

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-797**

**21-798**

**ADMINISTRATIVE DOCUMENTS AND  
CORRESPONDENCE**

Bristol-Myers Squibb Company

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06 See OMB Statement on Page 3.	
<b>PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT</b> For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use			
		NDA NUMBER 21-797	
		NAME OF APPLICANT / NDA HOLDER Bristol-Myers Squibb Co.	
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)			
ACTIVE INGREDIENT(S) Entecavir		STRENGTH(S) 0.5 mg tablet 1.0 mg tablet	
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 file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
<b>1. GENERAL</b>			
a. United States Patent Number 6,627,224		b. Issue Date of Patent 9/30/2003	c. Expiration Date of Patent 2/23/2021
d. Name of Patent Owner Bristol-Myers Squibb Co.		Address (of Patent Owner) Lawrenceville-Princeton Road (P.O. Box 4000)	
		City/State Princeton / New Jersey	
		ZIP Code 08543-4000	FAX Number (if available)
		Telephone Number 609-252-4000	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)  <input checked="" type="checkbox"/> Chief Patent Counsel, Bristol-Myers Squibb Co.		Address (of agent or representative named in 1.e.) Route 206 & Provinceline Road (P.O. Box 4000)	
		City/State Princeton / New Jersey	
		ZIP Code 08543-4000	FAX Number (if available) 609-252-4526
		Telephone Number 609-252-4825	E-Mail Address (if available) louis.wille@bms.com
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 checked="" type="checkbox"/> No	

Bristol-Myers Squibb Company

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 Patent Claim Number (as listed in the patent) 41 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)  
use of entecavir composition to treat chronic hepatitis B virus 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

Bristol-Myers Squibb Company

<b>6. Declaration Certification</b>	
<p><b>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.</b></p> <p><b>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</b></p>	
<p><b>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</b></p> <p><i>Stephen B. Davis</i></p>	<p>Date Signed</p> <p>9/08/04</p>
<p><b>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).</b></p>	
<p><b>Check applicable box and provide information below.</b></p>	
<input checked="" type="checkbox"/> NDA Applicant/Holder	<input 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
<p>Name Stephen B. Davis</p>	
<p>Address Route 206 &amp; Provinceline Road (P.O. Box 4000)</p>	<p>City/State Princeton / New Jersey</p>
<p>ZIP Code 08543-4000</p>	<p>Telephone Number 609-252-4338</p>
<p>FAX Number (if available) 609-252-4526</p>	<p>E-Mail Address (if available) stephen.davis@bms.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>	

Bristol-Myers Squibb Company

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06 See OMB Statement on Page 3.	
<b>PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT</b> For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use			
		NDA NUMBER 21-797	
		NAME OF APPLICANT / NDA HOLDER Bristol-Myers Squibb Co.	
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)			
ACTIVE INGREDIENT(S) Entecavir		STRENGTH(S) 0.5 mg tablet 1.0 mg tablet	
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 file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
<b>1. GENERAL</b>			
a. United States Patent Number 5,206,244		b. Issue Date of Patent 4/27/1993	c. Expiration Date of Patent 10/18/2010
d. Name of Patent Owner E.R. Squibb & Sons, Inc., a wholly owned subsidiary of Bristol-Myers Squibb Co.		Address (of Patent Owner) Lawrenceville-Princeton Road (P.O. Box 4000)	
		City/State Princeton / New Jersey	
		ZIP Code 08543-4000	FAX Number (if available)
		Telephone Number 609-252-4000	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)  <input checked="" type="checkbox"/> Chief Patent Counsel, Bristol-Myers Squibb Co.		Address (of agent or representative named in 1.e.) Route 206 & Provinceline Road (P.O. Box 4000)	
		City/State Princeton / New Jersey	
		ZIP Code 08543-4000	FAX Number (if available) 609-252-4526
		Telephone Number 609-252-4825	E-Mail Address (if available) louis.wille@bms.com
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 checked="" 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 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

**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

Bristol-Myers Squibb Company

<b>6. Declaration Certification</b>	
<p><b>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.</b></p> <p><b>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</b></p>	
<p><b>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</b></p> <p><i>Stephen B. Davis</i></p>	<p>Date Signed</p> <p>9/08/04</p>
<p><b>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).</b></p>	
<p><b>Check applicable box and provide information below.</b></p>	
<input checked="" type="checkbox"/> NDA Applicant/Holder	<input 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
<p>Name</p> <p>Stephen B. Davis</p>	
<p>Address</p> <p>Route 206 &amp; Provinceline Road (P.O. Box 4000)</p>	<p>City/State</p> <p>Princeton / New Jersey</p>
<p>ZIP Code</p> <p>08543-4000</p>	<p>Telephone Number</p> <p>609-252-4338</p>
<p>FAX Number (if available)</p> <p>609-252-4526</p>	<p>E-Mail Address (if available)</p> <p>stephen.davis@bms.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>	

Bristol-Myers Squibb Company

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06 See OMB Statement on Page 3.	
<b>PATENT INFORMATION SUBMITTED WITH THE                  FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT</b> For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use		NDA NUMBER 21-798	
		NAME OF APPLICANT / NDA HOLDER Bristol-Myers Squibb Co.	
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)			
ACTIVE INGREDIENT(S) Entecavir		STRENGTH(S) 0.05 mg/ml oral solution	
DOSAGE FORM oral solution			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
<b>1. GENERAL</b>			
a. United States Patent Number 5,206,244		b. Issue Date of Patent 4/27/1993	c. Expiration Date of Patent 10/18/2010
d. Name of Patent Owner E.R. Squibb & Sons, Inc., a wholly owned subsidiary of Bristol-Myers Squibb Co.		Address (of Patent Owner) Lawrenceville-Princeton Road (P.O. Box 4000)	
		City/State Princeton / New Jersey	
		ZIP Code 08543-4000	FAX Number (if available)
		Telephone Number 609-252-4000	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)  <input checked="" type="checkbox"/> Chief Patent Counsel, Bristol-Myers Squibb Co.		Address (of agent or representative named in 1.e.) Route 206 & Provinceline Road (P.O. Box 4000)	
		City/State Princeton / New Jersey	
		ZIP Code 08543-4000	FAX Number (if available) 609-252-4526
		Telephone Number 609-252-4825	E-Mail Address (if available) louis.wille@bms.com
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 checked="" 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 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

**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

<b>6. Declaration Certification</b>	
<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><b>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</b></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="text-align: center;"><i>Stephen B. Davis</i></p>	<p>Date Signed</p> <p style="text-align: center;">9/08/04</p>
<p><b>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).</b></p>	
<p>Check applicable box and provide information below.</p>	
<p><input checked="" type="checkbox"/> NDA Applicant/Holder</p> <p><input type="checkbox"/> Patent Owner</p>	<p><input 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>Stephen B. Davis</p>	
<p>Address</p> <p>Route 206 &amp; Provinceline Road (P.O. Box 4000)</p>	<p>City/State</p> <p>Princeton / New Jersey</p>
<p>ZIP Code</p> <p>08543-4000</p>	<p>Telephone Number</p> <p>609-252-4338</p>
<p>FAX Number (if available)</p> <p>609-252-4526</p>	<p>E-Mail Address (if available)</p> <p>stephen.davis@bms.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>	

Bristol-Myers Squibb Company

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 07/31/06 See OMB Statement on Page 3.	
<b>PATENT INFORMATION SUBMITTED WITH THE                  FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT</b> For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use		NDA NUMBER 21-798	
		NAME OF APPLICANT / NDA HOLDER Bristol-Myers Squibb Co.	
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)			
ACTIVE INGREDIENT(S) Entecavir		STRENGTH(S) 0.05 mg / ml oral solution	
DOSAGE FORM oral solution			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
<b>1. GENERAL</b>			
a. United States Patent Number 6,627,224		b. Issue Date of Patent 9/30/2003	c. Expiration Date of Patent 2/23/2021
d. Name of Patent Owner Bristol-Myers Squibb Co.		Address (of Patent Owner) Lawrenceville-Princeton Road (P.O. Box 4000)	
		City/State Princeton / New Jersey	
		ZIP Code 08543-4000	FAX Number (if available)
		Telephone Number 609-252-4000	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)  <input checked="" type="checkbox"/> Chief Patent Counsel, Bristol-Myers Squibb Co.		Address (of agent or representative named in 1.e.) Route 206 & Provinceline Road (P.O. Box 4000)	
		City/State Princeton / New Jersey	
		ZIP Code 08543-4000	FAX Number (if available) 609-252-4526
		Telephone Number 609-252-4825	E-Mail Address (if available) louis.wille@bms.com
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 checked="" 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 Patent Claim Number (as listed in the patent) 41 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.) use of entecavir composition to treat chronic hepatitis B virus 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

<b>6. Declaration Certification</b>	
<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><b>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</b></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><i>Stephen B Davis</i></p>	<p>Date Signed</p> <p>9/08/04</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>	
<input checked="" type="checkbox"/> NDA Applicant/Holder	<input 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
<p>Name Stephen B. Davis</p>	
<p>Address Route 206 &amp; Provinceline Road (P.O. Box 4000)</p>	<p>City/State Princeton / New Jersey</p>
<p>ZIP Code 08543-4000</p>	<p>Telephone Number 609-252-4338</p>
<p>FAX Number (if available) 609-252-4526</p>	<p>E-Mail Address (if available) stephen.davis@bms.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>	

Bristol-Myers Squibb Company

**NDA # 21-797 TRADENAME (entecavir, BMS-200475) Tablets**

**NDA # 21-798 TRADENAME (entecavir, BMS-200475) Oral Solution**

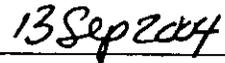
**FIELD COPY CERTIFICATION**

**Chemistry, Manufacturing, and Control Submission:**

Bristol-Myers Squibb Company certifies that a field copy of the Chemistry, Manufacturing and Control (CMC) section of each application was provided to the Food and Drug Administration, North Brunswick R. P., 120 Center Dr.,  North Brunswick, NJ 08902. An additional copy of the CMC section of each application was also provided to the Detroit, MI office of the Food and Drug Administration (DET-DO), 300 River Place, Suite 5900, Detroit, MI 48207. We further certify that these copies are true copies of the CMC section of each application.



