

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-937

ADMINISTRATIVE
DOCUMENTS/CORRESPONDENCE

Module 1.3a**Form FDA 356h Item 13 – Patent information**

Patent information is provided on FDA Forms 3542a for the following 11 patents relevant to efavirenz/emtricitabine/tenofovir disoproxil fumarate tablets.

Patents related to efavirenz:

- 5,811,423
- 5,663,169
- 5,519,021

Patents related to emtricitabine:

- 6,703,396
- 6,642,245
- 5,914,331
- 5,210,085
- 5,814,639

Patents related to tenofovir disoproxil fumarate:

- 6,043,230
- 5,977,089
- 5,935,946
- 5,922,695

Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>	Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/06 See OMB Statement on Page 3.
	NDA NUMBER 21-937
	NAME OF APPLICANT / NDA HOLDER Bristol-Myers Squibb & Gilead Sciences LLC

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)

To Be Determined

ACTIVE INGREDIENT(S)

efavirenz
emtricitabine
tenofovir disoproxil fumarate

STRENGTH(S)

efavirenz	600 mg
emtricitabine	200 mg
tenofovir disoproxil fumarate	300 mg

DOSAGE FORM

tablet

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 submit 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.

I. GENERAL

a. United States Patent Number 5,811,423	b. Issue Date of Patent 09/22/1998	c. Expiration Date of Patent 08/07/2012
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d. Name of Patent Owner Merck & Co., Inc.	Address (of Patent Owner) P.O. Box 2000	
	City/State Rahway, New Jersey	
	ZIP Code 07065	FAX Number (if available)
	Telephone Number (732) 594-8554	E-Mail Address (if available)

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

<p>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.</p>	
<p>2. Drug Substance (Active Ingredient)</p>	
<p>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?</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<p>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?</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<p>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).</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.</p> 	
<p>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.)</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<p>2.6 Does the patent claim only an intermediate?</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<p>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.)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>3. Drug Product (Composition/Formulation)</p>	
<p>3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<p>3.2 Does the patent claim only an intermediate?</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<p>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.)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>4. Method of Use</p>	
<p><i>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:</i></p>	
<p>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?</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<p>4.2 Claim Number (as listed in the patent) 1, 2, 3, 4, 5, and 6</p>	<p>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?</p> <p style="text-align: right;"><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>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.</p>	<p>Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)</p> <p>The proposed labeling under the "Indication and Usage" section, states that the TRADENAME is indicated for use alone or in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults.</p>
<p>5. No Relevant Patents</p>	
<p>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.</p>	
<input type="checkbox"/> 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.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

JAMES J. WONG

Dec 1, 2005

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.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

James J. Wong, J.D.

Address

Gilead Sciences, Inc.
333 Lakeside Drive

City/State

Foster City, California

ZIP Code

94404

Telephone Number

(650) 522-5823

FAX Number (if available)

(650) 522-5575

E-Mail Address (if available)

James.Wong@gilead.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/HFD-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/fdahm/fdahm.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.

Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/06 See OMB Statement on Page 3.
		NDA NUMBER 21-937
		NAME OF APPLICANT / NDA HOLDER Bristol-Myers Squibb & Gilead Sciences LLC
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>		
TRADE NAME (OR PROPOSED TRADE NAME) To Be Determined		
ACTIVE INGREDIENT(S) efavirenz emtricitabine tenofovir disoproxil fumarate	STRENGTH(S) efavirenz 600 mg emtricitabine 200 mg tenofovir disoproxil fumarate 300 mg	
DOSAGE FORM tablet		
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 <i>only</i> 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 submit 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 5,663,169	b. Issue Date of Patent 09/02/1997	c. Expiration Date of Patent 09/02/2014
d. Name of Patent Owner Merck & Co., Inc.	Address (of Patent Owner) P.O. Box 2000	
	City/State Rahway, New Jersey	
	ZIP Code 07065	FAX Number (if available)
	Telephone Number (732) 594-8554	E-Mail Address (if available)
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? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? <input type="checkbox"/> Yes <input type="checkbox"/> 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 type="checkbox"/> Yes <input checked="" 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 type="checkbox"/> Yes <input checked="" 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	
<i>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:</i>	
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 Claim Number (as listed in the patent) 1, 2, 3, 4	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? <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 proposed labeling.) The proposed labeling under the "Indication and Usage" section, states that the TRADENAME is indicated for use alone or in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults. Efavirenz is a non-nucleoside reverse transcriptase inhibitor of HIV-1.
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.	<input type="checkbox"/> 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.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

James J. Wong

Dec 1, 2005

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.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

James J. Wong, J.D.

Address

Gilead Sciences, Inc.
333 Lakeside Drive

City/State

Foster City, California

ZIP Code

94404

Telephone Number

(650) 522-5823

FAX Number (if available)

(650) 522-5575

E-Mail Address (if available)

James.Wong@gilead.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

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- 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.
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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)

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- 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

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/06 See OMB Statement on Page 3.	
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	
		21-937	
		NAME OF APPLICANT / NDA HOLDER	
		Bristol-Myers Squibb & Gilead Sciences LLC	
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)			
To Be Determined			
ACTIVE INGREDIENT(S)		STRENGTH(S)	
efavirenz		efavirenz 600 mg	
emtricitabine		emtricitabine 200 mg	
tenofovir disoproxil fumarate		tenofovir disoproxil fumarate 300 mg	
DOSAGE FORM			
tablet			
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 <i>only</i> 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 submit 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		b. Issue Date of Patent	c. Expiration Date of Patent
5,519,021		05/21/1996	05/21/2013
d. Name of Patent Owner		Address (of Patent Owner)	
Merck & Co., Inc.		P.O. Box 2000	
		City/State	
		Rahway, New Jersey	
		ZIP Code	FAX Number (if available)
		07065	
		Telephone Number	E-Mail Address (if available)
		(732) 594-8554	
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?		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes	<input type="checkbox"/> No

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.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

James J. Wong

Dec 1, 2005

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.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

James J. Wong, J.D.

Address

Gilead Sciences, Inc.
333 Lakeside Drive

City/State

Foster City, California

ZIP Code

94404

Telephone Number

(650) 522-5823

FAX Number (if available)

(650) 522-5575

E-Mail Address (if available)

James.Wong@gilead.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/HFD-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.

Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/06 See OMB Statement on Page 3.
		NDA NUMBER 21-937
		NAME OF APPLICANT / NDA HOLDER Bristol-Myers Squibb & Gilead Sciences LLC
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>		
TRADE NAME (OR PROPOSED TRADE NAME) To Be Determined		
ACTIVE INGREDIENT(S) efavirenz emtricitabine tenofovir disoproxil fumarate	STRENGTH(S) efavirenz 600 mg emtricitabine 200 mg tenofovir disoproxil fumarate 300 mg	
DOSAGE FORM tablet		
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 <i>only</i> 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 submit 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 6,703,396	b. Issue Date of Patent 03/09/2004	c. Expiration Date of Patent 03/09/2021
d. Name of Patent Owner Emory University	Address (of Patent Owner) 1784 N. Decatur Rd., Ste. 130	
	City/State Atlanta, Georgia	
	ZIP Code 30322	FAX Number (if available) (404) 727-1271
	Telephone Number (404) 727-2211	E-Mail Address (if available)
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?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input type="checkbox"/> 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? Yes 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? Yes 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). Yes 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.) Yes No

2.6 Does the patent claim only an intermediate? Yes 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.) Yes 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? Yes No

3.2 Does the patent claim only an intermediate? Yes 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.) Yes 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? Yes No

4.2 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? 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 proposed labeling.)

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.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

JAMES J. Wong

Dec 1, 2005

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.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

James J. Wong, J.D.

Address

Gilead Sciences, Inc.
333 Lakeside Drive

City/State

Foster City, California

ZIP Code

94404

Telephone Number

(650) 522-5823

FAX Number (if available)

(650) 522-5575

E-Mail Address (if available)

James.Wong@gilead.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/HFD-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.

Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>	Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/06 See OMB Statement on Page 3.
	NDA NUMBER 21-937
	NAME OF APPLICANT / NDA HOLDER Bristol-Myers Squibb & Gilead Sciences LLC

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) To Be Determined	
ACTIVE INGREDIENT(S) efavirenz emtricitabine tenofovir disoproxil fumarate	STRENGTH(S) efavirenz 600 mg emtricitabine 200 mg tenofovir disoproxil fumarate 300 mg
DOSAGE FORM tablet	

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 submit 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 6,642,245	b. Issue Date of Patent 11/04/2003	c. Expiration Date of Patent 11/04/2020
d. Name of Patent Owner Emory University	Address (of Patent Owner) 1784 N. Decatur Rd., Ste. 130	
	City/State Atlanta, Georgia	
	ZIP Code 30322	FAX Number (if available) (404) 727-1271
	Telephone Number (404) 727-2211	E-Mail Address (if available)
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?		
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		
<input type="checkbox"/> Yes <input type="checkbox"/> 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? Yes 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? Yes 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). Yes 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.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes 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.) Yes 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? Yes No
- 3.2 Does the patent claim only an intermediate? Yes 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.) Yes 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? Yes No

- | | |
|--|--|
| 4.2 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? |
| 1, 2, 4, 6, 7, 8 | <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 proposed labeling.) Treatment of HIV-1 infection in adults
---	--

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

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/HFD-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/fdahm/fdahm.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.

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/06 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>			
		NDA NUMBER 21-937	
		NAME OF APPLICANT / NDA HOLDER Bristol-Myers Squibb & Gilead Sciences LLC	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) To Be Determined			
ACTIVE INGREDIENT(S) efavirenz emtricitabine tenofovir disoproxil fumarate		STRENGTH(S) efavirenz 600 mg emtricitabine 200 mg tenofovir disoproxil fumarate 300 mg	
DOSAGE FORM tablet			
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 <i>only</i> 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 submit 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 5,914,331		b. Issue Date of Patent 06/22/1999	c. Expiration Date of Patent 09/29/2015
d. Name of Patent Owner Emory University		Address (of Patent Owner) 1784 N. Decatur Rd., Ste. 130	
		City/State Atlanta, Georgia	
		ZIP Code 30322	FAX Number (if available) (404) 727-1271
		Telephone Number (404) 727-2211	E-Mail Address (if available)
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?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input type="checkbox"/> 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? Yes 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? Yes 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). Yes 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.) Yes No

2.6 Does the patent claim only an intermediate? Yes 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.) Yes 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? Yes No

3.2 Does the patent claim only an intermediate? Yes 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.) Yes 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? Yes No

4.2 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? 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 proposed labeling.)

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	
<p>6.1 <i>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.</i></p> <p><i>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</i></p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p> <p style="font-size: 1.5em; font-family: cursive;">JAMES J. WONG</p>	<p>Date Signed</p> <p style="font-size: 1.2em; font-family: cursive;">DEC 1, 2005</p>
<p>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).</p>	
<p>Check applicable box and provide information below.</p>	
<p><input type="checkbox"/> NDA Applicant/Holder</p> <p><input type="checkbox"/> Patent Owner</p>	<p><input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official</p> <p><input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official</p>
<p>Name</p> <p>James J. Wong, J.D.</p>	
<p>Address</p> <p>Gilead Sciences, Inc. 333 Lakeside Drive</p>	<p>City/State</p> <p>Foster City, California</p>
<p>ZIP Code</p> <p>94404</p>	<p>Telephone Number</p> <p>(650) 522-5823</p>
<p>FAX Number (if available)</p> <p>(650) 522-5575</p>	<p>E-Mail Address (if available)</p> <p>James.Wong@gilead.com</p>
<p>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:</p> <p style="text-align: center;">Food and Drug Administration CDER (HFD-007) 5600 Fishers Lane Rockville, MD 20857</p> <p style="text-align: center;"><i>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.</i></p>	

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/HFD-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/fdahtml/fdahtml.html>.

First Section

Complete all items in this section.

I. 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:

Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>	Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/06 See OMB Statement on Page 3.
	NDA NUMBER 21-937
	NAME OF APPLICANT / NDA HOLDER Bristol-Myers Squibb & Gilead Sciences LLC

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) To Be Determined	
ACTIVE INGREDIENT(S) efavirenz emtricitabine tenofovir disoproxil fumarate	STRENGTH(S) efavirenz 600 mg emtricitabine 200 mg tenofovir disoproxil fumarate 300 mg

DOSAGE FORM
tablet

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 submit 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 5,210,085	b. Issue Date of Patent 05/11/1993	c. Expiration Date of Patent 05/11/2010
d. Name of Patent Owner Emory University	Address (of Patent Owner) 1784 N. Decatur Rd., Ste. 130	
	City/State Atlanta, Georgia	
	ZIP Code 30322	FAX Number (if available) (404) 727-1271
	Telephone Number (404) 727-2211	E-Mail Address (if available)
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?		
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		
<input type="checkbox"/> Yes <input type="checkbox"/> No		

<p>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.</p>	
<p>2. Drug Substance (Active Ingredient)</p>	
<p>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?</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<p>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?</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<p>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).</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.</p> 	
<p>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.)</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<p>2.6 Does the patent claim only an intermediate?</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<p>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.)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>3. Drug Product (Composition/Formulation)</p>	
<p>3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<p>3.2 Does the patent claim only an intermediate?</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<p>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.)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>4. Method of Use</p>	
<p><i>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:</i></p>	
<p>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?</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<p>4.2 Claim Number (as listed in the patent)</p> <p>1, 9, 14, 17</p>	<p>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?</p> <p style="text-align: right;"> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No </p>
<p>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.</p>	<p>Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)</p> <p>Treatment of HIV-1 infection in adults</p>
<p>5. No Relevant Patents</p>	
<p>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.</p>	
<input type="checkbox"/> 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.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below) <div style="font-size: 1.5em; font-family: cursive; margin-top: 10px;">JAMES J. WONG</div>	Date Signed <div style="font-size: 1.2em; font-family: cursive; margin-top: 10px;">Dec 1, 2005</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 James J. Wong, J.D.	
Address Gilead Sciences, Inc. 333 Lakeside Drive	City/State Foster City, California
ZIP Code 94404	Telephone Number (650) 522-5823
FAX Number (if available) (650) 522-5575	E-Mail Address (if available) James.Wong@gilead.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/HFD-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.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

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

21-937

NAME OF APPLICANT / NDA HOLDER

Bristol-Myers Squibb & Gilead Sciences LLC

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)

To Be Determined

ACTIVE INGREDIENT(S)

efavirenz
emtricitabine
tenofovir disoproxil fumarate

STRENGTH(S)

efavirenz	600 mg
emtricitabine	200 mg
tenofovir disoproxil fumarate	300 mg

DOSAGE FORM

tablet

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 submit 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
5,814,639

b. Issue Date of Patent
09/29/1998

c. Expiration Date of Patent
09/29/2015

d. Name of Patent Owner
Emory University

Address (of Patent Owner)
1784 N. Decatur Rd., Ste. 130

City/State
Atlanta, Georgia

ZIP Code
30322

FAX Number (if available)
(404) 727-1271

Telephone Number
(404) 727-2211

E-Mail Address (if available)

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? Yes 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? Yes 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). Yes 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.) Yes No

2.6 Does the patent claim only an intermediate? Yes 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.) Yes 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? Yes No

3.2 Does the patent claim only an intermediate? Yes 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.) Yes 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? Yes No

4.2 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? 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 proposed labeling.)

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.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

James J. Wong

Date Signed

Dec 1, 2005

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 James J. Wong, J.D.	
Address Gilead Sciences, Inc. 333 Lakeside Drive	City/State Foster City, California
ZIP Code 94404	Telephone Number (650) 522-5823
FAX Number (if available) (650) 522-5575	E-Mail Address (if available) James.Wong@gilead.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/HFD-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/fdahtn/fdahim.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.

Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>	Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/06 See OMB Statement on Page 3.
	NDA NUMBER 21-937
	NAME OF APPLICANT / NDA HOLDER Bristol-Myers Squibb & Gilead Sciences LLC

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) To Be Determined	
ACTIVE INGREDIENT(S) efavirenz emtricitabine tenofovir disoproxil fumarate	STRENGTH(S) efavirenz 600 mg emtricitabine 200 mg tenofovir disoproxil fumarate 300 mg
DOSAGE FORM tablet	

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 submit 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 6,043,230	b. Issue Date of Patent 03/28/2000	c. Expiration Date of Patent 07/25/2017
d. Name of Patent Owner Gilead Sciences, Inc.	Address (of Patent Owner) 333 Lakeside Drive	
	City/State Foster City, California	
	ZIP Code 94404	FAX Number (if available) (650) 522-5575
	Telephone Number (650) 522-5569	E-Mail Address (if available) ip@gilead.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?		
<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		
<input type="checkbox"/> Yes <input type="checkbox"/> No		

<p>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.</p>	
<p>2. Drug Substance (Active Ingredient)</p>	
<p>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?</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<p>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?</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<p>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).</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.</p> 	
<p>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.)</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<p>2.6 Does the patent claim only an intermediate?</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<p>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.)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>3. Drug Product (Composition/Formulation)</p>	
<p>3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<p>3.2 Does the patent claim only an intermediate?</p>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<p>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.)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>4. Method of Use</p>	
<p><i>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:</i></p>	
<p>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?</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<p>4.2 Claim Number (as listed in the patent)</p>	<p>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?</p>
<p>1</p>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<p>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.</p>	<p>Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)</p> <p>Treatment of HIV-1 infection in adults</p>
<p>5. No Relevant Patents</p>	
<p>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.</p>	
<input type="checkbox"/> Yes	

6. Declaration Certification	
<p>6.1 <i>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.</i></p> <p><i>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</i></p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p> <p style="font-size: 24pt; font-family: cursive;">James J. Wong</p>	<p>Date Signed</p> <p style="font-size: 24pt; font-family: cursive;">Dec 1, 2005</p>
<p>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).</p>	
<p>Check applicable box and provide information below.</p>	
<p><input type="checkbox"/> NDA Applicant/Holder</p> <p><input type="checkbox"/> Patent Owner</p>	<p><input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official</p> <p><input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official</p>
<p>Name</p> <p>James J. Wong, J.D.</p>	
<p>Address</p> <p>Gilead Sciences, Inc. 333 Lakeside Drive</p>	<p>City/State</p> <p>Foster City, California</p>
<p>ZIP Code</p> <p>94404</p>	<p>Telephone Number</p> <p>(650) 522-5823</p>
<p>FAX Number (if available)</p> <p>(650) 522-5575</p>	<p>E-Mail Address (if available)</p> <p>James.Wong@gilead.com</p>
<p>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:</p> <p style="text-align: center;">Food and Drug Administration CDER (HFD-007) 5600 Fishers Lane Rockville, MD 20857</p> <p style="text-align: center;"><i>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.</i></p>	

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/HFD-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/fdahim/fdahim.html>.

First Section

Complete all items in this section.

