CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-548

CORRESPONDENCE

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

FACSIMILE TRANSMITTAL SHEET

DATE: October 16, 2003

To: Ann Stokley	**From:** Destry Sillivan
Company: GlaxoSmithKline	Division of Antiviral Drug Products
Fax number: (919) 483-5756	**Fax number:** (301) 827-2471
Phone number: (919) 483-6972	**Phone number:** (301) 827-2335

Subject: CMC comments to the NDA

Total no. of pages including cover: 4

Comments:

Document to be mailed: NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: October 16, 2003

To: Anne N. Stokley
Antiviral/Antibacterial Regulatory Affairs

Address: GlaxoSmithKline
P.O. Box 13398
Five Moore Drive
Research Triangle Park
North Carolina, 27709

From: Destry Sillivan, MS, Regulatory Project Manager, HFD-530

Through: Steve Miller, Ph.D., Chemistry Team Leader, HFD-530
George Lunn, Ph.D. Chemistry Reviewer, HFD-530

Subject: Comments for NDA 21-548: CMC

Please refer to your Amendment of 9/29/03.

We agree with your responses to items 1-3.

Item 4 is pending.

With the modification shown below in bold we agree with your response to item 5. Please submit the following as an Amendment to the NDA.

GSK commits to negotiate in good faith with the FDA and other regulatory agencies to provide adequate labeling that ensures inappropriate dosing regimens are not followed in markets only using combination regimens with ritonavir (Variants A-C). A statement such as [redacted] will be proposed for the container labels in such countries. **GSK recognizes that [redacted] would not be sufficient in themselves.** GSK will also maintain a dialogue with the FDA on the progress for global long-term options regarding this issue.

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.

/S/

Destry Sillivan, M.S.
Regulatory Project Manager
Division of Antiviral Drug Products

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/s/

Destry Sillivan
10/22/03 11:51:43 AM
CSO

Dr. Miller, this is the cmc fax of October 16 for NDA 21548

Stephen Paul Miller
10/22/03 02:13:40 PM
CHEMIST

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

FACSIMILE TRANSMITTAL SHEET

DATE: June 25, 2003

To: Ann Stokley	**From:** Destry Sillivan
Company: GlaxoSmithKline	Division of Antiviral Drug Products
Fax number: (919) 483-5756	**Fax number:** (301) 827-2471
Phone number: (919) 483-6972	**Phone number:** (301) 827-2335

Subject: CMC and Pharmacology/Toxicology communication

Total no. of pages including cover: 3

Comments:

Document to be mailed: NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: June 24, 2003

To: Anne N. Stokley
Antiviral/Antibacterial Regulatory Affairs

Address: GlaxoSmithKline
P.O. Box 13398
Five Moore Drive
Research Triangle Park
North Carolina, 27709

From: Destry Sillivan, MS, Regulatory Project Manager, HFD-530

Through: Steve Miller, Ph.D., Chemistry Team Leader, HFD-530
George Lunn, Ph.D. Chemistry Reviewer, HFD-530
Hao Zhang, Ph.D., Pharmacology/Toxicology Reviewer, HFD-530
James Farrelly, Ph.D., Pharmacology/Toxicology Team Leader, HFD-530
Russell Fleischer, PA-C., M.P.H., Senior Clinical Analyst and Acting Medical Team Leader, HFD-530

Subject: Comments for NDA 21-548: CMC and Pharmacology/Toxicology communication

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Please refer to your Amendment of April 30, 2003 for NDA 21-548.

By our calculations, based upon the Human Equivalent Doses (HED) of the impurities at the No Observed Adverse Event Level (NOAEL) of the non-clinical toxicity studies in rats and dogs, the Maximum Qualified Dose of the impurities is less than the proposed Dose of Impurity in Humans that the current drug substance specifications permit.

We acknowledge that you calculated the drug substance qualification levels based on the high dose rather than the NOAEL in the non-clinical toxicology studies. However, such a calculation is not generally acceptable because at such doses toxicity was seen in animals.