Michael E. Brady, PhD  
Director, Global Regulatory Affairs  
Bristol-Myers Squibb Company  
5 Research Parkway, Dept. 718  
Signature 91 Building  
Wallingford, CT 06492  
(203) 677-3812



Date

EXCLUSIVITY SUMMARY FOR NDA # 21-797 and 21-798 SUPPL # \_\_\_\_\_

Trade Name BARACLUDE 0.5 mg and 1.0 mg Oral Tablets  
BARACLUDE 0.05 mg/mL Oral Solution

Generic Name entecavir (BMS 200-475)

Applicant Name Bristol-Myers Squibb Company HFD-530

Approval Date If Known March 29, 2005

**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 question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?  
YES // NO /\_\_\_/

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

505(b)(1)

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

YES // NO /\_\_\_/

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

\_\_\_\_\_  
\_\_\_\_\_

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

\_\_\_\_\_

---

d) Did the applicant request exclusivity?

YES /\_\_\_/      NO /\_\_\_/

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

---

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

YES /\_\_\_/      NO //

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

---

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

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

YES /\_\_\_/      NO //

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

## PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety,

e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /\_\_\_/      NO //

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

NDA# \_\_\_\_\_  
NDA# \_\_\_\_\_  
NDA# \_\_\_\_\_

2. Combination product.

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

YES /\_\_\_/      NO //

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

NDA# \_\_\_\_\_  
NDA# \_\_\_\_\_  
NDA# \_\_\_\_\_

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

**PART III THREE-YEAR EXCLUSIVITY FOR NDA'S 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.



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 /\_\_\_/ Explain \_\_\_\_\_ ! NO /\_\_\_/ Explain \_\_\_\_\_

! !

\_\_\_\_\_ ! \_\_\_\_\_

\_\_\_\_\_ ! \_\_\_\_\_

! !

Investigation #2 !

-----  
**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  
4/18/05 10:34:16 AM

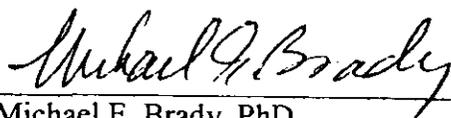
Bristol-Myers Squibb Company

**NDA NO. 21-797**

**ENTECAVIR TABLETS**

**CERTIFICATION: DEBARRED PERSONS**

As required by Section 306(k)(1) of the Federal Food, Drug and Cosmetics Act, Bristol-Myers Squibb Company certifies that it has not used and will not use in any capacity the services of any person listed as debarred as of the Date of Debarment List Debarment List under Section 306 (a) or (b) of the Federal Food, Drug and Cosmetics Act in connection with this Application.



Michael E. Brady, PhD  
Director, Global Regulatory Affairs  
Bristol-Myers Squibb Company  
5 Research Parkway, Dept 718  
Signature 91 Building  
Wallingford, CT 06492  
(203) 677-3812



Certification Date

## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-797 & 21-978 (NME) Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

Stamp Date: September 29, 2004 PDUFA Goal Date: March 29, 2005 HFD-530

Trade and generic names/dosage form: BARACLUDE™ (entecavir; BMS-200475) 0.5 mg and 1.0 mg Oral Tablets  
BARACLUDE™ (entecavir; BMS-200475) 0.05 mg/mL Oral Solution

Applicant: Bristol-Myers Squibb Pharmaceutical Company Therapeutic Class: Anti-hepatitis B drug product

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

Yes. Please proceed to the next section.

No. PREA does not apply. Skip to signature block.

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

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

(Each indication covered by this application must have pediatric studies: Completed, Deferred, and/or Waived.)

Number of indications for this application(s): one

For the treatment of chronic hepatitis B virus infection in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

Is this an orphan indication?

Yes. PREA does not apply. Skip to signature block.

No. Please proceed to the next question.

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

Yes: Please proceed to Section A.

No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

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

### Section A: Fully Waived Studies

Reason(s) for full waiver:

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

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

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

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

---

**Section B: Partially Waived Studies**

---

Age/weight range being partially waived:

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. from birth Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 16 years of age Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

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

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

Date studies are due (mm/dd/yy): # 1 July, 2007  
# 2 December, 2009

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

---

**Section D: Completed Studies**

---

Age/weight range of completed studies:

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.*

NDA 21-797  
NDA 21-798  
Page 3

**This page was completed by:**

*{See appended electronic signature page}*

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

cc: NDA 21-797  
NDA 21-798  
HFD-960/ Rosemary Addy or Grace Carmouze

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

**(revised 2-28-2005)**

**Attachment A**

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

Indication #2: NOT APPLICABLE

Is this an orphan indication?

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

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

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

NOTE: More than one may apply

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

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

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

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

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

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

Reason(s) for deferral:

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

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

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

---

**Section D: Completed Studies**

---

Age/weight range of completed studies:

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

Comments:

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

This page was completed by:

*{See appended electronic signature page}*

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

cc: NDA 21-797  
NDA 21-798  
HFD-960/ Rosemary Addy or Grace Carmouze

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

(revised 2-28-2005)

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

/s/

-----  
Virginia Behr  
4/18/05 01:33:26 PM

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

<b>NDA 21-797</b>		
<b>NDA 21-798</b>	Efficacy Supplement Type SE-	Supplement Number
Drug: <b>BARACLUDE (entecavir) 0.5 mg &amp; 1 mg Oral Tablets</b> <b>BARACLUDE (entecavir) 0.05 mg Oral Solution</b>		Applicant: <b>Bristol-Myers Squibb Pharmaceuticals</b>
RHPM: <b>Marsha S. Holloman, BS Pharm, JD</b>		HFD-530      Phone # <b>301-827-2418</b>
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.)  <b>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.</b>  <input type="checkbox"/> Confirmed and/or corrected		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
<b>❖ Application Classifications:</b>		
<ul style="list-style-type: none"> <li>• Review priority</li> <li>• Chem class (NDAs only)</li> <li>• Other (e.g., orphan, OTC)</li> </ul>		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
<b>❖ User Fee Goal Dates</b>		
<b>❖ Special programs (indicate all that apply)</b>		<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 type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
<b>❖ User Fee Information</b>		
<ul style="list-style-type: none"> <li>• User Fee</li> <li>• User Fee waiver</li> </ul>		<input checked="" type="checkbox"/> Paid UF ID number: <b>4780 &amp; 4820</b>
<ul style="list-style-type: none"> <li>• User Fee exception</li> </ul>		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
<b>❖ Application Integrity Policy (AIP)</b>		
		<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)



(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.)

03/29/2005  
 N/A

- 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 ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	<input checked="" type="checkbox"/> Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	<input checked="" type="checkbox"/> Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release <input checked="" type="checkbox"/> Talk Paper ( ) Dear Health Care Professional Letter <input checked="" type="checkbox"/> Info Alert
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	03/29/2005
• Most recent applicant-proposed labeling	03/29/2005
• Original applicant-proposed labeling	09/29/2004
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	03/29/2005
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	03/29/2005
• Applicant proposed	09/29/2004
• Reviews	03/29/2005
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	03/29/2005
• Documentation of discussions and/or agreements relating to post-marketing commitments	See facsimiles
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	Clinical 12/02/2002 CMC 08/27/2003
• Pre-NDA meeting (indicate date)	Clinical 04/27/2004 CMC 12/13/2003
• Pre-Approval Safety Conference (indicate date; approvals only)	January 24, 2005
• Other	Filing Meeting 10/26/2004
❖ Advisory Committee Meeting	
• Date of Meeting	03/11/2005
• <del>48 hour alert</del> Transcript	03/29/2005

NDA 21-797

NDA 21-798

Page 5

❖ 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)	03/29/2005
❖ Clinical review(s) (indicate date for each review)	03/29/2005
❖ Microbiology (efficacy) review(s) (indicate date for each review)	03/29/2005
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	03/29/2005
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	See Clinical Review
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	03/29/2005
❖ Demographic Worksheet (NME approvals only)	03/29/2005
❖ Statistical review(s) (indicate date for each review)	03/29/2005
❖ Biopharmaceutical review(s) (indicate date for each review)	03/29/2005
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	03/29/2005
• Bioequivalence studies	See Clinical Review
❖ CMC review(s) (indicate date for each review)	03/29/2005
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	Yes 03-29-2005
• 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: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ Methods validation	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	03/29/2005
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	03/29/2005 (See Pharm/Tox)

### 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).

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

/s/

-----  
Virginia Behr  
4/18/05 04:40:49 PM



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA: 21-797**  
**NDA: 21-798**

**Drug: BARACLUDE (entecavir) (ETV) (BMS-200475) (SQ 34,676)**

**Date: March 24, 2005**

**To: Joan C. Fung-Tomc, PhD, ABMM, Director, Global Regulatory Science**

**Sponsor: Bristol-Myers Squibb Company**

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

**Through: Linda L. Lewis, MD, Medical Officer**

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

**Subject: REVISED DRAFT PATIENT PRODUCT INFORMATION INSERT (PPI)**

Reference is made to Investigational New Drug (IND) application 52,196 dated and received December 20, 1996 for BMS-200475 (entecavir, ETV) (SQ 34,676) for the treatment of hepatitis B virus (HBV) infection. Also, reference is made to New Drug Application (NDA) 21-797 for BARACLUDE™ (BMS-200475, entecavir, ETV) Film-Coated Tablets and NDA-21798 Oral Solution dated and received September 29, 2004.