I. 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.

Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>	Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/06 <i>See OMB Statement on Page 3.</i>
	NDA NUMBER 21-937
	NAME OF APPLICANT / NDA HOLDER Bristol-Myers Squibb & Gilead Sciences LLC

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) To Be Determined	
ACTIVE INGREDIENT(S) efavirenz emtricitabine tenofovir disoproxil fumarate	STRENGTH(S) efavirenz 600 mg emtricitabine 200 mg tenofovir disoproxil fumarate 300 mg
DOSAGE FORM tablet	

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 submit 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 5,977,089	b. Issue Date of Patent 11/02/1999	c. Expiration Date of Patent 07/25/2017
d. Name of Patent Owner Gilead Sciences, Inc.	Address (of Patent Owner) 333 Lakeside Drive	
	City/State Foster City, California	
	ZIP Code 94404	FAX Number (if available) (650) 522-5575
	Telephone Number (650) 522-5569	E-Mail Address (if available) ip@gilead.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?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	<input type="checkbox"/> Yes	<input type="checkbox"/> 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? Yes 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? Yes 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). Yes 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.) Yes No

2.6 Does the patent claim only an intermediate? Yes 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.) Yes 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? Yes No

3.2 Does the patent claim only an intermediate? Yes 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.) Yes 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? Yes No

4.2 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?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3			

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 proposed labeling.) Treatment of HIV-1 infection in adults
---	--

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	
<p>6.1 <i>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.</i></p> <p><i>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</i></p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p> <p style="font-size: 1.2em; font-family: cursive;">James J. Wong</p>	<p>Date Signed</p> <p style="font-size: 1.2em; font-family: cursive;">Dec 1, 2005</p>
<p>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).</p>	
<p>Check applicable box and provide information below.</p>	
<p><input type="checkbox"/> NDA Applicant/Holder</p>	<p><input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official</p>
<p><input type="checkbox"/> Patent Owner</p>	<p><input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official</p>
<p>Name</p> <p>James J. Wong, J.D.</p>	
<p>Address</p> <p>Gilead Sciences, Inc. 333 Lakeside Drive</p>	<p>City/State</p> <p>Foster City, California</p>
<p>ZIP Code</p> <p>94404</p>	<p>Telephone Number</p> <p>(650) 522-5823</p>
<p>FAX Number (if available)</p> <p>(650) 522-5575</p>	<p>E-Mail Address (if available)</p> <p>James.Wong@gilead.com</p>
<p>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:</p> <p style="text-align: center;">Food and Drug Administration CDER (HFD-007) 5600 Fishers Lane Rockville, MD 20857</p> <p style="text-align: center;"><i>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.</i></p>	

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/HFD-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/fdahm/fdahm.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.

Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>	Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/06 <i>See OMB Statement on Page 3.</i>
NDA NUMBER 21-937	NAME OF APPLICANT / NDA HOLDER Bristol-Myers Squibb & Gilead Sciences LLC

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) To Be Determined	
ACTIVE INGREDIENT(S) efavirenz emtricitabine tenofovir disoproxil fumarate	STRENGTH(S) efavirenz 600 mg emtricitabine 200 mg tenofovir disoproxil fumarate 300 mg

DOSAGE FORM
 tablet

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 submit 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 5,935,946	b. Issue Date of Patent 08/10/1999	c. Expiration Date of Patent 07/25/2017
---	---------------------------------------	--

d. Name of Patent Owner Gilead Sciences, Inc.	Address (of Patent Owner) 333 Lakeside Drive City/State Foster City, California ZIP Code 94404 Telephone Number (650) 522-5569	
	FAX Number (if available) (650) 522-5575	E-Mail Address (if available) ip@gilead.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 Telephone Number	
	FAX Number (if available)	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? Yes 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? Yes 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). Yes 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.) Yes No

2.6 Does the patent claim only an intermediate? Yes 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.) Yes 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? Yes No

3.2 Does the patent claim only an intermediate? Yes 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.) Yes 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? Yes No

4.2 Claim Number (as listed in the patent) 9 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 proposed labeling.)
Treatment of HIV-1 infection in adults

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.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

JAMES J. WONG

Date Signed

Dec 1, 2005

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.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

James J. Wong, J.D.

Address

Gilead Sciences, Inc.
333 Lakeside Drive

City/State

Foster City, California

ZIP Code

94404

Telephone Number

(650) 522-5823

FAX Number (if available)

(650) 522-5575

E-Mail Address (if available)

James.Wong@gilead.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/HFD-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/fdahm/fdahm.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.

Department of Health and Human Services Food and Drug Administration PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>	Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/06 See OMB Statement on Page 3.
	NDA NUMBER 21-937
	NAME OF APPLICANT / NDA HOLDER Bristol-Myers Squibb & Gilead Sciences LLC

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) To Be Determined	
ACTIVE INGREDIENT(S) efavirenz emtricitabine tenofovir disoproxil fumarate	STRENGTH(S) efavirenz 600 mg emtricitabine 200 mg tenofovir disoproxil fumarate 300 mg

DOSAGE FORM
tablet

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 submit 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 5,922,695	b. Issue Date of Patent 07/13/1999	c. Expiration Date of Patent 07/25/2017
d. Name of Patent Owner Gilead Sciences, Inc.	Address (of Patent Owner) 333 Lakeside Drive	
	City/State Foster City, California	
	ZIP Code 94404	FAX Number (if available) (650) 522-5575
	Telephone Number (650) 522-5569	E-Mail Address (if available) ip@gilead.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? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? <input type="checkbox"/> Yes <input type="checkbox"/> 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 type="checkbox"/> Yes <input checked="" 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	
<i>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:</i>	
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 Claim Number (as listed in the patent) 25	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?
	<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 proposed labeling.) Treatment of HIV-1 infection in adults
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.	
	<input type="checkbox"/> 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.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)	Date Signed
<i>James J. Wong</i>	<i>Dec 1, 2005</i>

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 James J. Wong, J.D.	
Address Gilead Sciences, Inc. 333 Lakeside Drive	City/State Foster City, California
ZIP Code 94404	Telephone Number (650) 522-5823
FAX Number (if available) (650) 522-5575	E-Mail Address (if available) James.Wong@gilead.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.
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- 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/HFD-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.

Module 1.3a**Letters of Cross Reference**

Letters authorizing the Agency to refer to the following INDs and NDAs in support of the review of NDA 21-937 are provided in this section.

Efavirenz:

- IND 49,465
- NDA 20-972
- NDA 21-360

Emtricitabine:

- IND 53,971
- NDA 21-500

Tenofovir disoproxil fumarate:

- IND 52,849
- NDA 21-356

Emtricitabine/tenofovir disoproxil fumarate

- IND 67,671
- NDA 21-752

Atazanavir:

- IND 56,897
- NDA 21-567

**Bristol-Myers Squibb
Pharmaceutical Research Institute**

Richard L. Gelb Center for Pharmaceutical Research and Development

5 Research Parkway P.O. Box 5100 Wallingford, CT 06492-7660

LETTER OF CROSS REFERENCE

**IND 49,465 - efavirenz (DMP 266;
BMS-561525)**

November 29, 2005

Debra Birnkrant, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

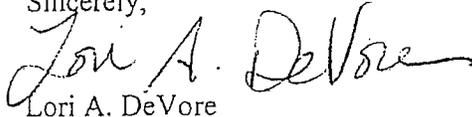
Dear Dr. Birnkrant:

This letter authorizes your Division to refer to Bristol-Myers Squibb's initial Investigational New Drug Application No. 49,465 for efavirenz (DMP 266; BMS-561525) and to all subsequent filings to this application when Gilead Sciences, Inc., acting on behalf of Bristol-Myers Squibb & Gilead Sciences, LLC, files a New Drug Application for the Fixed Dose Combination of efavirenz, emtricitabine and tenofovir disoproxil fumarate.

We request that all information in these files be treated as confidential and that no information from this file be provided to the applicant without our written consent to an authorized member of your Division.

Please contact the undersigned at (203) 677-6460 with any questions regarding the information provided herein. In the event that you are unable to reach me, please contact Dr. Margo Heath-Chiozzi at (203) 677-3819.

Sincerely,



Lori A. DeVore
Associate Director
Global Regulatory Strategy



**Bristol-Myers Squibb
Pharmaceutical Research Institute**

Richard L. Gelb Center for Pharmaceutical Research and Development

5 Research Parkway P.O. Box 5100 Wallingford, CT 06492-7660

LETTER OF CROSS REFERENCE

**NDA 20-972 SUSTIVA[®]
(efavirenz; BMS-561525) Capsules**

**NDA 21-360 SUSTIVA[®]
(efavirenz; BMS-561525) Tablets**

October 7, 2005

Debra Birnkrant, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Birnkrant:

This letter authorizes your Division to refer to Bristol-Myers Squibb's New Drug Application Nos. 20-972 (capsules) and 21-360 (tablets) for Sustiva (efavirenz; BMS-561525) and to all pending and approved Supplemental New Drug Applications associated with these applications when Gilead Sciences, Inc., acting on behalf of Bristol-Myers Squibb & Gilead Sciences, LLC, files a New Drug Application for the Fixed Dose Combination of efavirenz, emtricitabine and tenofovir disoproxil fumarate.

We request that all information in these files be treated as confidential and that no information from this file be provided to the applicant without our written consent to an authorized member of your Division.

Please contact the undersigned at (203) 677-6460 with any questions regarding the information provided herein. In the event that you are unable to reach me, please contact Dr. Margo Heath-Chiozzi at (203) 677-3819.

Sincerely,



Lori A. DeVore
Associate Director
Global Regulatory Strategy





27 December 2005

Food and Drug Administration, CDER
Division of Antiviral Drug Products
Attention: Ms. Marsha Holloman, Regulatory Health Project Manager
5901-B Ammendale Road
Beltsville, MD 20705-12

Subject: IND 53,971 emtricitabine – SN 751
General Correspondence: Authorization to Reference IND 53,971

Dear Ms. Holloman:

Gilead Sciences (Gilead) hereby authorizes the Food and Drug Administration (FDA) to refer to Gilead's IND 53,971 for information regarding emtricitabine. This authorization is provided in support of the review of NDA 21-937 for an efavirenz/emtricitabine/tenofovir disoproxil fumarate triple combination tablet that is being submitted to the Agency by Gilead on behalf of the joint venture of Bristol-Myers Squibb & Gilead Sciences, LLC.

The authorization granted by this letter does not include any right to access to, or reproduction of, any part of Gilead-sponsored IND 53,971 by the joint venture. It is understood and agreed that information contained in this application shall be treated as confidential in accordance with the provisions of the Federal Food, Drug and Cosmetic Act.

If you have any questions or need further information regarding this submission, please contact me at 650-522-6395 or via facsimile at 650-522-5489. You may also contact Martine Kraus, Ph.D., Director, Regulatory Affairs, at 650-522-5722. We share the same facsimile number.

Sincerely,

Pamela L. Danagher, MSc.
Associate Director, Regulatory Affairs

cc: 1 Original, 1 Copy, 1 Desk Copy for Ms. Holloman



Advancing Therapeutics.
Improving Lives.

27 December 2005

Food and Drug Administration, CDER
Division of Antiviral Drug Products
Attention: Ms. Marsha Holloman, Regulatory Health Project Manager
5901-B Ammendale Road
Beltsville, MD 20705-12

Subject: NDA 21-500 for Emtriva® (emtricitabine) Capsules
General Correspondence: Authorization to Reference NDA 21-500
(GSI Ref. No. 054)

Dear Ms. Holloman:

Gilead Sciences (Gilead) hereby authorizes the Food and Drug Administration (FDA) to refer to Gilead's NDA 21-500 for information regarding emtricitabine. This authorization is provided in support of the review of NDA 21-937 for an efavirenz/emtricitabine/tenofovir disoproxil fumarate triple combination tablet that is being submitted to the Agency by Gilead on behalf of the joint venture of Bristol-Myers Squibb & Gilead Sciences, LLC.

The authorization granted by this letter does not include any right to access to, or reproduction of, any part of Gilead-sponsored NDA 21-500 by the joint venture. It is understood and agreed that information contained in this application shall be treated as confidential in accordance with the provisions of the Federal Food, Drug and Cosmetic Act.

If you have any questions or need further information regarding this submission, please contact me at 650-522-6395 or via facsimile at 650-522-5489. You may also contact Martine Kraus, Ph.D., Director, Regulatory Affairs, at 650-522-5722. We share the same facsimile number.

Sincerely,

A handwritten signature in black ink, appearing to read "Pamela L. Danagher".

Pamela L. Danagher, MSc.
Associate Director, Regulatory Affairs

cc: 1 Original, 1 Copy, 1 Desk Copy for Ms. Holloman



Advancing Therapeutics.
Improving Lives.

27 December 2005

Food and Drug Administration, CDER
Division of Antiviral Drug Products
Attention: Ms. Marsha Holloman, Regulatory Health Project Manager
5901-B Ammendale Road
Beltsville, MD 20705-12

Subject: IND 52,849 tenofovir disoproxil fumarate – SN 683
General Correspondence: Authorization to Reference IND 52,849

Dear Ms. Holloman:

Gilead Sciences (Gilead) hereby authorizes the Food and Drug Administration (FDA) to refer to Gilead's IND 52,849 for information regarding tenofovir disoproxil fumarate. This authorization is provided in support of the review of NDA 21-937 for an efavirenz/emtricitabine/tenofovir disoproxil fumarate triple combination tablet that is being submitted to the Agency by Gilead on behalf of the joint venture of Bristol-Myers Squibb & Gilead Sciences, LLC.

The authorization granted by this letter does not include any right to access to, or reproduction of, any part of Gilead-sponsored IND 52,849 by the joint venture. It is understood and agreed that information contained in this application shall be treated as confidential in accordance with the provisions of the Federal Food, Drug and Cosmetic Act.

If you have any questions or need further information regarding this submission, please contact me at 650-522-5292 or via facsimile at 650-522-5489. You may also contact Martine Kraus, Ph.D., Director, Regulatory Affairs, at 650-522-5722. We share the same facsimile number.

Sincerely,

A handwritten signature in cursive script that reads "Dean M. Waters".

Dean M. Waters
Associate Director, Regulatory Affairs

cc: 1 Original, 1 Copy, 1 Desk Copy for Ms. Holloman



27 December 2005

Food and Drug Administration, CDER
Division of Antiviral Drug Products
Attention: Ms. Marsha Holloman, Regulatory Health Project Manager
5901-B Ammendale Road
Beltsville, MD 20705-12

Subject: NDA 21-356 for Viread[®] (tenofovir disoproxil fumarate) Tablets
General Correspondence: Authorization to Reference NDA 21-356
(GSI Ref. No. 351)

Dear Ms. Holloman:

Gilead Sciences (Gilead) hereby authorizes the Food and Drug Administration (FDA) to refer to Gilead's NDA 21-356 for information regarding tenofovir disoproxil fumarate. This authorization is provided in support of the review of NDA 21-937 for an efavirenz/emtricitabine/tenofovir disoproxil fumarate triple combination tablet that is being submitted to the Agency by Gilead on behalf of the joint venture of Bristol-Myers Squibb & Gilead Sciences, LLC.

The authorization granted by this letter does not include any right to access to, or reproduction of, any part of Gilead-sponsored NDA 21-356 by the joint venture. It is understood and agreed that information contained in this application shall be treated as confidential in accordance with the provisions of the Federal Food, Drug and Cosmetic Act.

If you have any questions or need further information regarding this submission, please contact me at 650-522-5292 or via facsimile at 650-522-5489. You may also contact Martine Kraus, Ph.D., Director, Regulatory Affairs, at 650-522-5722. We share the same facsimile number.

Sincerely,

Dean M. Waters
Associate Director, Regulatory Affairs

cc: 1 Original, 1 Copy, 1 Desk Copy for Ms. Holloman



27 December 2005

Food and Drug Administration, CDER
Division of Antiviral Drug Products
Attention: Ms. Marsha Holloman, Regulatory Health Project Manager
5901-B Ammendale Road
Beltsville, MD 20705-12

Subject: IND 67,671 emtricitabine/tenofovir disoproxil fumarate – SN 034
General Correspondence: Authorization to Reference IND 67,671

Dear Ms. Holloman:

Gilead Sciences (Gilead) hereby authorizes the Food and Drug Administration (FDA) to refer to Gilead's IND 67,671 for information regarding emtricitabine/tenofovir disoproxil fumarate. This authorization is provided in support of the review of NDA 21-937 for an efavirenz/emtricitabine/tenofovir disoproxil fumarate triple combination tablet that is being submitted to the Agency by Gilead on behalf of the joint venture of Bristol-Myers Squibb & Gilead Sciences, LLC.

The authorization granted by this letter does not include any right to access to, or reproduction of, any part of Gilead-sponsored IND 67,671 by the joint venture. It is understood and agreed that information contained in this application shall be treated as confidential in accordance with the provisions of the Federal Food, Drug and Cosmetic Act.

If you have any questions or need further information regarding this submission, please contact me at 650-522-5292 or via facsimile at 650-522-5489. You may also contact Martine Kraus, Ph.D., Director, Regulatory Affairs, at 650-522-5722. We share the same facsimile number.

Sincerely,

Dean M. Waters
Associate Director, Regulatory Affairs

cc: 1 Original, 1 Copy, 1 Desk Copy for Ms. Holloman



27 December 2005

Food and Drug Administration, CDER
Division of Antiviral Drug Products
Attention: Ms. Marsha Holloman, Regulatory Health Project Manager
5901-B Ammendale Road
Beltsville, MD 20705-12

Subject: NDA 21-752 for Truvada[®] (emtricitabine/tenofovir disoproxil fumarate) Tablets
General Correspondence: Authorization to Reference NDA 21-752
(GSI Ref. No. 178)

Dear Ms. Holloman:

Gilead Sciences (Gilead) hereby authorizes the Food and Drug Administration (FDA) to refer to Gilead's NDA 21-752 for information regarding emtricitabine/tenofovir disoproxil fumarate. This authorization is provided in support of the review of NDA 21-937 for an efavirenz/emtricitabine/tenofovir disoproxil fumarate triple combination tablet that is being submitted to the Agency by Gilead on behalf of the joint venture of Bristol-Myers Squibb & Gilead Sciences, LLC.

The authorization granted by this letter does not include any right to access to, or reproduction of, any part of Gilead-sponsored NDA 21-752 by the joint venture. It is understood and agreed that information contained in this application shall be treated as confidential in accordance with the provisions of the Federal Food, Drug and Cosmetic Act.

If you have any questions or need further information regarding this submission, please contact me at 650-522-5292 or via facsimile at 650-522-5489. You may also contact Martine Kraus, Ph.D., Director, Regulatory Affairs, at 650-522-5722. We share the same facsimile number.

Sincerely,

Dean M. Waters
Associate Director, Regulatory Affairs

cc: 1 Original, 1 Copy, 1 Desk Copy for Ms. Holloman

**Bristol-Myers Squibb
Pharmaceutical Research Institute**

Richard L. Gelb Center for Pharmaceutical Research and Development

5 Research Parkway P.O. Box 5100 Wallingford, CT 06492-7660

**OTHER:
Letter of Cross Reference**

**IND #56,897
Atazanavir (ATV, BMS-232632)
Serial No. 703**

December 20, 2005

Debra Birnkrant, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Birnkrant:

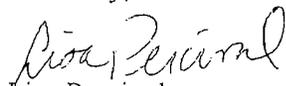
This letter authorizes your Division to refer to Bristol-Myers Squibb IND No. 56,897 for BMS-232632 (atazanavir) and to NDA No. 21-567 Reyataz[®] (atazanavir sulfate) Capsules and to all pending and approved Supplemental New Drug Applications associated with this application when Gilead Sciences, Inc., acting on behalf of Bristol-Myers Squibb & Gilead Sciences, LLC, files a New Drug Application for the Fixed Dose Combination of efavirenz, emtricitabine and tenofovir disoproxil fumarate.