We recommend you either reduce the acceptance criteria for these impurities to the qualification level, or conduct further studies to qualify these impurities, such as a 90 day study in rats that would be appropriate considering the dose, patient population, and treatment duration associated with this product. This could be accomplished as a Phase 4 commitment.

If you have qualification data on [redacted] from pre-clinical studies or clinical experience with amprenavir, at higher levels than the proposed acceptance criteria, this may be sufficient.

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.

/S/

Destry Sillivan, M.S.
Regulatory Project Manager
Division of Antiviral Drug Products

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/s/

Destry Sillivan
8/6/03 08:00:03 AM
CSO

Russ, this is a CMC/Pharm Tox fax for 433908

Russell Fleischer
8/6/03 09:17:33 AM
MEDICAL OFFICER

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

FACSIMILE TRANSMITTAL SHEET

DATE: June 19, 2003

To: Ann Stokley	**From:** Destry Sillivan
Company: GlaxoSmithKline	Division of Antiviral Drug Products
Fax number: (919) 483-5756	**Fax number:** (301) 827-2471
Phone number: (919) 483-6972	**Phone number:** (301) 827-2335

Subject: CMC information request

Total no. of pages including cover: 2

Comments:

Document to be mailed: NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: June 19, 2003

To: Anne N. Stokley
Antiviral/Antibacterial Regulatory Affairs

Address: GlaxoSmithKline
P.O. Box 13398
Five Moore Drive
Research Triangle Park
North Carolina, 27709

From: Destry Sillivan, MS, Regulatory Project Manager, HFD-530

Through: Steve Miller, Ph.D., Chemistry Team Leader, HFD-530
George Lunn, Ph.D. Chemistry Reviewer, HFD-530

Subject: Comment for NDA 21-548: CMC information request

Please refer to your Amendment of May 15, 2003 to NDA 21-548.

We consider that your [redacted] methods for [redacted] are robust for [redacted] of [redacted] It appears that control of the [redacted] should be fairly precise. Accordingly, please withdraw the change from [redacted] proposed in the Amendment of 4/16/03 for these methods (3.2.S.4.2 and 3.2.P.5.2).

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.

/S/

Destry Sillivan, M.S.
Regulatory Project Manager
Division of Antiviral Drug Products

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/s/

Destry Sillivan
8/4/03 02:20:57 PM
CSO

Dr. Miller, this is an old CMC fax for NDA 21-548

Stephen Paul Miller
8/27/03 03:58:42 PM
CHEMIST

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

FACSIMILE TRANSMITTAL SHEET

DATE: May 28, 2003

To: Ann Stokley	From: Destry Sillivan
Company: GlaxoSmithKline	Division of Antiviral Drug Products
Fax number: (919) 483-5756	Fax number: (301) 827-2471
Phone number: (919) 483-6972	Phone number: (301) 827-2335

Subject: CMC information request

Total no. of pages including cover: 3

Comments:

Document to be mailed: NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: May 23, 2003

To: Anne N. Stokley
Antiviral/Antibacterial Regulatory Affairs

Address: GlaxoSmithKline
P.O. Box 13398
Five Moore Drive
Research Triangle Park
North Carolina, 27709

From: Destry Sillivan, MS, Regulatory Project Manager, HFD-530

Through: Steve Miller, Ph.D., Chemistry Team Leader, HFD-530
George Lunn, Ph.D. Chemistry Reviewer, HFD-530

Subject: Comments for NDA 21-548: CMC information request

Please refer to your Amendment of April 30, 2003 to your NDA 21-548. While we have not yet had time to examine the [redacted] method in exhaustive detail a brief examination raised the following points:

1. We notice that you propose to test a minimum of [redacted] commercial batches then, when confidence in the product has been established, discontinue the test as a regulatory specification ([redacted] Test Package, p. 11). We do not feel that [redacted] batches are likely to be sufficient to establish that the manufacturing process consistently produces product with the desired behavior, given that the cause of the variability remains unknown. We recommend that, after the first [redacted] batches have been tested, periodic testing of batches using the [redacted] method be continued.