Specific PPI revised labeling changes from the Division of Surveillance, Research, and Communication Support (DSRCS) in the Office of Drug Safety (ODS) are detailed on the next page. These suggestions are intended to provide consistency in language and in content compared to similar products' PPIs.

5 Page(s) Withheld

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

       § 552(b)(5) Deliberative Process

       § 552(b)(5) 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

4/11/05 02:07:06 PM

CSO

This facsimile contains 2nd MO and PK revised draft  
PPI labeling and was sent to BMS 24-Mar-2005.

Kathrine Laessig

4/14/05 09:50:26 AM

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: March 23, 2005**

<b>To: Joan C. Fung-Tome</b>	<b>From: Marsha S. Holloman</b>
<b>Company: Bristol-Myers Squibb Co.</b>	<b>Title: Regulatory Health Project Manager, HFD-530</b>
<b>Fax number: 203-677-3818</b>	<b>Fax number: 301-827-2471</b>
<b>Phone number: 203-677-3817</b>	<b>Phone number: 301-827-2335</b>
<b>Subject: NDA 21-797 &amp; NDA 21-798 – MO &amp; PK CLINICAL 2<sup>nd</sup> REVISED DRAFT LABELING CHANGES – PACKAGE INSERT</b>	

**Total no. of pages including cover: 5**

**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. If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2335 Thank you.**

**DATE:** 03-23-05

**FROM:** Mark J Goldberger MD MPH.  
Director of Office of Drug Evaluation IV

**TO:** NDA 21-797 and 21-798

**SUBJECT:** Office Director Memo for NDA 21-797, entecavir 0.5 mg and 1.0 mg tablets, and NDA 21-798 entecavir oral solution for the Treatment of Chronic Hepatitis B Infection (tradename BARACLUDGE)

I agree with the overall assessments of this products as described by the primary reviewer staff, the medical team leader Dr. Laessig and that of Dr. Birnkrant. Entecavir represents a meaningful therapeutic advance in the treatment of Hepatitis B and I concur with the recommendations for its approval. Its efficacy exceeds that of the comparator product lamivudine and its overall safety profile is comparable to lamivudine. It also retains activity in lamivudine resistant patients. Resistance to lamivudine may develop in up to 25% of patients per year of treatment. Other products approved for treatment of hepatitis B are interferon which must be given by injection and has significant AEs that may limit the ability to complete a course of treatment and adefovir which is orally administered but can be associated with nephrotoxicity. Thus having another treatment option would be highly desirable.

Issues that will need to be addressed post approval include:

**Carcinogenicity:** Studies performed in multiple species show entecavir to be a carcinogen with the development of multiple tumor types though at exposures generally well in excess of likely human exposure. The specifics of this are described in Dr. Verma's review. Evaluation by the CAC and the executive CAC indicated that this may be significant for human health and that further evaluation should be performed. BMS has agreed to conduct a postmarketing pharmacovigilance trial comparing entecavir to standard of care (lamivudine and to a lesser degree adefovir). This trial will enroll sufficient patients to detect a 30% increase in cancer due to entecavir and has a planned 5-10 year follow-up.

I have several comments with regard to the carcinogenicity of entecavir and the proposed study to evaluate it. The AVAC expressed some concern that randomizing to lamivudine would be difficult and perhaps not ethical given the greater efficacy of entecavir. I believe their comments demonstrate that their concern for the carcinogenicity is quite low when considered in light of the totality of the data. The AVAC members and consultants also expressed concern that interpreting the results of this study might be complicated by the large number of switches from the lamivudine arm due to decreased effectiveness from development of resistance to lamivudine. This again places the carcinogenicity

potential in a broader perspective and suggests that this pharmacovigilance study should be considered as a broader look at the overall benefit-risk of the drug. Finally the potential carcinogenicity of the drug should be considered in light of the known carcinogenicity of hepatitis B infection and the evidence that successful treatment of this infection reduces the progression to hepatocellular carcinoma. It is nonetheless important to make every effort to conduct this trial.

**Development of Resistance:** Lamivudine, although it is well tolerated and active in the treatment of hepatitis B has a limited duration of effectiveness due to the development of resistance. Resistance to entecavir appears to develop more slowly, however longer term data are not yet available to assess the ultimate magnitude of same given that many patients will require long term treatment. Studies conducted with entecavir in lamivudine resistant patients demonstrate that entecavir retains activity in such patients but that this activity is reduced. It should be noted that the dose of entecavir in this trial was double that used in the clinical trials that enrolled treatment naïve patients. There is also some limited data suggesting this may also be true for use of adefovir in lamivudine resistant patients. This has several implications.

It would appear extremely important to begin the more organized study of combination therapy in the treatment of Hepatitis B. This appears essential in lamivudine based regimens and is likely to be true in other regimens as well given the high levels of circulating virus and the demonstrated ability of the virus to develop mutations rendering it less susceptible to therapy. It is probably also important to begin to consider whether additional information should be included in lamivudine labeling regarding its use as initial therapy as a single agent in hepatitis B. There may not yet be sufficient information to definitively state that this practice should no longer be recommended but it would appear prudent to begin considering what data is currently available on this point and what additional studies should be recommended to further address it. One of the Phase IV commitments in the entecavir approval letter is a request for the sponsor to propose and then conduct a trial using combination therapy.

Other broader issues in Hepatitis B drug development that appear in considering this as well as previous submissions and require additional attention include the need to continue to look at the correlation of histologic and virologic endpoints with the hope of making the latter the primary endpoints for future trials. The Division has a project underway to utilize recently submitted data to address this point. There is also the issue of when therapy can be discontinued. In clinical trials in this submission patients who were "e" antigen positive at time of randomization were less likely than "e" antigen negative patients to respond sufficiently (virologic and LFT endpoints) to allow discontinuation of Rx. Among all responders however "e" antigen positive patients were more likely to remain a responder after therapy was discontinued than were "e" antigen negative patients. Clearly additional information is required to determine treatment management strategies.

---

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

---

/s/

-----  
Mark Goldberger  
3/23/05 04:08:27 PM  
MEDICAL OFFICER



## MEMORANDUM OF FACSIMILE CORRESPONDENCE

**NDA:** 21-797  
**NDA:** 21-798

**Drug:** BARACLUDE (entecavir) (ETV) (BMS-200475) (SQ 34,676)

**Date:** March 23, 2005

**To:** Joan C. Fung-Tomc, PhD, ABMM, Director, Global Regulatory Science

**Sponsor:** Bristol-Myers Squibb Company

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

**Through:** Linda L. Lewis, MD, Medical Officer

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

**Subject:** MO and PK CLINICAL 2<sup>nd</sup> REVISED DRAFT LABELING CHANGES  
– PACKAGE INSERT

Reference is made to Investigational New Drug (IND) application 52,196 dated and received December 20, 1996 for BMS-200475 (entecavir, ETV) (SQ 34,676) for the treatment of hepatitis B virus (HBV) infection. Also, reference is made to New Drug Application (NDA) 21-797 for BARACLUDE™ (BMS-200475, entecavir, ETV) Film-Coated Tablets and NDA-21798 Oral Solution dated and received September 29, 2004.

Specific recommendations related to the clinical sections of the label are detailed below.

1. In the **INDICATIONS AND USAGE** section, delete the phrase ' — ' At the end of the last sentence, add the following language: "...and on more limited data in adult patients with HIV/HBV co-infection who have received prior lamivudine."
2. In the section describing Study 022, the study population should be described as he following: "The mean age of patients was 35 years, 75% were male, 57% were Asian, 40% were Caucasian, and 13% had previously received interferon- $\alpha$ . At baseline, subjects had a mean Knodell Necroinflammatory score of 7.8, mean serum HBV DNA as measured by Roche COBAS Amplicor PCR assay was 9.66 log<sub>10</sub> copies/mL, and mean

serum ALT was 143 U/L. Paired, adequate liver biopsy samples were available for 89% of subjects."

The proportion of subjects with cirrhosis on biopsy was too small to make any definitive conclusions regarding efficacy and too small to have a great impact on the overall study results. Ranges for each baseline characteristic are not necessary. Therefore, delete these items.

3. In the section describing Study 027, refer to editorial comments for Study 022. In addition, delete the phrase "..
4. In all tables, please avoid the use of multiple symbols for different p values in the same table. Use a single symbol for all significant differences in a table (i.e., " $p < 0.05$ ").
5. In Tables 2 and 4, footnote b carried over from the first version of the tables referred to the ~~the~~ category but are listed separately. Delete this footnote.
6. In Tables 3 and 5, delete footnote b regarding ~~the~~ This information does not represent a critical secondary endpoint and is not necessary for the label. Early virologic correlates of response were not part of the primary analysis plan.
7. Also, in Tables 3 and 5, please delete the row displaying ~~the~~ Very few subjects had loss of e antigen without appearance of e antibody. The occurrence of seroconversion is the event of more clinical relevance.
8. In the description of results of Study 022 and 027, delete the statement ~~the~~ This implies an indication for treatment in this cohort but the proportion of subjects enrolled in the Phase-3 studies is not adequate to determine efficacy in the subgroup.
9. In the same paragraph, delete the sentence that includes ~~the~~ This analysis is considered exploratory.
10. In the description of Study 026, refer to editorial comments above for Study 022 (See item 2 above).
11. In the description of results of Study 026, refer to the editorial comments above for similar wording of the nucleoside-naïve studies (See item 8 above).

12. In the section entitled \_\_\_\_\_ revise this section as follows:

*"The optimal duration of therapy with BARACLUDE is unknown. According to protocol mandated criteria in the Phase 3 clinical trials, subjects discontinued BARACLUDE or lamivudine treatment after 48 weeks according to a definition of response based on HBV virologic suppression (< 0.7 mEq/mL by bDNA assay) and loss of HBeAg (in HBeAg positive subjects) or ALT normalization (<1.25 X ULN, in HBeAg negative subjects).*

*\_\_\_\_\_ few LVD-refractory subjects met the response criteria and were eligible to discontinue treatment. These protocol specified patient management guidelines are not intended as guidance for clinical practice."*

Delete Table 6 in this section.

