8/27/08

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-224

Abbott Laboratories
Attention: Natalie Tolli
Associate Director, Dyslipidemia
200 Abbott Park Road
Dept. PA76, Bldg. AP30-1NE
Abbott Park, IL 60064-6157

Dear Ms. Tolli:

Please refer to your New Drug Application (NDA) submitted December 7, 2007 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fenofibric Acid Capsules 45 mg, 135 mg.

We have completed our review of your proposed tradename, TriLipix, and have the following comments regarding specifics labeling pieces.

A. **Retail Container Labels (45 mg and 135 mg)**
Present the proprietary name as Trilipix, in standard upper/lower case presentation.

B. **Sample Blister Labels**
Present the proprietary name as Trilipix, in standard upper/lower case presentation.

C. **Sample Carton Labeling (45 mg and 135 mg)**
1. Present the proprietary name as Trilipix, in standard upper/lower case presentation.
2. Present the proprietary name, TriLipix, in one color.
3. Improve the readability of the NDC number and the net quantity.

D. **Insert Labeling**
1. Present the proprietary name as Trilipix, in standard upper/lower case presentation.

If you have any questions, call Kati Johnson, Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
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/

Eric Colman
8/27/2008 09:18:24 AM
Eric Colman for Mary Parks

3/27/08

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-224 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Trilipix Delayed Release Capsules
Established Name: fenofibric acid
Strengths: 45 mg, 135 mg

Applicant: Abbott Laboratories
Agent for Applicant (if applicable): N/A

Date of Application: 12/7/07
Date of Receipt: 12/7/07
Date clock started after UN: N/A
Date of Filing Meeting: 1/31/08
Filing Date: 2/5/08
Action Goal Date (optional): User Fee Goal Date: 10/7/08

Indication(s) requested: dyslipidemia (mixed dyslipidemia [in combination with statins] or as monotherapy, primary hypercholesterolemia [as monotherapy], or hypertriglyceridemia [as monotherapy])

Type of Original NDA: (b)(1) ☐ (b)(2) X
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A 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). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S X P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 2
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES X NO ☐

User Fee Status: Paid X Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO X
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO X

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO X
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES X NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES X NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES X NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☐
   This application is: All electronic X Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format X
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES X NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   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 ☐
  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)? YES X 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 X

- 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: 70,345

- 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) July 20, 2007 NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) September 13, 2005 NO ☐
  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? AWAITING TRADENAME DECISION ☐ NO X
YES

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☐ NO x
REVISED LABELING (WITH TRADENAME) TO BE SUBMITTED 4/1/08
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☐ YES ☐ NO x

- 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:

- 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? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: 1/31/08

NDA #: 22-224

DRUG NAMES: Trilipix (fenofibric acid) Delayed Release Capsules

APPLICANT: Abbott

BACKGROUND: Fenofibric acid is the metabolite of fenofibrate, for which there are multiple approved 505(b)(1) and 505(b)(2) applications.

ATTENDEES:
Division of Metabolism and Endocrinology Products
Mary Parks, MD-Director
Eric Colman, MD-Deputy Director, Lipid Team Leader
Karen Davis Bruno, PhD-Supervisory PharmTox
Indra Antonipillai, PhD-PharmTox Reviewer
Kati Johnson-Project Manager

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

Discipline/Organization	Reviewer
Medical:	Julie Golden, MD
Secondary Medical:	Eric Colman, MD
Statistical:	Japo Choudhury, PhD
Pharmacology:	Indra Antonipillai, PhD
Statistical Pharmacology:	
Chemistry:	Yvonne Yang, PhD
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Manoj Khuranna, PhD
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI: Susan Leibenhaut (Clinical), Mike Skelly (Biopharm)	
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	☐	REFUSE TO FILE	☐	

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

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

- GLP audit needed? YES ☐ NO X

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.

- ☐ No filing issues have been identified.
- X 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. ☐ 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.

