

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-116**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE  
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and  
Composition) and/or Method of Use**

NDA NUMBER

22-116

NAME OF APPLICANT / NDA HOLDER

SmithKline Beecham Corp. dba  
GlaxoSmithKline

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)

LEXIVA

ACTIVE INGREDIENT(S)

fosamprenavir calcium

STRENGTH(S)

50 mg/ML

DOSAGE FORM

Oral Suspension

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number

6,436,989

b. Issue Date of Patent

8/20/2002

c. Expiration Date of Patent

12/24/2017

d. Name of Patent Owner  
Vertex Pharmaceuticals

Address (of Patent Owner)

130 Waverly St.

City/State

Cambridge, MA

ZIP Code

02139

FAX Number (if available)

617-444-7117

Telephone Number

617-444-6100

E-Mail Address (if available)

ken\_boger@vrtx.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**4. Method of Use**

**Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Patent Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
9	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) LEXIVA is indicated in combination with other antiretroviral agents for the treatment of HIV infection.	

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

<b>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</b>  <div style="font-family: cursive; font-size: 1.2em; margin-left: 20px;">Robert H. Brink</div>	Date Signed  <div style="font-family: cursive; font-size: 1.2em; margin-left: 20px;">21 Nov. 2006</div>
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**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

Check applicable box and provide information below.

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Robert H. Brink VP, Intellectual Property GlaxoSmithKline	
Address Five Moore Drive P.O. Box 13398	City/State Research Triangle Park, NC
ZIP Code 27709-3398	Telephone Number 919-483-3323
FAX Number (if available) 919-483-7977	E-Mail Address (if available) rob.h.brink@gsk.com

The public reporting burden for this collection of information has been estimated to average 9 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:

Food and Drug Administration  
 CDER (HFD-007)  
 5600 Fishers Lane  
 Rockville, MD 20857

*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.*

**INFORMATION AND INSTRUCTIONS FOR FORM 3542a**  
**PATENT INFORMATION SUBMITTED WITH THE FILING**  
**OF AN NDA, AMENDMENT OR SUPPLEMENT**

**General Information**

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HPD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahtm/fdahtm.html>.

**First Section**

Complete all items in this section.

**1. General Section**

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

**2. Drug Substance (Active Ingredient)**

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

**3. Drug Product (Composition/Formulation)**

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

**4. Method of Use**

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

**5. No Relevant Patents**

Complete this section only if applicable.

**6. Declaration Certification**

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

**4. Method of Use (continued)**

**Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:**

**4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?**  Yes  No

**4.2 Patent Claim Number (as listed in the patent)** 10 **Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?**  Yes  No

**4.2a** If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product *Use (Submit indication or method of use information as identified specifically in the approved labeling.)* LEXIVA is indicated in combination with other antiretroviral agents for the treatment of HIV infection.

**4. Method of Use (continued)**

**Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:**

**4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?**  Yes  No

**4.2 Patent Claim Number (as listed in the patent)** 11 **Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?**  Yes  No

**4.2a** If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product *Use (Submit indication or method of use information as identified specifically in the approved labeling.)* LEXIVA is indicated in combination with other antiretroviral agents for the treatment of HIV infection.

**4. Method of Use (continued)**

**Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:**

**4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment or supplement?**  Yes  No

**4.2 Patent Claim Number (as listed in the patent)** 12 **Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?**  Yes  No

**4.2a** If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product *Use (Submit indication or method of use information as identified specifically in the approved labeling.)* LEXIVA is indicated in combination with other antiretroviral agents for the treatment of HIV infection.

## EXCLUSIVITY SUMMARY

NDA # 22-116

SUPPL #

HFD # 530

Trade Name LEXIVA

Generic Name fosamprenavir calcium, FPV

Applicant Name GlaxoSmithKline, Inc

Approval Date, If Known 06/14/2007

### 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)(1)

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# 21-549

LEXIVA Oral Tablets

NDA#

NDA#

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:

Study APV20003  
Study APV29005

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 <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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 <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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"):

IND 58,637

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 # 58,627      YES       ! NO   
! Explain:

Investigation #2  
IND # 58,627      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:

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Name of person completing form:  
Marsha S. Holloman, BS Pharm, JD  
Title: Regulatory Health Project Manager  
Date: 06/14/2007

Name of Office/Division Director signing form:  
Jeffrey S. Murray, MD, MPH  
Title: Deputy Division Director

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

**PEDIATRIC PAGE**

(Complete for all filed original applications and efficacy supplements)

DA/BLA #: 22-116 Supplement Type (e.g. SE5): N/A Supplement Number: \_\_\_\_\_

Stamp Date: 12/14/2006 PDUFA Goal Date: 06/14/2007

HFD 530 Trade and generic names/dosage form: LEXIVA (fosamprenavir calcium, FPV) Oral Suspension

Applicant: GlaxoSmithKline, Inc Therapeutic Class: 7030202

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): \_\_\_\_\_

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: This application provides for the use of LEXIVA (fosamprenavir calcium) Oral Suspension in combination with other antiretroviral agents for the treatment of HIV-1 infection.

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. birth yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
 Max \_\_\_\_\_ kg \_\_\_\_\_ mo. one yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: Product unlikely to be used in children less than one month old because of probable need to dose with ritonavir which is not approved for use in patients less than one month of age.

*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. one yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
 Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. two 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: Some pediatric studies completed sooner than others. APV20002 is expected in December 2009 and will provide data on pediatric patients one month to two years of age.

Date studies are due (mm/dd/yy): 12/31/2007

*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. two Tanner Stage \_\_\_\_\_  
 Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 16 Tanner Stage \_\_\_\_\_

Comments: Studies submitted to the NDA provided 24-week data for pediatric patients two to 16 years of age. Long-term data from Study APV20095 will be submitted as it becomes available.

NDA 22-116

Page 3

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

**This page was completed by:**

*{See appended electronic signature page}*

---

**Marsha S. Holloman, BS Pharm, JD**  
**Regulatory Health Project Manager**

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

**(Revised: 10/10/2006)**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: \_\_\_\_\_

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. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Adult studies ready for approval

Formulation needed

Other: \_\_\_\_\_

*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. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for deferral:

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

Date studies are due (mm/dd/yy): \_\_\_\_\_

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

**Section D: Completed Studies**

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

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

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

\_\_\_\_\_  
Regulatory Project Manager

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

(Revised: 10/10/2006)

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/s/

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Marsha Holloman

6/20/2007 10:58:35 AM

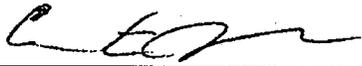
Confidential

Module 1.3.3 Debarment Certification

NDA 22-116  
Lexiva® (fosamprenavir calcium) 50mg/mL Oral Suspension  
Treatment of HIV-1 Infection

DEBARMENT CERTIFICATION

GlaxoSmithKline 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.



Charles Mueller or Mertie Snead  
Director, North America Clinical Compliance  
Worldwide Regulatory Compliance

4 PM 2006  
Date



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-116

**NDA ACKNOWLEDGMENT**

SmithKlineBeecham d/b as GlaxoSmithKline  
Attn: Eric B. Benson  
Senior Director, US Regulatory Affairs  
PO Box 13398  
Five Moore Drive  
Research Triangle Park, NC 27709

Dear Mr. Benson:

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

Name of Drug Product:	LEXIVA <sup>®</sup> (fosamprenavir calcium) Oral Suspension
NDA Number:	22-116
Review Priority Classification:	Priority
Date of Application:	December 14, 2006
Date of Receipt:	December 14, 2006

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 we file the application, the user-fee goal date will be June 13, 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 submitted pediatric studies with this application. Once the review of this application is complete we will notify you whether you have fulfilled 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 22-116

Page 2

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

If you have any questions, call Marsha Holloman, Regulatory Project Manager, at (301) 796-0731.