13. In the description of Study 038, include statements that \_\_\_\_\_ there is no data in HIV/HBV patients who have not received prior lamivudine.
14. In the WARNINGS section, after the reiteration of the boxed warning, delete the last sentence in the paragraph and insert a new paragraph:

Please delete the \_\_\_\_\_ from Table 8.

15. In the **Geriatric Use** section, please delete the sentence, ' \_\_\_\_\_
16. In the **Use in Racial/Ethnic Groups** section, please delete the last sentence and insert, "*There are no significant racial differences in entecavir pharmacokinetics.*" This will be consistent with terminology used in the Clinical Pharmacology section
17. In the **ADVERSE REACTIONS** section, description of Study 038, please replace " \_\_\_\_\_ with "*...in non-HIV infected patients.*"

18. In Table 10, explain how the proportions in the table were derived. The Clinical Reviewers confirmed proportions of patients with  $\geq$  Grade 3 laboratory abnormalities as presented in the final clinical study reports and the summary of safety for the NDA. These proportions are slightly different for many parameters, most notably ALT and AST.
19. In the PPI section, "**What are the possible side effects of Baraclude?**" include a statement regarding possible worsening of liver and pancreas-related blood tests. We will send additional recommendations regarding the PPI separately.
20. In the **Special Populations/Renal Impairment** section, re-insert the following deleted sentences ' 

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 at 301-827-2335 if you have any questions regarding the contents of this transmission

-----  
**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

4/11/05 01:20:51 PM

CSO

This facsimile contains 2nd MO & PK revised draft  
labeling and was sent to BMS 23-Mar-2005.

Kathrine Laessig

4/11/05 01:38:50 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: March 16, 2005**

<b>To: Joan Fung-Tomc</b>	<b>From: Marsha S. Holloman</b>
<b>Company: Bristol-Myers Squibb Co.</b>	<b>Title: Regulatory Health Project Manager, HFD-530</b>
<b>Fax number: 203-677-3818</b>	<b>Fax number: 301-827-2471</b>
<b>Phone number: 203-677-3817</b>	<b>Phone number: 301-827-2335</b>

**Subject: NDA 21-797 & NDA 21-798 – PHARMACOLOGY – 1<sup>st</sup> REVISED  
DRAFT LABELING – PACKAGE INSERT**

**Total no. of pages including cover: 4**

**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. If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2335 Thank you.**



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:** 21-797

**NDA:** 21-798

**Drug:** BARACLUDE™ (entecavir) (ETV) (BMS-200475) (SQ 34,676)

**Date:** March 15, 2005

**To:** Joan C. Fung-Tomc, PhD, ABMM, Director, Global Regulatory Science

**Sponsor:** Bristol-Myers Squibb Company

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

**Through:** James G. Farrelly, PhD, Pharmacology Team Leader

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

**Subject:** PHARMACOLOGY – 1<sup>st</sup> DRAFT REVISED LABELING – PACKAGE  
INSERT (PI)

---

Reference is made to Investigational New Drug (IND) application 52,196 dated and received December 20, 1996 for BMS-200475 (entecavir, ETV) (SQ 34,676) for the treatment of hepatitis B virus (HBV) infection. Also, reference is made to New Drug Application (NDA) 21-797 for BARACLUDE™ (BMS-200475, entecavir, ETV) Film-Coated Tablets and NDA-21798 Oral Solution dated and received September 29, 2004.

We have the following pharmacology draft revised labeling changes:

### PHARMACOLOGY

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

2 Page(s) Withheld

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

       § 552(b)(5) Deliberative Process

✓ § 552(b)(5) 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  
4/11/05 12:51:53 PM  
CSO

This facsimile contains the 1st Pharm revised draft labeling  
and was sent to BMS 16-Mar-2005.

Kathrine Laessig  
4/11/05 01:12:05 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: March 16, 2005**

<b>To: Joan C. Fung-Tome</b>	<b>From: Marsha S. Holloman</b>
<b>Company: Bristol-Myers Squibb Co.</b>	<b>Title: Regulatory Health Project Manager, HFD-530</b>
<b>Fax number: 203-677-3818</b>	<b>Fax number: 301-827-2471</b>
<b>Phone number: 203-677-3817</b>	<b>Phone number: 301-827-2335</b>
<b>Subject: NDA 21-797 &amp; NDA 21-798 – CLINICAL (MO) 1<sup>st</sup> REVISED DRAFT LABELING CHANGES – PACKAGE INSERT</b>	

---

**Total no. of pages including cover: 6**

**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. If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2335 Thank you.**



## MEMORANDUM OF FACSIMILE CORRESPONDENCE

**NDA:** 21-797  
**NDA:** 21-798

**Drug:** BARACLUDE (entecavir) (ETV) (BMS-200475) (SQ 34,676)

**Date:** March 16, 2005

**To:** Joan C. Fung-Tomc, PhD, ABMM, Director, Global Regulatory Science

**Sponsor:** Bristol-Myers Squibb Company

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

**Through:** Linda L. Lewis, MD, Medical Officer

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

**Subject:** CLINICAL (MO) 1<sup>st</sup> REVISED DRAFT LABELING CHANGES – PACKAGE INSERT

Reference is made to Investigational New Drug (IND) application 52,196 dated and received December 20, 1996 for BMS-200475 (entecavir, ETV) (SQ 34,676) for the treatment of hepatitis B virus (HBV) infection. Also, reference is made to New Drug Application (NDA) 21-797 for BARACLUDE™ (BMS-200475, entecavir, ETV) Film-Coated Tablets and NDA-21798 Oral Solution dated and received September 29, 2004.

In general, the proposed label is too long and contains some material that is considered either investigational or promotional. Specific recommendations related to the clinical sections of the label are detailed below.

1. All products with activity against HBV require a boxed warning regarding the potential for severe acute exacerbations of hepatitis (flares). This warning should also be reproduced in the WARNINGS section of the label where \_\_\_\_\_ 3 may be presented. Wording for the boxed warning has been standardized for all products and should be as follows:

**“Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti-hepatitis B therapy including entecavir. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue anti-hepatitis B therapy. If appropriate, initiation of anti-hepatitis B therapy may be warranted (See WARNINGS).”**

2. All nucleoside analogue products for treatment of chronic hepatitis B contain a boxed warning against lactic acidosis. Wording for this warning has been standardized and should be as follows:

**“Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with antiretrovirals.”**

3. In the INDICATIONS AND USAGE section, comments regarding efficacy should be removed. The indication for which entecavir is receiving approval is as follows:

**“Entecavir is indicated for the treatment of chronic hepatitis B virus infection in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.”**

***This indication is based on histological, virological, biochemical, and serological responses after one year of treatment in nucleoside treatment-naïve and lamivudine-resistant adult patients with HBeAg positive or HBeAg negative chronic HBV with compensated liver disease and more limited data in adult patients with HIV/HBV co-infection.***

4. In the *Description of Clinical Studies* section, we recommend that you include only the 3 Phase-3 studies (022, 027, and 026) and a brief description of Study 038 in HIV/HBV co-infected subjects. The safety data from the relevant cohorts of Study 014 should be included in Tables 7 and 8 and described in a table footnote.
5. In the *Description of Clinical Studies* section, for all studies described, please list the proportion of subjects who had paired adequate liver biopsy samples rather than the
6. In the *Description of Clinical Studies* section, please move all discussion of post-48 week management into a single section headed

format. Include a caveat that these protocol-mandated management guidelines are not

intended to direct providers to discontinue entecavir therapy for similarly responding patients in clinical practice (*i.e.*, these are not clinical practice guidelines).

7. In Table 2, please combine the missing or inadequate Week 48 liver biopsies into one row. Delete the columns containing the t — and include as footnotes p values indicating where significant differences were found.
8. In Table 3, in the table title and text add the word “**selected**” to describe the endpoints shown. Delete the rows displaying — add little to the interpretation of study efficacy. Please remove the results of — and present in a separate section as described in #6. Delete the footnote containing —. Move the description of the LOQ cut-off for the PCR assay to footnote —.
9. In the *Description of Clinical Studies* section, please delete the paragraph describing the —. This represents a secondary endpoint analysis of an assay available only for research purposes.
10. In Table 4, please combine missing or inadequate Week 48 liver biopsies in one row. Delete the column containing the — and indicate significance by citing relevant p values in table footnotes. Delete the row containing the — as this is likely to be confused with the *Patient Management Endpoints*.
11. In Table 5, please display results for only Study 026. See comment #8 for editing recommendations.
12. In the *Description of Clinical Studies* section, please delete the paragraphs describing —.
13. In the description of Study 038, the first sentence could be streamlined to read, “**Study AI463038 was a randomized....who experienced recurrence of HBV viremia while receiving a lamivudine-containing highly active antiretroviral regimen.**” Please include the proportion of subjects who were HBeAg positive rather than the —. Also, include in this section, either in table or text, the impact of entecavir treatment on HIV viral load.
14. In Table 6, please include the description of the LOQ of the PCR assay in footnote b. Delete the column containing the — and indicate significance by citing relevant p values in table footnotes. Please include the results of the analysis of proportion of subjects achieving HBV DNA < 300 copies/mL as in the previous efficacy tables.

15. In the PRECAUTIONS, Pregnancy Registry section, please advise us of the status of your proposal to monitor pregnant women who receive entecavir through an established registry. Do you intend to have health care providers register through the HIV Pregnancy Registry? Has this proposal been approved by the Pregnancy Registry administrators?