We are filing this letter under our IND 56,897 to be cross-referenced to NDA 21-567.

We request that all information in these files be treated as confidential and that no information from this file be provided to the applicant without our written consent to an authorized member of your Division.

If you have any questions regarding this submission, please contact the undersigned at (203) 677-6803.

Sincerely,



Lisa Percival
Associate Director
Global Regulatory Strategy

cc: LT. Paras Patel



Module 1.3a

**Letter on Joint Venture
Bristol-Myers Squibb & Gilead Sciences, LLC**

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

December 22, 2004

Food and Drug Administration, CDER
Division of Antiviral Drug Products (HFD-530)
Attention: Dr. Debra Birnkrant, Director, DAVDP
9201 Corporate Blvd., 1st Floor Document Room
Rockville, MD 20850

**Subject: Joint Venture Bristol-Myers Squibb & Gilead Sciences, LLC to
Develop Triple Fixed-Dose Combination Product of Efavirenz /
Emtricitabine / Tenofovir Disoproxil Fumarate**

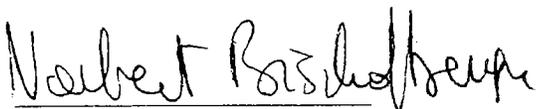
Dear Dr. Birnkrant:

We hereby inform the Division of Antiviral Drug Products that on December 17, 2004 Bristol-Myers Squibb and Gilead Sciences, Inc. (Gilead) and their wholly owned subsidiaries entered into agreements to form Bristol-Myers Squibb & Gilead Sciences, LLC. Bristol-Myers Squibb & Gilead Sciences, LLC was formed with the intent to develop, through the joint venture, a triple fixed-dose combination antiretroviral product of efavirenz, emtricitabine and tenofovir disoproxil fumarate. The joint venture partnership plans to submit an Investigational New Drug Application (IND) and eventually a New Drug Application (NDA) for this combination product.

By virtue of this letter, the joint venture advises the Food and Drug Administration (FDA) that Gilead Sciences through its authorized employees residing at 333 Lakeside Drive, Foster City, CA 94404 will represent the joint venture in all regulatory matters pertaining to the IND and NDA, as prescribed in 21 CFR 312 and 21 CFR 314 and related sections of the US Code of Federal Regulations and the US Food, Drug and Cosmetic Act. Employees of the Bristol-Myers Squibb Company will participate in meetings with and communications to FDA, through the coordination of Gilead.

Please contact me at 650-522-5717 or via facsimile at 650-522-5568 if you have any questions or need additional information. You may also contact Margo Heath-Chiozzi, Bristol Myers Squibb, at 203-677-3819 or via facsimile at 203-677-3834.

Sincerely,

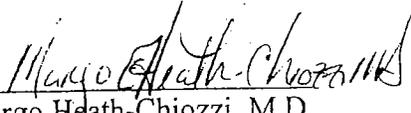


Norbert Bischofberger, Ph.D.

Executive Vice President, Research and Development

Gilead Sciences

Member of Joint Executive Committee of Bristol-Myers Squibb & Gilead Sciences LLC



Margo Heath-Chiozzi, M.D.

Executive Director, Global Regulatory Sciences

Bristol-Myers Squibb Company

Member of Joint Executive Committee of Bristol-Myers Squibb & Gilead Sciences LLC

Enclosure: 1 original, 1 review copy, 1 desk copy to Health Project Manager

EXCLUSIVITY SUMMARY

NDA # 21-937

SUPPL #

HFD # 530

Trade Name ATRIPLA Tablets

Generic Name efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg

Applicant Name Gilead Sciences, Inc/Bristol-Myers Squibb (GSI/BMS)

Approval Date, If Known July 13, 2006

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 is 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#

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# 20-972	SUSTIVA (efavirenz) 50 mg/100 mg/200 mg Tablets
21-360	SUSTIVA (efavirenz) 600 mg Capsules
NDA# 21-500	EMTRIVA (emtricitabine) 200 mg Capsules
NDA# 21-356	VIREAD (tenofovir disoproxil fumarate) 300 mg Tablets
21-752	TRUVADA (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) Tablets

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:

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

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 # YES ! NO
! Explain:

Investigation #2
IND # YES ! NO
! Explain:

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

Investigation #1

!

YES

!

! NO

Explain:

! Explain:

Investigation #2

!

YES

!

! NO

Explain:

! Explain:

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

YES

NO

If yes, explain:

=====
Name of person completing form: Marsha S. Holloman, BS Pharm, JD

Title: Regulatory Health Project Manager

Date: 07/13/2006

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

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

/s/

Jeffrey Murray
7/12/2006 10:49:15 AM

Module 1.3a

Statement of Claimed Exclusivity

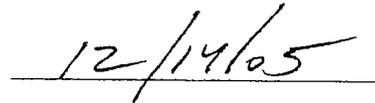
CONFIDENTIAL

21 CFR 314.50 (j) Claimed Exclusivity

With this new drug application (NDA 21-896), no additional exclusivity is claimed under the provisions of 21 CFR 314.108. The active ingredients tenofovir disoproxil fumarate and emtricitabine are both covered by New Chemical Entity (NCE) exclusivity under 21 CFR 314.108 (b)(2) with market exclusivities lasting until October 26, 2006 and July 2, 2008, respectively.



Allan Kutzenco
Senior Director - Intellectual Property
Bristol-Myers Squibb & Gilead Sciences LLC



Date

CONFIDENTIAL

Module 1.3a**Form FDA 356h item 16
Debarment Certification**

Neither Gilead Sciences, Inc. nor any of its contract operations, laboratories or individuals involved in the development or submission of records or data regarding efavirenz/emtricitabine/tenofovir disoproxil fumarate fixed-dose combination tablet has used or will use in any capacity the services of any person debarred under subsections (a) or (b) [section 306 (a) or (b)] or the Generic Drug Enforcement Act of 1992 (21 U.S.C. 335a(k)(1)).



Martine Kraus, Ph.D.
Director, Regulatory Affairs



Date

CONFIDENTIAL

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

v/BLA #: 21-937 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: 04/26/2006 Action Date: _____

HFD-530 Trade and generic names/dosage form: ATRIPLA (efavirenz/emtricitabine/tenofovir disoproxil fumarate) Tablets

Applicant: Gilead Sciences/Bristol-Myers Squibb Therapeutic Class: 7030202

Indication(s) previously approved:

Each approved indication must have pediatric studies: **Completed, Deferred, and/or Waived.**

Number of indications for this application(s): 1

Indication #1: for use alone as a complete regimen or in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults.

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:

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:

Min _____ kg _____ mo. _____ yr. birth Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 18 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: see below

Date studies are due (mm/dd/yy): see below

1. Deferred pediatric study under PREA for use of ATRIPLA alone as a complete regimen or in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric subjects ages from 2 to 18 years of age.

Pediatric studies are ongoing for the individual products, SUSTIVA (efavirenz) and VIREAD (tenofovir disoproxil fumarate).

SUSTIVA Final Study Report Submission for ages 3 months to 3 years of age: January 31, 2008

VIREAD Final Report Submission for ages 2 to 18 years of age: January 31, 2008

After submission of these studies, we will determine whether additional studies for ATRIPLA will be required. Should pediatric studies for ATRIPLA be required, the timeline for completion is as follows:

Final Study Report Submission for ages 2 to 18 years: January 31, 2011.

2. Deferred pediatric study under PREA for the use of ATRIPLA alone as a complete regimen or in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric subjects ages birth to 2 years of age.

Due to safety concerns for this age group, we are waiting for completion and review of studies of VIREAD in the 2 to 18 years age group before determining whether it is appropriate to study VIREAD or ATRIPLA in the birth to 2 years age group. Should further pediatric studies in this age group be required, the timeline for completion is as follows:

Final Study Report Submission for ages birth to 2 years of age: January 31, 2011.

udies 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:

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

Comments:

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

cc: NDA 21-937
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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

/s/

Jeffrey Murray
7/12/2006 10:46:25 AM

Module 1.3a

Request for Deferral of Requirement for Pediatric Studies

Request for Deferral of the Requirement to Conduct Pediatric Studies

A deferral of the requirement to conduct pediatric studies is requested for the efavirenz / emtricitabine / tenofovir disoproxil fumarate fixed-dose combination product, as required under the Pediatric Research Equity Act of 2003 (Public Law 108-155).

Age groups included in deferral request: All pediatric age groups.

Basis for request for deferral:

Reference is made to the Agency's minutes of the pre-NDA meeting held on April 18th, 2005 (see Module 1.3a), which reflect the Division's intent to defer further consideration regarding the requirement for the efavirenz/emtricitabine/tenofovir disoproxil fumarate fixed-dose until pediatric data for the individual components are submitted and reviewed. As such, deferral criteria (ii) of the Act, "pediatric studies should be delayed until additional safety or effectiveness data have been collected" have been fulfilled.

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-937	Efficacy Supplement Type SE-	Supplement Number
Drug: ATRIPLA (efavirenz/emtricitabine/tenofovir disoproxil fumarate) Tablets		Applicant: Gilead Sciences/Bristol-Myer Squibb/Merck
RPM: Marsha S. Holloman, BS Pharm, JD		HFD-530 Phone # 301-796-0731
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority • Chem class (NDAs only) • Other (e.g., orphan, OTC) 		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority 4 N/A
❖ User Fee Goal Dates		
❖ Special programs (indicate all that apply)		
		<input type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee • User Fee waiver • User Fee exception 		<input checked="" type="checkbox"/> Paid 12/29/2006 UF ID number PD3006280 <input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify) <input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)

Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> • Applicant is on the AIP 	() Yes (<input checked="" type="checkbox"/>) No
<ul style="list-style-type: none"> • This application is on the AIP 	() Yes (<input checked="" type="checkbox"/>) No
<ul style="list-style-type: none"> • Exception for review (Center Director's memo) 	N/A
<ul style="list-style-type: none"> • OC clearance for approval 	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(<input checked="" type="checkbox"/>) Verified
❖ Patent	
<ul style="list-style-type: none"> • Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. 	(<input checked="" type="checkbox"/>) Verified
<ul style="list-style-type: none"> • Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) () Verified
<ul style="list-style-type: none"> • [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	21 CFR 314.50(i)(1) () (ii) () (iii)
<ul style="list-style-type: none"> • [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i> 	() N/A (no paragraph IV certification) () Verified
<ul style="list-style-type: none"> • [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?</p> <p>(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)).</p> <p><i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i></p> <p>(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)?</p> <p><i>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 box below (Exclusivity).</i></p> <p><i>If "No," continue with question (3).</i></p>	() Yes () No
	() Yes () No

(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 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 box below (Exclusivity).

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

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the 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 applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

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.

❖ Exclusivity (approvals only)

- Exclusivity summary
- Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)

YES

- Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.

Yes, Application # _____
 No

❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	
❖ Actions	
• Proposed action	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	<input checked="" type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Not applicable
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> Press Release <input checked="" type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter <input checked="" type="checkbox"/> Press Conference 07/12/2006 <input checked="" type="checkbox"/> Q and A <input checked="" type="checkbox"/> Separate WebPage
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	07/12/2006
• Most recent applicant-proposed labeling	07/12/2006
• Original applicant-proposed labeling	04/04/2006
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DDMAC 07/06/2006 DMETS 06/16/2006 Labeling Meetings (See Faxed Correspondence) 05/07/2006 – 07/06/2006
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	07/12/2006
• Applicant proposed	07/10/2006
• Reviews	DDMAC 07/06/2006 DMETS 06/16/2006
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	Yes - See Approval Letter
• Documentation of discussions and/or agreements relating to post-marketing commitments	Yes - See Approval Letter
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	05/07/2006 – 07/06/2006
❖ Memoranda and Teleconferences	CMC Pre-NDA 0
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	CMC 04/11/2005 Clinical 04/18/2005
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	MOTL 07/12/2006
❖ Clinical review(s) (indicate date for each review)	07/12/2006
❖ Microbiology (efficacy) review(s) (indicate date for each review)	07/18/2006
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	See Clinical Review
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	07/10/2006
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	N/A
❖ Biopharmaceutical review(s) (indicate date for each review)	07/10/2006
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	07/12/2006
• Clinical studies	See Clinical Pharmacology Review
• Bioequivalence studies	See Clinical Pharmacology Review
❖ CMC review(s) (indicate date for each review)	05/09/2006
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	YES
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	Date completed: 05/03/2006 (<input checked="" type="checkbox"/>) Acceptable () Withhold recommendation
❖ Methods validation	N/A () Completed () Requested () Not yet requested
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	05/30/2006
❖ Nonclinical inspection review summary	N/A
Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
CAC/ECAC report	N/A

Appendix A to NDA/Efficacy Supplement Action Package Checklist

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

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

MEMORANDUM

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

DATE: July 07, 2006

FROM: Martin K. Yau, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

Jagan Mohan R. Parepally, Ph.D.
Staff Fellow
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Višwanathan, Ph.D. _____
Associate Director, Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Gilead's Written Response to Form FDA-483 Issued to the
Analytical Site of Study GS-US-177-0105 Filed Under NDA
21-937, Atripla™ Tablets

TO: Debra B. Birnkrant, M.D.
Director
Division of Antiviral Drug Products (HFD-530)

From June 12-16, 2006, DSI inspected the analytical portion of Study GS-US-177-0105 at Gilead Sciences Inc., Durham, NC (GSI). Following the inspection, Form FDA-483 (Attachment 1) was issued to GSI. GSI's written response to the Form FDA-483 was received on June 28, 2006 (Attachment 2). During a telephone conference on June 30, 2006, GSI was asked by DADP and DSI to provide additional data to resolve the issues cited in Form FDA-483 Items 1, 2, 5, and 6. The additional data was received by DSI on July 6, 2006 (Attachment 3). Our evaluations of the responses to the Form FDA-483 items are provided below:

Gilead Sciences, Inc., Durham, NC

483 Item 1. Following a review of GSI's written response, DSI maintains that data from Run 6 (efavirenz, subject 6),

Run 8 (efavirenz, subject 8), Run 58 (emtricitabine, subject 12) and Run 99 (tenofovir, subject 43) should be excluded from

bioequivalence determinations due to unacceptable QC results. During the telephone conference on June 30, 2006, GSI agreed to repeat the bioequivalence determinations. The results of the data re-analyses (provided to DSI on July 5, 2006) showed that excluding data from the 4 subjects listed above did not significantly affect the study outcomes.

483 Item 2. In the June 30, 2006 telephone conference, GSI clarified that the acceptance/rejection criteria for the runs cited on the Form FDA-483 was based on standards, QCs, and the observed interference in zero and pre-dose samples. Interference was considered significant only if the interference peak area was >20% of that of the LLOQ. Upon the request of DSI, GSI summarized results from all zero and pre-dose samples assayed in the runs cited in the 483 observation. Review of the data submitted to the Agency on July 6, 2006 (see tables 2 and 3 in Attachment 3) confirms that the acceptance/rejection criteria were consistently followed by GSI.

483 Item 3. A partial validation run was conducted by GSI to support minor changes in the LC-MS/MS method for emtricitabine and tenofovir. This run failed to meet acceptance criteria when all the QCs data were included in run evaluation. However, in light of the satisfactory assay performance during analysis of the study samples (i.e., 147 analytical runs met run acceptance criteria), DSI has decided that it is not critical to request GSI to further demonstrate the accuracy and precision of the modified emtricitabine and tenofovir LC-MS/MS assay.

483 Item 4. Additional 190 day long-term frozen stability data generated on 10/14/05 were provided to the Agency in response to this observation. The above stability data adequately covers the frozen storage time for the plasma samples obtained in this study.

483 Item 5. In the June 30, 2006 telephone conference, GSI agreed to repeat the bioequivalence determination using the original/initial data from samples re-assayed due to pharmacokinetic reasons. The results submitted to the Agency on July 6, 2006 confirmed that the re-assays did not have significant impact on the study outcomes.

483 Item 6. In response to this observation, two matrix studies were conducted to demonstrate the lack of matrix effect in the emtricitabine and tenofovir LC-MS/MS assay. In the study conducted by GSI following the June 30, 2006 telephone conference, six different lots of plasma obtained from _____ were evaluated

Page 3 - NDA 21-937, Atripla™ (Efavirenz 600 mg/Emtricitabine 200 mg/Tenofovir Disoproxil Fumarate 300 mg) Tablets

with spiked QC samples. No significant matrix effect was noted (see table 6 in Attachment 3)

483 Item 7. This 483 observation is concerning the occasional freezer temperature fluctuations (i.e., freezer temperatures reaching -50 degrees C for upto 10 hours) and related freezer alarms. In their written response, GSI informed the Agency that the bench-top stability data have shown that emtricitabine and tenofovir are stable in room temperature for up to 24 hours. Since the bench top stability data for emtricitabine and tenofovir adequately cover the period of temperature changes, this observation should not have significant impact on the integrity of the study samples.

Conclusion:

Following a review of the two written responses provided by GSI on June 28, 2006 and July 6, 2006, DSI concludes that GSI has adequately resolved the issues/concerns raised in the Form FDA-483.

After your review, please attach this transmittal memo the original NDA submission.

Martin K. Yau, Ph.D.

Jagan Mohan R. Parepally, Ph.D.

CC:

HFD-45/RF

HFD-48/Yau/Parepally/Himaya/CF

HFD-530/NDA 21-937/Holloman

HFD-880/DiGiacinto/Reynolds

HFR-SE150/Hubbard

HFR-SE1535/Frazier

Draft: JP 7/6/06

Edit: MKY 7/7/06

DSI: 5701; O:\BE\EIRCOVER\21937Atripla Response.doc

FACTS: 734997

Page 4 - NDA 21-937, Atripla™ (Efavirenz 600 mg/Emtricitabine 200 mg/Tenofovir Disoproxil Fumarate 300 mg) Tablets

Note: Due to the numerous pages in attachments 2 and 3, only the text portion of Gilead's response is included. The remaining pages will be available upon request.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

A

24 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

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

/s/

Jagan Parepally

7/11/2006 01:47:57 PM

PHARMACOLOGIST

Paper copy signed by Dr. Viswanathan on 7/10/06 and
available on request.



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: July 06, 2006

To: Pamela S. Danagher	From: Marsha Holloman
Company: Gilead Sciences, Inc	Title: Regulatory Health Project Manager, HFD-530
Fax number: 650-522-5489	Fax number: 301-796-8993
Phone number: 650-522-6395	Phone number: 301-796-0731
Subject: NDA 21-937 – DRAFT REVISED DAVP LABELING COMMENTS	

Total no. of pages including cover: 49

Comments: [REDACTED]

Document to be mailed: YES NO

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MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-937

Drug: ATRIPLA (emtricitabine/tenofovir disoproxil fumarate/efavirenz)

Date: July 06, 2006

To: Pamela S. Danagher, MS, Associate Director Regulatory Affairs

Sponsor: Gilead Sciences, Inc

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

Through: Jennifer DiGiacinto, Pharm D, Clinical Pharmacologist
Narayana Battula, PhD, Microbiologist

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

Subject: DRAFT REVISED DAVP LABELING COMMENTS

Reference is made to your New Drug Application (NDA) 21-937 dated April 25, 2006, and received April 26, 2006. Also, reference is made to SN-009 dated June 30, 2006, containing your response to DAVP's labeling review comments.

We also have the following changes in the labeling for ATRIPLA starting 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.