Sincerely,

*{See appended electronic signature page}*

Virginia Behr  
Chief, Project Management Staff  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/

-----  
Virginia Behr  
1/25/2007 03:58:01 PM

# MEMORANDUM

**To:** Marsha Holloman, BS Pharm, JD  
Division of Antiviral Products

**From:** Iris Masucci, PharmD, BCPS  
Division of Drug Marketing, Advertising, and Communications  
for the Study Endpoints and Label Development (SEALD) Team, OND

**Date:** June 13, 2007

**Re:** Comments on draft labeling for Lexiva (fosamprenavir)  
NDA 22-116

---

We have reviewed the proposed label for Lexiva (FDA version dated 6/13/07) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

Comments and recommendations are incorporated into the attached label.

49 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

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Iris Masucci  
6/21/2007 10:24:15 AM  
DDMAC REVIEWER

Laurie Burke  
6/21/2007 12:04:07 PM  
INTERDISCIPLINARY

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

**To:** Debra B. Birnkrant, MD  
Director, Division of Antiviral Products, HFD-110

**Through:** Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Errors and Technical Support, HFD-420

**From:** Kimberly Pedersen, RPh, Safety Evaluator  
Division of Medication Errors and Technical Support, HFD-420

**Date:** May 3, 2007

**Date of Document:** December 14, 2007

**Subject:** OSE Review 2007-830  
Proprietary Names: Lexiva Oral Suspension  
50 mg/mL (Fosamprenavir Calcium Oral Suspension)  
Sponsor: GlaxoSmithKline  
NDA #: 22-116

This memorandum is in response to an April 9, 2007 request from your Division for a review of the proposed labels and labeling for Lexiva Oral Suspension. This oral suspension is a product line extension of Lexiva tablets. Lexiva is currently marketed as a 700 mg oral tablet. The adult dose for Lexiva tablets ranges from 700 mg twice daily to 1400 mg twice daily, depending on whether it is administered with or without ritonavir. The proposed oral suspension has the same dosing for adults as the tablets, but provides for dosing for pediatric patients between the ages of two and eighteen years of age.

In review of the labels and labeling for this new dosage form, DMETS can anticipate errors with the introduction of this oral suspension. It is typical when new dosage forms are introduced that practitioners may be unaware of the introduction of this new formulation and dispense the tablets instead of the solution because this is what they are familiar with.

Additionally, there could be confusion between the doses of Lexiva oral suspension and Ritonavir (Norvir) oral solution concerning the existence of the new dosage form and potential dosing errors. Lexiva may be administered concurrently with Ritonavir. Both Lexiva and Ritonavir are available as oral liquid dosage forms. Potential confusion during the ordering, transcription, dispensing and administration of these two drug products may arise because of the overlap in dosage form and differences in dosing. The patients at highest risk for confusion are the pediatric population. DMETS' concern is that Ritonavir dosing for the pediatric patient will be less than five milliliters. In contrast, dosing for Lexiva will be 5 milliliters or more. Thus, Lexiva has a likelihood of being ordered in teaspoonsful. For example, a 30 pound (14 kilogram) child could be dosed at 5.6 mL or for administration convenience the practitioner could round this dose to one teaspoonful. This same patient's Ritonavir dose could be 0.5 mL or 1/2 mL. The difference in the dosing designation of milliliter and teaspoonsful could result in error. If the dose of teaspoonsful or milliliters were inadvertently switched or confused by a practitioner or caregiver; the patient could experience either an overdose or under dose of the intended drug product. This overdose or under dose could result in adverse events. Our concerns are based on post-marketing reports of similar dosing confusion that occurred with Ritonavir Oral Solution early after its approval. Practitioners were confusing the dose (e.g. 5 mL as 5 tsp).

DMETS recommends the sponsor develop a dosing device as a part of the physical container (i.e. cap) or that a device be co-packaged with Lexiva oral suspension. If the dosing device can not be a part of the physical container, there is still a possibility that the dosing devices for Lexiva and Ritonavir may be confused. Thus to minimize this risk if the dosing device is co-packaged with Lexiva oral suspension, DMETS recommends the sponsor add the proprietary name of "Lexiva" to the dosing device. Additionally, the device should be labeled in increments of milliliter to be in accordance with the recommended dose in the Dosage and Administration Section.

Furthermore, we have the following label and labeling recommendations for Lexiva oral suspension that may help to minimize other medication errors.

#### GENERAL COMMENTS

1. DMETS recommends that the sponsor implement an educational campaign that informs practitioners of the following:
  - The introduction of the new oral suspension of Lexiva;
  - The new recommended pediatric dosing; and
  - The differences in the administration of Lexiva oral suspension with/without food as compared to Lexiva tablets.
2. Lexiva Tablets are to be taken with or without food. However, Lexiva Oral Suspension should be taken with food in *pediatric* patients and without food in *adult* patients. DMETS assumes that dosing with food in pediatric patients pertains to the increased likelihood for gastrointestinal adverse reactions. However, this important difference should be explained in the labels and labeling. Therefore, the container labels and carton labeling should display a warning that pediatric patients take with food and that adult patients take without food. This warning should be given enough prominence to be observed and read by patients and practitioners.
3. Remove the teal colored “arc” before the proprietary name Lexiva, as it is distracting from the name and may be misinterpreted as a letter (e.g. capital “C”).
4. As currently presented, the 50 mg/mL strength is extremely small. DMETS recommends that the prominence of the strength be increased commensurate with the proprietary name.

#### B. CONTAINER LABELS

See General Comments A2 through A4.

#### CARTON LABELING

See General Comments A2 through A4.

#### D. INSERT LABELING

1. See General Comment A-2.
2. Highlights of Prescribing Information, Dosage and Administration Sub-Section
  - a. In reference to the Pediatric Dosing, the pediatric dose is ambiguous. A milligram per kilogram amount should be included and the milligram amount to not be exceeded should be designated rather than stated “not to exceed the recommended adult dose.” Additionally, as written the numbers (2.2) appear in parenthesis following the statement “recommended adult dose.” This number could be confused as the adult dose not to be exceeded.
  - b. In reference to the Pediatric Dosing, include the frequency of administration.
3. Highlights of Prescribing Information, Dosage Forms and Strengths Sub-Section

Delete the hyphen that appears between the number and mg (e.g. 700 mg rather than 700-mg or 50 mg/mL rather than 50-mg).
4. Full Prescribing Information, Dosage and Administration, Section 2.2

To simplify the presentation of the dosing for pediatric patients and reduce the potential for confusion with the dosing regimens, the sponsor should consider revising Table 1 from one box presentation to a two box presentation with Lexiva only dosing and then Lexiva and Ritonavir dosing. For example,

**Table 1: Lexiva Therapy Only**

Patient Population	Age	Lexiva
Therapy-Naïve	2-5 years	30 mg/kg Twice Daily
	≥6 years	30 mg/kg Twice Daily
Protease-Inhibitor Naïve	NA	NA
Protease-Inhibitor Experienced	NA	NA

**Table 2: Lexiva plus Ritonavir Therapy**

Patient Population	Age	Lexiva and Ritonavir Dosing Regimens	
		Once Daily	Twice Daily
Therapy-Naïve	2-5 years		
	≥6 years		Lexiva 18 mg/kg Ritonavir 3 mg/kg
Protease-Inhibitor Naïve	2-5 years		
	≥6 years		Lexiva 18 mg/kg Ritonavir 3 mg/kg
Protease-Inhibitor Experienced	2-5 years	NA	
	≥6 years	NA	Lexiva 18 mg/kg Ritonavir 3 mg/kg

b(4)

b(4)

b(4)

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any communication to the sponsor with regard to this review. If you have further questions or need clarifications, please contact Tanya Clayton, Project Manager, at 301-796-0871.