16. In the PRECAUTIONS section, please include a new subsection *Use in Racial/Ethnic Groups* and insert the following statement after the paragraph describing *Geriatric Use*:

***“Clinical studies of entecavir did not include sufficient numbers of subjects from some racial/ethnic minorities (black/African American, Hispanic) to determine whether they respond differently to treatment with the drug.”***

17. In the ADVERSE REACTIONS section, please include the median duration of treatment in the introductory paragraph rather than as

18. In Table 8, please re-title the table, ***“Selected laboratory abnormalities reported during treatment in four entecavir clinical trials”***. Please delete the

Include in

the table proportions of subjects with Grade 3 or 4 laboratory toxicity for ALT (may footnote that abnormal value was study entry criteria), AST, amylase, lipase, creatinine (include both > Grade 3 and > 0.5 mg/dL above baseline), hyperglycemia, total bilirubin, urine glucose (glycouria), and urine blood (hematuria). Please include the cut-off values for Grade 3 toxicity for each parameter.

19.

20.

21. In the DOSAGE AND ADMINISTRATION, Recommended Dosage section, please revise the wording of the first paragraph as follows:

***“The recommended dose of entecavir for chronic hepatitis B virus infection in nucleoside treatment-naïve adults and adolescents older than 16 years of age is 0.5 mg once daily.”***

***The recommended dose of entecavir in adults and adolescents with hepatitis B viremia while receiving lamivudine or with a history of known lamivudine resistance mutations is 1 mg once daily.***

22. Please correct the dosing recommendations for patients with renal impairment requiring dialysis as agreed in your communication dated March 14, 2005.
23. In the *Duration of Therapy* section, please revise the section to read:

***"The optimal duration of treatment with entecavir for patients*** \_\_\_\_\_

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 at 301-827-2335 if you have any questions regarding the contents of this transmission

Appears This Way  
On Original

-----  
**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

4/11/05 01:03:03 PM

CSO

This facsimile contains 1st MO revised draft labeling and  
was sent to BMS 16-Mar-2005.

Kathrine Laessig

4/11/05 01:26:30 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:** March 15, 2005

<b>To:</b> Joan Fung-Tomc	<b>From:</b> Marsha S. Holloman
<b>Company:</b> Bristol-Myers Squibb Co.	<b>Title:</b> Regulatory Health Project Manager, HFD-530
<b>Fax number:</b> 203-677-3818	<b>Fax number:</b> 301-827-2471
<b>Phone number:</b> 203-677-3817	<b>Phone number:</b> 301-827-2335

**Subject:** NDA 21-797 & NDA 21-798 – MICROBIOLOGY – 1<sup>st</sup> REVISED  
DRAFT LABELING – PACKAGE INSERT

**Total no. of pages including cover:** 4

**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. If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2335 Thank you.**



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA: 21-797**  
**NDA: 21-798**

**Drug: BARACLUDGE™ (entecavir) (ETV) (BMS-200475) (SQ 34,676)**

**Date: March 14, 2005**

**To: Joan C. Fung-Tomc, PhD, ABMM, Director, Global Regulatory Science**

**Sponsor: Bristol-Myers Squibb Company**

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

**Through: Lisa Naeger, PhD, Microbiologist**

**Concur: Julian J. O'Rear, PhD, Microbiology Team Leader  
Katherine A. Laessig, MD, Medical Team Leader**

**Subject: MICROBIOLOGY – 1<sup>st</sup> DRAFT REVISED LABELING – PACKAGE INSERT (PI)**

Reference is made to Investigational New Drug (IND) application 52,196 dated and received December 20, 1996 for BMS-200475 (entecavir, ETV) (SQ 34,676) for the treatment of hepatitis B virus (HBV) infection. Also, reference is made to New Drug Application (NDA) 21-797 for BARACLUDGE™ (BMS-200475, entecavir, ETV) dated and received September 29, 2004.

We have the following microbiology and resistance draft revised labeling changes:

**MICROBIOLOGY**

2 Page(s) Withheld

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

       § 552(b)(5) Deliberative Process

✓ § 552(b)(5) 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

4/11/05 01:08:49 PM

CSO

This facsimile contains 1st Micro revised draft labeling and  
was sent to BMS 15-Mar-2005.

Kathrine Laessig

4/11/05 01:34:50 PM

MEDICAL OFFICER

4 Page(s) Withheld

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

       § 552(b)(5) Deliberative Process

       § 552(b)(5) 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: March 03, 2005**

<b>To: Joan Fung-Tomc</b>	<b>From: Marsha S. Holloman</b>
<b>Company: Bristol-Myers Squibb Co.</b>	<b>Title: Regulatory Health Project Manager, HFD-530</b>
<b>Fax number: 203-677-3818</b>	<b>Fax number: 301-827-2471</b>
<b>Phone number: 203-677-3817</b>	<b>Phone number: 301-827-2335</b>
<b>Subject: NDA 21-797 &amp; NDA 21-798 – CLINICAL PHARMACOLOGY, MICROBIOLOGY, AND CMC REVIEW COMMENTS</b>	

**Total no. of pages including cover: 6**

**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. If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2335 Thank you.**



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA: 21-797**

**NDA: 21-798**

**Drug: BARACLUDE (entecavir) (ETV) (BMS-200475) (SQ 34,676)**

**Date: March 03 2005**

**To: Joan C. Fung-Tomc, PhD, ABMM, Director, Global Regulatory Science**

**Sponsor: Bristol-Myers Squibb Company**

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

**Through: Jenny H. Zheng, PhD, Clinical Pharmacologist  
Kimberly Bergman, Pharm D, Clinical Pharmacologist  
Lisa Naeger, PhD, Microbiologist  
Lorenzo Rocca, PhD, Chemist  
Linda L. Lewis, MD, Medical Officer  
Yoshihiko Murata, MD, PhD, Medical Officer**

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

**Subject: CLINICAL PHARMACOLOGY, MICROBIOLOGY, AND CMC  
REVIEW COMMENTS**

---

Reference is made to Investigational New Drug (IND) application 52,196 dated and received December 20, 1996 for BMS-200475 (entecavir, ETV) (SQ 34,676) for the treatment of hepatitis B virus (HBV). Also, reference is made to New Drug Application (NDA) 21-797 for BMS-200475 (entecavir, ETV) dated and received September 29, 2004.

We have the following review comments and recommendations:

**Clinical Pharmacology:**

1. Based on the simulated ETV areas under the curve (AUCs) from population pharmacokinetics (PK) analysis and the  $AUC_{inf}$  of entecavir from the non-

compartmental model, we recommend you change the dose adjustment for severely renally-impaired patients maintained with hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) to 10% of the recommended dose for patients with normal renal function (RF). This adjustment will provide entecavir exposure more closely related to that in patients with normal renal function after the full dose.

2. Using available electrocardiograms (ECG) and plasma-concentration data from all Phase-1 clinical pharmacology studies, please assess the predictive ability of the linear regression models for the corrected QT interval (Bazett's correction) (QTcB), the corrected QT interval (Fridericia's correction) (QTcF), and PR intervals defined in the retrospective ECG analysis of Protocol AI463041.
3. Please provide a comprehensive listing of subjects in all Phase-1 clinical pharmacology studies who experienced any of the following occurrences:
  - A. borderline or prolonged QTcB and QTcF [*i.e.*: intervals in the range 431 to 450 millisecond (msec) (borderline) or > 450 msec (prolonged) for male subjects, and QTcB intervals in the range 451 to 470 msec (borderline) or > 470 msec (prolonged) for females subjects];
  - B. categorical changes in QTcB and QTcF (<30, <=60, and >60 msec); and
  - C. borderline or prolonged PR [*i.e.* 201 to 250 msec (borderline) and >250 msec (prolonged)].

Please include an integrated dataset (SAS transport files or Excel) for the subjects listed above with the following subject information: study, subject number, age, gender, race, height, weight, and treatment.

4. Please provide a comprehensive listing of delta corrected QT intervals (QTc) values for all subjects in Phase- 1 clinical pharmacology studies. Please include an integrated dataset (SAS transport files or Excel) with the following patient information: study, subject number, age, gender, race, height, weight, and treatment.
5. Please provide a comprehensive listing of delta PR values for all subjects in Phase-1 clinical pharmacology studies. Please include an integrated dataset (SAS transport files or Excel) with the following patient information: study, subject number, age, gender, race, height, weight, and treatment.

**Microbiology:**

6. We have performed a meta-analysis using the combined ETV resistance datasets from studies 014, 015 and 026 in lamivudine-experienced (LAM) patients. This analysis determined that substitutions at I169 developed in 7 isolates on 1 mg ETV treatment in the

context of the LAM-resistant mutations L180M and M204V or I and ETV-associated substitutions at T184, M202 and/or M250. We note that you have not highlighted the I169 substitutions. The I169L/M/S/T substitutions occur in the context of LAM- and ETV-associated resistance substitutions and it is difficult to determine the contribution of the I169 substitutions to decreased ETV susceptibility from the limited clinical data. Because *in vitro* phenotypic data on ETV and ADV susceptibility of recombinant clones with I169 substitutions with and without LAM- and ETV-associated resistance substitutions is important data, please submit any available data examining the effect of the I169 substitutions on ETV susceptibility in *in vitro* phenotypic testing of recombinant clones alone and in the context of LAM- and ETV-associated resistance substitutions.

