

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-813

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 50-813

SUPPL #

HFD # 520

Trade Name Moxatag

Generic Name Amoxicillin extended-release tablet, 775 mg

Applicant Name MiddleBrooke Pharmaceuticals

Approval Date, If Known January 23, 2008

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

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

YES NO

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

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

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

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

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA# 50-754 Amoxil Tablet
NDA# 50-542 Amoxil Chewable Tablet
NDA# 50-460 Amoxicillin Oral Suspension

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

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

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

Sponsor conducted a Phase 3, double-blind, randomized, parallel-group, multicenter study to evaluate the safety and efficacy of Moxatag, 775 mg tablet, PO QD for 10 days, compared to penicillin VK, 250 mg PO QID for 10 days in the treatment of tonsillitis and or pharyngitis secondary to Streptococcus pyogenes in patients 12 years and older (Study 111.302).

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2

YES

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Same as 2C

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

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

Investigation #1
IND # 62,576 YES ! NO
! Explain:

Investigation #2
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Susmita Samanta

Title: Regulatory Project Manager

Date: January 24, 2008

Name of Office/Division Director signing form: Janice Soreth, MD

Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

A/BLA #: 50-813 Supplement Type (e.g. SE5): NA Supplement Number: NA

Stamp Date: March 23, 2007 PDUFA Goal Date: January 23, 2008

HFD 520 Trade and generic names/dosage form: APC-111 MP Tablet, 775 mg

Applicant: MiddleBrook Pharmaceuticals Therapeutic Class: Penicillin

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): NA

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Tonsillitis/pharyngitis

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
 No. Please proceed to the next question.

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

- Yes: Please proceed to Section A.
 No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 2 Tanner Stage _____

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. 2 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 11 Tanner Stage _____

Reason(s) for deferral:

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

Date studies are due (mm/dd/yy): 06/01/10

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

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. 12 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 18 Tanner Stage _____

Comments: Children in this age range included in adult Phase 3 studies.

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

This page was completed by:

NDA 50-813

Page 3

{See appended electronic signature page}

Susmita Samanta

Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND-MATERNAL HEALTH
STAFF at 301-796-0700**

(Revised: 10/10/2006)

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

/s/

Susmita Samanta
1/9/2008 12:00:58 PM

Samanta, Susmita

From: Araojo, Richardae
Sent: Wednesday, January 16, 2008 2:13 PM
To: Samanta, Susmita
Cc: Furness, Melissa; Feibus, Karen
Subject: Moxatag label content review

Attachments: AntibioticUseinPregnancy2006.NahumObstetGynecol.pdf; 20080116 Moxatag Amoxicillinfor tonsillitis andor pharyngitis _Content Review.doc

Hi Susmita,

Happy New Year! I have attached below the MHT and SEALD labeling review for Moxatag. In the Pregnancy and Nursing Mothers sub-sections of labeling, the MHT has included information from an article published by the former Pregnancy and Lactation Team on antibiotic use in pregnancy and lactation. Please let me know if you have any questions regarding our additions.

Thanks,
Chardae



AntibioticUse 20080116
Pregnancy2006;tag Amoxicilli

*Richardae Taylor Araojo, Pharm.D., LCDR USPHS
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff
FDA/CDER/OND, Immediate Office
Ph: (301) 796-1152
Fax: (301) 796-9744
Email:*

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT MiddleBrook Pharmaceuticals, Inc.	DATE OF SUBMISSION 01/16/2008
TELEPHONE NO. (Include Area Code) 301-944-6600	FACSIMILE (FAX) Number (Include Area Code) 301-944-6700
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 20425 Seneca Meadows Parkway Germantown, Maryland 20876	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 50-813		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Amoxicillin Tablet, Film Coated, Extended Release	PROPRIETARY NAME (trade name) IF ANY	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)	CODE NAME (If any)	
DOSAGE FORM: Tablet	STRENGTHS: 775 mg	ROUTE OF ADMINISTRATION: Oral
(PROPOSED) INDICATION(S) FOR USE: Tonsillitis and/or Pharyngitis Secondary to Streptococcus Pyogenes		

APPLICATION DESCRIPTION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input checked="" type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input type="checkbox"/> AMENDMENT TO PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)

REASON FOR SUBMISSION

Post-Marketing Pediatric Commitment
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (RN) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>1</u> THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact telephone number, registration number (CFR), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, stability testing) conducted at the site. Please indicate whether the site is ready for inspection (i.e. if not, when it will be ready).

Not applicable to this submission.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

Not applicable to this submission.

This application contains the following items: (Check all that apply)

<input checked="" type="checkbox"/>	1. Index
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/>	4. Chemistry section
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)
<input checked="" type="checkbox"/>	20. OTHER (Specify) Post-Marketing Pediatric Commitment

CERTIFICATION

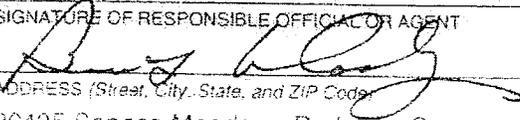
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Brenda L Wollong, Director, Regulatory Affairs	DATE: 01/16/2008
ADDRESS (Street, City, State, and ZIP Code) 20425 Seneca Meadows Parkway, Germantown, Maryland 20876		Telephone Number (301) 944-6600

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
1901 S. Amundson Road
Bethesda, MD 20892-1295

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-89)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

1. Conduct a phase 3 randomized, controlled, multicenter study to evaluate the safety and efficacy of an amoxicillin extended release formulation in the treatment of tonsillitis and/or pharyngitis secondary to *Streptococcus pyogenes* in pediatric patients ≥ 2 years to < 12 years.

Final Report Submission: by March, 2013

MiddleBrook

PHARMACEUTICALS

January 16, 2008

Food and Drug Administration - CDER
Janice M. Soreth, M.D., Director, DAIODP
ATTN: Susmita Samanta, M.D., Regulatory Project Manager
Division of Anti-Infective & Ophthalmologic Drug Products, HFD-520
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 50-813 - APC-111 MP Tablet, 775 mg

POST-MARKETING STUDY COMMITMENT

Dear Dr. Soreth:

Please refer to NDA 50-813 submitted to the FDA on March 23, 2007 for APC-111 MP Tablet, 775 mg, for the treatment of pharyngitis and/or tonsillitis secondary to *S. pyogenes* in adults and adolescents.

MiddleBrook Pharmaceuticals, Inc. commits to conduct a post-marketing Phase 3 randomized, controlled, multicenter study to evaluate the safety and efficacy of an amoxicillin extended release formulation in the treatment of tonsillitis and/or pharyngitis secondary to *Streptococcus pyogenes* in pediatric patients ≥ 2 years to < 12 years. The final study report will be submitted by March 2013.

If you have any questions or comments, please contact me at (301) 944-6614, facsimile (301) 944-6600 or via e-mail at bwolling@middlebrookpharma.com. In my absence please contact Susan P. Clausen, Ph.D., VP. Clinical Research & Regulatory Affairs at (301) 944-6660 or sclausen@middlebrookpharma.com.

Respectfully,



Brenda L. Wolling
Director, Regulatory Affairs

Samanta, Susmita

From: Colangelo, Kim M
nt: Tuesday, December 11, 2007 10:32 AM
: Bonapace, Charles; Alexander, John J; Samanta, Susmita
Cc: Robertson, Sarah
Subject: RE: NDA 50-813

All,

You are cleared for action from a (b) (2) perspective.

Happy action!
Kim

Kim Colangelo
Associate Director for Regulatory Affairs
Office of New Drugs, CDER, FDA
>301-796-0700 (OND IO main)
>301-796-0140 (direct)
>301-796-9856 (facsimile)
>Kim.Colangelo@fda.hhs.gov
>
>

-----Original Message-----

From: Bonapace, Charles
Sent: Friday, November 30, 2007 8:10 PM
To: Colangelo, Kim M; Alexander, John J
Cc: Robertson, Sarah; Bonapace, Charles
Subject: RE: NDA 50-813

John and Kim,

Sarah's response below is correct. 21 CFR 320.25 states that the reference material for an in vivo bioavailability study of an extended release formulation can be a solution or suspension of the active drug ingredient or therapeutic moiety. Thus, comparing the pharmacokinetics of amoxicillin pulsatile (NDA 50-813) to Amoxil suspension is appropriate for the in vivo bioavailability study.

Chuck

-----Original Message-----

From: Colangelo, Kim M
Sent: Friday, November 30, 2007 5:38 PM
To: Robertson, Sarah; Alexander, John J
Cc: Bonapace, Charles
Subject: RE: NDA 50-813

Great - thanks so much folks for your responses. Hopefully this will satisfy our attorneys!!!

Have a great weekend!

-----Original Message-----

From: Robertson, Sarah
Sent: Friday, November 30, 2007 3:13 PM
To: Alexander, John J
Cc: Bonapace, Charles; Colangelo, Kim M
Subject: RE: NDA 50-813

An MR product is typically compared to the suspension in order to provide a measure of relative bioavailability (in lieu of an IV dosage form).