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/s/  
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Kimberly Culley-Pedersen  
6/13/2007 02:39:55 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
6/13/2007 02:54:31 PM  
DRUG SAFETY OFFICE REVIEWER



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA:** 22-116

**Drug:** LEXIVA® (fosamprenavir, FPV) Oral Suspension

**Date:** June 8, 2007

**To:** Eric B. Benson, Senior Director, US Regulatory Affairs

**Sponsor:** GlaxoSmithKline (GSK)

**From:** Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project  
Manager, Division of Antiviral Products (DAVP)

**Through:** Yodit Belew, MD, Medical Officer, Pediatric Fellow  
Russell D. Fleischer, PA-C, MPH, Senior Clinical Analyst  
Vikram Arya, PhD, Clinical Pharmacologist

**Concur:** Linda L. Lewis, MD, Medical Team Leader (Acting)  
Kellie S. Reynolds, Pharm D, Clinical Pharmacology Team Leader  
Jeffrey S. Murray, MD, MPH, Deputy Division Director

**Subject:** REQUEST FOR LABELING REVISIONS

---

Reference is made to your new drug application (NDA) 22-116 for LEXIVA (fosamprenavir, FPV) Oral Suspension submitted and received December 14, 2006. Also, reference is made to the May 31, 2007 teleconference between participants from GSK and DAVP.

We have the following labeling revisions beginning on the next page.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

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Deliberative Process (b5)

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/s/

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Marsha Holloman  
6/8/2007 02:50:51 PM  
CSO

This document was faxed and emailed to GSK.



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA:** 22-116

**Drug:** LEXIVA® (fosamprenavir, FPV) Oral Suspension

**Date:** June 7, 2007

**To:** Eric B. Benson, Senior Director, US Regulatory Affairs

**Sponsor:** GlaxoSmithKline (GSK)

**From:** Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, Division of Antiviral Products (DAVP)

**Through:** Yodit Belew, MD, Medical Officer, Pediatric Fellow  
Russell D. Fleischer, PA-C, MPH, Senior Clinical Analyst

**Concur:** Linda L. Lewis, MD, Medical Team Leader (Acting)  
Jeffrey S. Murray, MD, MPH, Deputy Division Director

**Subject:** **COMMENTS ON LABELING BASED ON THE PHYSICIANS' LABELING RULE**

---

Reference is made to your new drug application (NDA) 22-116 for LEXIVA (fosamprenavir, FPV) Oral Suspension submitted and received December 14, 2006.

**Review Team Labeling Comments:**

These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance, and FDA recommendations to provide for labeling quality and consistency across review divisions.

We have the following labeling comments based on review under the Physicians' Labeling Rule (PLR):

**General Comments:**

1. As required by the regulations, the Highlights and Contents must fit on a single page, using the 2-column format in 8-point font. This conversion must be made prior to approval to ensure that the Highlights fit on a half-page. [See 21 CFR 201.57(d) (6)]

and (d) (8)] Although there is no requirement that the Contents of PLR labeling be ½ page, to optimize the readability and usefulness of labeling, the agency recommends that Contents be ½ page or less. The labeling examples of fictitious drugs on CDER's website at <http://www.fda.gov/cder/regulatory/physLabel/default.htm> provide guidance on the new requirements for prescribing information.

2. Throughout the label, bold type is sometimes used in both the text and in subheadings. The new regulations specifically define when bold type should be used (e.g., all numbered section headings) and discourages their use elsewhere. Text that has previously been bolded in the old version of the label should be un-bolded here. Any added subheadings within a section should not be bolded and should instead use other methods for emphasis (e.g., underlining, italicizing).
3. Throughout the label, adverse reactions are called adverse events. With the new regulations and the accompanying final guidance on the Adverse Reactions section of labeling, our intent is to include only those reactions reasonably causally related to the drug (i.e., reactions) and not all events seen in the clinical studies. Please change events to reactions throughout the label.
4. Please refer to the *Style-Sheet Prototype: Human Prescription Drug Labeling with Highlights* at:  
[http://www.fda.gov/oc/datacouncil/PROTOTYPE\\_Stylesheet\\_with\\_highlights.pdf](http://www.fda.gov/oc/datacouncil/PROTOTYPE_Stylesheet_with_highlights.pdf)

#### Highlights:

5. Please remove the section entitled RECENT MAJOR CHANGES.
6. Please insert a space between "Initial U.S. Approval: 2003" and the "INDICATIONS AND USAGE" section.
7. Please insert a space between the "INDICATIONS AND USAGE" section and the "DOSAGE AND ADMINISTRATION" section.
8. Please do not use bolding for the sub-headings in the "DOSAGE AND ADMINISTRATION" section. Instead, please underline this language.
9. Please insert a space between the "DOSAGE AND ADMINISTRATION" section and the "DOSAGE FORMS AND STRENGTHS" section.
10. Please insert a space between the "DOSAGE FORMS AND STRENGTHS" section and the "CONTRAINDICATIONS" section.
11. Please insert a space between the "CONTRAINDICATIONS" section and the "WARNINGS AND PRECAUTIONS" section.

12. Please delete the language in the first bullet in the "WARNINGS AND PRECAUTIONS" section and insert "Do not co-administer with (list the drugs.)"
13. Please insert a space between the "WARNINGS AND PRECAUTIONS" section and the "ADVERSE REACTIONS" section.
14. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It does not provide a structured format for reporting. [See 21 CFR 201.57(a) (11)]
15. Please insert a space between the "ADVERSE REACTIONS" section and the "DRUG INTERACTIONS" section.
16. Please insert a space between the "DRUG INTERACTIONS" section and the "USE IN SPECIFIC POPULATIONS" section.

**Full Prescribing Information: Contents**

17. Please insert a space immediately following the line between the end of the "HIGHLIGHTS" section and before the beginning of this section.
18. Throughout this section, please insert spaces between the end of one numbered section and the beginning of the next.
19. In subsection 7.2, please format so that the word "LEXIVA" is parallel or in line with the word "Drugs."
20. In subsection 8.7, please format so that the words "Elevations of Liver Transaminases" are in parallel or in line with the word "Patient."
21. In subsection 13.1, please format so that the words "Fertility" is parallel or in line with the word "Carcinogenesis."
22. Please right-justify the sentence "\*\*Sections or subsections omitted from the full prescribing information are not listed." in the second column.

**Full Prescribing Information (FPI):**

23. Please begin this section on the next page following the "HIGHLIGHTS" and the "FULL PRESCRIBING INFORMATION: CONTENT" sections.
24. Please do not bold the information in the "INDICATIONS AND USAGE" section.
25. Please use brackets for all cross-references throughout the text.

26. Please underline but do not bold the information in the "Patients with Hepatic Impairment" in subsection 2.3.

27. Please remove the "Rx only" at the end of the package insert and the patient package insert.

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/s/

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Marsha Holloman  
6/8/2007 10:13:51 AM  
CSO



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA:** 22-116

**Drug:** LEXIVA® (fosamprenavir, FPV) Oral Suspension

**Date:** June 1, 2007

**To:** Eric B. Benson, Senior Director, US Regulatory Affairs

**Sponsor:** GlaxoSmithKline (GSK)

**From:** Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, Division of Antiviral Products (DAVP)

**Through:** Yodit Belew, MD, Medical Officer, Pediatric Fellow  
Russell D. Fleischer, PA-C, MPH, Senior Clinical Analyst  
Vikram Arya, PhD, Clinical Pharmacologist

**Concur:** Linda L. Lewis, MD, Medical Team Leader (Acting)  
Kellie S. Reynolds, Pharm D, Clinical Pharmacology Team Leader  
Jeffrey S. Murray, MD, MPH, Deputy Division Director

**Subject:** REQUEST FOR CLINICAL LABELING REVISIONS AND CLINICAL PHARMACOLOGY INFORMATION

---

Reference is made to your new drug application (NDA) 22-116 for LEXIVA (fosamprenavir, FPV) Oral Suspension submitted and received December 14, 2006. Also, reference is made to the May 31, 2007 teleconference between participants from GSK and DAVP.