Kati Johnson
Regulatory Project Manager

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 ☐

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(e))

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 X NO ☐

(***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 X NO ☐

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

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): nda 21-656, Tricor (fenofibrate) Tablets

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)?
FIRM IS REFERENCING PUBLISHED ARTICLE FOR DRUG DRUG INTERACTION STUDY WITH SIMVASTATIN. NOT YET CLEAR IF NECESSARY FOR APPROVAL
YES ☐ NO ☐

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"). REFERENCING A DRUG DRUG INTERACTION STUDY

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 YES ☐ NO x

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)).

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 ☐ NO x

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): FIRM SAID THEY WILL BE SUBMITTING A PARAGRAPH II CERTIFICATION

☐ 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 x NO ☐

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 –DRUG DRUG INTERACTION STUDY WITH SIMVASTATIN
Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES ☐ NO x

- 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
3/27/2008 01:12:03 PM
CSO

2/12/08

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-224

Abbott Laboratories
Attention: Natalie Tolli
Associate Director, GPRA
Dept. RA76, Bldg. AP30-1E
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Ms. Tolli:

Please refer to your new drug application (NDA) dated December 7, 2007, received December 7, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Fenofibric Acid Capsules, 45 mg, 135 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is October 7, 2008.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

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 acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients 0 to < 10 years, and for a deferral of pediatric studies for this application for pediatric patients 10 to 18 years.

We have the following requests for information:

Chemistry, Manufacturing and Controls

1. Because the dosage strengths 45 mg and 135 mg are based on "fenofibric acid", the established name of your product is "fenofibric acid". Revise all labeling, where applicable, to replace "choline fenofibrate" with the correct established name "fenofibric acid".
2. The dosage form of your product is a delayed-release capsule. Revise all labeling, where applicable, to state "delayed release capsules".
3. Provide to the NDA the general properties of the drug substance and the regulatory specification of the drug substance.
4. Provide to the NDA the complete quantitative and qualitative composition of the drug product (i.e., to include the composition of the "mini-tablet"). Revise all labeling, where applicable, to add the inactive ingredients present in the gelatin capsule shell.

5. Provide additional stability data for the product batches manufactured at the commercial sites prior to Month 5 of the NDA review clock.
6. Provide additional information to show that the test method RTM.C311 (Identity and Assay) was adequately validated for the determination of degradation products in support of your stability data that show no degradation of the product.

Clinical Statistics

Please provide both the tables and graphs for the cumulative distribution functions (CDF) for the endpoints (LOCF at the end of the study) of primary efficacy variables.

3/24/08 Submission

If you have any questions, call Kati Johnson, Regulatory Project Manager, at 301-796-1234.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolism & 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
2/12/2008 01:42:14 PM
signing for Enid Galliers

1/3/08

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-224

NDA ACKNOWLEDGMENT

Abbott Laboratories
Attention: Natalie Tolli
Associate Director, Dyslipidemia
Dept. RA76, Building AP30-1NE
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Ms. Tolli:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Fenofibrate Capsules, 45 mg. and 135 mg.

Date of Application: December 7, 2007

Date of Receipt: December 7, 2007

Our Reference Number: NDA 22-224

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 February 5, 2008 in accordance with 21 CFR 314.101(a).

The NDA number provided above be cited 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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-

standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

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

Sincerely,

{See appended electronic signature page}

Kati Johnson
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
1/3/2008 12:45:59 PM

8/16/07

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 70,345

Abbott Laboratories
Attention: Natalie Tolli
Associate Director, Dyslipidemia
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Ms. Tolli:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ABT-335 (Choline fenofibrate) Capsules.

We also refer to the pre-NDA meeting between representatives of your firm and the FDA on July 20, 2007. The purpose of the meeting was the following:

1. To review the preliminary efficacy and safety results of the 3 co-administration Phase 3 studies of ABT-335 with statins, in support of the proposed co-administration indication.
2. To obtain agreement with the Agency on the pediatric study plans for ABT-335.
3. To confirm that the Agency is in agreement with the proposed content and structure of the planned NDA, including the content of the nonclinical and clinical sections.