2. Please submit any available data where the same batch was tested using the [redacted] model and the [redacted] method.

3. Please submit any [redacted] data obtained for batches of drug product, other than B037578 or B050889, manufactured using Variant B or C drug substance.

4. We notice that the [redacted] method will not be used on stability. Please commit to testing the first [redacted] commercial-scale batches at some time points using this method.

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.

/S/

Destry Sillivan, M.S.
Regulatory Project Manager
Division of Antiviral Drug Products

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/s/

Destry Sillivan
5/28/03 10:49:39 AM
CSO

Dr. Miller , this is the CMC fax for
the april 30 amendment for NDa 21-548

Stephen Paul Miller
6/2/03 11:41:34 AM
CHEMIST

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Joseph C. Gathe, Jr., M.D.
4900 Fannin
Houston, Texas 77004

MAY 12 2003

Dear Dr. Gathe:

Between April 7 and 10, 2003, Mr. Patrick D. Stone, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol APV30002 entitled: "A Randomized, Open-Label, Two Arm Trial to Compare the Safety and Antiviral Efficacy of GW433908/Ritonavir QD to Nelfinavir BID When Used in Combination with Abacavir and Lamivudine BID for 48 Weeks in Antiretroviral Therapy Naïve HIV-1 Infected Subjects") of the investigational drug Telzir (fosamprenavir calcium), performed for GlaxoSmithKline. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Stone during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

AE

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003943859
Field Classification: NAI
Headquarters Classification:
_X __1)NAI
_____2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

cc:
HFA-224
HFD-530 Doc.Rm. NDA #21-548
HFD-530 Division Director Birnkrant
HFD-530 MO Fleischer
HFD-530 PM Sullivan
HFD-47c/r/s/ GCP File #4004
HFD-47 El-Hage
HFD-47 Hajarian
HFR-SW150 DIB Thornburg
HFR-SW1540 BIMO Monitor Martinez
HFR-SW1580 Field Investigator Stone
GCF-1 Seth Ray

r/d:GRH:5/6/03
f/t:ML:5/7/03

O:\GRH\GATHE NAI.DOC

Reviewer's Note to Review Division Medical Officer

Protocol APV30002

Of 62 subjects screened, 49 were randomized. Forty-one subjects completed the study. The records of 17 subjects were reviewed in detail. Informed consents were on file for all subjects. Primary and secondary efficacy endpoints on source documents and case report forms were consistent.

No deficiencies were observed and no Form FDA 483 was issued. The data from subjects at this site can be used for evaluation of Protocol APV30002 submitted in support of NDA 21-548 for review by FDA.

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/s/

Antoine El-Hage
5/20/03 06:27:37 AM

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

FACSIMILE TRANSMITTAL SHEET

DATE: April 30, 2003

To: Ann Stokley	From: Destry Sillivan
Company: GlaxoSmithKline	Division of Antiviral Drug Products
Fax number: (919) 483-5756	Fax number: (301) 827-2471
Phone number: (919) 483-6972	Phone number: (301) 827-2335

Subject: CMC information request

Total no. of pages including cover: 3

Comments:

Document to be mailed: NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: April 30, 2003

To: Anne N. Stokley
Antiviral/Antibacterial Regulatory Affairs

Address: GlaxoSmithKline
P.O. Box 13398
Five Moore Drive
Research Triangle Park
North Carolina, 27709

From: Destry Sillivan, MS, Regulatory Project Manager, HFD-530

Through: Steve Miller, Ph.D., Chemistry Team Leader, HFD-530
George Lunn, Ph.D. Chemistry Reviewer, HFD-530

Subject: Comments for NDA 21-548: CMC information request

We have been studying the impurities found in fosamprenavir (NDA 21-548) and comparing them with the corresponding impurities found in amprenavir (approved NDA 21-007). Therefore, we have the following information requests:

1. In amprenavir, the [redacted], is a specified impurity (NDA 21-007, Amendment of 7/27/98, pages 144 and 171), but there appears to be no corresponding [redacted] impurity in fosamprenavir. Would such a compound be determined by one of the fosamprenavir [redacted] methods?