We have the following requests for clinical pharmacology information:

1. Please provide the following information (in the format shown below) related to analytical method(s) used in the following studies: APV10017, APV10024, APV20003, and APV29005:

Parameter	APV10017	APV10024	APV20003	APV29005
Concentrations of standard used				
Mobile Phase				
Internal Standard				
QC Concentrations				
Calibration Range				
Intra/Inter Day Precision (% CV)				
Intra/Inter Day Accuracy (% CV)				

2. Please provide the long-term storage stability data related to the samples stored during the analysis and indicate if the stability data covers the time from the first sample collection until the completion of the analysis for all the studies indicated above.
3. Recommended content revisions of the LEXIVA labeling begins on the next page. Please note that we will probably request further revisions as we proceed with our review.
4. Recommended format revisions of the LEXIVA labeling under the Physicians' Labeling Rule (PLR) will be sent to you late next week.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

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✓           Draft Labeling (b4)

           Draft Labeling (b5)

           Deliberative Process (b5)

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/s/

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Marsha Holloman  
6/1/2007 05:22:06 PM  
CSO

Linda Lewis  
6/2/2007 08:32:37 AM  
MEDICAL OFFICER



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA:** 22-116

**Drug:** LEXIVA® (fosamprenavir, FPV) Oral Suspension

**Date:** May 22, 2007

**To:** Eric B. Benson, Senior Director, US Regulatory Affairs

**Sponsor:** GlaxoSmithKline

**From:** Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, Division of Antiviral Products (DAVP)

**Through:** Yodit Below, MD, Medical Officer (Pediatric Fellow)

**Concur:** Kellie S. Reynolds, Pharm D, Clinical Pharmacology Team Leader  
Linda L. Lewis, MD, Medical Team Leader (Acting)

**Subject:** CLINICAL REQUEST FOR FURTHER INFORMATION

Reference is made to your new drug application (NDA) 22-116 for LEXIVA (fosamprenavir, FPV) Oral Suspension submitted and received December 14, 2006. Also, reference is made to your May 16, 2007 response to our request for information.

We have the following clinical comments and recommendations:

AGE	UNBOOSTED Lexiva Twice Daily*	BOOSTED LEXIVA/ritonavir <sup>±</sup>	
		BID	QD
<b>2-5 years old</b>			
Treatment-naive	30 mg/kg  <i>Label would describe vomiting and carry a caveat that patients who experience repeated vomiting may be at risk for virologic failure.</i>	No dose recommendation	No dose recommendation

b(4)

		<i>safety data is submitted from additional patients</i>	<i>safety data is submitted from additional patients</i>
PI-naïve	No dose recommendation per proposed labeling	No dose recommendation T	No dose recommendation
PI- experienced	No dose recommendation per proposed labeling	No dose recommendation T	No dose recommendation per proposed labeling
<b>&gt;6 years old</b>			
Treatment-naïve	FPV 30 mg/kg BID	FPV 18 mg + RTV 3 mg BID	T

b(4)

b(4)

			<i>additional patients.</i>
PI-naive	No dose recommendation per proposed labeling	FPV 18 mg/kg + RTV 3 mg BID	┌
PI-experienced	No dose recommendation per proposed labeling	FPV 18 mg/kg + RTV 3 mg/kg BID	No dose recommendation per proposed labeling

b(4)

\* Maximum dose not to exceed the recommended adult dose. The adult regimen of LEXIVA Tablets 1,400 mg twice daily may be used for pediatric patients weighing at least 47 kg.  
 † Maximum dose not to exceed the recommended adult dose. When administered in combination with ritonavir, LEXIVA Tablets may be used for pediatric patients weighing at least 39 kg; ritonavir capsules may be used for pediatric patients weighing at least 33 kg.

b(4)

1. Please provide any information you have on the ability to score LEXIVA Tablets for possible use as a reduced dose in younger children.
2. The Written Request states that safety from patients receiving the proposed dose for marketing for at least six months should be submitted to support approval. Please be aware that we do not make the decision to grant exclusivity. That determination will be made by the Pediatric Exclusivity Board. The Board generally interprets the language in Written Requests very literally, and any deviance from the data requests may cause them to reach a negative conclusion.
3. Please provide subject identification numbers and case narratives for all patients who discontinued from the study for reasons other than virologic failure, adverse events, or pregnancy.
4. Please provide further details for subjects who received unboosted FPV (paragraph three of your response) who had completed questionnaires:
  - How many subjects had completed questionnaires?

- How many subjects with data completed questionnaires?
  - What was the outcome for those who had non-adherence or refusal of medication?
  - What was the response of guardians at Week 48 (or Week 24) regarding their children's ability to take the oral suspension?
5. Please provide the following information for all subjects with emesis:
- What was the re-dosing protocol, if any?
  - Is there virologic resistance noted in those subjects with emesis?
6. Please provide case narratives summarizing all concomitant medications and CBC values for all subjects in study APV20003 who experienced Grade 3 or 4 neutropenia.

We are providing the above information via telephone facsimile for your convenience.  
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Please feel free to contact me if you have any questions regarding the contents of this transmission.

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/s/

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Marsha Holloman  
5/22/2007 03:20:50 PM  
CSO

Linda Lewis  
5/22/2007 04:11:27 PM  
MEDICAL OFFICER



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA:** 22-116

**Drug:** LEXIVA<sup>®</sup> (fosamprenavir, FPV) Oral Suspension

**Date:** May 7, 2007

**To:** Eric B. Benson, Senior Director, US Regulatory Affairs

**Sponsor:** GlaxoSmithKline

**From:** Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, Division of Antiviral Products (DAVP)

**Through:** Yodit Below, MD, Medical Officer, Pediatric Fellow  
Russell D. Fleischer, PA-C, MPH, Senior Clinical Analyst  
Vikram Arya, PhD, Clinical Pharmacologist

**Concur:** Katherine A. Laessig, MD, Medical Team Leader  
Derek Yuanchao Zhang, PhD, Clinical Pharmacology Team Leader (Acting)  
Debra B. Birnkrant, MD, Division Director

**Subject:** CLINICAL REQUEST FOR FURTHER INFORMATION

---

Reference is made to your new drug application (NDA) 22-116 for LEXIVA (fosamprenavir, FPV) Oral Suspension submitted and received December 14, 2006.

We have reviewed the available pharmacokinetic, safety, and antiviral activity data contained in the NDA. Unfortunately, we do not believe we will be able to approve a number of your requested doses of LEXIVA Oral Solution. The table on the following pages outlines our current thinking on each proposed dose for each age group. We are concerned about the high rates of emesis and lack of pharmacokinetic and safety data for some regimens. We are available by phone for a teleconference to discuss these issues, should you be interested in further discussion.

**Unboosted Fosamprenavir**

Age	GSK proposed dose	DAVP response
2-5 years	Suspension: 30 mg/kg BID  Tablet: None proposed	Patients received either 30 BID (n=8), 40 BID (n=1) or both (n=9). DAVP is concerned about very high rate of emesis in this age group (10/18, 56%).
>6 years	Suspension: 30 mg/kg BID  Tablet: None proposed	No pediatric patients received this dose. Dose extrapolated from Agenerase data and actual dose not studied in intended population. Under review.