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 Kati Johnson, Regulatory Project Manager, 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

Appears This Way
On Original

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	July 20, 2007
TIME:	9:30 am – 10:30 am
LOCATION:	White Oak Campus Building 22, Room 1313 10903 New Hampshire Avenue Silver Spring, MD 20903
APPLICATION:	IND 70,345
DRUG NAME:	Choline Fenofibrate (ABT-335) Capsules
TYPE OF MEETING:	Pre-NDA
MEETING CHAIR:	Eric Colman, MD
MEETING RECORDER:	Kati Johnson

FDA ATTENDEES:

Office of Drug Evaluation II
Robert Meyer, MD-Director
Curtis Rosebraugh, MD-Deputy Director

Division of Metabolism & Endocrinology Products
Mary Parks, MD-Director
Eric Colman, MD-Deputy Director, Lipid Team Leader
Julie Golden, MD-Clinical Reviewer
Karen Davis Bruno, PhD-Pharmacology/Toxicology Team Leader

Office of Translational Sciences
Office of Biostatistics
Japobatra Choudhury, PhD-Statistical Reviewer
Office of Clinical Pharmacology
Sang Chung, PhD-Clinical Pharmacology Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Abbott Laboratories
Susan Buttler, Associate Director (Clinical Research), Dyslipidemia
Maureen Kelly, M.D., Medical Director, Dyslipidemia
Martin King, Ph.D., Associate Director, Statistics
Melodi McNeil, R.Ph., M.S., Director, FDA Liaison Office
Rajendra Pradhan, Ph.D., Director, Clinical Pharmacokinetics
David Ross, Pharm.D., MBA, Director, Regulatory Affairs
Carolyn Setze, M.S., Manager, Statistics
Darryl Sleep, M.D., Global Project Head, Dyslipidemia
James Stolzenbach, Ph.D., Divisional Vice President, Dyslipidemia and Heart Failure
Natalie Tolli, B.Pharm, M.S., Associate Director, Regulatory Affairs

Solvay Pharmaceuticals
Laurence Brugere, Project Manager, Regulatory Affairs, Solvay Pharmaceuticals

BACKGROUND:

Fenofibric acid (ABT-335) is the active metabolite of fenofibrate, currently marketed by others in addition to Abbott, the latter under the trade name TriCor Tablets. TriCor is currently approved for the treatment o f hypercholesterolemia and hypertriglyceridemia.

In anticipation of submission of the NDA (given the pre-assigned number NDA 22-224) in December 2007, the firm has requested a pre-NDA meeting.

Fenofibric acid is being investigated in co-administration with low or moderate doses of 3 different statins (rosuvastatin calcium [10 mg or 20 mg], simvastatin [20 mg or 40 mg], and atorvastatin calcium [20 mg or 40 mg] in three separate Phase 3 studies. Each of the following studies is a double-blind, active controlled study with a long-term open-label extension study and all were conducted under IND 70,345:

1. Study M05-748, titled "A Multicenter, Randomized, Double-Blind, Prospective Study Comparing the Safety and Efficacy of Fenofibric Acid and Rosuvastatin Calcium Combination Therapy to Fenofibric Acid and Rosuvastatin Calcium Monotherapy in Subjects with Mixed Dyslipidemia";
2. M05-749, titled "A Multicenter, Randomized, Double-Blind, Prospective Study Comparing the Safety and Efficacy of Fenofibric Acid and Simvastatin Combination Therapy to Fenofibric Acid and Simvastatin Monotherapy in Subjects with Mixed Dyslipidemia";
3. M05-750, titled "A Multicenter, Randomized, Double-Blind, Prospective Study Comparing the Safety and Efficacy of Fenofibric Acid and Atorvastatin Calcium Combination Therapy to Fenofibric Acid and Atorvastatin Calcium Monotherapy in Subjects with Mixed Dyslipidemia"; and
4. M05-758, titled "A Long-Term, Open-Label, Safety Extension Study of the Combination of Fenofibric Acid and Statin Therapy for Subjects With Mixed Dyslipidemia."

MEETING OBJECTIVES:

1. To review the preliminary efficacy and safety results of the three co-administration Phase 3 studies of ABT-335 with statins, in support of the proposed co-administration indication.
2. To obtain agreement with the Agency on the pediatric study plans for ABT-335.
3. To confirm that the Agency is in agreement with the proposed content and structure of the planned NDA, including the content of the nonclinical and clinical sections.

