph.D., Acting Chemistry Team Leader, DNDCIII, HFD-830
Norman See, Ph.D., Pharmacology/Toxicology Reviewer, DDDDP, HFD-540
Dennis Bashaw, Pharm.D., Biopharmaceutics Team Leader, DPEIII, HFD-880
Ribhi Shawar, Ph.D., Clinical Microbiology Reviewer, DAIDP, HFD-520
Markham Luke, M.D., Ph.D., Clinical Team Leader, DDDDP, HFD-540
Brenda Vaughan, M.D., Clinical Reviewer, DDDDP, HFD-540
Mohamed Alosh, Ph.D., Biostatistics Team Leader, DBIII, HFD-725
Kathleen Fritsch, Ph.D., Bostatistics Reviewer, DBIII, HFD-725
Terri Rumble, Associate Director for Reggulatory Affairs, ODEV, HFD-105
Frank H. Cross, M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

Collagenex Pharmaceuticals, Inc:

Klaus Theobald, M.D., Chief Medical Officer, Collagenex Pharmaceuticals, Inc.
Christopher Powala, Vice President, Drug Development and Regulatory Affairs, Collagenex Pharmaceuticals, Inc.
Phillip Freidenreich, Ph.D., Director, Quality Assurance and Compliance, Collagenex Pharmaceuticals, Inc.
John McPartland, Director, Manufacturing, Collagenex Pharmaceuticals, Inc.
[redacted]
James Leyden, M.D., Dermatologist, Consultant

With reference to the Sponsor's March 16, 2004, Pre-IND/End of Phase 2 Meeting Request/Briefing Package, the following discussion took place:

Chemistry, Manufacturing and Controls:

1. Regarding the certificate of analysis in Attachment #8 of the March 16, 2004, Briefing Package, the Sponsor should indicate in the NDA what testing will be done by [redacted] on receipt of the drug substance from [redacted]
2. The drug substance specification should include acceptance criteria for total impurities, and should reflect specified and unspecified impurities specific to the route of synthesis.

3. In addition, the particle size distribution should be justified by development studies, and should include a bracket range or range for a median particle size.

4. The acceptance criteria for diethylamide should be justified, based on historical data.

5. Page 4 of the Sponsor's cover letter in the March 16, 2004, Briefing Package indicates that stability data reported in Attachment #13 is for a clinical lot. It appears that neither the drug substance nor the drug product, for this lot was manufactured at the proposed commercial site. Consequently, comparative drug substance and drug product data for the clinical lots, and proposed commercial materials should be included in your application.

Pharmacology/Toxicology:

As a review issue under the IND, the Agency may request that the database be improved to include teratology data from studies conducted with doxycycline in both rodents and non-rodents. This decision will, in part, be based upon assessment of the patient population that appears likely to use the product if it is approved. If the population would include teenagers or others that would be at a high risk for unexpected pregnancies, then teratology data specific to doxycycline may be warranted.

Biopharmaceutics:

1. The two pk studies, a multiple-dose steady-state BE study, and a food effect study are appropriately designed and should be sufficient for determining the biopharmaceutic aspects of the proposed COL-101 dosage form.

2. While not related to the fileability of this application, the current package insert contains the standard tetracycline warning about the potential loss of activity of hormonal contraception when tetracyclines are give concomitantly. Given the relatively low doses of doxycycline used here, the Sponsor may wish to investigate the need for such a warning with this product under its current conditions of use.

Clinical Microbiology:

During the meeting, the Sponsor indicated that the dosage of the new formulation results in systemic exposure that is either less than or equal to that obtained with the existing approved product Periostat (Doxycycline hyclate). The Sponsor will provide for review information that this dose and formulation of Doxycycline monohydrate will not adversely affect the microbial flora in a way that could potentially cause harmful effects to the patient or cause increase in bacterial resistance."

Clinical:

Question 2, 3 and 4 from Sponsor's March 16, 2004, Briefing Package:

2. "Does the Division agree with the design and endpoints for the proposed Phase 3 clinical trials?
3. Does the Division agree that 2 Phase 3 trials will be adequate to support approval provided the outcome is positive?
4. Does the Division agree that the design of the Phase 3 protocols will support the indication sought?"

The Sponsor indicated that treatment of papules and pustules of mild to moderate is the intended indication. The Sponsor is not seeking treatment of erythema as an indication.