B

47 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

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

/s/

Marsha Holloman
7/10/2006 05:46:59 PM
CSO

This document was sent via email and facsimile 07/06/2006.

Kathrine Laessig
7/11/2006 04:18:27 PM
MEDICAL OFFICER

C

6 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 ✓ § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV
Division of Antiviral Drug Products**

FACSIMILE TRANSMITTAL SHEET

DATE: June 29, 2006

To: Pamela S. Danagher	From: Marsha Holloman
Company: Gilead Sciences, Inc	Title: Regulatory Health Project Manager, HFD-530
Fax number: 650-522-5489	Fax number: 301-796-8993
Phone number: 650-522-6395	Phone number: 301-796-0731

Subject: NDA 21-937 – DRAFT REVISED DAVP LABELING COMMENTS

Total no. of pages including cover: 49

Comments:

Document to be mailed: YES NO

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MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-937

Drug: ATRIPLA (emtricitabine/tenofovir disoproxil fumarate/efavirenz)

Date: June 28, 2006

To: Pamela S. Danagher, MS, Associate Director Regulatory Affairs

Sponsor: Gilead Sciences, Inc

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

Through: Jennifer DiGiacinto, Pharm D, Clinical Pharmacologist
Narayana Battula, PhD, Microbiologist

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

Subject: DRAFT REVISED DAVP LABELING COMMENTS

Reference is made to your New Drug Application (NDA) 21-937 dated April 25, 2006, and received April 26, 2006. Also, reference is made to SN-007 dated June 26, 2006, containing your response to DAVP's labeling review comments.

Please note that where the term "TRADENAME" appears, it should be replaced with "ATRIPLA".

We also have the following changes starting 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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§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: June 26, 2006

To: Pamela Danagher	From: Marsha Holloman
Company: Gilead Sciences, Inc	Title: Regulatory Health Project Manager, HFD-530
Fax number: 650-522-5489	Fax number: 301-796-8993
Phone number: 650-522-6395	Phone number: 301-796-0731

Subject: NDA 21-937 – DMETS Review Comments

Total no. of pages including cover: 6

Comments:

Document to be mailed: YES NO

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MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-937

Drug: ATRIPLA (efavirenz /emtricitabine/tenofovir disoproxil fumarate)

Date: June 23, 2006

To: Pamela S. Danagher, MS, Associate Director, Regulatory Affairs, CMC

Sponsor: Gilead Sciences, Inc

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

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

Subject: TRADENAME REVIEW COMMENTS

Reference is made to NDA 21-937 dated April 25, 2006, and received April 26, 2006.

The Division of Medication Errors and Technical Support (DMETS) does not recommend the use of the proprietary name, _____. However, DMETS has no objections to the use of the proprietary name, Atripla. In reviewing the proprietary name _____ the primary concerns related to look-alike confusion with _____

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§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

Additionally, DMETS reviewed the — /Atripla labels and labeling from a safety perspective. DMETS has identified the following areas of possible improvement, which may minimize the potential for user error.

A. CONTAINER LABEL (US Market and Access Program)

1. Increase the prominence of the established name to at least ½ the size of the proprietary name per 21 CFR 201.10(g)(2).
2. The product strength does not appear on the primary display panel of the container label. Add the strength prominently on the primary display panel as follows. Since — Atripla is a combination product, it should appear as follows: 600 mg/200 mg/300 mg.
3. Once the strength has been added to the principle display panel, relocate the net quantity statement away from the strength in order to avoid confusion.
4. Decrease the font or de-bold the net quantity statement (30 tablets) as it appears as prominent as the established name.
5. The statement on the export product: "Gilead Access Program for Export Only" may be easily overlooked because the — ont appears very similar to the — font on the container label. Increase the prominence of this statement (e.g., revise the color of the font) as this statement is intended to differentiate the US product from the product to be exported. Increasing the prominence of this statement may help to minimize selection errors at the point of distribution.

B. CARTON LABELING (US Market and Access Program)

1. The — interferes with the readability of carton labeling. Revise the — so it does not interfere with the verbiage on the label.
2. See comments A1 through A5.
3. Relocate the "Each tablet contains..." statement on the primary display panel to the side panel in order to increase the amount of space on the primary display panel and to ease readability.

C. PACKAGE INSERT

At the top of the package insert, include the product strength following the

established name.

D. PATIENT PACKAGE INSERT

No comment.

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/s/

Marsha Holloman
6/26/2006 10:59:33 AM
CSO

Kathrine Laessig
6/26/2006 11:57:37 AM
MEDICAL OFFICER

MEMORANDUM

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

DATE: June 22, 2006

TO: Debra B. Birnkrant, M.D.
Director
Division of Antiviral Drug Products (HFD-530)

FROM: Martin K. Yau, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

Jagan Mohan R. Parepally, Ph.D.
Staff Fellow
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 21-937,
(Efavirenz 600 mg/Emtricitabine 200 mg/Tenofovir
Disoproxil Fumarate 300 mg) Tablets, Sponsored by
Gilead Sciences, Inc., Durham, NC

At the request of Division of Antiviral Drug Products (DADP), the Division of Scientific Investigations (DSI) conducted an audit of the clinical and analytical portions of following bioequivalence study:

Protocol GS-US-177-0105: A Phase 1 Pharmacokinetic Study in Healthy Subjects to Evaluate the Bioequivalence of a Fixed-Dose Triple-Combination Tablet of Efavirenz, Emtricitabine, and Tenofovir Disoproxil Fumarate Compared With the Concurrent Administration of the Individual Dosage Forms

The clinical portion of Protocol GS-US-177-0105 was conducted at

The analytical portion of Protocol GS-US-177-0105 was conducted at Gilead Sciences, Inc., Durham, NC (GSI). Following the inspection at — (June 05-22, 2006) and GSI (June 12-16, 2006), Form FDA-483 was issued at each site. The objectionable items and our evaluation are provided below:

Clinical Site: _____

1. An investigation was not conducted in accordance with the investigational plan. Specifically,

For — study number AA28769 (GS-US-177-0105):

- a. Subject 13 — : Information concerning a spontaneous abortion as known to the study site on/about Nov. 30, 2005. The protocol defines spontaneous abortion as a serious adverse event, and gives a time frame of 24 hours for reporting such a serious adverse events to the sponsor. The sponsor was not notified until Dec. 22, 2005. (Due to the pregnancy, the subject had been discontinued from the study Oct. 11, 2005.)

Protocol deviation listed above is related to the safety of study subjects and should not significantly affect the bioequivalence study. The firm should avoid such deviations in future studies.

- b. Subjects 1 — and 2 — Period 1: Pre-dose blood draws were performed just after the first dose of study drug was given to these subjects, instead of one-half hour prior to the first dose.

Concentrations of the analytes in these samples are below limit of quantitation and hence they do not affect the study.

Analytical Site: Gilead Sciences, Inc., Durham, NC

1. Failure to reject an analytical run when >50% of quality control (QC) samples fail at the same level. For example, Run 6 (efavirenz subject 6), Run 8 (efavirenz subject 8), Run 58 (emtricitabine subject 12) and Run 99 (tenofovir subject 43).

Analytical runs listed above were accepted when 2 of the 3 (66%) QCs at the same level failed. Due to the unacceptable QC results, data from the following subjects should be excluded from the bioequivalence determination.

Analyte	Run	Subjects
Efavirenz	6, 8	6, 8
Emtricitabine	58	12
Tenofovir	99	43

2. Review of tenofovir/emtricitabine analytical runs found some inconsistencies in run acceptance/rejection when QC's failed for one of the analytes.

For example, tenofovir data from Run 57 was accepted and all data from Runs 60, 74, and 75 was rejected, although in all four runs, standards and QC's for tenofovir met run acceptance criteria:

Run 57 (subject 11) - QC's for emtricitabine failed, and only the emtricitabine data was rejected.

Run 60 (subject 15) - QC's for emtricitabine failed, and all standards and 8 out of 9 QC's for tenofovir were acceptable, but the entire run was rejected.

Run 74 (subject 27) - QC's for emtricitabine failed, and all standards and 8 out of 9 QC's for tenofovir were acceptable, but the entire run was rejected.

Run 75 (subject 28) - QC's for emtricitabine failed, and 12 out of 16 standards and 8 out of 9 QC's for tenofovir were acceptable, but the entire run was rejected.

Also, Run 56 (subject 10) - QC's for tenofovir failed, and only the tenofovir data was rejected.

During the inspection, the site explained that data for both emtricitabine and tenofovir in Runs 60, 74, and 75 were rejected due to contamination problems. As these contamination issues identified in Runs 60, 74, and 75 might also exist in Runs 56 and 57, DSI is of the opinion that all the tenofovir data from Run 57 (subject 11) and emtricitabine data from Run 56 (subject 10) should also be rejected at this time.

At the inspection close out meeting, the site stated they will provide written response to the Form FDA-483 items. Upon receipt of the written response, DSI will evaluate and will determine if there are adequate justifications for accepting the emtricitabine data in Run 56 (subject 10) and the tenofovir data in Run 57 (subject 11).

3. **Failure to include all QC results in the determination of assay accuracy and precision. For example, a partial validation consisting of only one run to determine intra-assay accuracy and precision was conducted to support method changes in the emtricitabine and tenofovir LC/MS/MS assay (Validation Report Addendum 2). In this partial validation run, two failed QC (one low QC and one mid QC) were identified as outliers and discarded from accuracy and precision determination. When all QC results were included, the mid QC exhibited an intra-run precision of 16.7% CV and failed to meet the site's validation acceptance criteria of <15% CV.**

A single partial validation run was conducted to support the following changes in the emtricitabine and tenofovir LC/MS/MS assay: (1) Using _____ was used instead of the _____ for the MS detection, (2) using an expanded calibration range for emtricitabine, (3) using _____ for reconstitution of evaporated sample preparation. Since this is the only validation run to support the precision and accuracy of the modified assay, and the precision of the assay failed the acceptance criteria when the failed QC was included (see attachment 1). DSI is concerned that modified assay is not adequately validated. Additional data to demonstrate the accuracy and precision of the modified emtricitabine and tenofovir LC/MS/MS assay should be provided to the Agency for evaluation.

4. **Failure to properly document the 460 days long term frozen stability study for emtricitabine and tenofovir. There is no written record showing that the stability samples were stored at -80°C for 460 days.**

The validity and integrity of the long term frozen stability data can not be confirmed, as there is no document to show that the stability samples were indeed stored at -80°C for 460 days.

In Study GS-US-177-0105, the time period when the study subject samples were collected at the clinical site to the time when all study subject samples were assayed is about 100 days. In light of the documentation problem uncovered at the site, DSI recommends that the long term frozen stability study for emtricitabine and tenofovir be conducted again and to cover a period of at least 100 days of frozen storage at -80 degrees C.

5. Many study samples were re-assayed for efavirenz, emtricitabine and tenofovir due to pharmacokinetic reasons. No objective criteria were established a priori to justify selection of these study samples.

To determine the impact of the re-assays on the study outcomes, DSI recommends that the original concentrations be used for the bioequivalence determination (see attachment 2).

6. Failure to conduct study to demonstrate the lack of matrix effect in the emtricitabine and tenofovir LC/MS/MS assay.

Matrix effect study should be conducted to confirm the lack of matrix effect in the emtricitabine and tenofovir LC/MS/MS assay.

7. Review of temperature charts/alarm records for freezers — (used to store plasma samples from study GS-US-177-0105 found:

The temperature recording chart for freezer — for 11/30/'05-12/7/'05 shows that the temperature rose to -70°C at about noon on 12/1, with an alarm at 1 pm (-67°). But, the temperature for this freezer went to -58° on 12/5 (above -70 for approximately 6 hours) and -55° on 12/6 (above -70° for approximately 6 hours), with no alarms logged.

On 12/9, the temperature for freezer — started increasing at 8am, to a high of -48° at 4:30pm, with -80° not achieved until 6am the next day; the temperature was above -70° from 10am 12/9 until approximately 1 am 12/10. There is no entry on the alarm log for this event.

The chart for 12/7 - 14/05 also shows 4 additional instances where the temperature rose to approximately -60°, -50°, -60°, and -52°, with no alarms logged, and with the temperature above -70° for 5 to 10 hours each time.

During the inspection, the FDA investigators found that long term frozen stability study at -20°C for efavirenz is available and showed that efavirenz is stable at -20 °C for 532 days. Thus, the above observation should have no impact on the integrity of the study subject samples regarding efavirenz. However, it is unknown what impact the above observation might have on the integrity of the study samples concerning emtricitabine and tenofovir. The firm should resolve this issue by providing additional stability data for emtricitabine and tenofovir at a warmer temperature (e.g., -20 °C).

Conclusion:

The data from Study GS-US-177-0105 needs resolution of the Form FDA-483 issues. Specifically, data of subjects identified in analytical 483 Item 1 should be excluded from the bioequivalence determination. The OCPB reviewer needs to evaluate the impact of the re-assays of subject samples by using the original instead of the re-assayed analyte concentrations in the bioequivalence determination. Furthermore, the site should resolve analytical 483 Items 2, 3, 4, 6, and 7.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Martin K. Yau, Ph.D.

Jagan Mohan R. Parepally, Ph.D.

Final Classifications:

Page 7 of 10 - NDA 21-937, (Efavirenz 600 mg/Emtricitabine
200 mg/Tenofovir disoproxil Fumerate 300 mg) Tablets

Gilead Sciences, Inc., Durham, NC - VAI

Note:

cc:

HFD-45/RF

HFD-48/Yau/Parepally/Himaya/CF

HFD-530/NDA 21-937/Holloman

HFD-880/DiGiacinto/Reynolds

HFR-PA200/Koller

HFR-PA2540/Johnson

HFR-SE150/Hubbard

HFR-SE1535/Frazier

Draft: JP 6/19/06

 MKY 6/20/06

Edit: MKY 6/22/06

DSI: 5701; O:\BE\EIRCOVER\21937 Triple Combo.doc

FACTS: 734997

Attachment 1

Emtricitabine with outliers included in calculations

Nominal conc. of QCs	(ng/mL)	QC LLOQ	QC Low	QC Mid	QC High
Validation Run 04/07/05	Rep 1	5	15	500	2500
	Rep 2				
	Rep 3				
	Rep 4				
	Rep 5				
	Rep 6				
	n	6	6	6	6
Intra-run Mean ^a	(ng/mL)	4.9	13.4	454.3	2472.7
Intra-run Precision	(%RSD)	11.4	18.7	10.6	5.3
Intra-run Accuracy	(%bias)	-2.0	-10.7	-9.1	-1.1

^a The calculated mean was rounded to the nearest tenth of a unit.

*Statistical outlier not included in statistics

Precision and accuracy were calculated using the rounded values for mean.

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Emtricitabine without outliers included in the calculations

Nominal conc. of QCs (ng/mL)	QC LLOQ	QC Low	QC Mid	QC High
Validation Run 04/07/05	5	15	500	2500
Rep 1				
Rep 2				
Rep 3				
Rep 4				
Rep 5				
Rep 6				
n	6	5	5	6
Intra-run Mean ^a (ng/mL)	4.9	14.3	473.7	2472.7
Intra-run Precision (%RSD)	11.4	2.8	2.2	5.3
Intra-run Accuracy (%bias)	-2.0	-4.7	-5.3	-1.1

^a The calculated mean was rounded to the nearest tenth of a unit.

*Statistical outlier not included in statistics

Precision and accuracy were calculated using the rounded values for mean.

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Attachment 2

Subject	Analyte	Time (h)	Run ID	Treatment ID	Period	Original Concentration ng/mL
06	EFV	504	6	A	1	
06	EFV	504	6	B	2	
10	EFV	6	9	B	2	
13	EFV	8	46	B	1	
14	EFV	0	34	B	2	
16	EFV	36	36	B	1	
19	EFV	10	39	B	2	
20	EFV	2.5	40	B	1	
22	EFV	8	12	B	1	
25	EFV	4.5	15	A	2	
26	EFV	24	16	A	1	
27	EFV	2	17	A	2	
30	EFV	0	20	A	2	
30	EFV	3	20	B	2	
32	EFV	1.5	22	B	2	
46	EFV	4.5	43	B	1	
48	EFV	24	45	A	1	
48	EFV	0	45	B	2	
03	FTC	48	50	B	1	
23	FTC	3.5	70	B	2	
03	FTC	2.5	50	A	2	
11	FTC	1	77	A	1	
14	FTC	2	59	A	1	
25	FTC	4	72	A	2	
27	FTC	4.5	90	A	2	
32	FTC	2	87	A	2	
48	FTC	24	104	A	1	
47	TFV	1.5	103	B	1	
25	TFV	4	72	A	2	
32	TFV	2	87	A	1	
48	TFV	24	104	B	1	

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/s/

Amalia Himaya

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CSO

Paper copy signed by Dr. Viswanathan on 6/22/06 and
available upon request.

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§ 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

REQUEST FOR CONSULTATION

TO (Office/Division): DDMAC
 From: Lynn Panholzer
 103 New Hampshire Ave.
 Building 22 Room 1400
 Silver Spring, MD 20903-0002

FROM (Name, Office/Division, and Phone Number of Requestor):
 Marsha S. Holloman, BS Bharm, JD
 Regulatory Health Project Manager
 Division of Antiviral Products (DAVP)
 10903 New Hampshire Ave.
 Building 22 Room 6321
 Silver Spring, MD 20903-000

DATE June 19, 2006	IND NO. 71,420	NDA NO. 21-937	TYPE OF DOCUMENT Labeling	DATE OF DOCUMENT April 26, 2006
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NAME OF DRUG ATRIPLA (efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300mg) Tablets	PRIORITY CONSIDERATION Priority - Expedited	CLASSIFICATION OF DRUG Treatment HIV-1	DESIRED COMPLETION DATE June 23, 2006
---	--	---	--

NAME OF FIRM: Gilead Sciences, Inc/Bristol-Myers Squibb Company

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input checked="" 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 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 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 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 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

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: The draft revised labeling will be sent in a separate email.

SIGNATURE OF REQUESTOR
/s/ Marsha S. Holloman

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

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/s/

Marsha Holloman

6/19/2006 11:23:13 AM

Labeling for this consult to follow.

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; Write Oak 22; Mail Stop 4447)

DATE RECEIVED: Dec. 12, 2005

DATE OF DOCUMENT: Dec. 2, 2005

DESIRED COMPLETION DATE:

Feb. 26, 2006

PDUFA: Feb. 26, 2007

OSE REVIEW #:

05-0267

05-0267-1

TO: Debra Birnkrant, MD
Director, Division of Anti-Viral Products
HFD-530

THROUGH: Alina Mahmud, RPh, MS, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Felicia Duffy, RN, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME:

— (primary name)

Atripla (alternate name)

(Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate) Tablets
600 mg/200 mg/300 mg

SPONSOR: Gilead Sciences, Inc.

NDA #: 21-937

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name, —. However, DMETS has no objections to the use of the proprietary name, Atripla. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to in order to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary names — and Atripla acceptable from a promotional perspective.

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. If you have further questions or need clarifications, please contact Diane Smith, Pre-marketing Project Manager, at 301-796-5038.

Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
HFD-420; W022; Mail Stop 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: February 15, 2006
NDA #: 21-937
NAME OF DRUG: _____ (primary name)
Atripla (alternate name)
(Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate) Tablets
600 mg/200 mg/300 mg
IND SPONSOR: Gilead Sciences, Inc.