**Boosted Fosamprenavir**

Age	GSK proposed dose	DAVP response
2-5 years	Tablet: None proposed	Patients received 30/6 QD and some are now receiving 20/4 BID. Safety, PK and antiviral activity data pending from 20/4. The proposed doses are based on pharmacometric modeling, but have not been administered to patients; as such there is no PK, safety or activity data.
6-11 years	Suspension: FPV 18 mg + RTV 3 mg BID  Tablet: None proposed	Patients received 15/3 or 18/3 BID or 30/6 QD. Safety, PK and antiviral activity data available for 15/3, 18/3 and 30/6 doses, but no safety, PK or activity data for proposed doses which was extrapolated from pharmacometric modeling. Generally high rates of GI intolerance and poorer antiviral response compared to other age groups. Thus is it unknown what the PK or safety effect of the additional 6 mg FPV will have.

b(4)

b(4)

12-18 years	Suspension: FPV 18 mg + RTV 3 mg BID ↓  Tablet: None proposed	Studied 15/3 suspension and 700/100 BID and 1400/200 QD tablets in this age group. 18/3 not studied so there are no safety, PK or activity data. Suspension data remains under review. Would find it acceptable for this age group to receive Lexiva Tablet formulation at currently approved adult doses.
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b(4)

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/s/

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Marsha Holloman  
5/7/2007 02:52:56 PM  
CSO

Kathrine Laessig  
5/7/2007 03:00:10 PM  
MEDICAL OFFICER

## MEMORANDUM

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

**DATE:** May 4, 2007

**TO:** Debra Birnkrant, M.D., Director  
Division of Antiviral Products

**VIA:** Marsha Holloman BS Pharm, JD, Regulatory Health Project  
Manager  
Division of Antiviral Products

**FROM:** Jeanine Best, M.S.N., R.N., P.N.P.  
Patient Product Information Specialist  
Division of Surveillance, Research, and Communication Support

**THROUGH:** Toni Piazza-Hepp, Pharm.D., Deputy Director  
Division of Surveillance, Research, and Communication Support

**SUBJECT:** OSE/DSRCS Review of Patient Labeling for Lexiva  
(fosamprenavir calcium) 50mg/mL Oral Suspension, NDA 22-116

### **Background and Summary**

GlaxoSmithKline submitted an NDA for Lexiva (fosamprenavir calcium) 50mg/mL Oral Suspension, NDA 22-116, on December 13, 2006. An NDA (21-548) was approved for Lexiva Tablets on October 20, 2003.

Submitted labeling includes revised Product Information (PI) and a revised Patient Package Insert (PPI). The sponsor will have one label for Lexiva that incorporates the Lexiva Tablet and Lexiva Oral Suspension information.

DSRCS reviewed the current approved PPI for Lexiva Tablets. (See PPI review dated September 11, 2003).

### **Comments and Recommendations**

The minor revisions to the PPI for the addition of information pertaining to Lexiva Oral Suspension are acceptable, although, we do suggest simplifying the word 'vigorously' to 'well' in the following sentence under, "**How should I take LEXIVA?**":

- Shake LEXIVA Oral Suspension ~~vigorously~~ well before each use.

Please call us if you have any questions.

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/s/

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Jeanine Best  
5/4/2007 03:29:58 PM  
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp  
5/4/2007 04:41:40 PM  
DRUG SAFETY OFFICE REVIEWER



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA:** 22-116  
**Drug:** LEXIVA® (fosamprenavir, FPV) Oral Suspension  
**Date:** May 1, 2007  
**To:** Eric B. Benson, Senior Director, US Regulatory Affairs  
**Sponsor:** GlaxoSmithKline  
**From:** Kenny Shade, JD, BSN  
**Through:** Vikram Arya, PhD  
**Concur:** Katherine Laessig, MD  
Kellie Reynolds, PharmD  
**Subject:** Review Team Comments

---

The following comments are being conveyed to you on behalf of the review team. Please refer to your new drug application (NDA) 22-116 for LEXIVA (fosamprenavir, FPV) Oral Suspension submitted and received December 14, 2006.

**Pharmacometrics comments (NDA 022116)**

Please provide all the requested information on or before May 18, 2007.

**1. Population PK model**

Please submit diagnostic plots (similar to Figures 5,6, 7, 15, 16, 17, 18 and 19 of the population PK report) for two interim models, (1) a model that excludes age effect and (2) a model that excludes AAG effect on clearance from the final model. Please submit relevant control streams, key output files and datasets.

**2. Additional simulations**

Using the **base** (run 127) and the **final** (run 242) population PK model, please perform additional simulations to compare exposures between pediatric and adult population.

**Use the following dosing strategies for simulations of pediatric exposure**

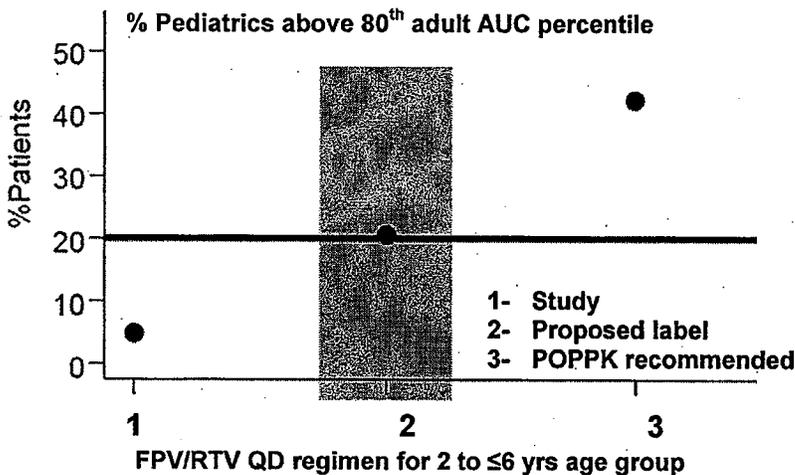
- a. Dose studied in clinical trials (APV20003 and APV29005). If the dose or the dosing regimen were revised based on the preliminary PK data generated during the study, use both doses for simulations.
- b. Dose recommended by the population PK model (population PK report page no. 32).

- c. Dose proposed in the label, if different than the above doses.
- d. Dose disregarding age effect in the proposed label- For example,  $\Gamma$   
 $\downarrow$  is proposed for 2-5 yrs and  $\geq 6$  yrs, respectively. For simulations, use  $\Gamma$   
 $\downarrow$

b(4)

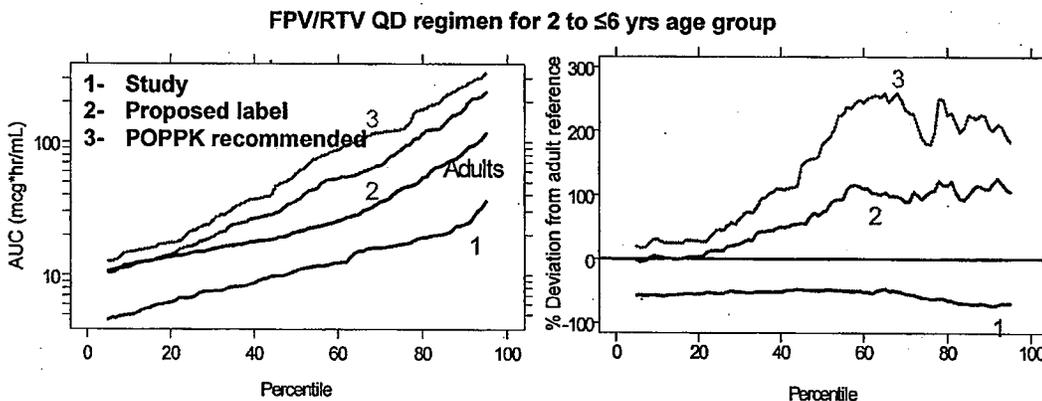
Use Cr, Cmax and AUC(0- $\tau$ ) as exposure variables for comparison

**Metric 1:** For each age group (2 to  $\leq 6$  yrs,  $>6$  to  $\leq 12$  yrs and  $>12-18$  yrs) and dosing regimen, calculate: % pediatric subjects above 80<sup>th</sup>, below 20<sup>th</sup> and within 20<sup>th</sup> and 80<sup>th</sup> percentile of adult exposure. The following graph indicates the comparison of adult and pediatric exposures assessing % peditrics above 80<sup>th</sup> adult AUC percentile for 3 dosing strategies. (Note: the graph is for illustration purposes only).