2. Similarly, [redacted] are specified impurities in amprenavir. These [redacted] cannot form the [redacted] Would they be detected by the fosamprenavir [redacted] methods, if present?

3. In fosamprenavir, [redacted] are specified impurities. We note that they have no analogues in amprenavir. In Amendment 074 (May 7, 2001) of the fosamprenavir IND 58,627, you deal with the specifications for [redacted] You state:

> [redacted] GW4339086, we propose that the current specification for [redacted] registered in approved NDA 21-007 will continue for the manufacture of amprenavir. Careful selection of [redacted] used in the synthesis of amprenavir will ensure that levels of [redacted]

[redacted] impurities in amprenavir are kept below [redacted] area. Therefore the revised specification for [redacted] will only be applied in the manufacture of GW433908G.

However, the [redacted] are common to both amprenavir and fosamprenavir. In the fosamprenavir NDA they have a specification for the [redacted] in the amprenavir NDA they do not. Would this situation lead to batches of [redacted], from which fosamprenavir but not amprenavir could be manufactured? Please comment on this situation.

4. In the Amendment of 3/21/03 Study APV10021 was carried out using Variant A tablets used to initiate pivotal Phase III studies (Batch E00B149) and commercial Variant A tablets (Batch B086052). From the NDA we see that Batch E00B149 was made on a [redacted] scale. What was the scale of tablet manufacture of batch B086052?

5. Please refer to our fax of 4/1/03 (specifically question 4) and your response of 4/16/03. You have not demonstrated that the [redacted] methods for [redacted] for the drug substance and drug product are robust. So that we may better understand what is happening, please supply the full report(s) that evaluated the robustness of these methods.

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.

/S/

Destry Sillivan, M.S.
Regulatory Project Manager
Division of Antiviral Drug Products

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/s/

Destry Sillivan
5/5/03 11:29:25 AM
CSO

STeve, CMC fax for 21-548

Stephen Paul Miller
5/5/03 04:58:11 PM
CHEMIST

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

FACSIMILE TRANSMITTAL SHEET

DATE: April 1, 2003

To: Ann Stokley	From: Destry Sillivan
Company: GlaxoSmithKline	Division of Antiviral Drug Products
Fax number: (919) 483-5756	Fax number: (301) 827-2471
Phone number: (919) 483-6972	Phone number: (301) 827-2335

Subject: CMC information request

Total no. of pages including cover: 4

Comments:

Document to be mailed: NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: April 1, 2003

To: Anne N. Stokley
Antiviral/Antibacterial Regulatory Affairs

Address: GlaxoSmithKline
P.O. Box 13398
Five Moore Drive
Research Triangle Park
North Carolina, 27709

From: Destry Sillivan, MS, Regulatory Project Manager, HFD-530

Through: Steve Miller, Ph.D., Chemistry Team Leader, HFD-530
George Lunn, Ph.D. Chemistry Reviewer, HFD-530

Subject: Comments for NDA 21-548: CMC information request

The following comments are forwarded on behalf of Dr. George Lunn:

1. Please provide evidence to show that the potential impurities described in 1.1.1 to 1.1.14 can be quantitated by one of the [redacted] methods (3.2.S.3.2, pp. 1-3). Additionally please provide data to show that the [redacted] are removed during work-up.

2. On page 2 of the justification of the specifications (3.2.S.4.5) it is stated that the [redacted] are separated by [redacted] and are not observed at [redacted] Thus they are controlled by the unspecified impurity specification of [redacted] Please provide data to show that these compounds can be quantitated by one of the [redacted] methods.