Agency:

Concerns regarding study design are noted below.

The endpoints are not as recommended at the January 28, 2002, Pre-IND/End of Phase 2 Meeting with comments noted below. At the previous meeting, the Agency recommended that the Sponsor should conduct adequate dose-ranging. It is understood that the Sponsor is relying in part on previous experience with doxycycline and rosacea. However, additional information regarding dose and treatment efficacy and safety for rosacea could be useful (What is the differential effect between the 40 mg dose and other doses used historically? What effect do the different doses have on longevity of response after discontinuing medication? What effect do the different doses have on specific patient conditions, such as mild ocular symptoms associated with rosacea?).

The Sponsor is not planning to explore treatment at higher dose levels for this application because some efficacy has been demonstrated at the proposed level. After much discussion with the Agency regarding the effects of resistance at lower levels of exposure; the Sponsor offered to submit reference materials addressing the issue of development of microbial resistance at the proposed levels.

The Agency indicated that longevity of effect was not needed for drug approval; however, would be useful for labeling. For future development,

1. Comments on Study Design:

   a. Inclusion/Exclusion Criteria:

      i. The Precautions Section of the Package Insert states that concurrent use of tetracyclines may render oral contraceptives less effective; therefore, the inclusion criterion #4 (pg. 173 of Sponsor's March 16, 2004, Briefing Package) should be modified to recommend use of an additional barrier form of contraception if the female volunteer is using an oral contraceptive (as in the PK study, pg. 131 of Sponsor's March 16, 2004, Briefing Package). This recommendation may be revisited if reclassification of the Pregnancy Category for Periostat (Category D) is reconsidered by the Agency.

      ii. Exclusion criteria:

      - Exclusion Criterion #2 provides a washout period of 2 weeks of baseline for use of topical acne treatments. The washout periods should reflect drug pharmacokinetics and pharmacodynamics. Inadequate washout periods may have an unwanted effect on efficacy. The following washout periods have been suggested:

        Topical acne treatment - 4 weeks
        Topical or systemic corticosteroids - 4 weeks
        Topical or systemic anti-inflammatories - 4 weeks
        Topical or systemic antibiotics - 4 weeks
        Systemic retinoids - 3 months

The Sponsor indicated that continuous use of some anti-inflammatory medication would be permitted. The

Sponsor also will permit use of anti-inflammatory medication such as aspirin at doses recommended for cardiovascular health.

- Exclusion criterion #14, Tab 7, pg. 8: "Patients with significant ocular rosacea and/or blepharitis/meibomianitis are to be excluded." "Significant" should be defined. Will patients receive an ophthalmologic examination prior to study entry? Does the study drug at the doses studied improve the ocular symptoms of rosacea?

The Sponsor indicated that patients needing referral to Ophthalmology for blepharitis/meibomianitis at baseline or who needs a referral during the study will be excluded from the study. No claim for treatment of blepharitis/meibomianitis will be made.

b. Study Procedures:

i. A full-face photograph will be taken at the baseline visit and at each visit. How are photographs to be used (e.g., clinical evaluations, marketing tool, etc.)? If the Sponsor is planning to use the photographs for marketing purposes, the Agency would like to participate in the selection of photographs that would be considered to be representative. Photographs taken of subjects should not be used during patient evaluations. Investigators should be blinded to prior efficacy evaluations and each evaluation should use a static global assessment.

The Sponsor indicated that photographs will not be used for study evaluation and that they will be available for submission to the Agency. The Agency requested that all photographs including those selected for marketting be submitted for review.

Section 7, pg. 175 of Sponsor's March 16, 2004, Briefing Package: The protocol indicates that women cannot be evaluated within one week of their period or during their period during pre-study screening and baseline evaluations. For post-baseline visits, the Agency recommends that restrictions should not be placed on evaluations within one week of menses or during their menses (potential increase in erythema). However, notation could be made in the CRF regarding such a condition. It will be useful to know whether the study drug alters the disease process in women that are peri-menstrual.