Sarah

-----Original Message-----

From: Alexander, John J
Sent: Friday, November 30, 2007 3:09 PM
To: Colangelo, Kim M; Robertson, Sarah; Bonapace, Charles
Cc: Imoisili, Menfo; Samanta, Susmita; Duvall Miller, Beth A; Laessig, Katherine A
Subject: RE: NDA 50-813

Kim,

I believe that reliance on the Augmentin products is necessary for a couple of reasons. As you noted, the Augmentin XR formulation is an extended release formulation. In addition, the Augmentin XR and regular Augmentin formulation provide exposure to amoxicillin that is much higher than the doses used in the NDA 50-813 product. I don't think we need specific studies of comparative pharmacokinetics to the Augmentin products for this reliance on safety, since for Augmentin XR the total daily dose is 4 grams of amoxicillin in comparison to less than 775 mg for the NDA 50-813 product. (We do know that the presence of clavulanate in Augmentin doesn't alter the PK for amoxicillin.)

Further, doses of up to 875 mg in the Amoxil NDA labeling are based on studies that were done for the Augmentin products back in the early 90's. I don't think that this is as important an issue, since we are relying on the Agency's previous findings of safety and effectiveness for the Amoxil and Augmentin products, rather than the data contained in the NDA for those GSK products.

I can't explain why they made the PK comparison with the suspension. Sarah or Chuck, do you know?

Sorry for the late reply.
-John

-----Original Message-----

From: Colangelo, Kim M
Sent: Friday, November 30, 2007 11:43 AM
To: Alexander, John J
Cc: Imoisili, Menfo; Samanta, Susmita; Duvall Miller, Beth A; Laessig, Katherine A
Subject: RE: NDA 50-813

PS: If we can get responses by COB Tuesday of next week that would be great - we meet with ORP/OCC to discuss (b)(2)s on Wednesday.

Have a great weekend!

-----Original Message-----

From: Colangelo, Kim M

Sent: Tuesday, November 27, 2007 2:57 PM

To: Alexander, John J

Imoisili, Menfo; Samanta, Susmita; Duvall Miller, Beth A; Laessig, Katherine

Subject: RE: NDA 50-813

John,

A follow-up question or two if I may.

Why is reliance on the approval of Augmentin and Augmentin XR needed to support the safety of the proposed product? In other words, why is the approval of Amoxil insufficient to support the safety of the proposed product? (We think we know, but you know what they say about assumptions...)

At issue is the need for a scientific "bridge" to justify the relevancy of the products being relied upon to support the approval of the proposed product. We have a "bridge" in the form of comparative PK to the Amoxil suspension. What allows us (scientifically) to say the reliance on Augmentin is relevant to support the safety of the proposed product? Again, not wanting to assume, based on your response below, is it because Augmentin XR is an approved extended-release version of amoxicillin (albeit in combination with clavulante potassium)?

Finally (I hope), can you explain why they chose to compare themselves to the Amoxil suspension instead of the tablet?

Thank you in advance,

Kim

-----Original Message-----

From: Alexander, John J

Sent: Monday, November 19, 2007 10:44 AM

To: Colangelo, Kim M

Cc: Imoisili, Menfo; Samanta, Susmita; Duvall Miller, Beth A; Laessig, Katherine A

Subject: RE: NDA 50-813

Kim,

The product in this 505(b)(2) NDA contains the same active ingredient (amoxicillin) as the previously approved Amoxil and Augmentin NDA applications. The Augmentin XR application is another approved extended release formulation (although Augmentin XR is a combination product). We are relying on the FDA's previous findings of safety for these products to support the approval of this product.

Although the sponsor provided the results of 7 clinical studies, only one of the trials (Study 111-302) was considered a pivotal efficacy trial for approval of the product given once daily in a ten-day course for treatment of Streptococcal pharyngitis. There was another clinical study of the new product given for 7 days (Study 111-301), but this trial was not successful.

We are therefore relying, in part, on the FDA's previous findings of efficacy for the Amoxil products in the treatment of Streptococcal Throat infections as supportive evidence of efficacy. They have also provided literature reports for this supportive evidence of efficacy, reporting the results of studies that used these Amoxil products for treatment of Streptococcal pharyngitis.

I don't think we are looking for specific supportive information from the NDA applications for the chewable tablets and suspensions. The previous findings of efficacy and safety of amoxicillin for treatment of Streptococcal pharyngitis is not linked to those specific formulations.

I hope this answers your questions.

-John

-----Original Message-----

From: Colangelo, Kim M
Sent: Wednesday, November 14, 2007 1:46 PM
To: Alexander, John J; Samanta, Susmita
Cc: Duvall Miller, Beth A
Subject: RE: NDA 50-813

Thanks, John. That is also how I interpret the response. The reference to Spectracef and Omnicef appears to be limited to informing the study design to support the approval of this product, which is not a (b)(2) reference, per se.

I do need to follow-up on this further (unfortunately!) Given that the applicant conducted 7 clinical trials, including two randomized, double-blind, active control trials to support safety and efficacy of the proposed product, what information is provided from the approvals of Augmentin, Amoxil chewable, Amoxil tablets, Augmentin XR, and Amoxil suspension? (They are all listed as references by the applicant.) Without annotated labeling, it is hard for me to sort out. Note that the chewable tablets and suspensions have both been discontinued from marketing, and if they specifically provided support not available via reliance on the Amoxil tablet, we will need to ensure that neither product was withdrawn for reasons of safety or efficacy (and document as such.) I doubt this is the case, but if it is...

Also, can you describe how we scientifically justify using the data discussed above from the Augmentin and Amoxil products to support the approval of this product? Often such support is provided via comparative BA trials, but I don't believe they were conducted nor are they necessary in this case. But we do have to articulate how we have determined that the information from Augmentin/Amoxil is relevant to support the approval of this product. (An example of one possible response would be that exposures of amoxicillin in the proposed product do not (significantly) exceed that seen with the approved products, therefore nonclinical data provided in the labels of the Amoxil and Augmentin products is sufficient to support the proposed product.)

I appreciate your assistance as we navigate the (b)(2) rapids!

-----Original Message-----

From: Alexander, John J
Sent: Tuesday, November 13, 2007 3:28 PM
To: Samanta, Susmita; Colangelo, Kim M
Subject: RE: NDA 50-813

Kim,

From the response, it does not appear that the sponsor is relying on FDA's findings of safety and effectiveness for any of these cephalosporins. The sponsor is pointing to information about prior studies in the SBA's for Spectracef and Omnicef, but I don't think they need to rely on FDA's previous findings of safety and effectiveness for those drugs to direct our attention to that information.

I think we are mainly relying on FDA's previous findings for safety and effectiveness for the amoxicillin-containing products to support the approval of this formulation.

-John

-----Original Message-----

From: Samanta, Susmita
Sent: Tuesday, November 13, 2007 2:52 PM
To: Colangelo, Kim M
Cc: Alexander, John J
Subject: NDA 50-813
Importance: High

Kim,

Here is the response from the Sponsor of NDA 50-813 regarding the references to omnicef, spectracef and cephalixin.

Thank you
Susmita

November 16, 2007

Food and Drug Administration - CDER
Janice M. Soreth, M.D., Director, DAIODP
ATTN: Susmita Samanta, M.D., Regulatory Project Manager
Division of Anti-Infective & Ophthalmologic Drug Products, HFD-520
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 50-813 - APC-111 MP Tablet, 775 mg

**GENERAL CORRESPONDENCE
DRAFT MOCK-UP LABELING**

Dear Dr. Soreth:

Please refer to NDA 50-813 submitted to the FDA on March 23, 2007 for APC-111 MP Tablet, 775 mg, for the treatment of pharyngitis and/or tonsillitis secondary to *S. pyogenes* in adults and adolescents.

On November 1, 2007, MiddleBrook received a request from the Agency to provide mock-up draft labeling for APC-111 MP Tablets, 775 mg. We have provided colored hard-copies of the labeling and have included a CD-ROM for ease of review.

Please see the below list of draft labeling provided in this submission.

DRAFT 10 Count Blister Card – TRADE
DRAFT 10 Count Blister Card Display Tray – TRADE
DRAFT 30 Count Bottle Label/Fold-Out-Insert – TRADE
DRAFT 10 Count Blister Card – SAMPLE
DRAFT 10 Count Blister Card Display Tray – SAMPLE
DRAFT 1 Count Blister Card – SAMPLE
DRAFT 1 Count Blister Card Display Tray - SAMPLE
DRAFT Flat Insert for Blisters with identifiable folds

If you have any questions or comments, please contact me at (301) 944-6614, facsimile (301) 944-6600 or via e-mail at bwolling@middlebrookpharma.com. In my absence please contact Susan P. Clausen, Ph.D., VP, Clinical Research & Regulatory Affairs at (301) 944-6660 or sclausen@middlebrookpharma.com.

Respectfully,

Brenda L. Wolling
Director, Regulatory Affairs

8 Page(s) Withheld

 Trade Secret / Confidential (b4)

 X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Withheld Track Number: Administrative- 1

Samanta, Susmita

From: Wolling, Brenda [bwolling@middlebrookpharma.com]
Sent: Thursday, November 01, 2007 4:31 PM
To: Samanta, Susmita
Cc: Wolling, Brenda
Subject: NDA 50-813
Importance: High

Hi Susmita,

With regards to MiddleBrook's 505(b)2 application, two Reference Listed Drugs (RLD) were used to assist us in our preparation of the APC-111 MP Tablet, 775 mg package insert for NDA 50-813. These RLD, Amoxil® NDA 50-754 and Augmentin® XR NDA 50-785, were discussed in the Pre-NDA Briefing Package and agreed upon by the Agency as adequate RLDs for use in support of the NDA.