3. We concur with your proposal for controlling the [redacted] by controlling the [redacted] Please consider controlling the [redacted] in the same way since it is not detected by the [redacted] method. This information could also be included as a footnote. As an alternative to the use of a footnote these parameters could be included in the specification. For example:

Test	Procedure	Specification
Impurities:	[redacted]	[redacted]

4. During the [redacted] testing of the [redacted], it was found that the [redacted]). This also applies to the similar drug product method [redacted] (3.2.P.5.3, p.18). Does this mean that the [redacted]?

5. We note that the [redacted] are controlled by the specifications for the precursors and are not monitored on stability. Please provide some evidence to show that the levels of [redacted] do not increase on storage of the drug substance or drug product.

6. The in-process controls applied during the [redacted] fosamprenavir tablets are carried out at the [redacted] and at appropriate intervals thereafter. (3.2.P.3.4, p. 2). Please define "appropriate intervals".

7. We note that there was no dissolution testing for tablets stored [redacted]. Please supply this data if available, or justify the lack of testing.

8. According to Table 2 in 3.2.S.4.5 the following compounds do not appear to be qualified.

[redacted]	Highest concentration tested [redacted]	Acceptance criterion [redacted]	
[redacted]	Highest concentration tested [redacted]	Acceptance criterion [redacted]	

By our calculations based upon the Human Equivalent Doses (HED) of these impurities at the None Observed Adverse Event Level (NOAEL) in the rat toxicity studies, the Maximum Qualified Dose of Impurities for humans are less than the proposed Dose of Impurity in Humans that the current drug substance specification permit.

Please indicate whether additional qualification data are available to support the proposed acceptance criteria, or whether the acceptance criteria can be reduced to levels that are qualified

Additionally, we notice from Table 2 that the levels of [redacted] actually found are given as [redacted]. However, [redacted] using the [redacted] method (3.2.S.4.3, page 3), the [redacted] method (3.2.S.4.3, page 3), and the [redacted] method (3.2.S.7.3, page 52). Please describe the analytical method used to obtain the data in Table 2.

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.

/S/

Destry Sillivan, M.S.
Regulatory Project Manager
Division of Antiviral Drug Products

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/s/

Destry Sillivan
4/2/03 01:32:37 PM
CSO

Dr. Miller, this is the CMC information request fax for GSK for 433908

Stephen Paul Miller
4/3/03 03:00:26 PM
CHEMIST

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING REVIEW ISSUES IDENTIFIED

NDA 21-548

GlaxoSmithKline
Attention: Anne Stokely, M.S.P.H.
Director, Antiviral/Anti-infective Regulatory Affairs
Five Moore Drive
Research Triangle Park
North Carolina 27709

Dear Ms. Stokely:

Please refer to your December 19, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fosamprenavir calcium-GW433908) 700 mg Tablets.

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 19, 2003 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Chemistry, Manufacturing, and Control (CMC):

1. The major CMC issue identified at the time of filing is the question of the bioequivalence of different batches of tablets made from different batches of variant A drug substance. If the results of the study APV10021, to be reported in May, indicate that the recently manufactured batch is not bioequivalent to the previously manufactured batch, then the approvability of this NDA may be adversely affected.

Clinical Pharmacology:

2. There are insufficient data to support the claim that

   If the effect is not the same, the data should be submitted that explain the mechanism of the effect of Kaletra on fosamprenavir. If the mechanism of the interaction has not been determined, it will be difficult to extrapolate drug interaction data from the Agenerase label to the fosamprenavir label.

3. There are insufficient data to support the claim that there is adequate characterization of GW433908, with respect to drug interactions, compared to amprenavir. If the results of Study APV 10022 indicate that the interaction between amprenavir and ritonavir differs

between Agenerase and GW433908, there will be a significant impact on the review of this application. Additional drug interaction studies may be needed prior to the final approval of this application.