The Sponsor indicated that the requirement that women cannot be evaluated within one week of their period or during their period during pre-study screening and baseline evaluations will be removed.

iii. The study drug is taken once daily for 16 weeks (efficacy end point). The patient should return for assessment at 4 weeks post treatment for duration of treatment effect assessment.

iv. Diet, the use of non-soap cleansers, and the use of sunscreens should be addressed in the protocol. For example for rosacea any protocol instruction concerning diet or use of sunscreens might be included or stated as not an exclusion criterion. No particular rosacea diet is recommended; however, in some studies patients were instructed to avoid any foods and beverages that, in their own experience, might provoke erythema, flushing, and blushing (including spicy food and alcoholic beverages). Patients were instructed to avoid thermally hot drinks, including hot coffee and tea. A list of acceptable sunscreens

and non-soap cleansers should be provided to study participants, rather than recommending one sunscreen or cleanser.

The Sponsor does not plan to include commonly recommended rosacea management guidelines as listed above. The Sponsor agreed to provide protocol instructions to the investigators not to recommend diet, the use of non-soap cleansers, and the use of sunscreen in management of study patients. The protocol will instruct investigators to instruct the study participants that these measures will not reduce pimples or protect from doxycycline photosensitivity. Most sunscreens do not provide protection in the visiblelight range; therefore, sunscreen use will not protect from doxycyline photosensitivity reaction since activation is in the visible light range. The Sponsor agreed to list sunscreens as concomitant medications and to provide listings of the types used. The Sponsor stated that photosensitization has not been observed in over 500 pateints studied.

c. Investigator's Global Assessment/Erythema Scale:

i. The inclusion criterion allows for the presence of ≤ 2 nodules; however, the Clinician's Global Severity Score does not include the presence of nodules.

ii. Appendix A, pg. 193 of Sponsor's March 16, 2004, Briefing Package: The Agency recommends that the Clinician's Global Severity Score be modified to include static clinical descriptors and categories (e.g., Clear, Almost Clear, Mild, Moderate, and Severe). The Clinician's Global Severity Score appears to be similar to an Investigator's Global Assessment (IGA) scale; however, as an IGA the Agency recommends use of clinical descriptors (e.g., papules, nodules, slight pinkness, fiery redness, telangiectasia, etc.) The Sponsor's Clinician's Global Severity Score includes an area specific "score" which is not a clinical global assessment.

iii. On the IGA, "clear" category should not include mild erythema. For a systemic drug, no erythema or minimal pinkness with 0 - 2 scattered papules/pustules present is recommended to describe "clear".

Addendum: No papules/pustules present should be present in the "Clear" category on the IGA.

The Sponsor proposes to remove erythema from the Clinician's Global Severity Scale and evalute erythema as a secondary variable since the Sponsor is not seeking the treatment of erythema as an indication. The Agency informed the Sponsor that this issue will be discussed and addressed in an addendum to the minutes of today's meeting.

Addendum:

Erythema may be evaluated separately as a secondary variable and not be included in the Clinician's Global Severity Scale as proposed by the Sponsor. Erythema will be addressed as a secondary variable for labeling and erythema should not get worse.

The Sponsor should also address the asymmetry of the Clinician's Global Severity Scale in that patients with 10 lesions at entry could have a reduction of one lesion and be considered a success on the Clinician's Global

Severity Scale if the scale is dichotomized at Grade 0 or1. As previously mentioned, the Agency recommends that success be considered "Clear" and "Almost clear" with all others as failure.

iv. The Agency recommends that the IGA be dichotomized a priori to success (clear, almost clear) and failure.

v. Appendix B, pg. 193 of Sponsor's March 16, 2004, Briefing Package: Clinician's Erythema Assessment Scale is a scoring system. Sponsor is reminded that if a reduction of erythema is sought as part of the indication, then this parameter should be incorporated into the IGA as a static assessment made by the investigator rather sum of a score. The erythema scale should also be dichothomized into success and failure a priori.

d. Comments on Endpoints:

The endpoints are not as recommended at the January 28, 2002, Pre-IND/End of Phase 2 Meeting to support the rosacea indication.

i. The Agency recommends the following two primary efficacy endpoints for demonstrating efficacy in treatment of rosacea: 1) inflammatory lesion counts (papules, pustules, and nodules) and 2) the investigator's static global assessment (IGA). Clinical signs (erythema and telangiectasia) should be incorporated into the static global assessment.

ii. As noted above, the Agency recommends that the IGA be a static scoring system. The IGA should be dichotomized a priori to success and failure.

iii. For approval, success must be demonstrated in both the IGA and in lesion counts. There should be a statistically significant reduction in inflammatory lesions at study endpoint.