The proposed draft labeling provided in the NDA was prepared following the New Labeling Rule format. It was provided in PDF, SPL, and MS WORD as an annotated label. A comparison table between Amoxil® and Augmentin® XR was not prepared due to the new labeling format of our product, and as agreed upon by the Agency, we provided the RLD package inserts in PDF in the literature reference section (m5\clinstata\clintoc.pdf in Section 5.4 Publications).

In addition, you requested artwork for the final packaging of APC-111 MP Tablet, 775 mg. We will have documents to you shortly.

Thank you, and please let me know if you have additional questions.

Sincerely,
Brenda

Brenda L Wolling
Director, Regulatory Affairs

MiddleBrook Pharmaceuticals, Inc.
20425 Seneca Meadows Parkway
Germantown, Maryland 20876

(301) 944-6600 MAIN
(301) 944-6703 FAX

www.middlebrookpharma.com
bwolling@middlebrookpharma.com

11/30/2007

REQUEST FOR CONSULTATION

TO (Division/Office):

ORDER USE CONSULTS

FROM: Susmita Samanta, Regulatory Project Manager,
Division of Anti-Infective and Ophthalmology Products

DATE November 1, 2007	IND NO. NA	NDA NO. 50-813	TYPE OF DOCUMENT Proposal for Tradename	DATE OF DOCUMENT October 5, 2007
NAME OF DRUG APC-111 MP tablet		PRIORITY CONSIDERATION P	CLASSIFICATION OF DRUG Penicillin	DESIRED COMPLETION DATE December 15, 2007

NAME OF FIRM: Middlebrok Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

<input type="checkbox"/> NEW PROTOCOL	<input type="checkbox"/> PRE--NDA MEETING	<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> PROGRESS REPORT	<input type="checkbox"/> END OF PHASE II MEETING	<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> NEW CORRESPONDENCE	<input type="checkbox"/> RESUBMISSION	<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> DRUG ADVERTISING	<input type="checkbox"/> SAFETY/EFFICACY	<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> ADVERSE REACTION REPORT	<input type="checkbox"/> PAPER NDA	<input type="checkbox"/> FORMULATIVE REVIEW
<input type="checkbox"/> MANUFACTURING CHANGE/ADDITION	<input type="checkbox"/> CONTROL SUPPLEMENT	<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review
<input type="checkbox"/> MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES	<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST
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IV. DRUG EXPERIENCE

<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS
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V. SCIENTIFIC INVESTIGATIONS

<input type="checkbox"/> CLINICAL	<input type="checkbox"/> PRECLINICAL
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COMMENTS/SPECIAL INSTRUCTIONS: We would appreciate a priority review. Thank you

PDUFA DATE: 1/23/08

ATTACHMENTS: Draft Package Insert, Container and Carton Labels

CC: Archival IND/NDA 50-813

HFD-520/Division File

HFD-520/RPM

HFD-520/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER Susmita Samanta	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS ONLY <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
---	--

TITLE OF RECEIVER	SIGNATURE OF DELIVERER
-------------------	------------------------

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

/s/

Susmita Samanta
11/1/2007 11:30:43 AM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 50813 Supplement # NA Efficacy Supplement Type SE- NA

Proprietary Name: APC-111 MP Tablet, 775 mg
Established Name: Amoxicillin Tablet
Strengths: 775 mg

Applicant: Middlebrook Phramaceutical Corporation
Agent for Applicant (if applicable): NA

Date of Application: 12/14/2006
Date of Receipt: 12/14/2006
Date clock started after UN: 03/23/2007
Date of Filing Meeting: 05/09/2007
Filing Date: 05/22/2007
Action Goal Date (optional): 01/23/2008

User Fee Goal Date: 1/23/2008

Indication(s) requested: Tonsillitis and/or pharyngitis

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? X
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.) NA

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 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
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
- 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
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES 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 Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES 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? All

Additional comments: Amendments are submitted in paper

3. This application is an eCTD NDA. YES
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 NO
- Exclusivity requested? YES, _____ Years 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 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 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 NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO
If yes, contact PMHT in the OND-IO
- Financial Disclosure forms included with authorized signature? YES 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
- PDUFA and Action Goal dates correct in tracking system? YES 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: 62,576
- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) 11/3/2005 NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 09/14/2006 NO
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) _____ 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: NA
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES X NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES X NO
- 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: NA

- 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 NA 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? NA YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 05/09/2007

NDA #: 50-813

DRUG NAMES: APC-111 MP Tablet, 775 mg

APPLICANT: Middlebrook Pharmaceutical

BACKGROUND: Amoxicillin has already been approved. This is an extended release product. (Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Janice Soreth, John Alexander, Menfo Imoisili, Maria Rivera, Thamban Valappil, Charles Bonapace, Jeffrey Tworzanski, Frederic Marsik, Rapti Madurawe, Colangelo, Yan Wang, Shrikant Pagay

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

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	Menfo Imoisili
Secondary Medical:	John Alexander
Statistical:	Yan Wang
Pharmacology:	Wendy Schmidt
Statistical Pharmacology:	NA
Chemistry:	Suresh Pagay
Environmental Assessment (if needed):	NA
Biopharmaceutical:	Sarah Robertson
Microbiology, sterility:	NA
Microbiology, clinical (for antimicrobial products only):	Fred Marsik
DSI:	Mathew Thomas
OPS:	NA
Regulatory Project Management:	Susmita Samanta
Other Consults:	NA

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 FILE X REFUSE TO FILE

STATISTICS	N/A <input type="checkbox"/>	FILE X	REFUSE TO FILE <input type="checkbox"/>
BIOPHARMACEUTICS		FILE X	REFUSE TO FILE <input type="checkbox"/>
• Biopharm. study site audits(s) needed? YES			<input type="checkbox"/> NO X
PHARMACOLOGY/TOX	N/A <input type="checkbox"/>	FILE X	REFUSE TO FILE <input type="checkbox"/>
• GLP audit needed?		YES <input type="checkbox"/>	NO X
CHEMISTRY		FILE X	REFUSE TO FILE <input type="checkbox"/>
• Establishment(s) ready for inspection?		YES X	NO <input type="checkbox"/>
• Sterile product?		YES <input type="checkbox"/>	NO X
If yes, was microbiology consulted for validation of sterilization?		YES <input type="checkbox"/>	NO <input type="checkbox"/>

ELECTRONIC SUBMISSION:

Any comments: NO

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

Susmita Samanta
Regulatory Project Manager
Version 6/14/2006

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): Amoxicillin, 62-118, 50-755, 50-749, 50-542, 50-754, 21-222, 50-460, 50-785

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 X NO

If "Yes," skip to question 7.

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

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

(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

(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

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"). Change in dosage form

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

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

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

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

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):

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

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 NO

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

N/A YES NO

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

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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/s/

Susmita Samanta
10/31/2007 04:32:24 PM
CSO

Samanta, Susmita

From: Marsik, Frederic J
Sent: Tuesday, August 28, 2007 9:02 AM
To: Samanta, Susmita
Subject: RE: NDA 50-813: Response to FDA 74-day Letter

8/28/07

Susmita,

The response is adequate to give them Group G streptococci in the PI but not Group C streptococci. They know that from their response.

Fred

From: Samanta, Susmita
Sent: Monday, August 27, 2007 2:14 PM
To: Marsik, Frederic J
Subject: FW: NDA 50-813: Response to FDA 74-day Letter

Fred,

The attached document provides a response to your questions regarding the NDA 50-813. It is on page 44 of the document. Please let me know if the response is adequate.

Thank you

Susmita

From: Halim, Diana [mailto:dHalim@middlebrookpharma.com]
Sent: Monday, August 27, 2007 12:32 PM
To: Samanta, Susmita
Cc: Wolling, Brenda
Subject: NDA 50-813: Response to FDA 74-day Letter

Hi Dr. Samanta,

I wanted to follow-up with you regarding our response to the 74-day letter we submitted to the FDA on July 12, 2007. Attached please find a scanned copy of the submission along with the confirmation receipt we received from the Central Document Room. Please confirm that you have received this PDF copy of the submission.

Also to follow this email, I will forward an additional 3 regulatory documents that we have submitted to the FDA since the original new drug application submission on March 23, 2007.

Please let me know if you need anything further and if we need to do anything

8/28/2007

differently to avoid having this occur in the future.

Sincerely,
Diana

Diana M. Halim, M.S.
Assistant Director, Regulatory Affairs
MiddleBrook Pharmaceutical, Inc. (formerly Advancis Pharmaceutical Corporation)
20425 Seneca Meadows Parkway
Germantown, MD 20876
Phone: (301) 944-6608
Fax: (301) 944-6703

8/28/2007

DSI CONSULT: Request for Clinical Inspections

Date: June 8, 2007

To: Constance Lewin, M.D., M.P.H., Branch Chief, GCP1, HFD-46
Leslie Ball, M.D., Branch Chief, GCP2, HFD-47

cc: Gary Della'Zanna, D.O, Director, Division of Scientific Investigations, HFD-45

From: Susmita Samanta, Regulatory Project Manager, HFD-520
Division of Anti-Infective and Ophthalmology Products

Subject: **Request for Clinical Site Inspections**
NDA 50-813
Advancis Pharmaceutical Corporation
APC-111 MP Tablet

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Center 0391: Kentucky Pediatric/Adult Research 201 South 5th St., Suite 102 Bardstown, KY 40004	111.302	58	Tonsillitis and/or pharyngitis
Center 0388: Foothill Family Clinic 2295 Foothill Drive Salt Lake City, UT 84109	111.302	51	Tonsillitis and/or pharyngitis

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) October 8, 2007. We intend to issue an action letter on this application by (division action goal date) January 23, 2008. The PDUFA due date for this application is January 23, 2008.