**Metric 2:** For each age group (2 to  $\leq 6$  yrs,  $>6$  to  $\leq 12$  yrs and  $>12-18$  yrs), plot exposure variable on y-axis and percentile on x-axis. Overlay adult and pediatric data for all dosing strategies. Also, calculate % deviation from adult reference.

The following graph indicates the comparison of adult and pediatric exposures distribution of pediatric and adult AUC percentile. (Note: the graph is for illustration purposes only).



Follow simulation methods and constraints as outlined in the population PK report (section 3.7) ensuring that the distribution of covariates matches with that of the study population.

Please submit all relevant codes (for example to recreate NONMEM output as well as graphic output) and datasets that would enable us to recreate simulation re

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---

Kenny Shade, JD, BSN  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/

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Kenny Shade  
5/1/2007 02:00:25 PM  
CSO

Kathrine Laessig  
5/1/2007 02:12:12 PM  
MEDICAL OFFICER



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA:** 22-116

**Drug:** LEXIVA<sup>®</sup> (fosamprenavir, FPV) Oral Suspension

**Date:** April 9, 2007

**To:** Eric B. Benson, Senior Director, US Regulatory Affairs

**Sponsor:** GlaxoSmithKline

**From:** Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project  
Manager, Division of Antiviral Products (DAVP)

**Through:** Yodit Below, Medical Officer (Pediatric Fellow)

**Concur:** Katherine A. Laessig, MD, Medical Team Leader

**Subject:** CLINICAL REQUEST FOR FURTHER INFORMATION

---

Reference is made to your new drug application (NDA) 22-116 for LEXIVA (fosamprenavir, FPV) Oral Suspension submitted and received December 14, 2006.

We have the following requests for further clinical information:

Please submit case report forms (CFR) for the following subjects:

6336, 6338, 6433, 6442, 6475, 6991, 6422, 6992, 6993, 6996, 6999, 7004, 7059

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/s/

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Marsha Holloman  
4/11/2007 10:59:27 AM  
CSO

Kathrine Laessig  
4/12/2007 10:08:28 AM  
MEDICAL OFFICER

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** February 26, 2007  
**TIME:** 12 noon – 1 PM  
**LOCATION:** WO, Bldg 22, Room 6305  
**APPLICATION:** 22-116  
**DRUG NAME:** LEXIVA (fosamprenavir calcium; FPV) 50 mg/mL Suspension  
**TYPE OF MEETING:** New NDA Filing Meeting

**MEETING CHAIR:** Russell D. Fleischer, PA-C, MPH, Senior Clinical Analyst

**MEETING RECORDER:** Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager

**FDA ATTENDEES:** (Division of Antiviral Products; DAVP)

Vikram Arya, PhD, Clinical Pharmacologist  
Virginia Behr, Chief, Project Management Staff  
Yodit Belew, MD, Pediatric Fellow  
Debra B. Birnkrant, MD, Division Director  
James G. Farrelly, PhD, Pharmacology/Toxicology Team Leader  
Russell D. Fleischer, PA-C, MPH, Senior Clinical Analyst  
Thomas Hammerstrom, PhD, Mathematical Statistician  
Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager  
Katherine A. Laessig, MD, Medical Team Leader  
George Lunn, PhD, CMC Reviewer  
Stephen P. Miller, PhD, CMC Team Leader  
Lalji Mishra, PhD, Microbiologist  
Jeffrey S. Murray, MD, MPH, Deputy Division Director  
Julian O'Rear, PhD, Microbiology Team Leader  
Kellie S. Reynolds, Pharm D, Clinical Pharmacy Team Leader  
Guoxing (Greg) Soon, PhD, Biometrics Team Leader  
Ita Yuen, PhD, Pharmacologist/Toxicologist  
Monica Zeballos, Pharm D, Chief, Project Management Staff (Acting)

**BACKGROUND:**

**BACKGROUND:** Reference is made to IND 58,637 for fosamprenavir calcium (FPV) dated July 16, 1999, and received July 19, 1999 for the treatment of HIV-1. Also, reference is made to NDA 21-548 for LEXIVA<sup>®</sup> (fosamprenavir calcium; FPV) 700 mg tablets dated December 19, 2002, received December 20, 2002, and approved October 20, 2003. Additionally, reference is made to NDA 22-116 for LEXIVA<sup>®</sup> Suspension dated December 13 and received December 14, 2006. This NDA was given Priority Review status with the PDUFA action date of June 14, 2007.

**MEETING OBJECTIVES:**

To decide whether this new NDA contains the required elements needed for filing.

**DISCUSSION POINTS:**

Discussion was conducted by all review disciplines (See information below.)

**DECISIONS (AGREEMENTS) REACHED:**

1. **Clinical Filing Review:** The reviewers found no filing issues. The application, on its face, is well-organized and indexed. Therefore, the application is suitable for filing.
2. **Chemistry, Manufacturing, and Controls (CMC) Filing Review:** The reviewers found no filing issues. The application, on its face, is well-organized and indexed. Therefore, the application is suitable for filing.
3. **Pharmacology/Toxicology Filing Review:** The reviewers found no filing issues. The application, on its face, is well-organized and indexed. Therefore, the application is suitable for filing.
4. **Microbiology Filing Review:** The reviewers found no filing issues. The application, on its face, is well-organized and indexed. Therefore, the application is suitable for filing.
5. **Clinical Pharmacology Filing Review:** The reviewers found no filing issues. The application, on its face, is well-organized and indexed. Therefore, the application is suitable for filing.
6. **Statistical Filing Review:** The reviewers found no filing issues. The application, on its face, is well-organized and indexed. Therefore, the application is suitable for filing.

**UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:**

There are no unresolved issues or issues requiring further discussion.

**ACTION ITEMS:**

The filing letter will be sent and the minutes of the filing meeting will be completed. Both documents will be archived.

**ATTACHMENTS/HANDOUTS:**

There are no attachments and/or handouts for these minutes.

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/s/

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Victoria TysonMedlock  
4/10/2007 01:23:59 PM

## REQUEST FOR CONSULTATION

TO (Division/Office):  
Division of Drug Marketing, Advertising and Communications (DDMAC),  
Attn: Lynn Panholzer, Pharm D, Consumer Safety Officer, 10903 New  
Hampshire Ave, Bldg 22, Rm 1460, Silver Spring, MD 20993  
301-796 0616 Phone [lynn.panholzer@fda.hhs.gov](mailto:lynn.panholzer@fda.hhs.gov)

FROM:  
Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager,  
Division of Antiviral Products (DAVP), 10903 New Hampshire Ave, Bldg 22,  
Rm 6321 Silver Spring, MD 20993 [marsha.holloman@fda.hhs.gov](mailto:marsha.holloman@fda.hhs.gov)  
301-796-0731 Phone 301-796-9883 Fax

DATE  
04/10/2007

IND NO.

