Additional comments:

3. This application is an eCTD NDA. YES X ☐

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES X ☐ NO ☐

- Exclusivity requested? YES, X Years 3 NO X ☐

NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES X[NO ☐
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
YES X☐ NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? N/A YES ☐ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO X ☐

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES X ☐ NO ☐

(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☐ NO ☐
N/A

- PDUFA and Action Goal dates correct in tracking system? YES X NO ☐
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: Simcor (65,187), Niaspan (34,613), Advicor (56,027)

- Are the trade, established/proper, and applicant names correct in COMIS? YES X☐ NO ☐
  If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 9/26/06 NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) NO X ☐
  _____
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES X ☐ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES X ☐ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? Will be ☐ NO ☐
YES

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☐ NO ☐
  Will be
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A X ☐ YES ☐ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A X ☐ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA X ☐ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application: N/A

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X ☐ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES X ☐ NO ☐
- If a parenteral product, consulted to Microbiology Team? N/A YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: 6/14/07

NDA #: 22-078

DRUG NAMES: Simcor (niacin extended-release/simvastatin) Tablets

APPLICANT: Abbott Laboratories

BACKGROUND: This is a fixed dose combination of 2 approved products: Niacin (Niaspan) and Simvastatin (Zocor). The firm is seeking approval of 500mg/20 mg, 750 mg/20mg, and 1000mg/20 mg Tablets for use in patients with primary hypercholesterolemia, mixed dyslipidemia, and hypertriglyceridemia.

ATTENDEES: Julie Golden, MD-Clinical Reviewer
Janice Derr, PhD-Clinical Statistical Reviewer
Sally Choe, PhD-Acting Team Leader, Biopharmaceutics
Sang Chung, PhD-Biopharmaceutics Reviewer
Indra Antonipillai, PhD-PharmTox Reviewer
Kati Johnson-Project Manager

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	Reviewer
Medical:	Iffat Chowdhury, MD
Secondary Medical:	Eric Colman, MD
Statistical:	Janice Derr, PhD
Pharmacology:	Indra Antonipillai, PhD
Statistical Pharmacology:	N/A

Chemistry: John Hill, PhD
Environmental Assessment (if needed): N/A
Biopharmaceutical: Sang Chung, PhD
Microbiology, sterility: N/A
Microbiology, clinical (for antimicrobial products only): N/A
DSI: Andrea Slavin
OPS:
Regulatory Project Management: Kati Johnson
Other Consults:

Per reviewers, are all parts in English or English translation? YES X NO ☐

If no, explain:

CLINICAL FILE X☐ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES X NO ☐

  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO X

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

  N/A X YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A X☐ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE X REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE X REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? ☐ NO ☐
  YES

PHARMACOLOGY/TOX N/A ☐ FILE X☐ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☐

CHEMISTRY FILE X☐ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES X NO ☐
- Sterile product? YES ☐ NO X

  If yes, was microbiology consulted for validation of sterilization?

  YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

X The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

X☐ No filing issues have been identified.

☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1.X Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3.☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4.X☐ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5X☐ Convey document filing issues/no filing issues to applicant by Day 74.

_____
Regulatory Project Manager

**APPEARS THIS WAY
ON ORIGINAL**

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES X NO ☐

*If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): NDA 19-766, Zocor (simvastatin) Tablets

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES ☐ NO X

*If "**Yes**," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product? YES ☐ NO X

*If "**Yes** "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES ☐ NO X

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

   *If "**No**," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

   *If "**Yes**," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

   *If "**No**," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*

   Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO X ☐

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," to (c), proceed to question 7.*

***NOTE:** If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No**," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☐ NO X ☐

*If "**No**," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). **This is a fixed dose combination product of Simvastatin + Niacin ER**

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO X ☐

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO X

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO X

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES X NO ☐

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

X 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES ☐ NO X

*If "**Yes**," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*
Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES X NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A ☐ YES ☐ NO X