Should you require any additional information, please contact Susmita Samanta.

Concurrence: (if necessary):

John Alexander, M.D., M.P.H., Medical Team Leader

Menfo Imoisili, M.D., M.P.H., Medical Reviewer

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/s/

John Alexander
6/18/2007 04:38:53 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 50-813

Advancis Pharmaceutical Corporation
Attention: Brenda L. Wolling
Associate Director, Regulatory Affairs
20425 Seneca Meadows Parkway
Germantown, MD 20876

Dear Ms. Wolling:

Please refer to your March 23, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for APC-111 MP Tablet, 775 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on May 22, 2007 in accordance with 21 CFR 314.101(a).

Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We request that you submit the following information:

Chemistry:

1. Please list equipments used for each of the unit operations with justification for scalability based on equipment design and type of operation.
2. Page 37 in m3 document provides data for evaluation of _____
Please confirm if the compacted grade amoxicillin was also formulated with _____ similar to the powder grade amoxicillin? **b(4)**
3. Provide appropriate drug release data to demonstrate that Pulse 2 and Pulse 3 coatings remain intact during tablet compression. For example, it can be demonstrated using the final blend in a _____ **b(4)**
4. Provide drug release profile (at least 3 sample points) individually for Pulse 1, Pulse 2 and Pulse 3 each in the gastric pH range at _____ for up to 2 hours. **b(4)**
5. Provide drug release (at least 3 sample points) individually for Pulse 2 and Pulse 3 each at _____ for up to 2 hours.

6. Provide drug release (at least 3 sample points) individually for Pulse 3 at _____ for up to 2 hours.
7. The in-process specification for the total amoxicillin _____ How is this material accounted, i.e., % yield in the batch record? Is this material considered as a waste? **b(4)**
8. Please list for each of the 6 batches manufactured _____ the amount of usable amoxicillin _____, i.e. amount of Pulse 1 available from _____ batch size. **b(4)**
9. The in-process specification for the total amoxicillin core pellets _____ How is this material accounted, i.e., % yield in the batch record? Is this material considered as a waste? **b(4)**
10. Please list for each of the 6 batches manufactured _____ the amount of usable amoxicillin _____ for Pulse 2 and Pulse 3 that was available from the batch size. **b(4)**
11. What is the actual yield of usable Pulse 2 pellet from each of the 6 batches (batch size listed as _____).
12. What is the actual yield of usable Pulse 3 pellet from each of the 6 batches (batch size listed as _____).
13. Provide observed particle size distribution including limits on _____ utilized for Pulse 1. **b(4)**
14. Provide observed particle size distribution including limits on _____ utilized for Pulse 2 and Pulse 3. **b(4)**
15. Provide observed particle size distribution including limits on the Pulse 2 and Pulse 3 _____. **b(4)**
16. Since , NDA batch size is _____ (NDA Table 3.2.P.3-7) requiring multiple and fractional intermediate batches, provide how these batches are tracked and your plans for utilization of unused fractions, e.g., amoxicillin Pulse 3 pellets – nominal number of batches required are _____ batches, then what happens to the remaining _____ fraction of the batch? **b(4)**
17. Since multiple sub-batches of Pulse 2 are combined in a batch, the in-process test should include dissolution profile for both _____ rather than single point proposed in Table 3.2.P.3-28. Please explain your rationale for single point dissolution. **b(4)**
18. Since multiple sub-batches of Pulse 3 are combined in a batch, the in-process test should include dissolution profile rather than single point proposed in Table 3.2.P.3-29. This table should also include _____ Please explain your rationale for a single point dissolution test. **b(4)**

19. If available, provide representative SEM of Pulse 2 and Pulse 3 pellets.
20. Since the formulation was designed on the basis of biopharmaceutical studies and formal formulation optimization studies (level of excipient and processes) do not appear to have been carried out, please list all those studies that were carried out for the evaluation of any excipient at high, low and middle levels as well as evaluation of any of the unit processes.
21. Provide drug release profile of the uncoated amoxicillin core pellets used for Pulse 2 and Pulse 3. This is a critical step to demonstrate reproducibility of pellets from batch to batch or provide any other testing to demonstrate that core pellets used for Pulse 2 and Pulse 3 are reproducible from batch to batch.
22. Explain how the in-process — test and acceptance criteria (see item 7 and 9) provide adequate control for pellet coating. Also, explain if the — are controlled for optimal tablet compression.

b(4)

Microbiology:

2. Please provide the reference Jones et al., 2006. This reference is listed as “pub ahead of print” in the references for the above cited section of the application.

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

If you have any questions, call Susmita Samanta, Regulatory Project Manager, at 301-796-1400.

Sincerely,

(See appended electronic signature page)

Frances V. LeSane
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

b(4)

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/s/

Frances LeSane
6/4/2007 03:42:12 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-813

Advancis Pharmaceutical Corporation
Attention: Brenda L. Wolling
Associate Director, Regulatory Affairs
20425 Seneca Meadows Parkway
Germantown, MD 20876

Dear Ms. Wolling:

We have received your new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act in response to our February 12, 2007 refusal to file letter for the following:

Name of Drug Product: APC-111 MP Tablet, 775 mg

Review Priority Classification: Standard (S)

Date of Application: March 23, 2007

Date of Receipt: March 23, 2007

Our Reference Number: NDA 50-813

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 May 22, 2007, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be January 23, 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 requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have deferred the pediatric study requirement for this application.

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:

NDA 50-813

Page 2

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

If you have any questions, call Susmita Samanta, Regulatory Project Manager, at 301-796-1400.

Sincerely,

{See appended electronic signature page}

Frances V. LeSane
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Frances LeSane
4/17/2007 05:51:27 PM

MEMORANDUM OF TELECONFERENCE

MEETING DATE: February 26, 2007
TIME: 12:00-1:15 P.M.
APPLICATION: 50-813
DRUG NAME: APC-111 MP Tablet, 775 mg
SPONSOR: Advancis Pharmaceutical Corporation

FDA Attendees:

Menfo Imoisilli, M.D. Clinical Reviewer
Rapti Madurawe, Ph.D., Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment II
Elaine Morefield, Ph.D., Director, Division of Pre-Marketing Assessment II
Suresh Pagay, Ph.D., Chemistry Reviewer, Division of Pre-Marketing Assessment II
Norman Schmuff, Ph.D., Branch Chief, Division of Pre-Marketing Assessment II
Susmita Samanta, M.D, Regulatory Project Manager, Division of Anti-Infective and Ophthalmologic Drug Products

Advancis Pharmaceutical Corporation Representatives:

Susan P. Clausen, Ph.D., Vice President, Clinical Research & Regulatory Affairs
Nicholas J. Garito, Senior Director, Compliance and Quality
Donald J. Treacy, Ph.D., Vice President, Analysis and Pharmaceutical Quality
Sandra E. Wassink, Vice President, Pharmaceutical Development Operations
Brenda L. Wolling, Associate Director, Regulatory Affairs

Background:

On February 13, 2007, the Sponsor requested a meeting with the Agency to understand and to come to an agreement to resolve the deficiencies identified in the February 12, 2007 refusal to file letter for NDA 50-813, submitted December 14, 2006. A teleconference was scheduled to occur on February 26, 2007.

Discussion points:

The teleconference started with the introduction of the attendees. The Agency had the following comments regarding the deficiencies and requirements for resubmission:

- No commercial process has been identified in the current NDA submission. The current submission did not include proposed master batch records or a sufficiently detailed process description for the proposed commercial manufacturing process. The NDA resubmission should include a commercial manufacturing process and the approved, ready to execute, master batch records for the commercial process.
- In the NDA re- submission, the master batch records provided should describe all commercial process steps in appropriate level of detail.
- The proposed process controls for the manufacturing process were insufficient to provide assurance that the intermediates and finished drug products would be produced consistently. The

Agency provided examples of deficiencies in controls. Sufficient process controls should be provided to ensure manufacturing consistency.

- The Sponsor had not provided sufficient equipment operating parameters and intermediate batch utilization information. The commercial process in the NDA resubmission should contain sufficient operating parameters, acceptance criteria, etc.
- A summary of controls strategy should be included in the submission, which should include a more thorough description of the proposed in-process controls for the manufacturing process. The specifics of the control strategy and rationale are review issues.
- At the time of NDA re-submission, the commercial manufacturing site should be ready for inspection with the commercial equipment in place and qualified, process controls in place, master batch records, SOPs, process validation plans and validation protocols available for review, and the lab ready to support manufacturing.

The Sponsor outlined two scenarios for the proposed commercial manufacturing process.

Scenario 1:

The proposed commercial manufacturing process will be identical to the pilot scale/submission batches. The same batch sizes and equipment used in the manufacture of pilot scale for the proposed commercial scale.