DISCUSSION POINTS: The firm's questions are in regular text, and the preliminary responses are in ***bold italics***. The meeting discussion is <u>underlined</u>.

Note: Solvay Pharmaceuticals was in attendance because they are Abbott's international development partner for choline fenofibrate.

<u>Clinical</u>

1. Abbott believes that the preliminary results from the three double-blind, multi-center, active-controlled Phase 3 efficacy studies (M05-748, M05-749, M05-750) demonstrate the safety and efficacy of combination therapy of ABT-335 co-administered with statins in patients with mixed dyslipidemia (Fredrickson Type IIb). Abbott further believes that the data from these studies adequately support the following proposed indication for ABT-335 co-administration therapy with a statin:

   "ABT-335 co-administered with an HMG-CoA reductase inhibitor, is indicated as adjunctive therapy to diet for the reduction of elevated triglycerides, LDL-C, non-HDL-C, VLDL-C, ApoB and total cholesterol and to increase HDL-C in adult patients with mixed dyslipidemia (Fredrickson Type IIb)."

The three double-blind studies have demonstrated that co-administration of ABT-335 and a statin provides significant additional benefit over statin monotherapy in the reduction of elevated triglycerides and elevating low HDL-C in the treatment of patients with mixed dyslipidemia. In addition, adding a statin to ABT-335 monotherapy provides significant additional benefit on lowering elevated LDL-C compared to ABT-335 monotherapy. Further information is provided in Section 12.0 of this Information Package.

Does the Agency agree that the preliminary results of these studies support the proposed indication, pending review of the clinical data?

Agency Response: The proposed indications under section 6.0 of your briefing document do not help the prescriber distinguish between patients with mixed dyslipidemia who should be treated with ABT-335 monotherapy vs. those treated with ABT-335 + a statin. The intent of co-administration is to treat patients who were on one agent and would benefit from the addition of the second agent (i.e., patients treated with a statin who require further TG-lowering or HDL-raising and patients treated with ABT-335 and would require further LDL-lowering). You should refer to the Advicor label for direction on co-administration labeling language.

Meeting Discussion: None

2. As previously discussed and agreed to with the Agency at the May 25, 2004 Pre-IND Meeting, Abbott plans to request monotherapy indications for ABT-335 that are the same as the current TriCor® monotherapy indications, approved under NDA 21-656. This is supported by the demonstration of bioequivalence of ABT-335 to the reference 200 mg capsule formulation of fenofibrate. The proposed indication is presented below:

   "ABT-335 is indicated as adjunctive therapy to diet to reduce elevated LDL-C, total cholesterol, triglycerides and ApoB, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb). Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone have been inadequate.
   ABT-335 is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia)."

   Does the Agency agree that these indications may be approved for ABT-335, pending review of the biopharmaceutics data?

   Agency response: Yes

   Meeting Discussion: None

3. **We are requesting a partial waiver for pediatric studies required under the Pediatric Equity Research Act (PREA) for patients younger than 10 years of age, and a deferral for pediatric studies in patients aged 10-18 years. As the ABT-335 studies in adults are being completed during 2007, and submission of the ABT-335 NDA is planned for December 2007, Abbott is requesting a deferral of the PREA study requirements for the monotherapy indication for this age group. To meet all PREA obligations for ABT-335, Abbott requests a partial waiver for pediatric studies (both monotherapy and co-administration therapy) in patients aged 0-9 years, as current pediatric treatment guidelines do not recommend treatment of elevated TG and LDL-C in patients younger than 10 years of age. Abbott requests a deferral for co-administration studies in pediatric patients aged 10-18 years, to be conducted after approval of the ABT-335 NDA, and after completion of the pediatric monotherapy study. The partial waiver and deferral requests are provided in accordance with the guidance document *How to Comply with the Pediatric Research***

Equity Act (September 2005). Supporting information for these requests are provided in Section 17.0 of this Information Package.

A Proposed Pediatric Study Request of ABT-335 monotherapy was submitted to IND 70,345 on May 30, 2007 (Serial Number 097). The results of the monotherapy pediatric study program are anticipated to be submitted within 36 months of the issue date of the Written Request. It is anticipated that the double-blind placebo-controlled ABT-335 monotherapy study (in patients aged 10-18 years with hypertriglyceridemia) submitted in this PPSR will fulfill the PREA requirements for the monotherapy indication for ABT-335.