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO X

If "**Yes**," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

---

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

/s/

Kati Johnson
6/25/2007 01:54:33 PM
CSO

Building 22, Rm 3113
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-2419
Fax: 301-796-9712
Email: Iffat.Chowdhury@fda.hhs.gov

From: Johnson, Kati
Sent: Tuesday, June 26, 2007 5:26 AM
To: Chowdhury, Iffat
Subject: RE: DSI possible inspection list and question for applicant

list of possible inspection sites. Does that mean it isn't final? DSI will inspect whatever sites we ask them to.
KJ

NOTE NEW E-MAIL ADDRESS BELOW

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Phone-301-796-1234
Fax-301-796-9722
Kati.Johnson@fda.hhs.gov

From: Chowdhury, Iffat
Sent: Monday, June 25, 2007 3:26 PM
To: Johnson, Kati
Subject: DSI possible inspection list and question for applicant

Hi Kati,
The request I would like to ask the applicant: "Please clarify the location in the NDA or submit a rationale for assuming the applicability of foreign data in the submission to the U.S. population."

Attached is the list of possible DSI inspection sites:
<< File: possible site inspections 2.doc >>
Thanks,
Iffat

Johnson, Kati

From: Chung, Sang
Sent: Thursday, June 21, 2007 9:37 AM
To: Johnson, Kati
Subject: RE: NDA 22-078, Simcor, 74-day letter

Let me explain the situation and I'll follow your guide from there. The sponsor conducted 3 PK studies and [redacted] will be in the proposed labeling. Third study was prematurely terminated. In the EDR, I found only one electronic data file (019-03-04-CP). The sponsor might submit data from other 2 studies as PDF/paper. In these regards, I feel my request is not related to filing issue/deficiency and is more or less review aids. Please, let me know if you need any further in these regards.

Thanks,

Sang

From: Johnson, Kati
Sent: Thursday, June 21, 2007 8:41 AM
To: Chung, Sang
Subject: RE: NDA 22-078, Simcor, 74-day letter

I will include that in the letter, but make it clear that it is just a request
Thanks.
KJ

NOTE NEW E-MAIL ADDRESS BELOW

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Phone-301-796-1234
Fax-301-796-9722
Kati.Johnson@fda.hhs.gov

From: Chung, Sang
Sent: Thursday, June 21, 2007 8:09 AM
To: Johnson, Kati
Cc: Colman, Eric C; Choe, Sally
Subject: RE: NDA 22-078, Simcor, 74-day letter

Kati,

There was no filing issue from clinical pharmacology perspectives.

Meanwhile, I would like to request electronic data files (e.g., plasma concentrations and PK parameters) for Phase I studies (i.e., CP-03-012004, 019-04-05-CP) if possible.

Thanks,

Sang

From: Johnson, Kati
Sent: Thursday, June 21, 2007 7:50 AM
To: Colman, Eric C; Chowdhury, Iffat; Derr, Janice; Chung, Sang; Antonipillai, Indra; Davis Bruno, Karen L

Subject: NDA 22-078, Simcor, 74-day letter

Hi guys,
There weren't any potential problems identified in this application at our filing meeting. The 74-day letter must issue by COB next Friday, 5/29. I am planning to issue it on Wednesday. If you identify any issue by then, let me know so that I can include them in the letter.

Thanks everyone, Kati

NOTE NEW E-MAIL ADDRESS BELOW

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Phone-301-796-1234
Fax-301-796-9722
Kati.Johnson@fda.hhs.gov

4/20/07

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-078

NDA ACKNOWLEDGMENT

Abbott Laboratories
Attention: Jeanne M. Fox
Sr. Director, Global Pharmaceutical Regulatory Affairs
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Ms. Fox:

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

Name of Drug Product: Simcor (niacin extended-release and simvastatin) Tablets 500 mg/20 mg, 750 mg/20 mg and 100 mg/20 mg

Review Priority Classification: Standard

Date of Application: April 17, 2007

Date of Receipt: April 17, 2007

Our Reference Number: NDA 22-078

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 16, 2007 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 17, 2008.