Scenario 2:

The proposed commercial records and scale-up will be a "hybrid" of the pilot scale/submission batches and the original proposed scale-up process. The proposed commercial manufacturing process will be identical to the process submitted in the NDA in December with the exception of the Pulse 2 and Pulse 3 processes. The proposed processes for Pulse 2 and Pulse 3 manufacturing will be the same equipment and scale used for the Pilot Scale/Submission batches which would require the production of multiple batches and sub-batches to obtain the necessary quantity.

The Agency stated that the acceptability of the plan would depend upon development and justification of the appropriate controls for the proposed commercial manufacturing process. Additionally, the processing parameters for the scaled-up processes outlined in Scenario 2 should be justified and the uniformity of the multiple batches/sub-batches used in the process established.

The Agency noted the CMC submission should be significantly revised to reflect these changes.

The Sponsor agreed to provide proposed master batch records, a controls strategy, and a more thorough analysis and justification of the controls for the proposed commercial manufacturing process in the revised CMC submission to ensure that the resubmitted NDA is complete for filing in order to permit a substantive review.

Other Comments:

The Agency stated that there were no other major filing issues noted during the initial fileability evaluation. The timing for filing of the resubmission will be 60 days from the date received. At this time, no change in the review team is anticipated.

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/s/

Norman Schmuff
3/13/2007 12:23:31 PM

Frances LeSane
3/13/2007 11:36:12 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

REFUSAL TO FILE

NDA 50-813

Advancis Pharmaceutical Corporation
Attention: Brenda L. Wolling
Associate Director, Regulatory Affairs
20425 Seneca Meadows Parkway
Germantown, MD 20876

Dear Ms. Wolling:

Please refer to your December 14, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for APC-111 MP Tablet, 775 mg.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

Chemistry:

For proposed commercial-sized drug product manufacture, neither a proposed commercial batch record nor a detailed commercial process description with process parameters and in-process controls is included in the application. Consequently, the application is deficient in that it fails to meet the requirements of 21 CFR 314.50(d)(1)(ii)(c) and 21 CFR 314.50(d)(1)(ii)(a).

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

NDA 50-813

Page 2

If you have any questions, call Susmita Samanta, Regulatory Project Manager, at (301)–796-0803

Sincerely,

{See appended electronic signature page}

Janice M. Soreth, MD

Director

Division of Anti-Infective and Ophthalmology Products

Office of Antimicrobial Products

Center for Drug Evaluation and Research

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/s/

Janice Soreth
2/12/2007 05:07:21 PM

Samanta, Susmita

From: Wolling, Brenda [bwolling@advancispharm.com]
Sent: Wednesday, February 07, 2007 2:20 PM
To: LeSane, Frances V; Samanta, Susmita
Cc: Wolling, Brenda
Subject: NDA 050-813: Additional Information to Facilitate Review
Importance: High
Attachments: Advancis NDA 50813 Manufacturing Operations Table.doc

Dear Frances,

Pursuant to our conversation on Tuesday, February 6, we have summarized information already provided in the Original NDA 50-813 to facilitate review of the proposed commercial manufacturing operations.

We have attached a WORD table entitled "Comparison of the Drug Product Manufacturing for Submission and Proposed Commercial Batches" that shows the active component, unit operation, equipment and batch sizes for the submission and proposed commercial batches at Clonmel Healthcare. This information was compiled from information provided in the NDA (Reference file path: 050813\m3\cmc\product) in Tables 3.2.P.2-3 through 3.2.P.2-7. Many of the unit operations proposed for the commercial manufacturing process at Clonmel use the same equipment that was used to manufacture the submission batches at Clonmel. For the ~~_____~~ and Tablet Coating processes, the batch size for commercial is the same as manufactured for the submission batches, with the commercial process requiring multiple batches from each unit operation. For many of the unit operations the equipment used for the commercial process is identical to that used for the submission batches at Clonmel, and the throughput rate at which the batch is processed is the same. For these unit operations, the equipment and process are being run in the same manner for the submission batches as well as the proposed commercial batches.

b(4)

As discussed in the teleconference, scale-up and process optimization activities are ongoing and will be completed prior to process validation.

b(4)

If you have any additional questions please contact me at my number below, or via e-mail. We look forward to further discussion regarding the acceptability of our NDA for filing.

Regards,
Brenda

Brenda L Wolling
Associate Director, Regulatory Affairs
Advancis Pharmaceutical Corporation
20425 Seneca Meadows Parkway
Germantown, Maryland 20876

2/22/2007

1 Page(s) Withheld

 x Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Samanta, Susmita

From: Wolling, Brenda [bwolling@advancispharm.com]
Sent: Tuesday, February 06, 2007 4:01 PM
To: francis.lasane@fda.hhs.gov
Cc: Samanta, Susmita; Wolling, Brenda
Subject: NDA 50-813 Response to FDA Inquiry
Importance: High

Hi Francis,

Regarding the question of "Missing" data for 23 of 37 patients enrolled at Site 0305 in Protocol 111.302, these subjects had a telephone call as opposed to an in-clinic visit for Visit 2 (During Therapy Visit) which was allowed per protocol. Vital signs, clinician assessment of symptoms, HEENT and clinical response assessment by the clinician were not performed for subjects that had a telephone call for Visit 2 and are reported as "Missing" in the relevant listings. Please see listing 16.2.8.2 for more details.

Sincerely,
Brenda

Brenda L Wolling
Associate Director, Regulatory Affairs
Advancis Pharmaceutical Corporation
20425 Seneca Meadows Parkway
Germantown, Maryland 20876
(301) 944-6600 MAIN
(301) 944-6703 FAX

www.advancispharm.com
bwolling@advancispharm.com

2/22/2007



NDA 50-813

NDA ACKNOWLEDGMENT

Advancis Pharmaceutical Corporation
Attention: Brenda L. Wolling
Associate Director, Regulatory Affairs
20425 Seneca Meadows Parkway
Germantown, MD 20876

Dear Ms. Wolling:

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

Name of Drug Product: APC-111 MP Tablet, 775 mg

Review Priority Classification: Standard (S)

Date of Application: December 14, 2006

Date of Receipt: December 14, 2006

Our Reference Number: NDA 50-813

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 12, 2007, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 12, 2007.

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 requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have deferred the pediatric study requirement for this application.

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:

NDA 50-813

Page 2

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

If you have any questions, call Susmita Samanta, Regulatory Project Manager, at 301-796-1400.

Sincerely,

Frances V. LeSane
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**

/s/

Frances LeSane
1/24/2007 12:23:04 PM



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

FACSIMILE TRANSMITTAL SHEET

DATE: September 12, 2006

To: Wolling Brenda L.	From: Susmita Samanta
Company: Advancis Pharmaceutical Corporation	Division of Anti-Infective and Ophthalmology Products
Fax number: 301- 944-6703	Fax number: 301-796-9881
Phone number: 301-944-6614	Phone number: 301-796-1400
Subject: Responses to the Questions in the Pre-NDA Package, IND 62,576, #065, Dated August 16, 2006	

Total no. of pages including cover: 8

Comments:

Document to be mailed: YES NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-813

Advancis Pharmaceutical Corporation
Attention: Brenda L. Wolling
Associate Director, Regulatory Affairs
20425 Seneca Meadows Parkway
Germantown, MD 20876

Dear Ms. Wolling:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for APC-111 MP Tablet, 775 mg.

We also refer to the teleconference between representatives of your firm and the FDA on February 26, 2007. The purpose of the meeting was to understand and to come to an agreement to resolve the deficiencies identified in the February 12, 2007 refusal to file letter.

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 Susmita Samanta, Regulatory Project Manager, at 301-796-1400.

Sincerely,

{See appended electronic signature page}

Frances V. LeSane
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

1.6 Comprehensive List of Questions and Responses, 9/12/06

1.6.1 Regulatory and Format Questions

1. Advancis intends to file a 505(b)(2) NDA supported by the following:

- The successful pivotal study (Protocol 111.302) evaluating the safety and efficacy of APC-111 QD for 10 days compared to Pen VK QID for 10 days for the treatment of tonsillitis and/or pharyngitis secondary to *S. pyogenes* in adolescents and adults. (Refer to Appendix I for a brief summary of top-line results.)
- Published literature for immediate-release amoxicillin 750 mg QD for 10 days, to which Advancis has not obtained a right of reference.
- The completed Phase III study (Protocol 111.301) evaluating APC-111 QD for 7 days.
- Five pharmacokinetic studies conducted with APC-111 (Protocols 111.109, 111.110, 111.111, 111.112 and 111.115).
- The Division's previous findings on the safety and effectiveness of amoxicillin and Augmentin XR® for treatment of ear, nose, and throat infections due to *S. pyogenes*.

b(4)

Does the Division agree that this is an adequate package to support the proposed labeling of APC-111 775 mg once daily for 10 days for the treatment of tonsillitis and/or pharyngitis secondary to *S. pyogenes* in adolescents and adults?

Division response: *Yes, per our previous communication with you regarding this question (March 7, 2006), a 505 (b)(2) NDA application containing the items listed above would be considered adequate by the Division.*

2. The content and format of the NDA as outlined in this briefing document are based on our understanding of agreements reached during the November 17, 2004, Pre-Phase III CMC meeting, November 2, 2005, Pre-Phase III Meeting Clinical, key correspondence with the Division and the ICH Common Technical Document format, respectively.

Does the Division agree that the information provided in this document and all items specified herewith, will constitute a fileable and reviewable application?