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

We also request that your submit the following information:

Clinical:

1. Please provide an explanation for the differential efficacy results observed in the Nelfinavir containing arm of studies APV30001 and APV30002. Specifically, please address why the regimen of NLF plus ABC plus 3TC appeared to perform differently in the two studies that were similarly conducted.

Microbiology:

2. Please provide data on the uptake and intracellular concentration(s) of GW433908 and amprenavir following exposure to GW443908 in cell culture.

3. Please provide data on the *in vitro* cytotoxicity of GW433908 in appropriate cells.

4. Please provide data on the *in vitro* anti-HIV-1 activity of amprenavir in combination with approved nucleoside analogue reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs).

5. Please specify the date for the submission of 48-week resistance data for the study APV30003.

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

If you have any questions, please call Destry Sillivan, Regulatory Project Manager, at (301) 827-2376.

Sincerely,

{See appended electronic signature page}

/S/

Anthony DeCicco, RPh.
Chief Regulatory Project Management
Division of Antiviral Drug Products

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/s/

Tony DeCicco
3/13/03 10:45:12 AM

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

FACSIMILE TRANSMITTAL SHEET

DATE: February 20, 2003

To: Ann Stokley	**From:** Destry Sillivan
Company: GlaxoSmithKline	Division of Antiviral Drug Products
Fax number: (919) 483-5756	**Fax number:** (301) 827-2471
Phone number: (919) 483-6972	**Phone number:** (301) 827-2335

Subject: Trade Name review comments

Total no. of pages including cover: 4

Comments:

Document to be mailed: NO

4 Page(s) Withheld

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

FACSIMILE TRANSMITTAL SHEET

DATE: January 30, 2003

To: Ann Stokley	From: Destry Sillivan
Company: GlaxoSmithKline	Division of Antiviral Drug Products
Fax number: (919) 483-5756	Fax number: (301) 827-2471
Phone number: (919) 483-6972	Phone number: (301) 827-2335

Subject: Clinical Pharmacology information request

Total no. of pages including cover: 2

Comments:

Document to be mailed: NO

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: January 30, 2003

To: Anne N. Stokley
Antiviral/Antibacterial Regulatory Affairs

Address: GlaxoSmithKline
P.O. Box 13398
Five Moore Drive
Research Triangle Park
North Carolina, 27709

From: Destry Sillivan, MS, Regulatory Project Manager, HFD-530

Through: Russell Fleischer, PA-C., M.P.H., Senior Clinical Analyst, HFD-530
Kellie Reynolds, Pharm.D. Clinical Pharmacology Team Leader, HFD-530
Steven Gitterman, M.D., Ph.D., Medical Team Leader, HFD-530

Subject: Comments for NDA 21-548: Clinical Pharmacology information request

---

The following is forwarded on behalf of Dr. Kellie Reynolds:

We want to discuss the implications of the fosamprenavir-Kaletra drug interaction studies (APV10011 and APV10012). In IND 58627 SN 197 you indicate the low amprenavir exposure observed in those studies is likely due to an absorption interaction, or decreased conversion of fosamprenavir to amprenavir in the enterocyte. Please update us on plans to evaluate the mechanism of the interaction. Also, indicate how you will determine whether other drugs may interact with fosamprenavir in the same manner.

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.

Destry Sillivan, M.S.
Regulatory Project Manager
Division of Antiviral Drug Products

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/s/

Destry Sillivan
1/30/03 04:19:22 PM
CSO

Dr. Gitterman, this is the clin pharm fax for 908 dated Jan 30, 2003

Steven Gitterman
2/5/03 05:10:36 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-548

GlaxoSmithKline
Attention: Anne N. Stokley
Antiviral/Antibacterial Regulatory Affairs
P.O. Box 13398
Five Moore Drive
Research Triangle Park
North Carolina, 27709

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: TELZIR™ (fosamprenavir calcium-GW433908) 700 mg Tablets

Review Priority Classification: Standard (S)

Date of Application: December 19, 2002

Date of Receipt: December 20, 2002

Our Reference Number: NDA 21-548

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 18, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 20, 2003.