NOTE: This review contains proprietary and confidential information that should not be released to the public.

I. INTRODUCTION

This consult was written in response to a request from the Division of Anti-Viral Products (HFD-530), for an assessment of the proprietary names _____ and "Atripla" regarding potential name confusion with other proprietary or established drug names. A draft package insert was submitted for review and comment. Additionally, an independent name analysis of the proposed names, conducted by _____ and _____, was submitted by the sponsor.

The sponsor indicated that they originally intended to submit _____ as their first preference for the name of this drug product. However, the name _____ was reconsidered upon the _____

proposed _____ as the primary alternate to their original first preference, _____. The sponsor also submitted the name Atripla as their second option in case _____ is not acceptable. Thus, the sponsor

PRODUCT INFORMATION

_____ Atripla is a fixed-dose triple drug combination containing efavirenz, emtricitabine and tenofovir disoproxil fumarate. It is indicated for the treatment of HIV-1 infection in adults. _____ Atripla can be used alone as a complete regimen or in combination with other anti-retroviral agents. The dose is one tablet once daily by mouth taken on an empty stomach. Each tablet contains 600 mg of efavirenz, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate. _____ Atripla will be available in child resistant unit-of-use bottles containing 30 tablets.

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference textsⁱⁱⁱ as well as several FDA databases^{iii,iv} for existing drug names which sound-alike or look-alike to " — " and "Atripla" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted^v. The Saegis^{vi} Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving healthcare practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names " — " and Atripla. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC did not have any concerns from a promotional perspective regarding the proposed names, " — " and Atripla.
2. The Expert Panel identified six proprietary names that were thought to have potential for confusion with " — ". These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.
3. The Expert Panel identified six proprietary names that were thought to have potential for confusion with Atripla. These products are listed in Table 2 (see pages 4 & 5), along with the dosage forms available and usual dosage.

ⁱ MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

ⁱⁱ Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

ⁱⁱⁱ The Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-06, and the electronic online version of the FDA Orange Book.

^{iv} Phonetic and Orthographic Computer Analysis (POCA).

^v WWW location <http://www.uspto.gov/tmdb/index.html>.

^{vi} Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names for ~~Identified~~ Identified by DMETS Expert Panel

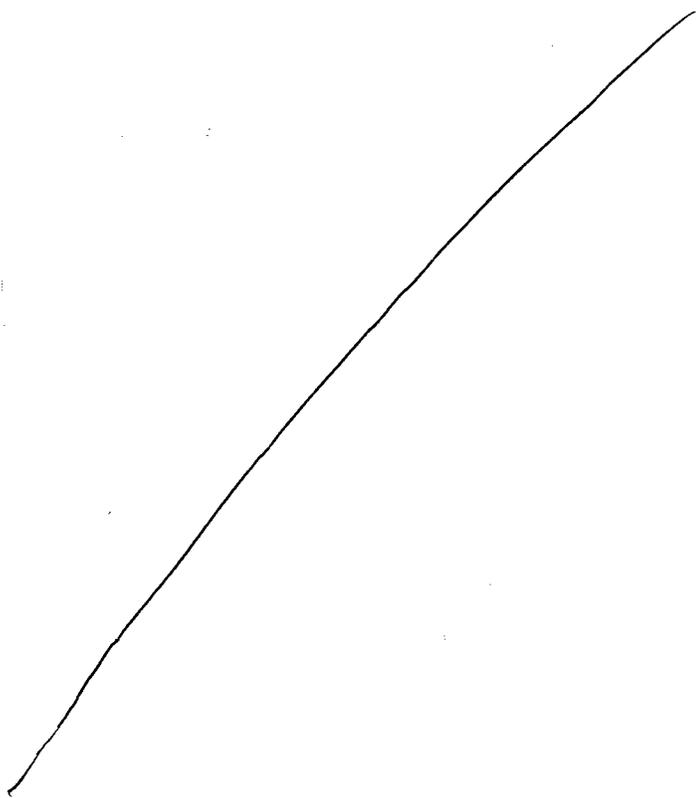


Table 2: Potential Sound-Alike/Look-Alike Names for Atripla Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Atripla	Emtricitabine/Rilpivirine/tenofovir DF Tablets: 600 mg/200 mg/300 mg	One tablet by mouth once daily on an empty stomach	
Atropen	Atropine Injection: 0.25 mg, 0.5 mg, 1 mg, and 2 mg	Adults and children over 90 lbs: 2mg Children 40-90 lbs: 1 mg Children 15-40 lbs: 0.5 mg Infants less than 15 lbs: 0.25 mg Mild symptoms: Administer (IM) one Atropen for two or more mild symptoms. Two additional Atropen injections given in	LA

*** NOTE: This review contains proprietary and confidential information that should not be released to the public.***

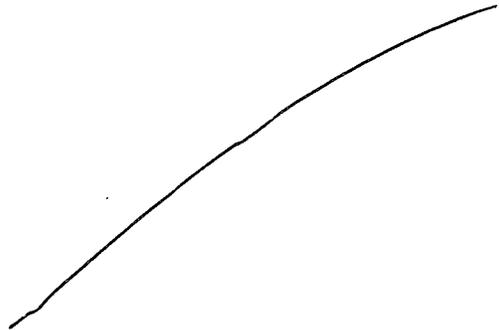
Product Name	Established Name	Adult Dose	Other**
Atripla	Emtricitabine/Rilpivirine/Didanosine Tablets: 600 mg/200 mg/25 mg	1 tablet by mouth once daily on an empty stomach	
		rapid succession 10 minutes after receiving the first Atropine injection if the patient exhibits severe symptoms. <u>Severe symptoms:</u> Administer (IM) 3 Atropine injections in rapid succession.	
Atropine	Atropine Sulfate Injection: 0.05 mg/mL, 0.1 mg/mL, 0.4 mg/mL, 0.5 mg/mL, 0.8 mg/mL, 1 mg/mL Ophthalmic solution: 0.5%, 1%, 2% Ophthalmic ointment: 1%	<u>Oral:</u> Adult: 0.1 to 1.2 mg, every 4-6 hours as needed. Peds: 0.01 mg/kg or 0.3mg/m ² , every 4-6 hours as needed. <u>Parenteral:</u> Adult: 0.3 to 1.2 mg, may be repeated every 4-6 hours. Peds: 0.01 mg/kg or 0.3mg/m ² , every 4-6 hours as needed. <u>Ophthalmic:</u> Solution: 1-2 drops in the eye(s) TID Ointment: Apply a small amount in the conjunctival sac once or twice a day.	LA
Apidra	Insulin Glulisine (rDNA origin) Injection: 100 units/mL	Individualized dose based on patients needs. Intended for subcutaneous administration and for use by external infusion pump. Give 15 min before a meal or within 20 min after eating.	LA/SA
Emtriva	Emtricitabine Capsules: 200 mg Oral Solution: 10 mg/mL	Capsules: 1 tablet by mouth once daily. Solution: 240 mg (24 mL) by mouth once daily.	SA
Etreva	Lubiprostone Capsules: 24 mcg	Once capsule twice a day for a total daily dose of 48 mcg.	SA
Atreza	Atropine Sulfate Tablets: 0.4 mg	0.4 mg every 4 to 6 hours as needed.	LA
*Frequently used, not all-inclusive. **LA (look-alike), SA (sound-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Six separate studies were conducted within the Centers of the FDA for the proposed proprietary names to determine the degree of confusion of — and Atripla with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 119 health care professionals (pharmacists, physicians, and nurses) for each name. This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for — and Atripla (see page 6). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
--------------------------	---------------------



ATRIPLA	
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<u>Outpatient RX:</u> Atripla #30 TQD	Atripla Dispense #30 Take one tablet by mouth once daily.
<u>Inpatient RX:</u> Atripla, 1 tab daily	

2. Results - —



3. Results – Atripla:

One participant in the written outpatient study interpreted the proposed name as Atropen, a currently marketed US product. See Appendix B for the complete listing of interpretations from the verbal and written studies.

G

3 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

2. Atripla Evaluation

In reviewing the proprietary name "Atripla", the primary concerns relating to look-alike and sound-alike confusion with Atripla are Atreza, Etreva, Emtriva, Atropen, Atropine and Apidra.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that Atripla could be confused with Atropen. One respondent from the outpatient written study interpreted the name as Atropen, a currently marketed US product. Although there are limitations to the predictive value of these studies, primarily due to the sample size, we have acquired safety concerns due to the positive interpretation of the drug product, Atropen. The remaining interpretations from the written and verbal studies were misspelled/phonetic variations of the proposed name, Atripla.

- a. Atreza was identified as a name with similar appearance to Atripla when scripted. Atreza is indicated for the reduction of excessive salivation and bronchial secretions. Atreza is available as 0.4 mg tablets and the usual dose is 0.4 mg. The dose may be repeated every 4 to 6 hours as needed.

Atreza and Atripla both begin with "Atr-". Although the endings are different ("-za" vs. "-pla"), they may look similar when scripted (see below). Atreza and Atripla share the following overlapping product characteristics: route of administration (oral), usual dosage and dosage form (1 tablet). There may also be an overlapping patient population since many patients infected with HIV contract pneumonia, which can result in bronchial secretions. Despite the different strengths of each drug (0.4 mg vs. 600 mg/200 mg/300 mg), both are available in only one strength, thus, prescriptions for Atreza and Atripla may be written without the strength. Both drugs also differ in indication for use (excessive salivation/bronchial secretions vs. treatment of HIV), and frequency of administration (every 4-6 hours as needed vs. once daily). Although the frequency of administration for Atreza is every 4-6 hours as needed, it is possible to receive a one time order for Atreza in the inpatient setting if the medication is dropped on the floor or if it is inadvertently omitted from the patient's medication drawer at the time of filling in the pharmacy. Furthermore, a patient may potentially be taking both medications concomitantly. Thus, a prescription for Atreza may be misinterpreted as Atripla and vice versa. In either case, the patient would receive a double dose of medication. Due to the overlapping product characteristics in addition to the orthographic similarities between Atreza and Atripla, DMETS has concerns with the potential for confusion between the two drug products.

Atreza
Atripla

- b. Etreva was identified as a name having sound-alike similarities with Atripla. Etreva is indicated for the rapid and sustained relief of chronic idiopathic constipation and associated symptoms including abdominal bloating, abdominal discomfort, straining, stool consistency, and constipation severity. It is supplied in 24 mcg capsules that are orally administered twice a day.

Etreva and Atripla contain 3 syllables and may have a similar phonetic beginning if the "E" in the beginning of Etreva is pronounced as "Ah". The last syllables are different, yet they rhyme ("va" vs. "pla"). The rhyming quality may slightly contribute to their phonetic similarities. However, the second syllable of each name is phonetically different ("tre" vs. "trip"). Thus, the distinct middle syllable helps to differentiate the names ("ah-TREE-va" vs. "ah-TRIP-la"). Etreva and Atripla overlap in product characteristics such as usual dosage (1 capsule/tablet), route of administration (oral), and dosage form (capsule/tablet). The differentiating product characteristics include indication for use (constipation vs. HIV), and frequency of administration (twice a day vs. once daily). Although Etreva and Atripla share some overlapping product characteristics, the lack of convincing phonetic similarities minimize the potential for confusion between these two drug products.

- c. Emtriva was identified as a name having sound-alike similarities with Atripla. Emtriva is indicated for the treatment of HIV of children over the age of 3 months and adults. It is available as 200 mg capsules and as a 10 mg/mL oral solution. Emtriva and Atripla both contain 3 syllables. The third syllables rhyme with one another ("va" vs. "pla"), which contribute to their phonetic similarity. However, the first syllable ("Em" vs. "A") helps to provide some phonetic differentiation between the names. Additionally, the pronunciation of the second syllable is phonetically different ("tree" vs. "trip"). Emtriva and Atripla contain overlapping product characteristics such as indication for use (HIV), active ingredient (emtricitabine), usual dose (1 capsule/tablet), route of administration (oral), frequency of administration (once daily), and dosage form (capsule/tablet). Although Emtriva and Atripla share some overlapping product characteristics, the phonetic distinction between the names ("Em-TREE-va" vs. "Ah-TRIP-la") may help to minimize the potential for confusion and error with these two drug products.
- d. Atropen was identified as having look-alike similarities to Atripla. Atropen is an atropine injection that is a first-line antidote for victims affected by chemical nerve agent poisoning. It is currently made available only to federal, state and local governments and emergency responders. Atropen is available in 0.25 mg, 0.5 mg, 1 mg and 2 mg pre-filled auto-injectors. One respondent from the outpatient prescription study interpreted Atripla as Atropen.

Atropen and Atripla contain 7 letters and begin with "Atr-". The ending of each name ("-pen" vs. "-pla") may look similar when scripted (see page 12). Additionally, the letters "o" and "i" may resemble one another when scripted. Atropen and Atripla have many differentiating product characteristics such as indication for use (nerve poisoning vs. HIV treatment), strength (0.25 mg, 0.5 mg, 1 mg, 2 mg vs. 600 mg/200 mg/300 mg), usual dosage (1 or 3 doses vs. 1 tablet), route of administration (intramuscular vs. oral), frequency of administration (one time or x3 vs. once daily), and dosage form (pre-filled pen injector vs. tablet). Additionally, Atropen is limited in distribution as it is available only to federal, state, and local governments and emergency responders. Despite the strong orthographic similarities between Atropen and Atripla, the potential for confusion between the two drug products is minimized by the use of Atropen in only emergency situations. Furthermore, the strength for Atropen will likely be indicated as it is available in four different strengths, whereas the strength for Atripla may be omitted on a prescription as it is available in only one strength. Therefore, DMETS believes the differentiating product characteristics (indication for use, strength, route of administration, frequency of administration, usual dose, dosage form, and area of distribution) will minimize the risk of confusion between Atropen and Atripla.

Atropine
Atropine

- e. Atropine was identified as a name with similar appearance to Atripla. Atropine is indicated when excessive muscarinic effects are judged to be life threatening, or are producing symptoms severe enough to call for temporary, reversible muscarinic blockade. Additionally, Atropine can be used as an ophthalmic agent for mydriasis or cyclopegia. Atropine and Atripla begin with "Atr-" and share the letter "p" in the fourth position. Additionally, the letters "o" and "i" may look similar when scripted. Although Atropine and Atripla have different endings ("-pine" vs. "-pla"), the endings may resemble one another at a quick glance. Atropine and Atripla may be administered orally. However, the differentiating product characteristics include indication for use (reversal of muscarinic effects vs. treatment of HIV), usual dose, frequency of administration (one time or every 4-6 hours as needed vs. once daily), and dosage form (injection/solution vs. tablet). Since Atropine is available in multiple strengths and dosage forms, the intended dose and dosage form will be specified on a prescription. However, prescriptions for Atripla may be written without the strength as it is available in only one strength. Although Atropine and Atripla share some orthographic similarities, the differentiating product characteristics will help to minimize the potential for confusion between the two drug products.

Atropine
Atropine

Atropine
Atropine

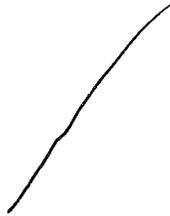
- f. Apidra was identified as a name with having look-alike and sound-alike similarities with Atripla. Apidra is indicated for the treatment of diabetes mellitus in adults and is available as 100 units/mL in 10 mL vials. The usual dose is individualized based on the patient's needs. Apidra and Atripla begin with the letter "A", have the letter "i" in the middle of the name and ends with an "a". However, the upstrokes and downstrokes of Apidra and Atripla appear in different positions, which help to distinguish the names. Both names contain 3 syllables and the ending of each name rhymes (-dra vs. -pla), which contributes to their sound-alike quality. Additionally, the middle of the names may sound similar when they are pronounced with the 'i' sound as in the word the word 'sit'. Apidra and Atripla differ in many product characteristics such as indication for use (diabetes mellitus vs. treatment of HIV), strength (100 units/mL vs. 600 mg/200 mg/300 mg), usual dose (individualized dose/pt vs. 1 tablet), route of administration (subcutaneous vs. oral), frequency of administration (15 min before meals or within 20 minutes of eating vs. once daily), and dosage form (injection vs. tablet). The lack of convincing orthographic and phonetic similarities, in addition to the differentiating product characteristics between Apidra and Atripla, will help to minimize the potential for confusion between the two drug products.

Atripla *Apidra*

D. — EVALUTION

The sponsor contracted — to conduct a name evaluation in support of the proprietary names — and Atripla.

1. —



2. Atripla

— identified the following names as having the potential for confusion with Atripla: Amitriptyline, Atropine, Arixtra, Abilify, Trileptal, Atrovent, Altace, Aldara, Emla, Atabrine, Aricept, Aspirin, Advil, Elavil, and Ativan. — concluded that the likelihood of Atripla being confused with other pharmaceuticals or leading to dispensing errors is extremely low.

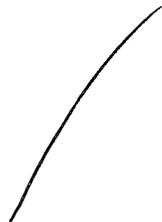
DMETS' comments

Both the DMETS and — evaluations identified the existing name, Atropine, as having potential confusion with Atripla. DMETS discussed Atropine and Atripla in section IIC2e of this review. We concur that these drug products can co-exist in the marketplace.

Additionally, DMETS identified Atropen, Atropine, Apidra, Atreza, Etreva, and Emtriva as having phonetic and/or orthographic similarities with Atripla. These names were not identified in the — evaluation. DMETS believes the aforementioned drug products may co-exist in the marketplace with minimal potential for confusion and error with Atripla (see section IIC2).

E. — EVALUATION

1. —



2. Atripla

The analysis conducted by [redacted] identified Atropen and Atropine as potential look-alike drugs to Atripla. [redacted] concluded that Atripla does not pose a strong look-alike or sound-alike similarity to other pharmaceuticals on the market.

DMETS' comments

DMETS identified Apidra, Atreza, Etreva, and Emtriva as having phonetic and/or orthographic similarities with Atripla. These names were not identified in the [redacted] evaluation. DMETS believes the aforementioned drug products may co-exist in the marketplace with minimal potential for confusion and error with Atripla (see section IIC2).

Both DMETS and [redacted] identified Atropen and Atropine, as having potential confusion with Atripla. DMETS discussed Atropen, Atropine and Atripla in section IIC2(d)(e) of this review. Following review of the proprietary name analysis submitted by [redacted] we concur that these drug products may co-exist in the marketplace.

III. COMMENTS TO THE SPONSOR

DMETS does not recommend the use of the proprietary name, [redacted]. However, DMETS has no objections to the use of the proprietary name, Atripla. In reviewing the proprietary name [redacted], the primary concerns related to look-alike confusion with [redacted].

1. [redacted]

*** NOTE: This review contains proprietary and confidential information that should not be released to the public.***



Additionally, DMETS reviewed the — Atripla labels and labeling from a safety perspective. DMETS has identified the following areas of possible improvement, which may minimize the potential for user error.

A. CONTAINER LABEL (US Market and Access Program)

1. Increase the prominence of the established name to at least ½ the size of the proprietary name per 21 CFR 201.10(g)(2).
2. The product strength does not appear on the primary display panel of the container label. Add the strength prominently on the primary display panel as follows. Since — Atripla is a combination product, it should appear as follows:

600 mg/200 mg/300 mg

3. Once the strength has been added to the principle display panel, relocate the net quantity statement away from the strength in order to avoid confusion

4. Decrease the font or de-bold the net quantity statement (30 tablets) as is appears as prominent as the established name.
5. The statement on the export product: "Gilead Access Program For Export Only" may be easily overlooked because the — font appears very similar to the —font on the container label. Increase the prominence of this statement (e.g., revise the color of the font) as this statement is intended to differentiate the US product from the product to be exported. Increasing the prominence of this statement may help to minimize selection errors at the point of distribution.