Division response: *From the clinical standpoint, the content and format of the NDA as presented in the briefing document would be considered a fileable and reviewable application.*

3. Advancis will be submitting an electronic-NDA (based on the FDA guidance "Providing Regulatory Submissions in Electronic Format – NDAs January 1999") following the format of the Common Technical Document.

Does the Division find this acceptable?

Division response: *Electronic NDA submissions that follow the format of the Common Technical Document are acceptable to the Division.*

4. Does the Division agree with the Common Technical Document Table of Contents for the NDA as shown in Appendix II?

Division response: *Yes.*

5. Advancis intends to make a general reference to FDA's findings on safety, clinical efficacy, clinical pharmacology, microbiology, and pharmacology/toxicology for amoxicillin and Augmentin XR®.

Does the Division find this acceptable?

Division response *Yes, this approach is consistent with a 505 (b)(2) application.*

6. Advancis intends to use the innovator's current package inserts (Amoxil® and Augmentin XR®), as appropriate, as the basis of the APC-111 package insert.

Does the Division find this acceptable?

Division response: *Yes.*

7. The draft package insert provided in Appendix III will be outlined as described in FDA's New Labeling Rule dated February 2006.

Does the Division find this acceptable?

Division response: *Yes, this would be acceptable.*

8. As noted in the above questions, Advancis intends to use the innovator's package inserts as the basis of the APC-111 package insert. Due to the significant labeling format changes, Advancis will be unable to provide a side-by-side comparison. As a result of these different presentations, Advancis now intends to provide PDF copies of the package inserts for Amoxil® and Augmentin XR® for your information to allow direct comparison between appropriate sections of these package inserts and the proposed Advancis labeling for APC-111.

Does the Division find this acceptable?

Division response: *This appears to be an acceptable approach. Instead of a side-by-side comparison, we request that you provide an annotated copy of your package insert, noting the source for specific statements (your own studies, literature, etc.).*

9. Advancis intends to provide SAS (V 8.02) transport files containing randomization numbers and treatment groups for the ITT population for Protocols 111.301 and 111.302, as requested

by the Division on June 2, 2006, see Appendix IV. This transport file, *submitted prior to the NDA submission*, will allow the Division to randomly select 10% of the Case Report Forms for each of the studies, as part of the NDA submission.

Does the Division find this acceptable?

Division response: *Yes.*

10. Advancis plans to list and format the references within the NDA by number and in alphabetical order by primary author last name?

Does the Division find this acceptable?

Division response: *That would be acceptable to the Division.*

11. Advancis intends to provide SAS (V 8.02) transport files of raw datasets and derived datasets for the biopharmaceutical/clinical pharmacology (Phase I studies: Protocols 111.109, 111.110, 111.111, 111.112 and 111.115) and for the Phase III studies (Protocols 111.302 and 111.301). Data Definition Tables (DDTs) describing variable contents (variable names, type, length, format, labels, and source) will be provided for each raw and derived dataset for each study. Programs creating the derived datasets and table outputs for the individual study reports will not be provided unless specifically requested. As no dataset integration is being performed, there will be no transport files or DDTs for any integrated datasets.

Does the Division find this acceptable?

Division response: *The proposal for the data definition tables is adequate.*

12. Advancis intends to provide documents requiring original signatures in hard copy as well as in PDF format for the following documents: cover letter, FDA Form 356h, patent certification, debarment certification, field copy certification, user fee cover sheet, financial disclosure information, letters of authorization, environmental assessment certification, and claimed exclusivity.

Does the Division find this acceptable?

Division response: *Yes.*

1.6.2 Pharmacology/Toxicology Questions

1. The scope and proposed detail of the pharmacology/toxicology summary is outlined in CTD Section 2.6. Does the Division agree that the scope and proposed detail of the pharmacology/toxicology summary is adequate to support the registration of APC 11?

Division response: *The sponsor's plan to rely on the Division's previous findings of safety for approved amoxicillin products and to present an integrated summary review of published*

literature on the nonclinical pharmacology, PK, and toxicology of amoxicillin is acceptable. The sponsor also intends to provide pdf copies of the references used to write this summary. The sponsor did not conduct any of their own nonclinical studies with amoxicillin to support the development of APC-111 and none were necessary.

2. Advancis intends to present a justification for the use of _____ in APC-111 and a toxicology assessment to support the safety of the low amount used. An overview will be presented in CTD Section 2.4 with more detail provided in CTD Section 2.6. Does the Division find this acceptable? b(4)

Division response: *The Division and the sponsor agreed to this plan prior to the initiation of Phase 3 clinical trials. It is acceptable. The scope and proposed detail of the pharmacology/toxicology summary is outlined in CTD Section 2.6.*

1.6.3 Biopharmaceutics and Clinical Pharmacology Questions

1. The scope and proposed detail of the biopharmaceutics and clinical pharmacology summary is outlined in CTD Section 2.7.

Does the Division agree that the scope and proposed detail of the biopharmaceutics and clinical pharmacology summary is adequate to support the registration of APC-111?

Division response: *It is adequate.*

1.6.4 Microbiology Questions

1. The scope and proposed detail of the In Vitro and Clinical Microbiology sections of the CTD are in Appendix V and will be contained within CTD Module 5 Section 5.3.5.4. A summary of the in vitro microbiology information will be included in CTD Section 2.7.2.4. A summary of the clinical microbiology from Protocols 111.301 and 111.302 will be included in CTD Section 2.7.3.

Does the Division find this acceptable?

Division response: *It is acceptable. For tables 2.7.3.3 thru 2.7.3.8 and 2.7.3.10 and 2.7.3.11, it would be helpful if the clinical outcome could be included along with the bacteriological outcome in the same tables.*

1.6.5 Clinical Questions

1. Advancis plans to provide a summary of clinical efficacy and safety per the CTD guidance in CTD Sections 2.7.3 and 2.7.4, respectively, summarizing the two Phase III studies sequentially. The results will not be integrated since the APC-111 treatment durations used were different in the two studies. A once daily 10-day treatment regimen of APC-111 was used in Protocol 111.302 whereas a once daily 7-day treatment regimen was used in Protocol 111.301.

Does the Division find this acceptable?

Division response: *Providing a summary of clinical efficacy and safety in accordance with the CTD guidance, Sections 2.7.3 and 2.7.4 respectively, and summarizing the two Phase III studies separately, would be acceptable to the Division. Although the treatment durations recommended for use of your product by the patients in the two Phase III studies differed, having an integrated summary of safety for the two studies would be recommended by the Division. The datasets for the two trials should use the same variables and formats to allow reviewers to concatenate files from the two trials for safety and laboratory data analyses.*

2. Advancis does not plan on presenting the safety findings from the Phase I studies in CTD Section 2.7.4.2. Safety data will be presented in the individual clinical study reports in CTD Section 5.3.

Does the Division find this acceptable?

Division response: *This, also, would be acceptable to the Division. In addition, an integrated safety database for Phase 1 studies should be provided. Files for phase 1 studies should be similar in format, also to allow ease of concatenation by reviewers during safety and laboratory data analyses.*

3. Advancis intends to provide Individual Patient Profiles for Protocol 111.302 *only* in CTD Section 5.3.7 as outlined in Appendix VI. Individual patient profiles for Protocol 111.301 and the Phase I studies will not be provided.

Does the Division find this acceptable?

Division response: *The Division requests Individual Patient Profiles (IPP) for Protocol 111.301 patients. Case report forms for deaths, serious adverse events and discontinuations should be included in CTD section 5.3.7, regardless of study in which the patient was enrolled.*

1.6.6 Statistical Questions

1. Advancis has made the following revisions to the Statistical Analysis Plan (SAP), including the Division's comments received on July 6, 2006:
 - The scientific rationale for the non-inferiority margin chosen has been included.
 - Further to the statistical populations (ITT/Safety, mITT, PPc and PPb) previously defined in the SAP dated March 14, 2006, four additional populations (PPc1, PPb1, PPc2 and PPb2) are defined in SAP Amendment 1, dated July 25, 2006 (see Appendix VII), with the intent of ensuring the per-protocol analysis populations were inclusive of subjects compliant with the *active* study medication to which they were randomized. Assignment of the ITT, mITT, PPc1 and PPb1 populations will occur prior to database lock and unblinding of randomized treatment allocation. Assessment of compliance and subsequent assignment to the PPc1 and PPb1 populations will be based on the tablet and capsule counts, without regard to actual randomized treatment

allocated. The ITT, mITT, PPc1 and PPb1 populations will be discussed at the final data review meeting and will be authorized thereafter. Assignment of PPc2 and PPb2 will occur after database lock and unblinding of the randomized treatment allocated, with compliance based on actual randomized *active* treatment received. The PPc2 and PPb2 populations will exclude those subjects considered to be non-compliant to their active study medication only, in accordance with the actual study medication that they were randomized to. This implies that a subject, who is non-compliant with placebo medication but compliant with active study medication, could now be included in both the PPc2 and PPb2 analysis populations, if otherwise valid. The PPc2 and PPb2 will be the principle efficacy analysis populations PPc and PPb, respectively.