Does the Agency agree that a partial waiver can be granted for pediatric monotherapy and co-administration studies required under the Pediatric Research Equity Act for patients younger than 10 years of age, and a deferral can be granted for pediatric monotherapy and co-administration studies in patients aged 10-18 years?

Agency response: We agree to grant the waiver for pediatric monotherapy for patients younger than 10 years of age. We are not prepared, at this time, to grant the deferral.

Meeting Discussion: In response to a question from the firm, the agency said that the waiver also applied to co-administration with statins. With regard to the deferral, the agency said that it has not been determined whether the 10-18 years of age group warrants pharmacologic treatment. The firm could assist us in making this determination by providing an estimate of the number of pediatric patients in the U.S. with triglycerides in the 400-700 mg/dL range. It was agreed that the submitted NDA could contain this deferral request, although the firm needs to provide some timeline for when the information would be submitted.

Clinical Pharmacokinetics and Pharmacology

4. The results from the definitive food effect study of ABT-335 (Study M06-831) indicate the following:
   - The Cmax and AUC for the ABT-335 formulation in the high-fat arm are bioequivalent to those in the fasting arm;
   - The AUC for the ABT-335 formulation in the low-fat arm is bioequivalent to that in the fasting arm; and
   - The point estimate of the Cmax after a low-fat meal was 78% relative to the fasting conditions.

   Patients enrolled in the pivotal phase 3 safety and efficacy studies were instructed to take all study drugs, including ABT-335, together at the same time of day without regard to meals. Further details on the findings of the food-effect study are presented in Section 14.0 of this Information Package.

   Does the Agency agree that these results will support a statement in the *Dosage and Administration* section of the prescribing information that ABT-335 may be administered without regard to meals?

   Agency response: It appears acceptable, despite a food effect on Cmax.

   Meeting Discussion: None

5. Abbott has developed a 45 mg capsule dosage strength of ABT-335, for use in patients with moderate renal impairment. No clinical or pharmacokinetic studies are planned for this dosage strength. Compared to the 135 mg formulation, the 45 mg strength formulation has one-third the number of mini-tablets. Furthermore, the composition of the mini-tablets is identical between the two strengths. In accordance with the FDA guidance (*Guidance for Industry: Bioavailability and*

Bioequivalence Studies for Orally Administered Drug Products — General Considerations [March 2003]), Abbott believes that the *in vivo* biostudy requirement for the 45 mg strength can be waived based on the *in vitro* dissolution data generated using the recommended dissolution method. Further information is provided in Section 13.0 of this Information Package.

Does the Agency agree that a biowaiver can be granted for the 45 mg dose strength of ABT-335?

Agency Response; A waiver of the in vivo biostudy requirement for the 45 mg strength dose is based on the following:
-composition similarity and proportionality
-data to demonstrate linear pK
-in vitro dissolution data

Meeting Discussion: The firm said that this information would be provided from cross study comparison and historical information from early development formulations. The agency said this was acceptable.

Labeling

6. Since ABT-335 is the active metabolite of fenofibrate (TriCor), and the results of Study M06-830 have demonstrated bioequivalence of 135 mg ABT-335 to the reference 200 mg fenofibrate product, we plan to include the following clinical pharmacology sections from the TriCor prescribing information in the ABT-335 label:
    - *Protein binding*
    - *Metabolism*
    - *Excretion*
    - *Special Populations: Geriatric, pediatric, gender, race, renal and hepatic insufficiency*
    - *Drug-Drug Interactions*

    Does the Agency agree with this strategy, pending review of the biopharmaceutics data?

    Agency Response: This is a review issue.