B. CARTON LABELING (US Market and Access Program)

1. The — interferes with the readability of carton labeling. Revise the — so it does not interfere with the verbiage on the label.
2. See comments A1 through A5.
3. Relocate the "Each tablet contains..." statement on the primary display panel to the side panel in order to increase the amount of space on the primary display panel and to ease readability.

C. PACKAGE INSERT

At the top of the package insert, include the product strength following the established name.

D. PATIENT PACKAGE INSERT

No comment.

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§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

Appendix B
Atripla Prescription Study Results

Written Inpatient	Written Outpatient	Verbal
Altripta	Atriplen	Atripla
Atinpla	Atripla	Atripla
Atinpla	Atripla	atripla
Atripla	Atripla	Atripla
Atripla	Atripla	Atripla
Atripta	Atripla	Atripla
Atinpla	Atripla	Atripla
Attripta	Atripla	Atripla
Attripta	Atriplan	Atripla
Attripta	Atriplan	Atripla
Attripta	Atriplen	Atripla
Attripta	Atriplen	Atripta
Attripta	Atripler	Atroblock
Attripta	Atripler	Echerpla
Attripta	atriplu	HR Block
Attripta	Atropen	
Attripta	Atryplen	
Attripta	Attripla	
Attripta		
Attupla		

**This is a representation of an electronic record that was signed electronically and
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/s/

Felicia Duffy
6/16/2006 03:38:35 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
6/16/2006 03:46:16 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/16/2006 04:00:44 PM
DRUG SAFETY OFFICE REVIEWER

REQUEST FOR CONSULTATION

TO (Division/Office):
**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420
WO22, RM 4447**

FROM: **Marsha S. Holloman, BS Pharm, JD**
Regulatory Health Project Manager, Division of Anti-
viral Products, HFD-530, WO22, RM 6321

DATE
May 1, 2006

IND NO.
71,420

NDA NO.
21-937

TYPE OF DOCUMENT
Consult

DATE OF DOCUMENT
May 1, 2006

NAME OF DRUG
Efavirenz/Emtricitabine/Ten
ofovir DF fixed-dose
combination product

PRIORITY CONSIDERATION
Yes - Expedited Review
(8 weeks)

CLASSIFICATION OF DRUG
7030140

DESIRED COMPLETION DATE
June 19, 2006

NAME OF FIRM: **Gilead Sciences/Bristol-Myers Squibb**

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- 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

- DISSOLUTION
 BIOAVAILABILITY STUDIES
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
 PROTOCOL-BIOPHARMACEUTICS
 IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
 CASE REPORTS OF SPECIFIC REACTIONS (List below)
 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
 SUMMARY OF ADVERSE EXPERIENCE
 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: I am sending the electronic NDA labeling (PI, PPI, Container and Carton Labels) submitted May 1, 2006 via email. I will also deliver a paper copy to you. Please let me know if you have any questions.

PDUFA DATE: N/A

ATTACHMENTS: Draft Package Insert, Container and Carton Labels

CC: Archival IND/NDA IND 71,420/NDA 21-937

HFD-530/Division File

HFD-530/RPM

HFD-530/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER
// Marsha S. Holloman, BS Pharm, JD

METHOD OF DELIVERY (Check one)

DFS ONLY

MAIL

HAND

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

/s/

Marsha Holloman

6/16/2006 03:25:24 PM

— Atripla Tradename consult



MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-937

Drug: efavirenz/emtricitabine/tenofovir disoproxil fumarate tablets

Date: June 14, 2006

To: Pamela S. Danagher, MS, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

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

Through: Scott Proestel, MD, Medical Officer
Narayana Battula, PhD, Microbiologist
Jennifer DiGiacinto, Pharm D, Clinical Pharmacologist

Concur: Katherine A. Laessig, MD, Medical Team Leader
Julian J. O'Rear, PhD, Microbiology Team Leader
Kellie S. Reynolds, Pharm D, Clinical Pharmacology Team Leader

Subject: FDA REVISED DRAFT LABELING CHANGES, Version 1

Reference is made to your new drug application (NDA) 21-937 for efavirenz/emtricitabine/tenofovir disoproxil fumarate submitted April 25, 2006, and received April 26, 2006.

We have the changes in your revised draft labeling starting on page 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.

I

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_ § 552(b)(4) Trade Secret / Confidential

_ § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-937

Gilead Sciences, Inc.
Attention: Pamela S. Danagher, MS
Associate Director
Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Danagher:

Please refer to your April 25, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg fixed-dose combination tablet.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on May 31, 2006, in accordance with 21 CFR 314.101(a).

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.

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

Sincerely,

(An approved electronic signature is present.)

Anthony W. DeCicco, RPh
CAPT, USPHS
Chief, Project Management Staff
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Research and Evaluation

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

/s/

Tony DeCicco
6/1/2006 03:53:02 PM

Module 1.3a

**Form FDA 356h item 19
Financial Information**

One clinical trial submitted with this application meets the definition of a covered clinical trial under 21 CFR 54.

- Study GS-US-177-0105, A Phase 1 Pharmacokinetic Study in Healthy Subjects to Evaluate the Bioequivalence of a Fixed-dose Triple Combination Tablet of Efavirenz, Emtricitabine, and Tenofovir Disoproxil Fumarate Compared With the Concurrent Administration of the Individual Dosage Forms.

A completed Form FDA 3454 attesting to the absence of financial interests and arrangements described in 21 CFR 54.5(a)(3) for the Investigators participating in study GS-US-177-0105 is provided.

**APPEARS THIS WAY
ON ORIGINAL**

CONFIDENTIAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Martine Kraus, Ph.D.		TITLE Director, Regulatory Affairs	
FIRM / ORGANIZATION Gilead Sciences, Inc.			
SIGNATURE <i>Martine Kraus</i>		DATE March 29, 2006	

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: June 16, 2006

To: Pamela Danagher	From: Marsha Holloman
Company: Gilead Sciences, Inc	Title: Regulatory Health Project Manager, HFD-530
Fax number: 650-522-5489	Fax number: 301-796-8993
Phone number: 650-522-6395	Phone number: 301-796-0731
Subject: NDA 21-937 – FDA Revised Draft Labeling Changes, Version 1	

Total no. of pages including cover: 51

Comments: 

Document to be mailed: YES NO

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/s/

Marsha Holloman
6/21/2006 01:55:17 PM
CSO

This facsimile was sent to GSI Friday, June 16, 2006.

Kathrine Laessig
6/23/2006 02:12:15 PM
MEDICAL OFFICER



NDA 21-937

NDA ACKNOWLEDGMENT

Gilead Sciences, Inc
Attn: Pamela S. Danagher, MD
Associate Director
Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Danagher:

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:	Efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg fixed-dose combination
Review Priority Classification:	Priority (P)
Date of Application:	April 25, 2006
Date of Receipt:	April 26, 2006
Our Reference Number:	NDA 21-937

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 24, 2006 in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be October 26, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are deferring submission of your pediatric studies until review of this NDA is completed.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. Please note that

NDA 21-937

Page 2

satisfaction of the requirements in section 2 of the Pediatric Research Equity Act alone may not qualify you for pediatric exclusivity.

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

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

If you have any questions, call Marsha Holloman, Regulatory Health Project Manager, at (301) 796-0741.

Sincerely,

Anthony W. DeCicco, RPh

Anthony W. DeCicco, RPh
CAPT, USPHS
Chief, Project Management Staff
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Tony DeCicco
5/19/2006 01:34:54 PM

DSI CONSULT: Request for Clinical Inspections

Date: May 10, 2006

To: Martin K. Yau, PhD, DSI/GCPBB, HFD-48
Ct Viswanathan, PhD, DSI/GCPBB, HFD-48

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager
Division of Antiviral Drug Products (DAVP HFD-530)

Subject: Request for Clinical Site Inspections

NDA 21-937
Gilead Sciences, Inc
(efavirenz 600 mg/emtricitabine 200mg/tenofovir disoproxil fumarate 300 mg) Tablets

Protocol/Site Identification:

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

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Clinical Site: 	GS-US-177-0105	48	treatment of HIV-1
BioAnalytical Site: Gilead Sciences BioAnalytical Laboratory 4 University Place 4611 University Drive Durham, NC 27707 919-493-5980 - phone 919-493-5925 - fax	GS-US-177-0105	48	treatment of HIV-1

Goal Date for Completion: June 19, 2006

We request that the inspections be performed and the Inspection Summary Results be provided by June 19, 2006. We intend to issue an action letter on this application by June 23, 2006.

Should you require any additional information, please contact Marsha S. Holloman at 301-796-0731 or marsha.holloman@fda.hhs.gov.

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Marsha Holloman

5/17/2006 10:36:10 AM

Review package delivered to DSI at Metro Park North

1 on May 11, 2006



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: May 1, 2006

To: Peter Karlton	From: Marsha Holloman
Company: Gilead Sciences, Inc	Title: Regulatory Health Project Manager, HFD-530
Fax number: 650-522-5489	Fax number: 301-796-8993
Phone number: 650-522-5305	Phone number: 301-796-0731
Subject: NDA 21-937: CMC REQUEST FOR INFORMATION	

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-937
Drug: efavirenz/emtricitabine/tenofovir disoproxil fumarate tablets
Date: May 1, 2006
To: Peter Karlton, PhD, Director, Global Regulatory Affairs, CMC
Sponsor: Gilead Sciences, Inc
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) 21-937 for efavirenz/emtricitabine/tenofovir disoproxil fumarate submitted April 25, 2006, and received April 26, 2006.

Please indicate if you intend to place any tablets in the alternate trade dress for export on stability. If so, please indicate the stability testing protocol that you intend to use and the means by which the data will be reported.

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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/s/

Marsha Holloman
5/1/2006 04:04:26 PM
CSO

Norman Schmuff
5/3/2006 06:58:35 AM
CHEMIST



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: April 10, 2006

To: Peter Karlton	From: Marsha Holloman
Company: Gilead Sciences, Inc	Title: Regulatory Health Project Manager, HFD-530
Fax number: 650-522-5489	Fax number: 301-796-8993
Phone number: 650-522-5305	Phone number: 301-796-0731

Subject: NDA 21-937/Rolling Review, Presubmission, Tier 2: CMC REQUEST
FOR INFORMATION

Total no. of pages including cover: 4

Comments:

Document to be mailed: YES NO

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MEMORANDUM OF FACSIMILE CORRESPONDENCE

NDA: 21-937/Rolling Review, Presubmission, Tier 2

Drug: — (emtricitabine/tenofovir disoproxil fumarate/efavirenz)

Date: April 7, 2006

To: Peter Karlton, PhD, Director, Global Regulatory Affairs, CMC

Sponsor: Gilead Sciences, Inc

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

Through: George Lunn, PhD, Chemist

Concur: Stephen P. Miller, PhD, CMC Team Leader
Norman Schmuff, PhD, CMC Branch Chief

Subject: CMC REQUEST FOR FURTHER INFORMATION

Reference is made to your rolling review, presubmission, tier 2 dated March 24 and received March 27, 2006.

We have the following comments and recommendations:

1. Please provide a narrative description of the tablet manufacturing process that specifies actual quantities, times, temperatures, etc. Also, please provide a description of the — process in more detail.
2. Please consider changing the product test and acceptance limit of "NMT a total of — TDF-related degradation products" to "NMT a total of — TDF-related and unidentified degradation products".
3. In the manufacturing process schematic, —
4. In the text (3.2.P.3.3, p. 8), — is monitored. No acceptance criterion or typical values are provided for — Please provide an acceptance criterion and the

values from the validation batches or a justification for not providing these data.
5. In the text (3.2.P.3.3, p. 8), the _____ measurement is " _____"
_____ and the _____ is also indicated on the
schematic. Please provide an explanation of how _____ is set.

We are providing the above information via telephone facsimile for your convenience.
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/s/

Marsha Holloman
4/7/2006 04:07:42 PM
CSO

This facsimile will be sent to Gilead following final
sign-off.

Norman Schmuff
4/10/2006 01:24:55 PM
CHEMIST

Module 1.3a

User Fee Coversheet

The original signed Prescription Drug User Fee Coversheet (Form 3397) along with a copy of the submission of the User Fee are provided in this item. The User Fee identification number for NDA 21-937 is PD3006280.

**APPEARS THIS WAY
ON ORIGINAL**



27 December 2005

Food and Drug Administration (360909)
Mellon Client Service Center – Room 670
500 Ross Street
Pittsburgh, PA 15262-0001

**Subject: NDA 21-937 Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate
Fixed-Dose Combination Tablets
User Fee Payment – Original NDA, ID# PD3006280**

Gilead Sciences (Gilead) hereby submits the user fee payment in the amount of \$ 383,700.00 for NDA 21-937, an original NDA not requiring clinical data for approval. The user fee ID number assigned to this NDA is PD3006280.

Please contact me at 650-522-6395 or via facsimile at 650-522-5489 if you have any questions or need additional information. You may also contact Martine Kraus, Ph.D., Director, Regulatory Affairs, at 650-522-5722. We share the same facsimile number.

Sincerely,

Pamela Danagher
Associate Director, Regulatory Affairs

Enclosures: 1 original with check

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: http://www.fda.gov/cder/pdufa/default.htm		
1. APPLICANT'S NAME AND ADDRESS GILEAD SCIENCES INC Pamela Danagher Gilead Sciences, Inc. 333 Lakeside Drive Foster City CA 94404 US		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 21-937
2. TELEPHONE NUMBER 650-522-6395		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input type="checkbox"/> YES <input checked="" 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 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 efavirenz/emtricitabine/tenofovir disoproxil fumarate		6. USER FEE I.D. NUMBER PD3006280
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 		TITLE Assoc. Dir. Regulatory Affairs DATE December 27, '05
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$383,700.00		
Form FDA 3397 (12/03)		

(IBE PRMT CLOSE G) (Print Cover sheet)

Gilead Sciences, Inc.

Efavirenz-Emtricitabine-Tenofovir Disoproxil Fumarate

THIS CHECK IS VOID WITHOUT A RED & BLUE BORDER AND BACKGROUND PLUS A KNIGHT & FINGERPRINT WATERMARK ON THE BACK - HOLD AT ANGLE TO VIEW

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404
Tel: 650/574-3000

WELLS FARGO BANK
400 HAMILTON AVENUE
PALO ALTO, CA 94301
11-24
1201(B)

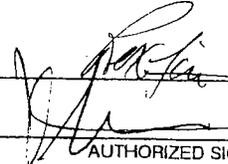
CHECK NO. 00138211

DATE	AMOUNT
11004655 12/15/05	\$\$\$383,700.00

PAY

THREE HUNDRED EIGHTY THREE THOUSAND SEVEN HUNDRED AND 00/100 *****

TO THE ORDER OF: U.S. FOOD & DRUG ADMINISTRATION
P.O. BOX 360909
500 ROSS STREET, ROOM 670
Pittsburgh, PA 15251-6909



AUTHORIZED SIGNATURES

SIGNATURE AREA CONTAINS A KNIGHT & FINGERPRINT CHECK WORDING

⑈00138211⑈ ⑆21000248⑆4277 157632⑈

ABSENCE OF PINK U.S. PATENT NUMBERS UNDER SIGNATURE INDICATES CHECK IS FRAUDULENT PATENT NUMBERS ARE PRINTED WITH HEAT SENSITIVE INK & WILL DISAPPEAR WHEN BLOWING OR RUBBING

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

CHECK NO. - 00138211
CHECK DATE - 12/15/05

DETACH STATEMENT BEFORE DEPOSITING

Stub 1 of 1

INVOICE NUMBER	DATE	DESCRIPTION	GROSS AMOUNT	DEDUCTIONS	AMOUNT PAID
CKRQ120605	120605	USER FEE PD3006280 NDA21-937	383700.00		383,700.00
			383700.00		383,700.00

FY 2005 and NEW FY 2006 USER FEE RATES

Effective October 1, 2005, applicants must send the full Fiscal Year 2006 application fee at the time of submission for fee liable applications and supplements. The fees for the appropriate fiscal year, announced in the Federal Register are:

Fiscal Year	FY 2006 Oct. 1, 2005 – Sep. 30, 2006	FY 2005 Oct. 1, 2004 – Sep. 30, 2005
Application/Clinical Data Required....	\$767,400	\$ 672,000
Application/No Clinical Data Required....	\$383,700	\$ 336,000
Supplement/Clinical Data Required.....	\$383,700	\$ 336,000
Federal Register Date	August 1, 2005	August 2, 2004

An application should be accepted for filing if a fee is submitted, even if the amount of the fee is incorrect (unless the company is in arrears). The firm should be contacted and told to promptly remit the balance (with the same user fee ID number).

[Alert the user fee staff if this should occur.]

New applications or supplements from companies on the *arrears list* (or from affiliates of companies on the arrears list) should NOT be accepted for filing per MAPP 6050.1. They should be UNd on the day they are received no matter whether they have paid the correct application fee or not.

Applications from companies that are not on the arrears list and for which NO FEE has been received by FDA within 5 days of the receipt date of the application should not be accepted for filing per MAPP 6050.1. They should be UNd on day 5 after they are received.

If you have any questions, please contact the user fee staff (301-594-2041).

APPLICATION PAYMENT

J

 1 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

REQUEST FOR CONSULTATION

(Division/Office):

**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420
WO22, RM 4447**

FROM: Marsha S. Holloman, BS Pharm, JD
Regulatory Health Project Manager, Division of Anti-
viral Products, HFD-530, WO22, RM 6321

DATE December 12, 2005	IND NO. 71420	NDA NO.	TYPE OF DOCUMENT Consult	DATE OF DOCUMENT December 12, 2005
NAME OF DRUG Efavirenz/Emtricitabine/Ten ofovir DF fixed-dose combination product		PRIORITY CONSIDERATION Yes	CLASSIFICATION OF DRUG 7030140	DESIRED COMPLETION DATE February 12, 2006

NAME OF FIRM: Gilead Sciences/Bristol-Myers Squibb

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- 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

- DISSOLUTION
 BIOAVAILABILITY STUDIES
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
 PROTOCOL-BIOPHARMACEUTICS
 IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
 CASE REPORTS OF SPECIFIC REACTIONS (List below)
 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
 SUMMARY OF ADVERSE EXPERIENCE
 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please let me know if you have any questions. Gilead sent a copy to Carol Holquist. The NDA for this product will be submitted later this month or early in January 2006. PI, PPI, Container and Carton Labels will be submitted with the NDA. Electronic version of this submission sent separately.

PDUFA DATE: N/A

ATTACHMENTS: Draft Package Insert, Container and Carton Labels

CC: Archival IND/NDA IND 71420

FD-530/Division File

HFD-530/RPM

HFD-530/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER

// Marsha S. Holloman, BS Pharm, JD

METHOD OF DELIVERY (Check one)

DFS ONLY

MAIL

HAND

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/s/

Marsha Holloman

12/12/2005 01:51:35 PM

Electronic copy of SN-023 DFSed separately.