iv. The Sponsor proposes a Clinician's Erythema Score (pg. 180 of Sponsor's March 16, 2004, Briefing Package) which is obtained at endpoint as a sum obtained from evaluation of five facial areas (scale of 0 to 4). The Sponsor is reminded that if a reduction of erythema is sought as part of the indication, then this parameter should be incorporated into the IGA. Erythema should also be a separate assessment with static descriptors and not assessed as improvement from baseline. The erythema scale should also be dichotomized into success and failure a priori. Erythema will only be considered if the trial is a success regarding the IGA and lesion counts.

e. Comment on Safety & Sample Size:

Repeated intermittent use of this drug product can be expected; therefore, the Sponsor should refer to ICH-E1A Guideline for Industry (The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions) regarding the bare minimum sample size for patients on active drug in trials to demonstrate safety. Investigators should actively ask subjects regarding vaginal candidiasis, photosensitivity, and other common side effects seen with doxycycline during the clinical studies.

The Sponsor said that it has right of reference to data regarding a previously approved drug product with higher bioavailability than the currently proposed dose. The Sponsor was advised that safety could be extrapolated from higher to lower bioavailability found in a comparative biostudy.

Biostatistics:

Question 2 from Sponsor's March 16, 2004, Briefing Package: "Does the Division agree with the design and end points for the proposed Phase 3 clinical trials?"

Agency:

1. Please refer to the clinical comments (above) for the recommended primary endpoints. The study should be adequately powered for the endpoints recommended by the Agency.

2. The protocol includes a large number of secondary endpoints. The Sponsor should consider a limited number of clinically relevant endpoints or an adjustment for multiplicity may be needed.

During the meeting the Sponsor said that it could classify clinically relevant secondary endpoints into two groups: a small number that might be considered for labeling, and those with only exploratory interest.

3. The ITT population should be defined as all subjects randomized and dispensed treatment medication, rather than as randomized patients for whom it cannot be excluded that they have taken the study medication at least once.

4. The protocol states that "Patients who discontinue treatment prior to week 16 will be included in the PP analysis. For patients with missing data at week 16, no imputation technique to compensate for missing data will be used in the PP analysis." (Section 11.4.2 of Sponsor's March 16, 2004, Briefing Package) The protocol should clarify how the patients with missing data will be included in the per protocol analysis if no data imputation will be done. In addition, the protocol should include a list of protocol violations that will exclude subjects from the per protocol analysis.

During the meeting the Agency said that any patients who otherwise meet all criteria for inclusion in the per protocol analysis and yet have missing data should have their results imputed in a way consistent with the imputation for the ITT population. This is not likely to involve many patients as most patients who meet the criteria for the per protocol population will have observed data.

5. The recommended significance level for testing treatment by center interaction is 0.10 rather than 0.05. If the interaction is significant, the protocol should plan for a sensitivity analysis to assure that results are not driven by only a few centers.
6. The protocol should include subgroup analyses by race and age in addition to gender. The Sponsor should clarify why subgroup analyses will be performed for patients with baseline lesion counts above 17 for the primary endpoint and above 20 for the secondary endpoints. For consistency, the same cutoff point should be used for both the primary and secondary endpoint subgroup analyses.

7. The protocol states that no formal interim analyses are planned for the study. The Sponsor should clarify whether they intend to conduct any "informal" interim analyses. Any looks at the interim data should be justified within the goals of the study and adequately described in the protocol and adjusted for in the analysis.

8. It appears unlikely that the individual counts of papules, pustules, and especially nodules are normally distributed. The protocol should also specify an alternative methodology to analyze these endpoints in case normality is not achieved.

9. The protocol stated that "all alternative or additional statistical analyses that may be performed will be laid down in amendments prior to unblinding of the randomization code" (p. 178 of Sponsor's March 16, 2004, Briefing Package). The Agency requests that all analyses be pre-specified in the protocol, as only pre-specified analyses can be used to support efficacy claims.

Project Management:

1. All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.

2. The Sponsor is encouraged to submit its revised protocol for the indication of rosacea as a Special Protocol to its original IND through the 45-day Special Protocol Assessment (SPA) mechanism for Agency review and comment, prior to study initiation.

3. The Sponsor's Pre-IND/End of Phase 2 Meeting has been assigned IND 67,833. The Sponsor should reference this number when submitting the proposed IND.

The meeting ended amicably.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____