NDA NO.  
22-116

TYPE OF DOCUMENT  
New NDA

DATE OF DOCUMENT 12/  
12/14/2007

NAME OF DRUG  
LEXIVA (fosamprenavir calcium) 50  
mg/mL Oral Suspension

PRIORITY CONSIDERATION  
Priority

THERAPEUTIC CLASSIFICATION  
7030202 (protease inhibitor)  
CHEMICAL CLASSIFICATION  
3 - New Dosage Form

DESIRED COMPLETION DATE  
05/29/2007  
(PDUFA date: 06/13/2007)

NAME OF FIRM:  
GlaxoSmithKline, Inc

### 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): |
| <input type="checkbox"/> MEETING PLANNED BY            |  |  |

#### II. BIOMETRICS

##### STATISTICAL EVALUATION BRANCH

##### STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW  
 END OF PHASE II MEETING  
 CONTROLLED STUDIES  
 PROTOCOL REVIEW  
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW  
 PHARMACOLOGY  
 BIOPHARMACEUTICS  
 OTHER (SPECIFY BELOW):

#### III. BIOPHARMACEUTICS

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

#### IV. DRUG EXPERIENCE

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

#### V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

#### COMMENTS/SPECIAL INSTRUCTIONS:

DAVP requests a labeling review of New NDA 22-116 for LEXIVA (fosamprenavir calcium; FPV) 50 mg/mL Oral Suspension. The first labeling meeting is Tuesday, 06/05/2007 and I will add you to the list of participants.

SIGNATURE OF REQUESTER  
// Marsha S. Holloman

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/s/

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Marsha Holloman

4/10/2007 12:13:13 PM

DDMAC consult request and labeling emailed to Lynn Panholzer

04/10/2007

**REQUEST FOR CONSULTATION**

TO (Division/Office):

**Mail: ODS (cders ose consults)**

FROM:

Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager,  
Division of Antiviral Products (DAVP), 10993 New Hampshire Ave, Bldg 22,  
Rm 6321 Silver Spring, MD 20993 [marsha.holloman@fda.hhs.gov](mailto:marsha.holloman@fda.hhs.gov)  
301-796-0731 Phone 301-796-9883 Fax

DATE  
04/09/2007

IND NO.

NDA NO.  
22-116

TYPE OF DOCUMENT  
New NDA

DATE OF DOCUMENT 12/  
12/14/2007

NAME OF DRUG  
**LEXIVA (fosamprenavir calcium)**  
50 mg/mL Oral Suspension

PRIORITY CONSIDERATION  
Priority

THERAPEUTIC CLASSIFICATION  
7030202 (protease inhibitor)  
CHEMICAL CLASSIFICATION  
3 – New Dosage Form

DESIRED COMPLETION DATE  
05/29/2007  
(PDUFA date: 06/13/2007)

NAME OF FIRM:

**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): |
| <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"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES      | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW         | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW):  |   |

**III. BIOPHARMACEUTICS**

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

**IV. DRUG EXPERIENCE**

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

**V. SCIENTIFIC INVESTIGATIONS**

CLINICAL

PRECLINICAL

**COMMENTS/SPECIAL INSTRUCTIONS:**

DAVP requests a labeling review of New NDA 22-116 for LEXIVA (fosamprenavir calcium; FPV) 50 mg/mL Oral Suspension. The first labeling meeting is Tuesday, 06/05/2007. Once I know the name of the reviewer, I will invite him/her.

SIGNATURE OF REQUESTER  
// Marsha S. Holloman

METHOD OF DELIVERY (Check one)  
 DFS  Electronic MAIL  HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

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Marsha Holloman

4/10/2007 10:46:46 AM

Consult request and labeling emailed to OSE.



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA:** 22-116

**Drug:** LEXIVA® (fosamprenavir, FPV) Oral Suspension

**Date:** March 9, 2007

**To:** Eric B. Benson, Senior Director, US Regulatory Affairs

**Sponsor:** GlaxoSmithKline

**From:** Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, Division of Antiviral Products (DAVP)

**Through:** George Lunn, PhD, Chemist

**Concur:** Norman Schmuff, PhD, CMC Branch Chief

**Subject:** CMC REQUEST FOR FURTHER INFORMATION

Reference is made to your new drug application (NDA) 22-116 for LEXIVA (fosamprenavir, FPV) Oral Suspension submitted and received December 14, 2006.

We have the following requests for further CMC information:

1. Please indicate how particle size is controlled in the drug substance used to manufacture the oral suspension and how the particle size distribution is related to product performance.
2. Please indicate how the bottles used for content uniformity and redispersibility testing at release are selected.
3. To help us understand the robustness of the manufacturing process please indicate if you have any data indicating how fast the suspension does (or does not) settle.
4. During the IND process, it was found that an adequate headspace in the bottle was necessary for acceptable redispersibility characteristics (IND 58,627 Amendment 089). Bottles that had a volume of 270 mL and contained 225 mL of suspension showed excellent redispersibility (Amendment 130). In this NDA you state that the fill volume is 225 mL (3.2.P.1) yet the package insert and container labels state that the bottles contain — Details are supplied for three — production-scale

b(4)

batches (1L723, 2A703, and 2A704) manufactured according to the proposed commercial method at the commercial production site and packaged in \_\_\_\_\_ bottles. Additionally, we note that at pre-defined intervals the fill weight is checked to be in the range \_\_\_\_\_ Please clarify the actual fill volumes and internal bottle volumes used for the stability batches (1L723, 2A703, and 2A704) and the batches used for the clinical studies (P.5.4).

b(4)

5. Please also clarify the actual fill volumes and internal bottle volumes to be used for the commercial product. During commercial production we assume that the in-process control will maintain the fill weight at \_\_\_\_\_ To what volume does that correspond? What is the internal volume of the bottle used for commercial production and how is this volume controlled? Although typical dimensions are given for the bottle we note that no tolerances are specified.
6. Please provide details of how the robustness testing was carried out for each HPLC method. Were univariate or multivariate experiments used? Under what conditions, if any, were unacceptable results obtained?
7. We note that Intermediate Precision was demonstrated for Laboratory 1 and Laboratory 2 \_\_\_\_\_ and Analyst 1 and Analyst 2 \_\_\_\_\_ Please indicate if Intermediate Precision was established for these methods using different days, analysts, and equipment as recommended by ICH Q2(R1).
8. Please provide a justification for not demonstrating Intermediate Precision for the HPLC method used for Dissolution.

b(4)

b(4)

We are providing the above information via telephone facsimile for your convenience.  
**THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**  
Please feel free to contact me if you have any questions regarding the contents of this transmission.

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

-----  
Marsha Holloman  
3/13/2007 02:26:36 PM  
CSO

Norman Schmuff  
3/13/2007 05:00:26 PM  
CHEMIST



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 22-116

GlaxoSmithKline, Inc  
ATTN: Eric B. Benson  
Senior Director, US Regulatory Affairs  
PO Box 13398  
Five Moore Drive  
Research Triangle Park, NC 27709

Dear Mr. Benson:

Please refer to your December 13, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LEXIVA<sup>®</sup> (fosamprenavir calcium; FPV) Oral Suspension.

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 February 13, 2007, in accordance with 21 CFR 314.101(a). This new drug application will receive a priority (6-month) review with an action date of June 13, 2007.

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

We note that you have submitted labeling compliant with the Structured Product Labeling (SPL) requirements and the Physician's Labeling Rule (PLR) format. We will have labeling comments and recommendations for you soon.

If you have any questions, call Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, at (301) 796-0731.