Under 21 CFR 314.102(c), you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Division Document Room 115
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, please call Destry Sillivan, Regulatory Project Manager, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Anthony W. DeCicco, R.Ph.
Chief, Project Management Staff
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

/s/

Tony DeCicco
2/3/03 01:46:13 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Antiviral Drug Products
Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: **January 14, 2002**

To: **Anne N. Stokley**
Antiviral/Antibacterial Regulatory Affairs

Address: **GlaxoSmithKline**
P.O. Box 13398
Five Moore Drive
Research Triangle Park
North Carolina, 27709

From: **Destry Sillivan, MS, Regulatory Project Manager, HFD-530**

Through: **Steve Miller, Ph.D., Chemistry Team Leader, HFD-530**
George Lunn, Ph.D. Chemistry Reviewer, HFD-530

Subject: **Comments for NDA 21-548: CMC information request**

Please confirm that the following facilities are the ONLY sites involved in the manufacturing, testing, and packaging of drug substance and drug product for your NDA 21-548 for Telzir (fosamprenavir calcium) Tablets. Please confirm that the address and the functions listed for each site are correct, and that all the facilities will be PAI-ready by February 14, 2003.

Manufacture of [redacted]

Glaxo Wellcome Operations
Temple Hill
Dartford
Kent DA1 5AH
UK

[redacted]

[redacted]

Manufacture of [redacted], manufacture of drug substance, quality control of drug substance, and drug substance stability testing:

Glaxo Wellcome Operations
Temple Hill
Dartford
Kent DA1 5AH
UK

Drug substance stability testing (NDA stability batches):

GlaxoSmithKline Research and Development Ltd.
Park Road
Ware
Hertfordshire SG12 0DP
UK

[redacted]

Manufacture, packaging, and testing of drug product:

Glaxo Wellcome Operations
Priory Street
Ware
Hertfordshire SG12 0DJ
UK

GlaxoSmithKline Research and Development Ltd.
Park Road
Ware
Hertfordshire SG12 0DP
UK

Stability testing of drug product:

Glaxo Wellcome Operations
Harmire Road
Barnard Castle
County Durham DL12 8DT
UK

[redacted]

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.

/S/

Destry Sillivan, M.S.
Regulatory Project Manager
Division of Antiviral Drug Products

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

/s/

Destry Sillivan
1/21/03 11:43:15 AM
CSO

Dr. Miller, this is the CMC information request facsimile sent 1/15/03 for NDA 21-548

Stephen Paul Miller
1/23/03 12:58:37 PM
CHEMIST

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

FACSIMILE TRANSMITTAL SHEET

DATE: January 15, 2003

To: Ann Stokley	From: Destry Sillivan
Company: GlaxoSmithKline	Division of Antiviral Drug Products
Fax number: (919) 483-5756	Fax number: (301) 827-2471
Phone number: (919) 483-6972	Phone number: (301) 827-2335

Subject: CMC information request

Total no. of pages including cover: 4

Comments:

Document to be mailed: NO

DAV. File

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 58,627

Glaxo Wellcome Research and Development
Attn: Robert Watson
Director, Regulatory Affairs
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

NOV 15 1999

Dear Mr. Watson:

Please refer to your Investigational New Drug Application (IND) 58627 submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act to study GW433908.

We also refer you to your August 19,1999 submission (serial number 0004) and to the September 22, 1999 meeting between Glaxo Wellcome and representatives of this Division.

In accordance with the Manual of Policies and Procedures (MaPP) 4512.1, the attachment contains FDA's meeting minutes. Should you have any questions, please contact Ms. Leslie Stephens, RN, MSN,Regulatory Health Project Manager, at (301) 827-2335.

Sincerely yours,

/S/

Anthony V. DeCicco, R.Ph.
Supervisory Consumer Safety Officer
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Attachment