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. We note that you have not fulfilled the requirements. **We note that a waiver of pediatric studies was granted for this application in a letter to your IND 65,187 dated December 12, 2006.**

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at 301-796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Kati Johnson
4/20/2007 11:31:23 AM

2/6/07

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 65,187

Responses to Q 15→22 not included. See preliminary responses.

Kos Life Sciences
Attention: Valerie Ahmuty
Director, Regulatory Affairs
2100 N. Commerce Parkway, Suite 300
Weston, FL 33326-3234

Dear Ms. Ahmuty:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Niacin ER/Simvastatin Tablets.

We also refer to the meeting between representatives of your firm and the FDA on September 26, 2006. The purpose of the meeting was to discuss your NDA submission planned for March 29, 2007.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 26, 2006
TIME: 10 am
LOCATION: White Oak Campus, Building 22, Conference Room 1309
APPLICATION: IND 65,187
DRUG NAME: Niacin ER/Simvastatin Tablets
TYPE OF MEETING: Pre-NDA

MEETING CHAIR: Mary Parks, MD

MEETING RECORDER: Kati Johnson

FDA ATTENDEES:
Division of Metabolism & Endocrinology Products
Mary Parks, MD-Director
Eric Colman, MD-Deputy Director
Julie Golden, MD-Clinical Reviewer
Karen Davis-Bruno, PhD-Supervisor, Pharmacology/Toxicology
Indra Antonipillai, PhD-Pharmacology/Toxicology Reviewer
Kati Johnson-Project Manager

Office of Translational Sciences, Office of Biostatistics
Todd Sahlroot, PhD-Team Leader
Janice Derr, PhD-Statistical Reviewer

Office of Translational Sciences, Office of Clinical Pharmacology
Hae Young Ahn, PhD-Team Leader
Wei Qiu, PhD-Primary Reviewer

Office of New Drug Quality Assessment
Su Tran, PhD-Product Assessment Lead

EXTERNAL CONSTITUENT ATTENDEES:
Kos Life Sciences, Inc.
Valerie Ahmuty-Director, Regulatory Affairs
Daiva Bajorunas, MD-VP, Product Realization
Marvin Blanford, PharmD-Sr. VP, Drug Safety and Regulatory
Michael Forem-Project Manager
Laurence Keller, MD-Sr. Medical Director, Product Realization
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Dwain Tolbert, PhD-Director of clinical Pharmacology
David Warnock, PhD-Executive Director, Regulatory Affairs

BACKGROUND:
This compound is a fixed dose combination tablet for the treatment of dyslipidemia. There are two Phase 3 studies:
-SEACOAST-The Safety and Efficacy of a combination of Niacin ER and Simvastatin in Patients with Dyslipidemia (Protocol 019-01-03-CR).
-OCEANS-An Open-Label Evaluation of the Safety and Efficacy of a Combination of Niacin ER and Simvastatin in Patients with Dyslipidemia.

The NDA is planned for submission March 29, 2007.

DISCUSSION POINTS:
The firm's questions are followed by our **bolded** responses.

General and Administrative

1. The product has been referred to as "NS tablets" (an abbreviation of the combination of the niacin and simvastatin active ingredients in the tablets). As noted in the original IND and various amendments, Kos would like the FDA to comment on the acceptability of the name "SIMCOR™" as a possible proprietary name for the product to be used for commercial purposes.

Response: The proposed tradename will be consulted to the Office of Drug Safety when the NDA is submitted. A determination as to the acceptability of that name will be made during the review process.
Meeting Discussion: None

2. Given previous discussions with the Agency with respect to the risk-benefit assessment of Niaspan use in pediatric populations, Kos plans to submit a waiver for the conduct of pediatric studies for NS. Does the Agency agree?

Response: We agree. Please submit this request under the IND and we will issue a letter. Cite our letter date in the cover letter of the NDA to be submitted.
Meeting Discussion: None

3. The NDA will be submitted as an e-CTD. Other than the FDA forms that require an actual signature, Kos intends that the submission be only electronic with no paper review copies submitted. Does the agency agree?