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: August 18, 2005

To: Pamela Danagher	From: Kenny Shade, JD, BSN Division of Antiviral Drug Products
Company: Gilead Sciences	Title: Regulatory Project Manager
Fax number: 650-522-5489	Fax number: 301-827-2471
Phone number: 650-522-5722	Phone number: 301-827-2335

Subject: Reviewer comments to IND 71,420/SN015

Total number of pages including cover: 2

Comments:

Document to be mailed: • YES NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

Date: August 18, 2005
IND: 71,420/SN-015
Drug: Efavirenz/Emtricitabine/Tenofovir DF
To: Pamela Danagher, MS
Sponsor: Gilead Science
From: Kenny Shade, JD, BSN
Through: Russell Fleischer, PA-C, MPH
Concurrence: Katherine Laessig, M.D.
Subject: Clinical Comments

The following comments are being conveyed to you on behalf of the review team. Please refer to your IND 71,420/ SN015 submitted on August 4, 2005.

1. The protocol and Investigator Brochure should clearly describe the results of the previous bioequivalence studies as well as the differences between formulations.

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

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/s/

Kenny Shade
8/18/2005 02:19:45 PM
CSO

Kathrine Laessig
8/22/2005 03:06:13 PM
MEDICAL OFFICER



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV
Division of Antiviral Drug Products**

FACSIMILE TRANSMITTAL SHEET

DATE: July 18, 2005

To: Pamela Danagher, M.Sc.,	From: Jeff D. O'Neill, ACRN
Company: Gilead Sciences, Inc.	Title: Regulatory Health Project Manager, HFD-530
Fax number: 650-522-5489	Fax number: 301-827-2510
Phone number: 650-522-5722	Phone number: 301-827-2362
Subject: Clinical comments regarding IND 71,420, submission number 013.	

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES NO

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MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: 71-420

Drug: efavirenz/emtricitabine/tenofovir DF

Date: July 18, 2005

To: Pamela Danagher, M.Sc., Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc.

From: Jeff D. O'Neill, ACRN, Regulatory Health Project Manager, DAVDP

Through: Russ Fleischer, PA-C, MPH, Clinical Reviewer, DAVDP

Concurrence: Jeffrey S. Murray, MD, MPH, Deputy Division Director, DAVDP
Katherine Laessig, MD, Medical Officer Team Leader, DAVDP

Subject: Comments regarding your IND 71,420, SN 013, for the combination tablet efavirenz/emtricitabine/tenofovir DF.

Please refer to your IND 71,420 for the combination tablet efavirenz/emtricitabine/tenofovir DF. The following responses are provided by the review team:

1. We find your proposed plan for the rolling NDA submission acceptable.
2. Regarding your request for a waiver of the user fee we have consulted with our User Fee Team. The conclusion is that waiving the user fee in this case is not appropriate because your proposed application does not meet all three criteria in the bulleted list at the end of section A of the Draft Guidance User Fee Waivers for FDC and Co-Packaged HIV Drugs for PEPFAR. The introduction to that list refers to the potential for "*waiver of PDUFA product and establishment user fees under the barrier to innovation waiver provision provided the applicant meets all of the following*" and the second criterion listed thereafter is "The applicant will only receive tentative approval in the United States for the product because, for example, it cannot market the product in the United States because of patents or exclusivity on the innovator product."
3. Regarding your proposal to include data from Study GS-01-934 in the proposed Package Insert for this product, we will not incorporate the data until :

IND 71,420
SN 013
July 18, 2005

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/s/

Jeff O'Neill
7/18/05 11:05:58 AM
CSO

Faxed comments IND 71,420 SN 013. Hard copy sign-off
7/18/05

Jeffrey Murray
7/18/05 01:49:13 PM
MEDICAL OFFICER



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: May 25, 2005

To: Pamela Danagher, M.Sc.,	From: Jeff D. O'Neill, ACRN
Company: Gilead Sciences, Inc.	Title: Regulatory Health Project Manager, HFD-530
Fax number: 650-522-5489	Fax number: 301-827-2510
Phone number: 650-522-5722	Phone number: 301-827-2362
Subject: Clinical comments regarding IND 71,420, submission number 011.	

Total no. of pages including cover: 2

Comments:

Document to be mailed: YES NO

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MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: 71-420

Drug: efavirenz/emtricitabine/tenofovir DF

Date: May 25, 2005

To: Pamela Danagher, M.Sc., Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc.

From: Jeff D. O'Neill, ACRN, Regulatory Health Project Manager, DAVDP

Through: George Lunn, Ph.D., Chemistry Reviewer, DAVDP

Concurrence: Stephen P. Miller, Ph.D., Chemistry Team Leader, DAVDP

Subject: Clinical comments regarding your IND 71,420, SN 011, for the combination tablet efavirenz/emtricitabine/tenofovir DF.

Please refer to your IND 71,420 for the combination tablet efavirenz/emtricitabine/tenofovir DF. The following clinical comments are provided on behalf of Russ Fleischer, PA-C, MPH:

- The protocol and Investigator Brochure should clearly describe the results of the original bioequivalence study as well as the differences between formulations.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 71,420

Gilead Sciences, Inc.
Attention: Martine Kraus, Ph.D.
Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Kraus:

Please refer to the meeting between representatives of your firm, Bristol-Myers Squibb, and FDA on April 18, 2005. The purpose of this Pre-NDA meeting was to discuss the format and content of your planned NDA for the fixed dose combination efavirenz, emtricitabine, and tenofovir disoproxil fumarate.

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

If you have any questions, call Jeff O'Neill, ACRN, Regulatory Health Project Manager, at 301-827-2362.

Sincerely,

{See appended electronic signature page}

Deb Birnkrant, MD
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure

RECORD OF INDUSTRY MEETING

Date: April 18, 2005

IND: 71,420

Sponsor: Gilead Sciences, Inc. (Representative for joint venture with Bristol-Myers Squibb)

Drug: efavirenz / emtricitabine / tenofovir disoproxil fumarate.

Indication: Treatment of HIV

FDA Attendees:

Mark Goldberger, MD, MPH, Director, Office of Drug Evaluation IV (ODEIV)
Edward Cox, MD, Deputy Director, ODEIV
Debra Birnkrant, MD, Director, Division of Antiviral Drug Products (DAVDP)
Jeffrey S. Murray, MD, MPH, Deputy Division Director, DAVDP
Katherine A. Laessig, MD, Medical Team Leader, DAVDP
Russ Fleischer, PA-C, MPH, Senior Clinical Analyst, DAVDP
Linda L. Lewis, MD, Medical Officer, DAVDP
Stephen Miller, PhD, Chemistry Team Leader, DAVDP
George Lunn, PhD, Chemistry Reviewer, DAVDP
Jennifer DiGiacinto, PharmD, Clinical Pharmacologist, DAVDP
Narayana Battula, PhD, Microbiologist, DAVDP
K.M. Wu, PhD, Pharmacologist, DAVDP
David Roeder, Assoc. Director, Regulatory Affairs, ODEIV
Virginia Behr, Chief, Project Management Staff, DAVDP
Jeff D. O'Neill, ACRN, Regulatory Health Project Manager, DAVDP

Bristol-Myers Squibb Attendees:

Laura Bessen, MD, VP, Global Medical Affairs, Virology
Lori Devore, BS, Associate Director, Global Regulatory Affairs
Margo Heath-Chiozzi, MD, Executive Director, Global Regulatory Affairs
Sanjeev Kaul, PhD, Director, Clinical Discovery
Amy Straub, Senior Project Manager, Project Planning and Management

Gilead Sciences Attendees:

Norbert Bischofberger, PhD, Executive VP, Research and Development
Andrew Cheng, PhD, MD, Senior Director, Clinical Research
Martine Kraus, PhD, Director, Regulatory Affairs
Michael Miller, PhD, Senior Director, Clinical Virology

Subject: Pre-NDA Industry Meeting

Background:

On December 27, 2004 an Investigational New Drug Application (IND) was received from Gilead Sciences Inc. (GSI), acting as representative for a joint venture with Bristol-Myers Squibb (BMS), for the combination product of efavirenz / emtricitabine / tenofovir disoproxil fumarate for the treatment of HIV. GSI was notified January 19, 2005 that the IND was safe to proceed.

On April 11, 2005 a meeting between representatives of GSI, BMS, and the FDA was held to discuss the CMC development plan and stability data to be included in the planned NDA submission.

The Sponsor's March 7, 2005 submission, received March 8, 2005, contained a Pre-NDA meeting request with clinical, preclinical, and regulatory questions for discussion.

Discussion:

In their introductory presentation, the Sponsor proposed that the NDA submission include both the final report for the bioequivalence Study GS-US-177-0101 and a 48-Week interim report for the clinical efficacy and safety Study GS-01-934. They proposed cross-referencing the approved NDAs 20-972 and 21-360 for efavirenz, NDA 21-500 for emtricitabine, and NDA 21-356 for tenofovir disoproxil fumarate.

In addition, the Sponsor presented a back-up formulation for the fixed-dose combination following preliminary data indicating that Study GS-US-177-0101 may not demonstrate bioequivalence of the fixed-dose to its individual components. Should they need to use the back-up formulation, the NDA, with stability data, will be submitted by the end of November instead of in August as originally planned.

The Sponsor proposed submitting information to the NDA as part of a Rolling Review. This was previously discussed during the April 11, 2005 CMC Pre-NDA meeting. The Sponsor proposed submitting the 48-week report for Study GS-01-934 in May, 2005. The proposal for a trade name and the final study report for GS-US-177-0101 will be submitted in June and August respectively. Lastly, submission of stability data will begin the regulatory review clock for the NDA.

After the presentation, the following questions were discussed in the order listed. The Sponsor's questions and comments are in bold type and the Division of Antiviral Drug Product's comments are in normal type.

Clinical

- 1. Does the Agency concur that the described submission of a dossier based on data from bioequivalence study GS-US-177-0101 and 48-week data from study GS-01-934 supports an evaluable NDA for the proposed indication?**

The bioequivalence and stability data will be sufficient to support the planned NDA submission. As stated in our draft guidance for Industry on Fixed Dose and Co-Packaged Drug Products for Treatment of HIV, the combination of efavirenz, emtricitabine and tenofovir DF is supported by current clinical data for a fixed-dose combination product.

Once the NDA for the combination is approved, what is your timeline for making the product available in the United States and the countries identified by the President's Emergency Plan for AIDS Relief (PEPFAR)?

Because Merck owns the rights to efavirenz in the PEPFAR countries, an agreement will need to be reached between Merck, BMS, and GSI before the fixed-dose combination product can be made available there. While this agreement may not be completed by the time of submission of the NDA, it is seen as an incentive for the companies to work together to make the product available to these countries.

The Draft Guidance for Industry on Fixed Dose Combination and Co-Packaged Drug Products for Treatment of HIV, offers an expedited review so these products can be made available to the PEPFAR countries. However, we realize that we have limited knowledge of the timelines following approval of alternate trade dress products for export to the PEPFAR countries (such as —). Therefore, we hope that an expedited review will serve as an incentive for the drug industry to develop similar products for this purpose.

The Sponsor will update the Division on their ongoing negotiations with Merck at the time their bioequivalence study is submitted.

- 2. The companies do not plan to summarize in Module 2 or include in Module 5 of the NDA any data that have been previously submitted. It is proposed that only data from Study GS-US-177-0101 and Study GS-01-934 will be summarized in Module 2 and their respective reports provided in Module 5. Does the agency concur with this proposal?**

The Division agrees with this proposal.

- 3. It is proposed not to provide an NDA Safety Update during the review of the NDA for the triple combination product as (1) individual components of product are approved / long-term safety data are included in respective PIs, (2) additional safety data (> 48 weeks) from study GS-01-934 are unlikely to alter safety conclusions reached based on 48-week data from study GS-01-934 and data from study GS-99-903, (3) SAE reports from ongoing studies and spontaneous reports are reviewed in PSURs for individual components of the product. Does the Agency agree with this proposal?**

The Division agrees with this proposal.

- 4. It is planned to request for the triple combination product a full waiver (all pediatric age groups) of the pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA). The request will be based on the following justification: (1) fixed-dose combination drug products do not allow for proper dose modification of their individual components and hence are not age-appropriate formulations for this populations, (2) studies**

to determine the safety, efficacy and pharmacokinetics of the individual components in pediatric patients across all age groups are currently under way and are subject to previously agreed upon Written Requests. The ongoing pediatric studies will provide dosing information for use of the individual components in children who require dose modification. (3) These studies will additionally identify the minimum body weights (or ages) that are sufficient to permit adult dosing of each component. Older children whose body weights allow for adult dosing with all three of the individual drugs and who can swallow an oral solid dosing formulation will be able to use the triple combination product safely because this product will be bioequivalent to its individual components. Does the Agency agree with this proposal?

The Division will defer this requirement until pediatric data for the individual components are submitted and reviewed. At that time we will determine whether pediatric studies will be required for the fixed dose combination. The Division may want to see studies in adolescents, and suggests that a combination pill with lower doses for pediatric patients may also be possible.

- 5. In section eight of the background package is a proposal for reporting of adverse events for the fixed dose combination product and the individual components thereof in accordance with 21 CFR 312.32 and 21 CFR 314.80. Gilead will submit spontaneous reports identifying any or all three components as suspect drug(s) to the NDA for the fixed dose triple combination product with a copy to BMS; reports from studies conducted under IND 71,420 will be submitted to the IND and NDA for the fixed dose combination product. The reports will not be concurrently submitted to the NDAs or INDs for the individual components of the triple combination product (i.e. NDA/IND for efavirenz, emtricitabine, or tenofovir disoproxil fumarate). Does the Agency agree with this proposal?**

The Division agrees with the proposal for reporting of adverse events. We will need further discussions regarding the content of the Periodic Safety Update Report (PSUR) for the combination product and reports for the individual component's NDAs, as well as their respective Annual Reports. The Sponsor will submit a proposal regarding the proposed reporting following approval of the fixed dose combination NDA.

Pre-clinical

- 6. It is proposed that available data from two-drug combination *in vitro* studies of efavirenz/emtricitabine, efavirenz/tenofovir and emtricitabine/tenofovir adequately document the lack of antagonism between the components of the triple combination product. Does the agency concur?**

The Division agrees that since there have been no interactions observed, no additional studies are needed.

- 7. It is proposed that clinical virology data from study GS-01-934 in conjunction with available data from *in vitro* resistance selection experiments conducted with the individual components as well as the combination of emtricitabine and tenofovir adequately characterize the resistance profile of the triple combination product. Does the Agency agree with this assessment?**

Since the data from Study 934 will not be submitted as a part of the combination NDA, this question is not relevant.

- 8. It is proposed that the NDA for the fixed-dose combination product cross-refer for all pre-clinical studies to the NDAs of the individual components of the product. We do not plan to summarize in Module 2 or include in Module 4 of the NDA any data that have been previously submitted. Does the Agency concur with this proposal?**

The Division requests that the Sponsor summarize in Modules 2.4 and 2.6 the data from *in vitro* studies and clinical virology data. The division agrees that the other data for Modules 2.4 and 2.6 can be supplied by cross-reference to the NDAs for the individual products. Module 4 can completely cross-reference the NDAs for the individual products.

In addition, we have concerns that some patients may have difficulty swallowing a pill of this size. Therefore, we would like an assessment of subject's ability to swallow for the combination tablet in Module 2.3, and any data supporting this in Module 3.

Regulatory

- 9. Does the Agency concur that the NDA for the fixed dose combination product qualifies for priority review? Does the Agency expect, as suggested in FDA guidance (May 2004), this NDA to be reviewed within an even shorter timeframe (<6 months)?**

The Division agrees that the fixed dose combination qualifies for priority review. The basis for this decision is because we believe the combination meets the criteria as outlined in the Draft Guidance for Industry for Fixed Dose Combination and Co-Packaged Drug Products for Treatment of HIV. As stated in the guidance, "The goal of having FDC or co-packaged HIV products is to simplify regimens to allow for easier distribution and improved patient adherence, particularly in resource poor settings." In addition, the combination of efavirenz / emtricitabine / tenofovir disoproxil fumarate is already listed in Attachment B of the guidance as an example of a combination for treatment of HIV supported by current clinical data for FDC/Co-Packaging and an alternative trade dress of the combination for export to resource poor settings which will be reviewed as a part of the planned NDA submission. Because the product will be reviewed under the FDC/Co-Packaged Draft Guidance, the Division intends to review the application with a six-week review clock (once the final piece of the Rolling Review is submitted).

The Division cautions the Sponsor that Priority Review is being granted based on the referenced guidance and not due to meeting an unmet medical need or increased adherence, which has not been proven. The Sponsor was advised to keep this in mind when releasing statements or promoting this product.

The Sponsor notes that this application will be reviewed under subpart H regulations and therefore, DDMAC will review all announcements and marketing materials.

- 10. Does the Agency agree with the Company's assessment that the fixed-dose combination product qualifies for Fast Track Designation? Does the Agency agree with the Company's submission plan and assessment that an early submission of the report of study GS-01-934 to the NDA for the fixed-dose combination product may allow the NDA to be reviewed**

within a shorter timeframe?

The Division agrees that the combination product should qualify for Fast Track Designation. In order to review the NDA in a six-week period, a Rolling Review will be necessary. The Sponsor should submit information on the manufacturing sites and clinical study and bio-analytical laboratory sites as soon as the information is available.

It is possible to include the 934 data in the PI for the combination if the NDA is submitted later than expected.

11. A proposed trade name for the fixed-dose combination product could be made available by June 2005. Would the Agency be amenable to accepting and working with the Division of Medication Errors and Technical Support to initiate the review of the proposed trade name prior to submission of all elements of the NDA?

The Division supports the Sponsor's plan to submit a proposed trade name in June, 2005, and strongly encourages that more than one proposed trade name be submitted in order to expedite the review process.

12. We plan to submit the application in the format of the CTD. A draft table of contents is provided in the pre-meeting information package. Does the Agency concur with the described table of contents?

Yes, the Division agrees with the Sponsor's proposed format.

The Sponsor inquired about the fees that will be assessed for the Traditional Approval Supplements for NDA 21-356 and NDA 21-752.

The Division believes it should only be one half of a user fee (standard fee for an efficacy supplement), and will work with the Sponsor and the User Fee group in order to identify the correct fees for these supplements.

Action Items

- The Sponsor will submit information on the manufacturing sites and clinical study and bio-analytical laboratory sites as soon as possible.

- The Sponsor will submit the outcome of the bioequivalence Study GS-US-177-0101 (May, 2005).
- The Sponsor will provide the Division with an update on their negotiations with Merck to make an alternate trade dress of the fixed dose combination available to the PEPFAR countries (May, 2005).
- The Division will work with the Sponsor to determine the correct User Fees associated with the submission of the Traditional Approval Supplements for NDA 21-356 and NDA 21-752.
- The Division will provide official meeting minutes.

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/s/

Jeffrey Murray
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IND 71,420

Martine Kraus, Ph.D.
Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Kraus:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for efavirenz / emtricitabine / tenofovir disoproxil fumarate combination tablets.

We also refer to your March 18, 2005 request for fast track designation.

We have reviewed your request and have concluded that it meets the criteria for fast track designation. Therefore, we are designating efavirenz / emtricitabine / tenofovir disoproxil fumarate combination tablets for the Treatment of HIV-1 infection as a fast track product.