- The primary efficacy analysis, based on both the PPb (i.e., PPb2) and mITT [b] populations as co-primary efficacy populations will be presented unadjusted for region, as per the Division's recommendation. The same analyses will be performed using region as a stratification factor and will be considered as secondary, supportive analyses.
- Secondary efficacy analyses will be unadjusted for region and will include a comparison of the following between treatment groups:
 - The bacteriological outcome in the mITT [a] population at TOC.
 - The bacteriological outcome in the mITT [b] and PPb populations at LPT.
 - The clinical outcome in the ITT/Safety, mITT [b], PPc and PPb populations at TOC and in the ITT/Safety and PPc populations at LPT.
 - Safety in the ITT/Safety population.
- A Data Review Meeting (DRM) has been conducted for the final assignment of the statistical analysis populations. The DRM document outlining assignment of the statistical analysis populations pre- and post-unblinding is included as an appendix to the Statistical Analysis Plan, see Appendix VII, with appropriate authorization signatures at each stage.

Does the Division find the changes implemented to the Statistical Analysis Plan, including the population assignment outline the DRM document, acceptable?

Division response: *It is acceptable. It should be noted that the missing/non-compliant/indeterminate responses would be classified as failures in the mITT population.*

1.6.7 Chemistry, Manufacturing & Controls

1. The format for Module 3 Quality, outlined in Section 3.3 of this briefing document, is based on the ICH/M4Q Quality guidance document. The proposed detail is based on withdrawn FDA draft Guidances for Drug Substance - Chemistry, Manufacturing and Controls information, January 2004 and Drug Product - Chemistry, Manufacturing and Controls information, January 2003.

Does the Division find this acceptable?

Division response: *The proposal is acceptable.*

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/s/

Susmita Samanta
9/12/2006 01:59:34 PM
CSO

Susmita Samanta
9/12/2006 02:03:11 PM
CSO



IND 62,576

Advancis Pharmaceutical Corporation
Attention: Brenda L. Wolling
Assistant Director, Regulatory Affairs
20425 Seneca Meadows Parkway
Germantown, Maryland 20876

Dear Ms. Wolling:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Amoxicillin Pulsatile Formulation.

We also refer to the clinical Pre-Phase III meeting between representatives of your firm and FDA on November 2, 2005.

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 Susmita Samanta, M.D., Regulatory Project Manager, at 301-796-1400.

Sincerely,

{See appended electronic signature page}

Frances LeSane
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 2, 2005
TIME: 1:30-3:00 PM
LOCATION: White Oak Building
APPLICATION: IND 62,576
DRUG NAME: Amoxicillin Pulsatile Formulation, APC-111 Tablet
SPONSOR: Advancis Pharmaceutical Corporation

TYPE OF MEETING: Pre-Phase III Meeting-Clinical

FDA Attendees:

Janice Soreth, MD, Division Director
John Alexander, MD, MPH, Medical Team Leader
Menfo Imoisili, MD, Medical Officer
Jeffrey Tworzanski, PhD, Clinical Pharmacology Reviewer
Venkat Jarugula, PhD, Clinical Pharmacology Team Leader
John Lazor, PhD, Director, BioPharmaceutics III
Frederic Marsik, PhD, Microbiology Team Leader
Sue Bell, PhD, Acting Statistical Team Leader
Yan Wang, PhD, Statistical Reviewer
Susmita Samanta, MD, Regulatory Project Manager

Advancis Pharmaceutical Corporation Representatives:

Susan Clausen, PhD, Vice President, Clinical Research and Regulatory Affairs
Henry Flanner, MS, Director, Pharmaceutical Research
Robert Guttendorf, PhD, Pharmacology and Biopharmaceutics Consultant
David Markowitz, Director, Clinical Research
Donald Treacy, PhD, Vice President, Analytical Sciences
Brenda Wolling, Associate Director, Regulatory Affairs
Frank Sasinowski, Regulatory Consultant

BACKGROUND

On September 1, 2005, Advancis Pharmaceutical requested a pre-phase 3 meeting. The meeting was granted and scheduled to occur on November 2, 2005. Advancis sent the meeting package on September 30, 2005.

DISCUSSION POINTS:

After the introduction of the attendees, the Sponsor presented an overview of the completed trial (111.301) and the regulatory strategy to support the 505(b)(2) NDA application for APC-111 MP

Tablet and the PK/PD analyses performed. The presentation was derived from the briefing document submitted on September 30.

The following is the summary of the main discussion points:

The Division cautioned that without a phase 2 trial, the Sponsor is taking a risk in assuming that that the PK argument is all they need. If the results of the pivotal trial are marginal, literature and PK/PD analysis data may not be sufficient. The Division agreed that a successful 111.302 trial combined with literature data for immediate-release amoxicillin 750 mg QD for 10 days as the supportive evidence of efficacy and the PK/PD data analysis should be adequate to submit an NDA for the treatment of pharyngitis and/or tonsillitis in adolescents and adults.

The design of protocol 111.302 is acceptable with the following comments:

- The Division will consider the analysis of bacteriological outcome at TOC Visit for the mITT population as co-primary analysis to ensure consistency in outcome between PPb and mITT populations.
- The Sponsor should mainly count the patients with documented eradication, not presumed eradication. Only very limited number (2-3) of patients should have presumed eradication (e.g., a patient whose throat culture specimen was lost) if the protocol is followed correctly.
- Since the absolute eradication rates for Pen VK and APC-111 may be less than 90%, the Division recommended increasing the number of patients in the study to ensure adequate power. It was agreed that a minimum of 600 patients and a maximum of 800 patients should be enrolled. The discussion included alternative schemes for deciding when to end enrollment in the trial (e.g, when either 800 patients have been enrolled or the end of the pharyngitis/tonsillitis season, which ever occurs first). Such schemes should be considered by the Sponsor to increase patient enrollment.

The Division requested the package insert for the Signify Test and the instructions on collection and transport of culture samples. The Sponsor agreed to submit the package insert for the Signify Test and appropriate sections for the clinical conduct manual pertaining to collection and transport of culture samples for 111.302.

Meeting minutes prepared by S. Samanta

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/s/

Frances LeSane
11/30/2005 04:01:13 PM

Janice Soreth
11/30/2005 05:11:45 PM



IND 62,576

Advancis Pharmaceutical Corporation
Attention: Brenda L. Wolling
Assistant Director, Regulatory Affairs
20425 Seneca Meadows Parkway
Germantown, Maryland 20876

Dear Ms. Wolling:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Amoxicillin Pulsatile Formulation.

We also refer to the pre-phase III meeting between representatives of your firm and FDA on September 22, 2004.

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 Susmita Samanta, M.D., Regulatory Project Manager, at 301-827-2125.

Sincerely,

{See appended electronic signature page}

Frances LeSane
Chief, Project Management Staff
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 22, 2004
TIME: 10:00-11:00 AM
LOCATION: Corporate Building
APPLICATION: IND 62,576
DRUG NAME: Amoxicillin Pulsatile Formulation, APC-111 Tablet
SPONSOR: Advancis Pharmaceutical Corporation

TYPE OF MEETING: Pre-Phase III

FDA Attendees:

Janice Soreth, MD, Division Director
John Alexander, MD, MPH, Medical Team Leader
Menfo Imoisili, MD, Medical Officer
Jeffrey Tworzyanski, PhD, Clinical Pharmacology Reviewer
Venkat Jarugula, PhD, Clinical Pharmacology Team Leader
Peter Coderre, PhD, Acting Microbiology Team Leader
Frederic Marsik, PhD, Microbiology Reviewer
Robert Osterberg, PhD, Pharmacology Team Leader
Christopher Khedouri, PhD, Statistical Reviewer
Suresh Pagay, PhD, Chemistry Reviewer
Dave Roeder, Assistant Director, Regulatory Affairs
Susmita Samanta, MD, Regulatory Project Manager
Frances LeSane, Chief, Project Management Staff

Advancis Pharmaceutical Corporation Representatives:

Beth Burnside, PhD, Vice President, Pharmaceutical Development
Susan Clausen, PhD, Senior Director, Clinical Research
Robert Guttendorf, PhD, Vice President, Preclinical Research / Biopharmaceutics
Barry Hafkin, MD, Senior Vice President and Chief Scientific Officer
David Markowitz, Associate Director, Clinical Research
Colin Rowlings, PhD, Senior Vice President, Pharmaceutical R&D / Project Management
Donald Treacy, PhD, Vice President, Analytical Sciences
Brenda Wolling, Assistant Director, Regulatory Affairs
Shankar Hariharan, PhD, Executive Vice President and Chief Scientific Officer, Par Pharmaceuticals

BACKGROUND

On August 4, 2004, Advancis Pharmaceutical requested a pre-phase 3 meeting. The meeting was granted and scheduled to occur on September 22, 2004. Advancis sent the meeting package on August 20, 2004.

DISCUSSION POINTS:

After the introduction of the attendees, the Sponsor presented a brief history of Advancis Pharmaceutical Corp., a review of the corporate goals for APC-111, and a review of the clinical and regulatory plan for development of the APC-111 Tablet. The presentation was derived from the briefing document submitted to the Division on August 20, 2004.

The Division was encouraged by the Sponsor's overall development plan for APC-111 and welcomed the idea of creating a novel formulation of amoxicillin. The discussion then focused on the three questions the Sponsor posed in the briefing package. The responses follow the questions.