Response: Yes
Meeting Discussion: None

Nonclinical Pharmacology and Toxicology

4. Consistent with the NS NDA being a 505(b)(2) application, Kos will provide legacy reports in Module 4 for niacin mutagenicity studies conducted by Kos in support of other applications (e.g., for European applications). Please note that summaries of these reports were previously provided to the Niaspan NDA 20-381 in the 2002-2003 annual report dated September 22, 2003. Also consistent with a 505(b)(2) application, no toxicology studies for either simvastatin alone or the combination of simvastatin and niacin have been conducted. Does the Agency agree with the proposed content of Module 4?

5. For the relevant sections of Module 2, brief summaries and overviews will be provided for the individual components of this combination product. These will be based primarily upon information referenced from the Zocor® (simvastatin) NDA, current Zocor approved labeling, and a recent literature search for relevant new nonclinical pharmacology and toxicology information.

Corresponding information for the niacin component from the Niaspan NDA 20-381, Niaspan current label, and a literature search will also be compiled and submitted. Kos does not expect to write extensive summaries and tables based upon either set of information. Does FDA agree with this approach to Module 2?

Response: The approach in general appears reasonable since both are approved drugs. Brief summaries and overviews for the individual components of this combination product will be adequate.
Meeting Discussion: None

Biopharmaceutics

6. Previous agreement with the Division was that Kos would provide results of a pilot relative bioavailability study using the lowest tablet strength (already submitted under the IND) and a pivotal four-way relative bioavailability study that would establish the lack of interactions using the highest tablet strength. No food effect study would be required.

   Subsequently, Kos added ——— to the formulation, and in IND amendments #043 dated December 22, 2005 (meeting request) and #052 dated March 02, 2006 (information package), requested that FDA consider whether an additional bioequivalence (BE) study would be necessary for filing. Per the FDA letter dated June 1, 2006, it is our understanding that a linking BE study is not required if simvastatin dissolution profiles are similar between the clinical formulations and the formulations containing the ———

   In the June 1, 2006 letter, FDA noted that a single pivotal (interactions) study conducted with the highest strength of the modified formulation should be sufficient, and recommended a single tablet administration for this study. However, Kos had already begun this study using two NS 1000/20 tablets since this dose represents the highest dose expected by label for the combination product. Does the Agency agree that this approach is acceptable? The study protocol was submitted in IND amendment #061, dated May 2, 2006.

Response: This is acceptable.
Meeting Discussion: None

7. The biopharmaceutics data will be provided in SAS transport files and terms will not be in CDISC format. Kos does not plan to submit Excel files in addition to SAS files. Does the Agency agree?

Response: Yes
Meeting Discussion: None

8. Bioequivalence of niacin extended-release —— as manufactured by the ——— —— facilities was established in the Niaspan and Advicor NDA submissions, 20-381 and 21-249, respectively. Should these reports be appended electronically in the SIMCOR CTD or is a simple reference in text sufficient? The Advicor NDA was an electronic submission compliant with the eNDA folder system.

Response: The reports should be appended electronically in the SIMCOR CTD.

Clinical Studies

9. Kos submitted a request for advice to the agency in IND amendment #025 on June 24, 2005 regarding our belief that a QTc evaluation is not required. As of this writing, no response has been provided. Since no issues have been raised by FDA we believe that no additional data are required. Does FDA agree?

Response: Yes
Meeting Discussion: An FDA request for a QTc study may be made if there is a significant drug interaction seen in the clinical studies. In general, drugs with wide therapeutic index demonstrating a twofold or greater increment in systemic exposure measures could be potentially significant. In response to a question from Kos, a 30-40% increase would not likely be an issue.

10. Kos plans to submit only the CRFs for deaths, SAEs, and for all adverse events resulting in discontinuation, except those discontinuations due only to flushing. Does the Agency agree?

Response: Yes, as this complies with the regulation.
Meeting Discussion: None

Statistics/Clinical Studies

The next two questions on statistical analysis are in reference to the SEACOAST study.