We are granting fast track designation for the following reasons:

1. The fixed dose combination of efavirenz / emtricitabine / tenofovir disoproxil fumarate tablets for the treatment of HIV is considered to benefit the public health because making it available in the fifteen countries that are targets of the PEPFAR program will have a significant impact on the global efforts to treat HIV.
2. As stated in the Guidance for Fixed Dose Combination and Co-Packaged Drug Products for Treatment of HIV, "The goal of having FDC or co-packaged HIV products is to simplify regimens to allow for easier distribution and improved patient adherence, particularly in resource poor settings." Of note, the combination of efavirenz / emtricitabine / tenofovir disoproxil fumarate is already listed in Attachment B of the guidance as an example of a combination for treatment of HIV supported by current clinical data for FDC/Co-Packaging. Further, you have proposed an alternative trade dress of the combination for export to resource poor settings which will be reviewed as a part of your planned NDA submission.

We have also reviewed your request for step-wise submission of sections of an NDA application for the indication described above and have concluded that the proposed plan, as discussed in the Pre-NDA meeting held April 18, 2005, for its step-wise submission is acceptable.

If you pursue a clinical development program that does not support use of efavirenz / emtricitabine / tenofovir disoproxil fumarate combination tablets for the Treatment of HIV-1 infection, we will not review the application or accept step-wise submission of sections of an NDA a supplemental new drug application under the fast track program.

**APPEARS THIS WAY
ON ORIGINAL**

If you have any questions, call Jeff O'Neill, Regulatory Project Manager, at 301-827-2362.

Sincerely,

Debra Birnkrant, M.D.
Debra Birnkrant, M.D.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Debra Birnkrant
5/11/05 02:54:44 PM
IND 71,420



Food and Drug Administration
Rockville MD 20857

IND 71,420

Gilead Sciences, Inc.
Attention: Peter Karlton
Director, Global Regulatory Affairs, CMC
333 Lakeside Dr.
Foster City, CA 94404

Dear Mr. Karlton:

Please refer to the teleconference between representatives of your firm, Bristol-Myers Squibb, and FDA on April 11, 2005. The purpose of the Pre-NDA meeting was to discuss chemistry and manufacturing issues related to the planned NDA submission for the combination product efavirenz / emtricitabine / tenofovir DF.

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

If you have any questions, call Jeff O'Neill, Regulatory Health Project Manager, at 301-827-2362.

Sincerely,

{See appended electronic signature page}

Jeffrey Murray, MD, MPH
Deputy Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure

RECORD OF FDA TELECONFERENCE

Date of Meeting: April 11, 2005
IND: 71,420
Drug: efavirenz / emtricitabine / tenofovir disoproxil fumarate
Sponsor/Applicant: Gilead Sciences, Inc.
Indication: Treatment of HIV

Division of Antiviral Drug Products (DAVDP) Participants:

Jeffrey Murray, MD, MPH, Deputy Division Director, HFD-530
Stephen Miller, PhD, Chemistry Team Leader, HFD-530
George Lunn, PhD, Chemistry Reviewer, HFD-530
Katherine Laessig, MD, Medical Team Leader, HFD-530
Jennifer DiGiacinto, PharmD, Clinical Pharmacologist, HFD-530
Jeff D. O'Neill, ACRN, Regulatory Health Project Manager, HFD-530

Gilead Sciences Participants:

Dr. Norbert Bischofberger, Executive Vice President, R&D
Dr. Taiyin Yang, Vice President, Pharmaceutical Development and Manufacturing
Dr. Terry Dahl, Sr. Director, Formulation
Dr. Tom Weber, Sr. Director, Chemistry
Mr. Peter Karlton, Director, Global Regulatory Affairs, CMC
Dr. Martine Kraus, Director, Regulatory Affairs
Ms. Pam Danagher, Associate Director, Regulatory Affairs

Bristol-Myers Squibb Participants:

Dr. Robert Lipper, Vice President Biopharmaceutics
Dr. Margo Heath Chiozzi, Executive Director, Global Regulatory Science
Dr. Munir Hussain, Sr. Research Fellow, Pharmaceutics
Dr. Robert Jerzewski, Director, Pharmaceutics
Ms. Lori Devore, Associate Director, Global Regulatory Science
Dr. Kwame Obeng, Director, Global Regulatory Science CMC
Dr. Meena Rao, Manager, Global Regulatory Sciences CMC
Dr. Amy Straub, Sr. Project Manager, Project Management

Background	
<p>Gilead Sciences, acting on behalf of Bristol-Myers Squibb, submitted an IND for the combination product efavirenz / emtricitabine / tenofovir DF for the treatment of HIV dated December 23, 2004. In addition to development of a trade dress for distribution in the U.S., an alternative trade dress for export to developing countries is also being developed and reviewed as part of the IND. Gilead requested a Pre-NDA meeting in their submission dated March 1, 2005 and the background document was submitted March 4, 2005. The background document contained chemistry related information and questions regarding the drug development program for the combination product efavirenz / emtricitabine / tenofovir DF for the treatment of HIV. In addition, the background submission provided answers to chemistry questions contained in a facsimile from the Division dated February 1, 2005.</p>	
Objectives	
<p>A Pre-NDA meeting to discuss chemistry and manufacturing issues related to the planned NDA submission for the combination product efavirenz / emtricitabine / tenofovir DF.</p>	
Questions /Issues/Topics	Discussion Points /Conclusions
<p>1. Will the Agency accept a stability data package that provides — data from three primary stability batches at the time of filing?</p>	<p>DAVDP: Yes, for this type of product we feel that — data is acceptable.</p>
<p>2. Will the Agency consider establishing the expiry period of the EFV/FTC/TDF combination tablet based on confirmed equivalent stability at — under accelerated condition of the combination tablet with the stability of the individual products and the marketed FTC/TDF combination tablet?</p>	<p>DAVDP: We agree that establishment of the shelf life be based on comparative data. The Division requests that the NDA include — stability data at 25 deg C/80% RH and 50 deg C. This data will be useful in evaluating the analytical assay method and product stability under stress conditions. We also acknowledge your concerns that the product would significantly change in assay after a — at 50 deg C and will not include the requested — stability data in the overall assessment of the product's stability profile.</p> <p>Gilead/BMS: Will the additional stability data effect the labeling expiration date for the product?</p> <p>DAVDP: Given that each country will have their own requirements for labeling and storage statements, if approved, we will most likely state approval but not indicate the specific zones for which they are approved. Based on the stability data, we will set expiration dating period(s) for the proposed storage statement(s). We do not anticipate that the 50 deg C data would adversely affect an expiration dating period for storage at USP controlled room temperature.</p> <p>Gilead/BMS: The Sponsor agrees to conduct the — stability testing and will also include a statement that the product should be stored in the original container to discourage distribution in alternative packaging (e.g. Plastic bags).</p> <p>DAVDP: The Division also requests that a document containing summaries/interpretation of stability data be included in the NDA submission for the purpose of public distribution.</p>

<p>3. NDA Submission and Content</p>	<p>DAVDP: The Division encourages a rolling NDA and requests that the following be submitted as soon as possible:</p> <ul style="list-style-type: none"> • Trade name. • List of manufacturing sites for API and drug product. • List of sites where clinical sample laboratory analysis is performed and sites used in the clinical studies. • Information on the clinical site name and lab site for the PK studies. <p>The Division also requests that the NDA submission contain a statement that the US and export products are manufactured according to identical standards with the only difference being the color.</p> <p>Gilead/BMS: The Sponsor notes that they will not have batch release data for the export product in the NDA.</p> <p>DAVDP: We will discuss this issue internally and get back to you with comments.</p> <p>Gilead/BMS: The Sponsor agrees to include the results from an study of — ; at 25 deg C/60% RH.</p> <p>DAVDP: The Division requests that the dissolution profiles presented in the NDA include a graphical indication of inter-tablet variability.</p> <p>The Division also encourages the Sponsor to share any knowledge of manufacturing and control that is not normally submitted with NDAs but that could be helpful in regulating this product.</p>
<p>4. Submission of post approval manufacturing and label changes pertaining to the export product.</p>	<p>DAVDP: The Division agrees that post approval manufacturing and label changes pertaining to the export product should be filed to the NDA (e.g., appropriate filing of new manufacturing facilities for export tablets). However, changes to the labels which are submitted to the NDA (as a labeling supplement for the U.S. distributed label) can be included in the annual report.</p>

Action Items:**Gilead will submit the following information as a part of the rolling review:**

- Trade name.
- List of manufacturing sites for API and drug product.
- List of sites where clinical sample laboratory analysis is performed and sites used in the clinical studies.
- Information on the clinical site name and lab site for the PK studies.

Gilead will submit as a part of the NDA:

- — stability data at 25 deg C/80% RH and 50 deg C.
- A statement that the product should be stored in the original container to discourage distribution in alternative packaging.
- Summaries/interpretation of stability data to be included in the NDA submission for the purpose of public distribution.
- Results from an — study of — at 25 deg C/60% RH.

DAVDP will provide the following:

- Following internal discussion, comments/recommendations regarding absence of batch release data for the export product in the NDA.
- Official meeting minutes.

Minutes drafted by: Jeff D. O'Neill, April 25, 2005

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Jeffrey Murray
5/6/05 04:19:13 PM



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV
Division of Antiviral Drug Products**

FACSIMILE TRANSMITTAL SHEET

DATE: April 19, 2005

To: Martine Kraus, Ph.D.	From: Jeff D. O'Neill, ACRN
Company: Gilead Sciences, Inc.	Title: Regulatory Health Project Manager, HFD-530
Fax number: 650-522-5489	Fax number: 301-827-2510
Phone number: 650-522-5722	Phone number: 301-827-2362
Subject: Chemistry comments.	

Total no. of pages including cover: 2

Comments:

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: 71-420

Drug: efavirenz/emtricitabine/tenofovir DF

Date: April 19, 2005

To: Martine Kraus, Ph.D., Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc.

From: Jeff D. O'Neill, ACRN, Regulatory Health Project Manager, DAVDP

Through: George Lunn, Ph.D., Chemistry Reviewer, DAVDP

Concurrence: Stephen P. Miller, Ph.D., Chemistry Team Leader, DAVDP

Subject: Chemistry comments regarding your planned NDA submission for the combination tablet efavirenz/emtricitabine/tenofovir DF.

Please refer to your IND 71,420 for the combination tablet efavirenz/emtricitabine/tenofovir DF. Please also refer to the 4/11/05 teleconference to discuss Pre-NDA CMC issues, and the 4/18/05 meeting to discuss Pre-NDA clinical issues. At both of these meetings DAVDP indicated that a rolling submission would facilitate the review process.

- From the CMC point of view, in addition to the list of manufacturing sites, it would be helpful if we could receive any other sections when they become ready. These sections might include a description of the product, a description of the manufacturing process, batch analyses, specifications, analytical methods, container-closure system, and — of stability data. Receipt of any of these sections would help expedite the review process.

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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/s/

Jeff O'Neill
4/19/05 04:11:31 PM
CSO

Chemistry comments reg. Pre-NDA meeting. Hard copy sign-off 4/19/05

Stephen Paul Miller
4/20/05 12:19:23 PM
CHEMIST



MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND:

Drug: Tenofovir DF (TDF) for the treatment of HIV infection

Date: April 11, 2005

To: Dean M. Waters, Associate Director, Regulatory Affairs

Sponsor: Gilead Sciences, Inc

From: Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, HFD-530

Through: Kimberly A. Struble, Pharm D, Senior Clinical Reviewer
Julian J. O'Rear, PhD, Microbiology Team Leader

Concurrence: Katherine A. Laessig, MD, Medical Team Leader

Subject: CLINICAL and MICROBIOLOGY REVIEW COMMENTS

Please refer to your new IND 72,420 for efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF) fixed-dose combination (FDC) for the treatment of HIV infection dated December 23, 2004 and received December 27, 2004. Reference is made to SN-021 dated November 23, 2005 and containing preliminary data generated in the bioequivalence study GS-US-177-0103.

Clinical:

1. We note your intention to submit an NDA for formulation three. We also note that there are ongoing bioequivalence studies evaluating formulations four and five.
 - When will these studies be completed?
 - What are your plans for formulations four and five should bioequivalence to the individual products be demonstrated?

2. Please clarify how much stability data you plan to submit to support whichever formulation you intend to market.
3. Please submit all safety data from all completed bioequivalence studies when you submit your NDA.

Clinical Pharmacology:

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.

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 71,420

Gilead Sciences Inc.
Attention: Martine Kraus, Ph.D.
Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Kraus:

Please refer to your Investigational New Drug Application (IND) submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for the combination product of efavirenz / emtricitabine / tenofovir disoproxil fumarate.

We also refer to your March 7, 2005 correspondence, received March 8, 2005, requesting a meeting to discuss pre-clinical and clinical sections of your planned New Drug Application.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: April 18, 2005
Time: 3:00-4:30pm
Location: 9201 Corporate Blvd, conference room S400

CDER participants:

Narayana Battula, PhD, Microbiologist, DAVDP
Virginia Behr, Chief Project Management Staff, DAVDP
Debra B. Birnkrant, MD, Division Director, DAVDP
Edward Cox, MD, MPH, Deputy Director, ODEIV
Jennifer DiGiacinto, PharmD, Clinical Pharmacology Reviewer, DAVDP
Russell D. Fleischer, C-PA, MPH, Senior Clinical Analyst, DAVDP
Mark Goldberger, MD, MPH, Director, ODEIV
Katherine A. Laessig, MD, Medical Team Leader, DAVDP
Linda L. Lewis, MD, Medical Officer, DAVDP
George Lunn, PhD, Chemistry Reviewer, DAVDP
Stephen Miller, PhD, Chemistry Team Leader, DAVDP
Jeffrey S. Murray, MD, MPH, Deputy Director, DAVDP
Julian O'Rear, PhD, Microbiology Team Leader, DAVDP
Jeff O'Neill, ACRN, Regulatory Health Project Manager, DAVDP
Kellie S. Reynolds, PharmD, Clinical Pharmacology Team Leader, DAVDP
Greg Soon, PhD, Statistical Team Leader, DAVDP

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at oneillj@cder.fda.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA give the guards either of the following numbers to request an escort to the conference room: Jeff O'Neill, ext. 2362, the division secretary, ext. 2335.

Provide the background information for this meeting (three copies to the IND and seventeen desk copies to me) at least one month prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by April 21, 2005, we may cancel or reschedule the meeting.

If you have any questions, call Jeff O'Neill, Regulatory Health Project Manager, at (301) 827-2362.

Sincerely,

{See appended electronic signature page}

Virginia Behr

Chief Project Management Staff

Division of Antiviral Drug Products

Office of Drug Evaluation IV

Center for Drug Evaluation and Research

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/s/

Virginia Behr
3/24/05 10:12:18 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 71,420

Gilead Sciences Inc.
Attention: Peter Karlton
Director, Global Regulatory Affairs, CMC
333 Lakeside Drive
Foster City, CA 94404

Dear Mr. Karlton:

Please refer to your Investigational New Drug Application (IND) submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for the combination product of efavirenz / emtricitabine / tenofovir disoproxil fumarate.

We also refer to your March 1, 2005 correspondence, received March 2, 2005, requesting a meeting to discuss the CMC development plan and the stability data that will be included in the NDA submission.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: April 11, 2005
Time: 3:00-4:30pm
Location: 9201 Corporate Blvd, conference room S400

CDER participants:

Debra B. Birnkrant, MD, Division Director
Jennifer DiGiacinto, PharmD, Clinical Pharmacology Reviewer
Russell D. Fleischer, C-PA, MPH, Senior Clinical Analyst
Katherine A. Laessig, MD, Medical Team Leader
George Lunn, PhD, Chemistry Reviewer
Stephen Miller, PhD, Chemistry Team Leader
Jeffrey S. Murray, MD, MPH, Deputy Director
Jeff O'Neill, ACRN, Regulatory Project Manager
Kellie S. Reynolds, PharmD, Clinical Pharmacology Team Leader

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at oneillj@cder.fda.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA give the guards either of the following numbers to request and escort to the conference room: Jeff O'Neill, ext. 2362, the division secretary, ext. 2335.

Provide the background information for this meeting (three copies to the IND and nine desk copies to me) at least one month prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by April 14, 2005, we may cancel or reschedule the meeting.

If you have any questions, call Jeff O'Neill, Regulatory Health Project Manager, at (301) 827-2362.

Sincerely,

{See appended electronic signature page}

Anthony DeCicco, RPh
Chief Project Management Staff
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Tony DeCicco
3/11/05 02:58:02 PM



IND 71,420

Gilead Sciences, Inc.
Attention: Martine Kraus, PhD
Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Kraus:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for the combination product of efavirenz/emtricitabine/tenofovir DF.

We have completed our 30-day safety review of your application and, as communicated to you during a telephone conversation with Jeff D. O'Neill of this Division on January 19, 2005, have concluded that you may proceed with your proposed clinical investigation.

The following comments are being provided on behalf of our review team:

Chemistry

1. Please describe your development timetable and indicate when we might expect to receive the NDA.
2. Please indicate how much stability data you expect to have at the time of NDA submission.
3. Please indicate if you expect to submit any stability data obtained in accordance with Q1F with the NDA.

Clinical Pharmacology

4. Please indicate whether you plan to evaluate the effect of food on the triple combination tablet. If you do not evaluate the effect of food, any approved label will indicate that the product should be taken on an empty stomach.
5. Please provide detailed information regarding the dissolution method development and the data that support the selected specification for the triple combination product.

According to 21 CFR regulation 312.32(c)(1)(i) *IND safety reports; Written reports*, the sponsor shall notify FDA and all participating investigators in a written IND safety report of any adverse experience associated with the use of the drug that is both serious and unexpected. According to 21 CFR 312.32(a), *associated with the use of the drug* is defined as, “there is a reasonable possibility that the experience may have been caused by the drug.” The Division interprets this definition under 21 CFR 312.32(c)(1)(i) such that the sponsor should adopt a conservative approach when determining the potential association of a serious and unexpected adverse event to the use of an investigational drug, particularly during early drug development. Events should be considered as possibly related, and thus reportable, unless an association has been reasonably ruled out using objective evidence.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports (21 CFR 312.33).

Please forward all future communications concerning this IND in quadruplicate, identified by the above IND number, to either of the following addresses:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Document Control 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, N115
9201 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions, call Jeff O'Neill, Regulatory Project Manager, at 301-827-2362.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Jeffrey Murray
2/1/05 11:29:30 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 71,420

Gilead Sciences, Inc
Attention: Martine Kraus, Ph.D.
Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Kraus:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 71,420
Sponsor: Gilead Sciences, Inc
Name of Drug: Combination product of efavirenz / emtricitabine / tenofovir disoproxil fumarate
Date of Submission: December 23, 2004
Date of Receipt: December 27, 2004

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, on or before January 26, 2005, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will notify you immediately that (1) clinical studies may not be initiated under this IND ("clinical hold") or that (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (<http://clinicaltrials.gov> & <http://prsinfo.clinicaltrials.gov/>). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site <http://prsinfo.clinicaltrials.gov/>.

Please forward all future communications concerning this IND in quadruplicate, identified by the above IND number, to either of the following addresses:

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, N115
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, N115
9201 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions, call Jeff O'Neill, ACRN, Regulatory Project Manager, at 301-827-2335.

Sincerely,

{See appended electronic signature page}

Anthony DeCicco, RPh
Chief, Project Management Staff
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Tony DeCicco
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