    Meeting Discussion: None

7. During the May 25, 2004 Pre-IND meeting, the Agency advised that they were not in a position to discuss the removal of the statements in the currently-approved package insert for TriCor regarding the risk of rhabdomyolysis with fibrate use, until such time as additional controlled study data are available. Since that Pre-IND meeting, the clinical development program for ABT-335 has studied approximately 2,700 patients, of whom over 1,900 have entered the long-term safety study (Study M05-758), and have received ABT-335 co-administered with a moderate dose of a widely-used statin (rosuvastatin 20 mg, simvastatin 40 mg, or atorvastatin 40 mg), for treatment periods of up to 15 months. No safety signals have been identified to date in this clinical program, suggesting that the co-administration of ABT-335 and statins can be used safely in the patient population studied, and Abbott believes the data support an indication for the concomitant use of ABT-335 and statins in the treatment of mixed dyslipidemia. Therefore, Abbott does not intend to include any statements in the *Warnings and Precautions* section of the ABT-335 package insert relating to the co-administration of ABT-335 and statins.

    Does the Agency agree?

    Agency Response: We may consider revising, but this is a review issue.

Meeting Discussion: None

Content and Format of the Application

8. Abbott proposes to submit the NDA for ABT-335 electronically in the Common Technical Document (eCTD) format. Abbott does not plan to provide any paper copies of the NDA, unless specifically requested.

   Does the Agency agree?

   Agency Response: Yes

   Meeting Discussion: None

9. The NDA submission package will include new nonclinical data generated on fenofibric acid, ABT-335 (choline fenofibrate), and other salts of fenofibric acid, as agreed to during the May 25, 2004 Pre-IND meeting. Nonclinical data for fenofibrate previously submitted to IND 19-056 and NDA 19-304 and reviewed by FDA will be incorporated only by cross-reference throughout the application, including in the Nonclinical Overview and Nonclinical Written and Tabulated Summary documents, and will not be resubmitted in the planned NDA.

   Does the Agency agree with this strategy?

   Agency Response: Yes

   Meeting Discussion: None

10. The NDA submission for ABT-335 will include new clinical data generated with ABT-335, to support the proposed indication for co-administration therapy with statins. As previously discussed and agreed upon at the Pre-IND meeting in May 2004, Abbott does not plan to submit clinical data for fenofibrate which has been previously submitted to NDA 19-304 and reviewed by FDA to support the proposed monotherapy indication for ABT-335. These data will be incorporated by cross-reference throughout the application, and will be discussed in the Clinical Overview document.

    Does the Agency agree with this strategy?

    Agency Response: Yes

    Meeting Discussion: None

11. As described in Section 15.0 of this Information Package, the Phase 1 program for ABT-335 consists of 13 studies. Of these, two studies are "definitive" studies, representing the pivotal bioequivalence and pivotal food-effect studies. Six studies are considered "supportive"; the results of these will be used to support the *in vitro-in vivo* correlation, or could be included in the package insert (e.g., drug-drug interaction studies). The remainder of the Phase 1 studies are considered "pilot" studies. Abbott proposes to provide PK datasets (as SAS transport files, with appropriate data definitions files) for the eight studies classified as definitive and supportive studies, but does not intend to provide PK datasets for the remaining five pilot PK studies. Abbott does not plan to provide CRT datasets for any of the Phase 1 studies. Analysis-ready datasets/programs and CRT datasets will be provided for all Phase 3 studies.

Is this strategy acceptable to the Agency?

Agency Response: Yes

Meeting Discussion: None

12. **Abbott does not plan to submit Appendix 16.4 (Individual Patient Data Listings) for the clinical studies contained in Module 5 of the NDA. However, individual patient data will be provided electronically as SAS transport files in Module 5 of the NDA for the Phase 3 studies, as well as in the Subject Data Listings (Appendix 16.2) for all studies.**

Does the Agency agree with this strategy?

Agency Response: Yes

Meeting Discussion: None

DECISIONS (AGREEMENTS) REACHED:

None

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

It was determined post-meeting that the application would be a 505(b)(2) application because the firm will cite a fenofibrate-simvastatin drug-drug interaction study (Bergman et al, J Clin Pharmacol 2004; 44: 1054-62, published by Merck) in their application. They conducted drug-drug interaction studies with fenofibric acid and both atorvastatin and rosuvastatin.