11. Subsequent to the discussions with the Agency on March 14, 2005, we intend to use the mixed-model repeated-measures approach as the primary method for handling missing data. We expect that the data will be Missing at Random or Missing Completely at Random, in which case this method gives us unbiased estimates. A supportive, or robustness, analysis by the Last Observation Carried Forward (LOCF) method will also be performed for the primary efficacy analysis. Please see the revised Statistical Analysis Plan provided for reference in Attachment 2. Does the Agency agree with this plan?

Response: We do not concur with using the ITT analysis population with no imputation for missing data as the primary analysis population. We continue to recommend the use of the ITT analysis population with Last Observation Carried Forward (LOCF) imputation as the primary analysis population. We made this recommendation in the telephone conference on March 14, 2005. We continue to be interested in comparing the results from each analysis population, using the proposed mixed effects repeated measures model (MMRM). We note that the SAP does include the use of the ITT/LOCF analysis population in a supportive analysis.

Meeting Discussion: FDA reiterated its concern with MMRM, as it may overestimate the treatment response if there is an imbalance in dropouts due to flushing in the treatment groups. A low percentage of dropouts combined with a similar number of dropouts across treatment groups might make the MMRM more reasonable, however, the ITT will remain the primary analysis looked at by the FDA. The firm should provide both analyses.

12. The statistical testing for the primary analysis in both the Simvastatin Low Dose (SLD) and Simvastatin High Dose (SHD) groups will be performed in a step-down manner, as suggested by Dr. Sahlroot at the meeting with the Agency on March 14, 2005. For the SLD group, the first step will be a superiority test of 2000/20 vs S20, followed by a test of 1000/20 vs. S20. For the SHD group, the first step will be a non-inferiority test of 2000/40 vs. S80, followed by a non-inferiority test of 1000/40 vs. S80. Each step will be a gate-keeper for the succeeding step (i.e., you cannot proceed to the next step unless the first step is significant). Does the agency agree that this is in-line with previous discussion?

Response: **We concur with the process described in the SAP for managing Type I error in the multiple statistical tests that are part of the primary efficacy evaluation.**
Meeting Discussion: None

13. Does the Agency agree with the bullets below?

- The SEACOAST and OCEANS data will use CDISC version 3.1 format
- The CDISC datasets will be in SAS transport files
- We do not plan to send domain data listings or patient profile listings
- The maximum size of the datasets will not exceed 100MB with the exception of the laboratory results file, which we expect to be between 300 to 400MB. May we submit this file in its current size or must it be separated into 100MB subsets? (Our understanding of the CDISC rules is that there should be only one laboratory dataset.)

Response: **Please contact Ken Edmunds at 301-796-0585.**
Meeting Discussion: None

14. Both SEACOAST and OCEANS had several protocol amendments during their conduct. We will submit only the last (current) versions of the CRFs as annotated CRFs. Does the Agency agree?

Response: **Yes; however, annotated CRFs from prior versions may be requested during the review cycle.**
Meeting Discussion: None

DECISIONS (AGREEMENTS) REACHED:

None

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

None

ATTACHMENTS/HANDOUTS:

None

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

/s/

Kati Johnson
2/6/2007 12:26:15 PM

Peds Waiver

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

12/7/06

IND 65,187

Kos Life Sciences, Inc.
Attention: Valerie Ahmuty
Director, Regulatory Affairs
2100 N. Commerce Parkway, Suite 300
Weston, FL 33326-3234

Dear Ms. Ahmuty:

Please refer to your submission dated October 26, 2006, requesting a waiver for pediatric studies for Niacin extended-release/Simvastatin Tablets.

We have reviewed the submission and agree that a waiver is justified for Niacin extended-release/Simvastatin Tablets for treatment of dyslipidemia for the entire pediatric population because of the following:

1. The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients;
2. Studies are highly impractical because the number of such patients is so small and geographically dispersed.

Accordingly, at this time, a waiver for pediatric studies for your application is granted under section 2 of the Pediatric Research Equity Act.

Please include a copy of this letter in any future NDA submission.

If you have questions, contact Kati Johnson, Chief, Project Management Staff at 301-796-1234.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, MD
Director
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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