## Chemistry, Manufacturing, and Controls

### Tablet Formulation

7. The area percentage for ETV monohydrate drug substance batches 002, 003, and 004 has area percentages of ca \_\_\_\_\_, \_\_\_\_\_, respectively (see Section 3.2.5.4.4, page 432). Please explain what these area percentage values represent. If they correspond to drug substance purity content, please explain the discrepancy between a total impurities content value of \_\_\_\_\_ (see Table 3.2.5.3.2.T04) for drug substance batch 002 and an area percentage of \_\_\_\_\_.
8. Please submit the \_\_\_\_\_ results for the drug substance stability samples at initial time and release. Please describe the sampling or monitoring frequency that was followed when manufacturing the registration batches (*i.e.*, LTSS batches) at the commercial site for manufacture of ETV Film Coated Tablets (FCT) 0.5 mg and 1 mg. For example were samples taken at the beginning, middle, and end of the run or were samples taken throughout the run? What were the criteria for the decision that there were a sufficient number of samples taken at different times to adequately evaluate the quality of the batch? Also, please describe the sampling or monitoring frequency that will be followed during commercial manufacture of ETV FCT 0.5 mg and 1 mg.
9. The drug product batch analysis results reported in Section 3.2.P.5.4, pages 346 – 357, show several clinical drug product batches manufactured at the commercial site released with a Total Impurities values higher than that seen in the registration batches of drug product used for LTSS (*i.e.*, \_\_\_\_\_ < \_\_\_\_\_). While all the drug product batches reported in the application meet the proposed Total Impurities release specification (NMT \_\_\_\_\_), please explain why there might be lot-to-lot variability for ETV FCT 0.5 mg and 1 mg manufactured at the commercial site. Also please advise us should you have concerns that lot-to-lot variability might prevent the commercial product from meeting specifications for the entire \_\_\_\_\_ proposed shelf life.
10. Please provide a description of the ETV FCT bulk container, including descriptions of the \_\_\_\_\_.

11

12. We recommend that you continue investigating alternative HPLC methodology that will improve the \_\_\_\_\_ when determining assay, total impurities/degradants, and individual impurities/degradants in ETV FCT 0.5 mg and 1 mg.
13. Please add an ETV drug substance \_\_\_\_\_ release specification for \_\_\_\_\_ and set release specifications for these \_\_\_\_\_ impurities that are consistent with the ICH guideline Q3C and manufacturing capability. Alternatively you may set in-process release specifications for \_\_\_\_\_ to ensure that these potential impurities are not present in the \_\_\_\_\_ drug substance at a level that exceeds the ICH guidelines.

#### **Oral Formulation**

14. Please revise the release specifications for \_\_\_\_\_ to read less than or equal to \_\_\_\_\_. This is consistent with the ICH Q3B(R) qualification threshold for degradants in a product with a maximum daily dose of less than 10 mg. Higher acceptance criteria may be proposed if toxicological qualification data for these two degradants are available.
15. Please describe the sampling or monitoring frequency that was followed when manufacturing the registration batches (*i.e.*, LTSS batches) at the commercial site for manufacture of Entecavir Oral Solution, 0.05 mg/mL (ETV OS). Also, please describe the sampling or monitoring frequency that will be followed during commercial manufacture of ETV OS.
16. Please correct the calculation for Potency (mg/mL) in Method \_\_\_\_\_ reflect that the sample is \_\_\_\_\_.
17. Please review for accuracy the information on the Purchase Specifications for the 10 mL dosing spoon (\_\_\_\_\_. In particular, please verify that the \_\_\_\_\_ used by the supplier to manufacture the dosing device is correct and, if necessary, update your Purchase Specification. Also, please submit any changes to the Purchase Specification for the 10 mL PP dosing spoon that will be packaged with ETV OS.

*NDA 21-797  
NDA 21-798  
February 14, 2005  
Page 5*

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 at 301-827-2335 if you have any questions regarding the contents of this transmission.

**Appears This Way  
On Original**

-----  
**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

3/3/05 10:44:57 AM

CSO

This facsimile contains CMC, Micro, PK Review RFI and  
will be sent to BMS following final sign-off.

Kathrine Laessig

3/3/05 10:56:00 AM

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: March 01, 2005

To: Joan Fung-Tomc	From: Marsha S. Holloman
Company: Bristol-Myers Squibb Co.	Title: Regulatory Health Project Manager, HFD-530
Fax number: 203-677-3818	Fax number: 301-827-2471
Phone number: 203-677-3817	Phone number: 301-827-2335

Subject: NDA 21-797 & NDA 21-798 – CLINICAL PHARMACOLOGY,  
MICROBIOLOGY, AND CMC REVIEW COMMENTS

Total no. of pages including cover: 7

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. If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2335 Thank you.



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA: 21-797**  
**NDA: 21-798**

**Drug: BMS-200475 (entecavir) (ETV) (SQ 34,676)**

**Date: February 14, 2004**

**To: Joan C. Fung-Tomc, PhD, ABMM, Director, Global Regulatory Science**

**Sponsor: Bristol-Myers Squibb Company**

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

**Through: Jenny H. Zheng, PhD, Clinical Pharmacologist**  
**Kimberly Bergman, Pharm D, Clinical Pharmacologist**  
**Lisa Naeger, PhD, Microbiologist**  
**Lorenzo Rocca, PhD, Chemist**  
**Linda L. Lewis, MD, Medical Officer**  
**Yoshihiko Murata, MD, PhD, Medical Officer**

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

**Subject: CLINICAL PHARMACOLOGY, MICROBIOLOGY, AND CMC REVIEW COMMENTS**

---

Reference is made to Investigational New Drug (IND) application 52,196 dated and received December 20, 1996 for BMS-200475 (entecavir, ETV) (SQ 34,676) for the treatment of hepatitis B virus (HBV). Also, reference is made to New Drug Application (NDA) 21-797 for BMS-200475 (entecavir, ETV) dated and received September 29, 2004.

We have the following review comments and recommendations:

**Clinical Pharmacology:**

1. Based on the simulated ETV areas under the curve (AUCs) from population pharmacokinetics (PK) analysis and the AUC<sub>inf</sub> of entecavir from the non-

compartmental model, we recommend you change the dose adjustment for severely renally-impaired patients maintained with hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) to 10% of the recommended dose for patients with normal renal function. This adjustment will provide entecavir exposure more closely related to that in patients with normal renal function after the full dose.

2. Using available electrocardiograms (ECG) and plasma-concentration data from all Phase-1 clinical pharmacology studies, please assess the predictive ability of the linear regression models for the corrected QT interval (Bazett's correction) (QTcB), the corrected QT interval (Fridericia's correction) (QTcF), and renal function (PR) as defined in the retrospective ECG analysis of Protocol AI463041.
3. Please provide a comprehensive listing of subjects in all Phase-1 clinical pharmacology studies who experienced any of the following occurrences:
  - A. borderline or prolonged QTcB and QTcF [*i.e.*: intervals in the range 431 to 450 millisecond (msec) (borderline) or > 450 msec (prolonged) for male subjects, and QTcB intervals in the range 451 to 470 msec (borderline) or > 470 msec (prolonged) for females subjects];
  - B. categorical changes in QTcB and QTcF (<30, <=60, and >60 msec); and
  - C borderline or prolonged PR [*i.e.* 201 to 250 msec (borderline) and >250 msec (prolonged)].

Please include an integrated dataset (SAS transport files or Excel) for the subjects listed above with the following subject information: study, subject number, age, gender, race, height, weight, and treatment.

4. Please provide a comprehensive listing of delta corrected QT intervals (QTc) values for all subjects in Phase- 1 clinical pharmacology studies. Please include an integrated dataset (SAS transport files or Excel) with the following patient information: study, subject number, age, gender, race, height, weight, and treatment.
5. Please provide a comprehensive listing of delta PR values for all subjects in Phase-1 clinical pharmacology studies. Please include an integrated dataset (SAS transport files or Excel) with the following patient information: study, subject number, age, gender, race, height, weight, and treatment.

**Microbiology:**

6. We have performed a meta-analysis using the combined ETV resistance datasets from studies 014, 015 and 026 in lamivudine-experienced (LAM) patients. This analysis determined that substitutions at I169 developed in 7 isolates on 1 mg ETV treatment in the

context of the LAM-resistant mutations L180M and M204V or I and ETV-associated substitutions at T184, M202 and/or M250. We note that you have not highlighted the I169 substitutions. The I169L/M/S/T substitutions occur in the context of LAM- and ETV-associated resistance substitutions and it is difficult to determine the contribution of the I169 substitutions to decreased ETV susceptibility from the limited clinical data. Because *in vitro* phenotypic data on ETV and ADV susceptibility of recombinant clones with I169 substitutions with and without LAM- and ETV-associated resistance substitutions is important data, please submit any available data examining the effect of the I169 substitutions on ETV susceptibility in *in vitro* phenotypic testing of recombinant clones alone and in the context of LAM- and ETV-associated resistance substitutions.

## Chemistry, Manufacturing, and Controls

### Tablet Formulation

7. The area percentage for ETV monohydrate drug substance batches 002, 003, and 004 has area percentages of ca. —, respectively (see Section 3.2.5.4.4, page 432). Please explain what these area percentage values represent. If they correspond to drug substance purity content, please explain the discrepancy between a total impurities content value of — (see Table 3.2.5.3.2.T04) for drug substance batch 002 and an area percentage of —.
8. Please submit the — results for the drug substance stability samples at initial time and release. Please describe the sampling or monitoring frequency that was followed when manufacturing the registration batches (*i.e.*, LTSS batches) at the commercial site for manufacture of ETV Film Coated Tablets (FCT) 0.5 mg and 1 mg. For example were samples taken at the beginning, middle, and end of the run or were samples taken throughout the run? What were the criteria for the decision that there were a sufficient number of samples taken at different times to adequately evaluate the quality of the batch? Also, please describe the sampling or monitoring frequency that will be followed during commercial manufacture of ETV FCT 0.5 mg and 1 mg.
9. The drug product batch analysis results reported in Section 3.2.P.5.4, pages 346 – 357, show several clinical drug product batches manufactured at the commercial site released with a Total Impurities values higher than that seen in the registration batches of drug product used for LTSS (*i.e.*, — vs. < —). While all the drug product batches reported in the application meet the proposed Total Impurities release specification (NMT —), please explain why there might be lot-to-lot variability for ETV FCT 0.5 mg and 1 mg manufactured at the commercial site. Also please advise us should you have concerns that lot-to-lot variability might prevent the commercial product from meeting specifications for the entire 24-month proposed shelf life.
10. Please provide a description of the ETV FCT bulk container, including descriptions of the

11.