1. Advancis will provide supporting pharmacokinetic studies and cross-reference the appropriate Amoxil and Augmentin NDA's for this 505(b)(2) submission. In addition, Advancis plans to conduct one pivotal phase III study for the treatment of tonsillitis and/or pharyngitis secondary to *S. pyogenes*. Assuming successful outcome of our pivotal study, does the Agency agree that this submission will represent an adequate development program to support approval of this indication?
 - The plan to rely on the Agency's finding on the safety and efficacy of the Amoxil and Augmentin NDAs along with conducting supporting pharmacokinetic and pivotal trials is acceptable as a basis for submitting a 505(b)(2) application. The Sponsor cannot cross reference the Amoxil and Augmentin NDAs unless right of reference is obtained.
 - The proposal to conduct phase I studies, 111.109, 111.110, and 111.111 are acceptable and adequate.
 - The Division stated that the Sponsor needs to provide additional data, besides the results of the single pivotal trial (Protocol 111.301), to support the assertion of efficacy for APC-111. The Division provided the following options:
 - a. A separate study of pediatric pharyngitis using a pediatric formulation of APC-111 would provide confirmatory evidence of efficacy.
 - b. Expanding the fully evaluable number of patients in the pivotal trial and splitting the trial into two separate cohorts, in effect creating two identical trials of APC-111 tablets, would be an option.
 - c. Provide other supportive data for efficacy of the proposed dosing regimen and duration. Since the Sponsor is proposing once daily dosing of APC-111 for seven days, the supportive evidence of efficacy from the Agency's previous findings from Amoxil and Augmentin is limited.
2. Does the Agency find the design of the pivotal study with Penicillin VK as the comparator to be appropriate?
 - Protocol 111.301 (phase III trial) seems to be acceptable in terms of design, size and end points.
 - The comparator, Penicillin VK, is appropriate for use in the pivotal trial.

- The Division recommended recording the type of food taken by the subjects in the phase III trial to explore potential food effect on efficacy.
 - The Division and the Sponsor agreed that for patients in Protocol 111.301, the predicted total time-above-MIC (*S. pyogenes*) over the course of the 7-day APC-111 treatment is comparable to that of the 10-day Penicillin treatment. The Division indicated to revisit the issue whether the total time-above-MIC analysis would provide adequate corroborative evidence to support the results of the single pivotal trial.
3. Does the Agency agree that the inactive components used in the APC-111 tablet formulation are acceptable for use in a product to be used for the oral treatment of pharyngitis?
- The Division reviewed the list and amount of excipients used in APC-111 tablet and has no immediate concern but suggested that the Sponsor request a meeting to review CMC issues in the near future. The ingredient _____ is a relatively toxic substance, however, the amount used _____ is small. The NDA submission should include justification for the use of _____, and information from the literature to support the safety of the amount of _____ used.
 - Concern expressed about the size of the tablet that it is too big and patients may cut it in half. The label should note that the tablet should not be cut or crushed.
 - The formulation should be finalized before the phase III trial.

b(4)

Note: The following comments were forwarded to the Sponsor before the meeting:

1. We do not know at this time the PK profile of APC-111 MP 775 mg tablet. Complete additional Phase 1 trials to characterize the specific PK/PD profile of this drug at this dose.
2. Provide the final study reports for study 111.105 and study 111.106.
3. Provide the detailed protocols for all future Phase 1 trials.
4. The Phase 3 protocol indicated that patients will be instructed that the medication's first dose of the day must be taken with food. Collect specific information regarding the meals the patients are to receive during dosing to assess the impact on safety and efficacy of the APC-111 MP 775mg tablet.
5. Provide information on the sensitivity and specificity of the SiGNIFY™ test being proposed for the detection of *S. pyogenes* associated with pharyngitis/tonsillitis.
6. Include in the clinical study protocol the suggested method for the collection and transport of tonsillar specimens to the laboratory, culture of the specimen, and the method to be used for identification of *S. pyogenes*.
7. Include as a section in the clinical study protocol the instructions for the non-culture test that will be used to detect the presence of *S. pyogenes* in tonsillar specimens.
8. It is suggested that isolates of *S. pyogenes* recovered from specimens be saved for future reference. Indicate in the clinical study protocol that isolates are to be saved and the method(s) by which isolates may be saved.
9. Include in the "Late Post Therapy" visit the need to obtain a specimen for culture in the event that the examining physician feels that infection is still present (protocol No. 111,301, dated 7/16/04, pg. 26). This will assure that the information on culture results is

available to help in classifying the patient as a "Failure", "Carrier/Re-colonization" or "Recurrence" (protocol No. 111,301, dated 7/16/04, pg. 42).

10. Clarify whether a patient will be considered for evaluation for bacteriological response based on a positive non-culture test and/or a positive culture test for *S. pyogenes* at base line. See sections 9.3.3 and 9.1.2 of protocol No. 111,301, dated 7/16/04. Section 9.3.3 refers to a section 9.1.10 of the protocol which is not present.

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

/s/

Frances LeSane
10/22/04 11:39:16 AM

Janice Soreth
10/22/04 01:33:30 PM

ACTION PACKAGE CHECKLIST

Application Information

BLA # NDA # 50-813	BLA STN# NDA Supplement # NA	If NDA, Efficacy Supplement Type NA
Proprietary Name: Established Name: APC-111, amoxicillin tablet, 775 mg Dosage Form: Tablet		Applicant: Middlebrook Pharmaceuticals
RPM: Susmita Samanta		Division: Division of Anti-Infective and Ophthalmology Products Phone # 301-796-1400
<p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)</p> <p>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(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.)</p>		<p>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)):</p> <p>NDA 50-755, Augmentin ES NDA 50-749, Omnicef NDA 50-542, Amoxil Chewable Tablet NDA 50-754, Amoxil Tablet NDA 50-785, Augmentin XR NDA 50-460, Amoxicillin Oral Suspension NDA 21-222, Spectracef</p> <p>Provide a brief explanation of how this product is different from the listed drug. This is once daily dose of amoxicillin</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>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.</p> <p>X Confirmed <input type="checkbox"/> Corrected Date: December 27, 2007</p>
❖ User Fee Goal Date		January 23, 2008
❖ Action Goal Date (if different)		January 23, 2008
❖ Actions		
• Proposed action		X AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		X 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 <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 3	
NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation	
NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies
NDAs and NDA Supplements: <input type="checkbox"/> OTC drug	
Other: Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<p>❖ Exclusivity</p>	
<ul style="list-style-type: none"> • NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>) 	<p>X Included</p>
<ul style="list-style-type: none"> • Is approval of this application blocked by any type of exclusivity? • NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>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.</i> • NDAs: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> • NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> • NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<p>X No <input type="checkbox"/> Yes</p> <p>X No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:</p> <p>X No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:</p> <p>X No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:</p> <p>X No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:</p>
<p>❖ Patent Information (NDAs and NDA supplements only)</p>	
<ul style="list-style-type: none"> • 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. 	<p><input type="checkbox"/> Verified X Not applicable because drug is an old antibiotic.</p>
<ul style="list-style-type: none"> • 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. • [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). 	<p>21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified</p> <p>21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)</p> <p><input type="checkbox"/> No paragraph III certification Date patent will expire</p>
<ul style="list-style-type: none"> • [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). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> • [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. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's</p>	<p><input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>

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

<p>within the 45-day period).</p> <p><i>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).</i></p> <p><i>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.</i></p>	
Summary Reviews	
❖ Summary Reviews: Team Leader, Division Director	1/18/08, 1/23/08
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)	NA
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	X
• Original applicant-proposed labeling	X
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	NA
Patient Package Insert	NA
• 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	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide	NA
• 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	
• 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
❖ Labeling reviews and minutes of any labeling meetings (indicate dates of reviews and meetings)	X DMETS 1/17/08 <input type="checkbox"/> DSRCS <input type="checkbox"/> DDMAC X SEALD 1/17/08 <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	October 31, 2007
NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	X Included
❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If AP: OC clearance for approval 	
❖ 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. (<i>Include certification.</i>)	X Verified, statement is acceptable
❖ Postmarketing Commitment Studies	X None
• Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>)	X
• Incoming submission documenting commitment	X
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	X
❖ Internal memoranda, telecons, email, etc.	X
❖ Minutes of Meetings	
• Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)	NA
• Pre-NDA/BLA meeting (<i>indicate date</i>)	<input type="checkbox"/> No mtg 9/12/06
• EOP2 meeting (<i>indicate date</i>)	<input type="checkbox"/> No mtg 9/22/04, 12/14/04, 11/2/05
• Other (e.g., EOP2a, CMC pilot programs)	NA
❖ Advisory Committee Meeting	X No AC meeting
• Date of Meeting	
• 48-hour alert or minutes, if available	
❖ <u>Federal Register</u> Notices, DESI documents, NAS/NRC reports (if applicable)	NA
CMC/Product Quality Information	
❖ CMC/Product review(s) (<i>indicate date for each review</i>)	1/1/08
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	X None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• X Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	1/1/08
• <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
• <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	X Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: 11/27/07 X Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (<i>indicate date(s)</i>) • Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>) 	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	1/2/08
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	X None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	X No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	X None requested
Clinical Information	
❖ Clinical review(s) (<i>indicate date for each review</i>)	1/18/08
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	1/18/08
❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)	X None
❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>)	<input type="checkbox"/> Not needed 12/19/07
❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)	1/18/08
Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>)	NA
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>)	X Not needed
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested
• Clinical Studies	12/4/07
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/21/07
❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/30/07