Sincerely,

*{See appended electronic signature page}*

Debra B. Birnkrant, MD  
Director  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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

-----  
Debra Birnkrant  
3/13/2007 03:49:51 PM  
NDA 22-116

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See Instructions for OMB Statement.		
DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		PRESCRIPTION DRUG USER FEE COVERSHEET
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <a href="http://www.fda.gov/cder/pdufa/default.htm">http://www.fda.gov/cder/pdufa/default.htm</a>		
1. APPLICANT'S NAME AND ADDRESS  SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE Parker Holmes ONE FRANKLIN PLAZA 16TH AND RACE STREETS PHILADELPHIA PA 19101 US		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER  022116
2. TELEPHONE NUMBER 919-483-0920		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:  <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION  <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:
3. PRODUCT NAME LEXIVA ( fosamprenavir calcium )		6. USER FEE I.D. NUMBER PD3006803
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.  <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE  <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY		
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO		
Public reporting burden for this collection of information is estimated to average 30 minutes 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 CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448  Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852  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.		
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE <i>David H. Conchetto, Ph.D.</i>		TITLE <i>US Regulatory Affairs</i>
		DATE <i>December 5, 2006</i>
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$896,200.00		
Form FDA 3397 (12/03)		

( BE PRMT CLOSE G ) ( Print Cover sheet )

## ACTION PACKAGE CHECKLIST

Application Information		
A # NDA # 22-116	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: fosamprenavir calcium Established Name: LEXIVA Dosage Form: Oral Suspension		Applicant: GlaxoSmithKline, Inc
RHPM: Marsha S. Holloman, BS Pharm, JD		Division: DAVP      Phone # 301-796-0731
NDAs: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):  Provide a brief explanation of how this product is different from the listed drug.  <input type="checkbox"/> If no listed drug, check here and explain:  <b>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.</b>  <input type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date:
❖ User Fee Goal Date		June 13, 2007
❖ Action Goal Date (if different)		
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions ( <i>specify type and date for each action taken</i> )		<input checked="" type="checkbox"/> None
❖ Advertising ( <i>approvals only</i> ) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed ( <i>indicate dates of reviews</i> )		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only):  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"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP                             <ul style="list-style-type: none"> <li>Exception for review (<i>file Center Director's memo in Administrative Documents section</i>)</li> <li>OC clearance for approval (<i>file communication in Administrative Documents section</i>)</li> </ul> </li> </ul>	<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"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input 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>❖ <b>Exclusivity</b></p>	
<ul style="list-style-type: none"> <li>• NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>)</li> </ul>	<p><input checked="" type="checkbox"/> Included</p>
<ul style="list-style-type: none"> <li>• Is approval of this application blocked by any type of exclusivity?             <ul style="list-style-type: none"> <li>• 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></li> <li>• 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>)</li> <li>• 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>)</li> <li>• 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>)</li> </ul> </li> </ul>	<p><input checked="" type="checkbox"/> No    <input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No    <input type="checkbox"/> Yes If, yes, NDA/BLA #                      and date exclusivity expires:</p> <p><input type="checkbox"/> No    <input checked="" type="checkbox"/> Yes If, yes, NDA #                      and date exclusivity expires:</p> <p><input type="checkbox"/> No    <input checked="" type="checkbox"/> Yes If, yes, NDA #                      and date exclusivity expires:</p> <p><input type="checkbox"/> No    <input checked="" type="checkbox"/> Yes If, yes, NDA #                      and date exclusivity expires:</p>
<p>❖ <b>Patent Information (NDAs and NDA supplements only)</b></p>	
<ul style="list-style-type: none"> <li>• 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.</li> </ul>	<p><input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.</p>
<ul style="list-style-type: none"> <li>• 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.</li> <li>• [505(b)(2) applications] If the application includes a <b>paragraph III</b> 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).</li> </ul>	<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"> <li>• [505(b)(2) applications] For each <b>paragraph IV</b> 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>)</li> <li>• [505(b)(2) applications] For each <b>paragraph IV</b> certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.</li> </ul> <p>Answer the following questions for each paragraph IV certification:</p>	<p><input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified</p>

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes  No

(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

<p>NDA file, confirm with the applicant whether a lawsuit was commenced 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>	
<b>Summary Reviews</b>	
<p>❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)</p>	MOTL 06/14/2007
<p>❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)</p>	
<b>Labeling</b>	
<p>❖ Package Insert</p>	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	06/14/2008
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	06/14/2008
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	November 2006 December 2006
<p>❖ Patient Package Insert</p>	
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	06/14/2007
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	06/14/2007
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	November 2006
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	December 2006
<p>❖ Medication Guide</p>	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling)</li> </ul>	
<p>❖ Labels (full color carton and immediate-container labels)</p>	
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labels (only if generated after latest applicant submission)</li> </ul>	06/14/2008
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling</li> </ul>	06/14/2007

❖ Labeling reviews and minutes of any labeling meetings ( <i>indicate dates of reviews and meetings</i> )	<input checked="" type="checkbox"/> DMETS 06/13/2007 <input checked="" type="checkbox"/> DSRCS 05/04/2007 <input checked="" type="checkbox"/> DDMAC 05/29/3007 <input checked="" type="checkbox"/> SEALD 06/21/2007 <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs
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**Administrative Documents**

❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) ( <i>indicate date of each review</i> )	06/14/2007
❖ NDA and NDA supplement approvals only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> <li>• Center Director's Exception for Review memo</li> <li>• If AP: OC clearance for approval</li> </ul>	N/A
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> 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> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies	<input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>)</li> <li>• Incoming submission documenting commitment</li> </ul>	<input checked="" type="checkbox"/> Approval Letter
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	<input checked="" type="checkbox"/>
❖ Internal memoranda, telecons, email, etc.	<input checked="" type="checkbox"/>
Minutes of Meetings	
<ul style="list-style-type: none"> <li>• Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)</li> <li>• Pre-NDA/BLA meeting (<i>indicate date</i>)</li> <li>• EOP2 meeting (<i>indicate date</i>)</li> <li>• Other (e.g., EOP2a, CMC pilot programs)</li> </ul>	<input checked="" type="checkbox"/> No mtg <input checked="" type="checkbox"/> No mtg <input checked="" type="checkbox"/> No mtg N/A
❖ Advisory Committee Meeting	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>• Date of Meeting</li> <li>• 48-hour alert or minutes, if available</li> </ul>	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

**CMC/Product Quality Information**

❖ CMC/Product review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 06/14/2008
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer ( <i>indicate date for each review</i> )	<input type="checkbox"/> 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)	
<ul style="list-style-type: none"> <li>• <input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)</li> <li>• <input type="checkbox"/> Review &amp; FONSI (<i>indicate date of review</i>)</li> <li>• <input type="checkbox"/> Review &amp; Environmental Impact Statement (<i>indicate date of each review</i>)</li> </ul>	<input checked="" type="checkbox"/> 01/19/2007
NDA: Microbiology reviews (sterility & apyrogenicity) ( <i>indicate date of each review</i> )	

❖ Facilities Review/Inspection	<input checked="" type="checkbox"/> Not a parenteral product Date completed: 01/30/2007 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Facilities inspections (include EER printout)	

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> <li>• Facility review (<i>indicate date(s)</i>)</li> <li>• Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>)</li> </ul>	<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> )	N/A
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	N/A
❖ Nonclinical inspection review Summary (DSI)	<input checked="" type="checkbox"/> None requested

**Clinical Information**

~ Clinical review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 06/14/2007
Financial Disclosure reviews(s) or location/date if addressed in another review	
❖ Clinical consult reviews from other review disciplines/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Microbiology (efficacy) reviews(s) ( <i>indicate date of each review</i> )	<input type="checkbox"/> Not needed <input checked="" type="checkbox"/> 06/13/2007
❖ Safety Update review(s) ( <i>indicate location/date if incorporated into another review</i> )	<input checked="" type="checkbox"/> 05/08/2007
❖ Risk Management Plan review(s) (including those by OSE) ( <i>indicate location/date if incorporated into another review</i> )	<input checked="" type="checkbox"/> See Consults
❖ Controlled Substance Staff review(s) and recommendation for scheduling ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested
<ul style="list-style-type: none"> <li>• Clinical Studies</li> <li>• Bioequivalence Studies</li> <li>• Clin Pharm Studies</li> </ul>	
❖ Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None <input checked="" type="checkbox"/> See Clinical Review 06/14/2007
❖ Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None <input checked="" type="checkbox"/> 06/14/2007

## Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

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

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

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

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

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

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

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

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