12. We recommend that you continue investigating alternative HPLC methodology that will improve the \_\_\_\_\_ when determining assay, total impurities/degradants, and individual impurities/degradants in ETV FCT 0.5 mg and 1 mg.

13. Please add an ETV drug substance \_\_\_\_\_ release specification for \_\_\_\_\_ and set release specifications for these \_\_\_\_\_ impurities that are consistent with the ICH guideline Q3C and manufacturing capability. Alternatively you may set in-process release specifications for \_\_\_\_\_ to ensure that these potential impurities are not present in the \_\_\_\_\_ drug substance at a level that exceeds the ICH guidelines.

#### **Oral Formulation**

14. Please revise the release specifications for \_\_\_\_\_ to read less than or equal to \_\_\_\_\_. This is consistent with the ICH Q3B(R) qualification threshold for degradants in a product with a maximum daily dose of less than 10 mg. Higher acceptance criteria may be proposed if toxicological qualification data for these two degradants are available.

15. Please describe the sampling or monitoring frequency that was followed when manufacturing the registration batches (*i.e.*, LTSS batches) at the commercial site for manufacture of Entecavir Oral Solution, 0.05 mg/mL (ETV OS). Also, please describe the sampling or monitoring frequency that will be followed during commercial manufacture of ETV OS.

16. Please correct the calculation for Potency (mg/mL) in Method \_\_\_\_\_ to reflect that the sample is \_\_\_\_\_.

17. Please review for accuracy the information on the Purchase Specifications for the 10 mL dosing spoon: \_\_\_\_\_. In particular, please verify that the \_\_\_\_\_ used by the supplier to manufacture the dosing device is correct and, if necessary, update your Purchase Specification. Also, please submit any changes to the Purchase Specification for the 10 mL PP dosing spoon that will be packaged with ETV OS.

NDA 21-797  
NDA 21-798  
February 14, 2005  
Page 4

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-827-2335 if you have any questions regarding the contents of this transmission.

Appears This Way  
On Original

6 Page(s) Withheld

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

       § 552(b)(5) Deliberative Process

       § 552(b)(5) 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: December 30, 2004**

<b>To: Michael E. Brady</b>	<b>From: Marsha S. Holloman</b>
<b>Company: Bristol-Myers Squibb Co.</b>	<b>Title: Regulatory Health Project Manager, HFD-530</b>
<b>Fax number: 203-677-3818</b>	<b>Fax number: 301-827-2471</b>
<b>Phone number: 203-677-3812</b>	<b>Phone number: 301-827-2335</b>
<b>Subject: NDA 21-797 – CLINICAL REQUEST FOR INFORMATION (RFI)</b>	

**Total no. of pages including cover: 4**

**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. If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2335 Thank you.**



## MEMORANDUM OF FACSIMILE CORRESPONDENCE

**NDA:** 21-797

**NDA:** 21-798

**Drug:** BMS-200475 (entecavir) (ETV) (SQ 34,676)

**Date:** December 30, 2004

**To:** Joan C. Fung-Tomc, PhD, ABMM, Director, Global Regulatory Science  
Michael E. Brady, PhD, Director, Regulatory Science

**Sponsor:** Bristol-Myers Squibb Company

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

**Through:** Linda L. Lewis, MD, Medical Officer

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

**Subject:** CLINICAL REQUEST FOR INFORMATION (RFI)

---

Reference is made to Investigational New Drug (IND) application 52,196 dated and received December 20, 1996 for BMS-200475 (entecavir, ETV) (SQ 34,676) for the treatment of hepatitis B virus (HBV). Also, reference is made to New Drug Application (NDA) 21-797 for BMS-200475 (entecavir, ETV) dated and received September 29, 2004.

Please submit the requested clinical information by Thursday, January 6, 2005.

1. In the study datasets, please clarify the difference between the variables for off treatment date (OFTRTD) and last dose date entered (LADSDDED) and also the difference between the variables for dose start date for randomized patient (STARTD) and first date of dosing (DOSED). Which of these variables were used in the analyses involving dates?
2. In the final study report for AI463022, patient #AI463022-68-10095 is listed as discontinuing study therapy in response to an AE described as cystitis. In the dataset, the patient is coded as 5 (discontinued) in the variable AEACTION (action taken in response to an AE). In the study addendum, the patient is coded as 1 (none, no action taken) in the same variable. Please explain the discrepancy.

3. Also related to patient discontinuations, 2 patients in Study 022 (#132-10857 and #185-10587) have narratives that describe discontinuing study drug due to AEs after 38 and 89 days on study medication. These patients are not listed in the AE datasets as discontinuing due to AEs. #132-10857 is not reported to have an AE of amylase/lipase elevation as the narrative describes. #185-10587 is listed as interrupting study treatment. Please clarify the status of these 2 patients.
4. The STAT files contain the patient disposition at different phases of study. Among patients in Study 022 who failed to complete the first year of dosing (first phase), why doesn't the reason for discontinuation (DCRNL) match the reason for non-completion (NNCPRNL) for some of the patients? For # for example, DCRNL is coded as "death" but NNCPRNL is coded as "adverse event." How are the patients who were never dosed with study drug identified?
5. Please provide a more detailed description of the different variables coded in the laboratory datasets (LBVAL, USSDVAL, ABSVAL) and how each was derived. In analyzing the laboratory value data, which variable was used to calculate mean values, etc?

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 at 301-827-2335 if you have any questions regarding the contents of this transmission

Appears This Way  
On Original

-----  
**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  
12/30/04 02:07:24 PM  
CSO

Linda Lewis  
12/30/04 02:27:07 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: December 23, 2004**

<b>To: Michael E. Brady</b>	<b>From: Jeff D. O'Neill</b>
<b>Company: Bristol-Myers Squibb Co.</b>	<b>Title: Regulatory Health Project Manager, HFD-530</b>
<b>Fax number: 203-677-3818</b>	<b>Fax number: 301-827-2471</b>
<b>Phone number: 203-677-3812</b>	<b>Phone number: 301-827-2335</b>
<b>Subject: NDA 21-797/21-798 - Clinical Pharmacology comments</b>	

**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. If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2335 Thank you.**



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA:** 21-797  
21-798

**Drug:** BMS-200475 (entecavir) (ETV) (SQ 34,676)

**Date:** December 23, 2004

**To:** Michael E. Brady, PhD, Director, Regulatory Science

**Sponsor:** Bristol-Myers Squibb Company

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

**Through:** Jenny Zheng, PhD, Clinical Pharmacologist

**Concur:** Linda L. Lewis, MD, Acting Medical Team Leader  
Yoshihiko (Yoshi) Murata, MD, PhD, Medical Officer  
Kellie S. Reynolds, PharmD, Clinical Pharmacology Team Leader

**Subject:** Clinical Pharmacology comments regarding your population PK studies  
A1463017 and 930007867.

---

The following comments are on behalf of Jenny Zheng, PhD, Clinical Pharmacologist:

Please submit the following information for Population PK studies AI463017 and 930007867:

- All raw data that were used for population PK analyses. The data should be submitted as SAS transport files.
- Data files (SAS transport files) used for NONMEM base model and final model.
- NONMEM model and output files. All model files should be submitted as "txt" files. For example filename "test1.ctl" should be renamed as "test1\_ctl.txt".

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 at 301-827-2335 if you have any questions regarding the contents of this transmission.

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

/s/

-----  
Jeff ONeill  
12/23/04 01:55:41 PM  
CSO

Clinical Pharmacology comments regarding NDAs 21797&21798. Hard copy sign-f  
12/23/04

Linda Lewis  
12/27/04 02:21:08 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: December 15, 2004**

<b>To: Joan C. Fung-Tomc</b>	<b>From: Marsha S. Holloman</b>
<b>Company: Bristol-Myers Squibb Co.</b>	<b>Title: Regulatory Health Project Manager, HFD-530</b>
<b>Fax number: 203-677-3817</b>	<b>Fax number: 301-827-2471</b>
<b>Phone number: 203-677-3812</b>	<b>Phone number: 301-827-2335</b>
<b>Subject: NDA 21-797 – MEDICAL &amp; CLINICAL PHARMACOLOGY REQUESTS FOR INFORMATION</b>	

**Total no. of pages including cover: 4**

**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. If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2335 Thank you.**



**MEMORANDUM OF FACSIMILE CORRESPONDENCE**

**NDA:** 21-797

**Drug:** BMS-200475 (entecavir) (ETV) (SQ 34,676)

**Date:** December 10, 2004

**To:** Joan C. Fung-Tomc, PhD, ABMM, Director, Global Regulatory Science

**Sponsor:** Bristol-Myers Squibb Company

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

**Through:** Linda L. Lewis, MD, Medical Officer  
Kimberly Bergman, Pharm D, Clinical Pharmacologist

**Concur:** Kellie S. Reynolds, Pharm D, Clinical Pharmacology Team Leader  
Katherine A. Laessig, MD, Medical Team Leader

**Subject:** MEDICAL & CLINICAL PHARMACOLOGY REQUESTS FOR INFORMATION

---

Reference is made to Investigational New Drug (IND) application 52,196 dated and received December 20, 1996 for BMS-200475 (entecavir, ETV) (SQ 34,676) for the treatment of hepatitis B virus (HBV). Also, reference is made to New Drug Application (NDA) 21-797 for BMS-200475 (entecavir, ETV) dated and received September 29, 2004.