ACTION ITEMS:

None

ATTACHMENTS/HANDOUTS:

None

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/s/

Kati Johnson
8/16/2007 10:58:21 AM

ACTION PACKAGE CHECKLIST

BLA # NDA # 22-224	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type	
Proprietary Name: Established Name: fenofibrate Dosage Form: Capsules		Applicant: Abbott Laboratories	
RPM: Kati Johnson		Division: DMEP (510)	Phone # 301-796-1234

NDAs: NDA Application Type: ☐ 505(b)(1) X 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A 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). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Zocor (simvastatin) tablets, NDA 19-766 Provide a brief explanation of how this product is different from the listed drug. Drug-drug interaction studies were referencec ☐ If no listed drug, check here and explain: **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** XConfirmed ☐ Corrected Date: 12/15/078

◆ User Fee Goal Date ◆ Action Goal Date (if different)	10/7/08 12/15/08
◆ Actions	
• Proposed action	X AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None
◆ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	X Requested in AP letter ☐ Received and reviewed

Application Characteristics	

Review priority: X Standard ☐ Priority
Chemical classification (new NDAs only): 2

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes X No
• This application is on the AIP	☐ Yes X No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☐ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes X No
• Press Office notified of action	☐ Yes X No
• Indicate what types (if any) of information dissemination are anticipated	X None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	X Included
• Is approval of this application blocked by any type of exclusivity?	X No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	X No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	X Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) X Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	X No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	X N/A (no paragraph IV certification) ☐ Verified
• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each paragraph IV** certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's	☐ Yes ☐ No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

If "Yes," skip to question (4) below. If "No," continue with question (2).

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

If "No," continue with question (3).

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

If "No," continue with question (5).

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).* *If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
◆ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	12/15/08
◆ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	N/A
◆ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	N/A
• Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	X
◆ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	X-later changed to Med Guide
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
◆ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	X-attached to AP letter
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
◆ Labels (full color carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	X-attached to AP letter
◆ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	X DMETS ☐ DSRCS ☐ DDMAC ☐ SEALD ☐ Other reviews ☐ Memos of Mtgs

◆ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	PM/Filing 3/27/08
◆ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	X Included
◆ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	N/A
◆ Pediatric Page (all actions)	X Included
◆ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	X Verified, statement is acceptable
◆ Postmarketing Commitment Studies	☐ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	X
◆ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	X
◆ Internal memoranda, telecons, email, etc.	N/A
◆ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg 7/20/07
• EOP2 meeting *(indicate date)*	X No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
◆ Advisory Committee Meeting	X No AC meeting
• Date of Meeting	
• 48-hour alert or minutes, if available	
◆ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
◆ CMC/Product review(s) *(indicate date for each review)*	2/1/08, 9/26/08, 10/1/08
◆ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	X None
◆ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No
◆ Environmental Assessment (check one) (original and supplemental applications)	
• X Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
• ☐ Review & FONSI *(indicate date of review)*	
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	
◆ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	X Not a parenteral product
◆ Facilities Review/Inspection	
◆ NDAs: Facilities inspections (include EER printout)	Date completed: 5/2/08 X Acceptable ☐ Withhold recommendation

◆ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)* ◆ NDAs: Methods Validation	☐ Requested ☐ Accepted ☐ Hold X Completed ☐ Requested ☐ Not yet requested ☐ Not needed
◆ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	2/7/08, 8/28/08, 10/1/08
◆ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	X None
◆ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	X No carc
◆ ECAC/CAC report/memo of meeting	
◆ Nonclinical inspection review Summary (DSI)	X None requested
◆ Clinical review(s) *(indicate date for each review)*	12/15/08
◆ Financial Disclosure reviews(s) or location/date if addressed in another review	See page 13
◆ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	X None
◆ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	X Not needed
◆ Safety Update review(s) *(indicate location/date if incorporated into another review)*	N/A
◆ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	See Deputy DD summary Review
◆ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	X Not needed
◆ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	9/17/08
• Bioequivalence Studies	9/12/08
• Clin Pharm Studies	
◆ Statistical Review(s) *(indicate date for each review)*	☐ None 10/10/08
◆ Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 2/21/08, 9/23/08

Appendix A to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
(3) **Or** 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) **And** 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.
(3) **And** 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) **Or** 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.
(3) **Or** 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.

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
12/16/2008 12:25:50 PM