**Medical:**

The Clinical Safety Summary indicates that, in addition to the individual study CRT datasets, the safety data are presented in three integrated datasets: the nucleoside-naive subjects, the lamivudine-refractory subjects, and the safety cohort subjects (Cohorts A, B, and C, respectively, in the CRT dataset "integ safety"). This file contains listings for 2427 subjects from the 10 identified Phase 2 and 3 studies. However, Cohort C only includes 2399 subjects. There are 28 subjects from rollover Study 007, who are not included in any cohort. These subjects appear to be included in the total patient population number used to calculate rates of malignancies but not in the other safety analyses. Please submit the following information:

1. Please explain why these patients are not included in Cohort C.

2. Please summarize which analyses were performed using Cohort C and which analyses included the subjects in rollover Study 007.
3. Please explain whether all patients who initially received placebo, subsequently received ETV (the malignancy analysis suggests that 105 of 108 placebo patients later received entecavir) and how these patients were included in the safety analyses.

**Clinical Pharmacology:**

4. Based on the dosage and administration recommendations for dose adjustment in patients with renal impairment, please provide the predicted exposures for subjects with varying degrees of renal function (including the highest and lowest CLcr for each dose group).
5. Please provide demographic/baseline information, including weights, for all subjects in studies in Japanese healthy volunteers (Protocols AI463-021 and AI463-029).

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 at 301-827-2335 if you have any questions regarding the contents of this transmission.

-----  
**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

12/15/04 11:10:25 AM

CSO

This facsimile contains MO & PK RFIs about the  
clinical safety update and will be sent immediately  
following final sign-off.

Kathrine Laessig

12/15/04 11:16:21 AM

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: November 18, 2004**

<b>To: Michael E. Brady</b>	<b>From: Marsha S. Holloman</b>
<b>Company: Bristol-Myers Squibb Co.</b>	<b>Title: Regulatory Health Project Manager, HFD-530</b>
<b>Fax number: 203-677-3818</b>	<b>Fax number: 301-827-2471</b>
<b>Phone number: 203-677-3812</b>	<b>Phone number: 301-827-2335</b>

**Subject: NDA 21-797 - CLINICAL & STATISTICAL REVIEW COMMENTS**

**Total no. of pages including cover: 13**

**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. If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2335 Thank you.**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 21-797  
NDA 21-798

Bristol-Myers Squibb Company  
Attention: Michael E. Brady, PhD  
Director, Global Regulatory Affairs  
5 Research Parkway  
PO Box 5100  
Wallingford, CT 06492-7660

Dear Dr. Brady:

Please refer to your September 29, 2004 new drug applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Entecavir (BMS-20075) 0.5 mg and 1 mg Oral Tablets and Solution.

We also refer to your pre-submissions dated: June 17, 2004, July 2, 2004, July 14, 2004, July 27, 2004, August 2, 2004, August 6, 2004, August 23, 2004, September 3, 2004, September 9, 2004, and September 10, 2004.

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 November 3, 2004 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. Also, we do have the following review comments and recommendations.

1. We notice that you failed to enroll any significant numbers of African Americans or other black minorities in your clinical trials. This deficiency may need to be addressed at a later time.
2. Please explain what role, if any, \_\_\_\_\_ will play in the testing of commercial entecavir drug substance and drug product.
3. Please modify the clinical resistance dataset so that amino acids are in numerical order rather than alphabetical order. The template is not usable in the current format. In addition to the official submission of these data to the NDA, please attach the same information to an email and send it to Marsha Holloman by November 10, 2004.

NDA 21-797

NDA 21-798

Page 2

4. Please examine the activity of entecavir against the adefovir-resistant mutations rtN236T and rtA181V.
5. Please determine the *in vitro* combination activity relationship of entecavir and adefovir dipivoxil.
6. Please explain why there are two different PCR assay limits — 300) in your database.
7. Please submit the assay performance characteristics for the PCR assay.

We agree with your request for a deferral of pediatric studies (PREA) until the risk/benefit assessment in adults is complete.

Also, we agree with your request for priority review. Therefore, the action date for both NDAs is March 29, 2005.

These two new NDAs will be the subject of an Antiviral Advisory Committee (AVAC) meeting currently scheduled for March 10 or 11, 2005. We will advise you once we have the final date scheduled. Finally, please submit the safety update for entecavir on or before January 10, 2005, approximately two months prior to the AVAC meeting.

If you have any questions, call Marsha Holloman, Regulatory Health Project Manager, at (301) 827-2335.

Sincerely,

*{See appended electronic signature page}*

Debra B. Birnkrant, MD  
Director  
Division of Antiviral Drug Products HFD-530  
Office of Drug Evaluation IV  
Office of New Drugs  
Center for Drug Evaluation and Research

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

/s/

-----  
Debra Birnkrant  
11/5/04 11:38:12 AM  
NDA 21-797

ADDENDUM TO  
FILING LETTER

**From:** Holloman, Marsha S  
**Sent:** Friday, November 05, 2004 12:32 PM  
**To:** 'Michael E Brady'  
**Subject:** ETV Trade Name

Mike:

I just faxed you the Filing Meeting Letter that answers most of your questions.

Additionally, please submit two more trade names, just in case your 1st choice is not approved. We do not want anything to interfere with the 6-month priority review goal date.

Jim Farrelly is handling the CAC meeting details. Please note that this meeting is before the full CAC since the Exec CAC has already reviewed your data twice. I will send the meeting information ASAP.

Finally, the date for submission for the safety update is January 10, 2005 (60 days prior to advisory committee meeting). Data for presentation to the AVAC must be the most currently available.

Please email me if you have further questions.

Thanks....Marsha

Marsha S. Holloman, BSpHarm, JD  
Regulatory Health Project Manager  
Division of Antiviral Drug Products  
(HFD-530) ODEIV/CDER/FDA  
phone: 301-827-2335  
fax: 301-827-2471  
email: [hollomanm@cderr.fda.gov](mailto:hollomanm@cderr.fda.gov)

-----  
**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  
11/5/04 12:46:57 PM  
CSO  
ADDENDUM TO 74-day Filing Letter



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

**FACSIMILE TRANSMITTAL SHEET**

**DATE: March 24, 2005**

<b>To: Joan C. Fung-Tomc</b>	<b>From: Marsha S. Holloman</b>
<b>Company: Bristol-Myers Squibb Co.</b>	<b>Title: Regulatory Health Project Manager, HFD-530</b>
<b>Fax number: 203-677-3818</b>	<b>Fax number: 301-827-2471</b>
<b>Phone number: 203-677-3817</b>	<b>Phone number: 301-827-2335</b>

**Subject: NDA 21-797 & NDA 21-798 – MO & PK CLINICAL 2<sup>nd</sup> REVISED DRAFT LABELING CHANGES – PACKAGE INSERT**  
*1 PATIENT*

**Total no. of pages including cover: 7**

**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. If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2335 Thank you.**



## MEMORANDUM OF FACSIMILE CORRESPONDENCE

**NDA:** 21-797

**Drug:** BMS-200475 (entecavir) (ETV) (SQ 34,676)

**Date:** November 17, 2004

**To:** Michael E. Brady, PhD, Director, Regulatory Science

**Sponsor:** Bristol-Myers Squibb Company

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

**Through:** Linda L. Lewis, MD, Medical Officer  
Yoshihiko (Yoshi) Murata, MD, PhD, Medical Officer  
Thomas Hammerstrom, PhD, Mathematical Statistician

**Concur:** Katherine A. Laessig, MD, Medical Team Leader  
Guoxing (Greg) Soon, PhD, Biometrics Team Leader

**Subject:** Clinical & Statistical Review Comments

---

Reference is made to Investigational New Drug (IND) application 52,196 dated and received December 20, 1996 for BMS-200475 (entecavir, ETV) (SQ 34,676) for the treatment of hepatitis B virus (HBV). Also, reference is made to New Drug Application (NDA) 21-797 for BMS-200475 (entecavir, ETV) dated and received September 29, 2004.

Please provide the requested information by 5 PM, Monday, November 22, 2004.

We have the following comments and recommendations:

**Clinical:**

1. Please forward the most recent MedWatch/safety reports that were previously submitted to the ETV IND for the following subjects: AI463026-101-80042, AI463014-39-6039, AI463022-136-10204, and AI463027-12-51342.
2. For patient AI463014-39-6039, please explain why the subject stopped study drug, why the subject started lamivudine (LAM) following cessation of ETV, and whether or not this subject bore sequence-confirmed lamivudine-resistant HBV.

10 Page(s) Withheld

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

\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(5) 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  
11/18/04 10:00:36 AM  
CSO

This facsimile contains MO & Stats RFIs regarding the  
new NDA and will be sent following final  
sign-off.

Kathrine Laessig  
11/18/04 01:41:15 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 21, 2004**

<b>To: Michael E. Brady</b>	<b>From: Jeff D. O'Neill</b>
<b>Company: Bristol-Myers Squibb Co.</b>	<b>Title: Regulatory Health Project Manager, HFD-530</b>
<b>Fax number: 203-677-7867</b>	<b>Fax number: 301-827-2471</b>
<b>Phone number: 203-677-6734</b>	<b>Phone number: 301-827-2362</b>

**Subject: NDA 21797/ CLINICAL PHARMACOLOGY REVIEW  
 COMMENTS AND RECOMMENDATIONS**

**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. If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2335 Thank you.**



## MEMORANDUM OF FACSIMILE CORRESPONDENCE

**IND:** 21-797

**Drug:** entecavir (ENT)

**Date:** July 21, 2004

**To:** Michael E. Brady, Ph.D., Director, Regulatory Science

**Sponsor:** Bristol-Myers Squibb Company

**From:** Jeff D. O'Neill, ACRN, Regulatory Health Project Manager, HFD-530

**Through:** Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader, HFD-530  
Derek Zhang, Ph.D., Clinical Pharmacology, HFD-530

**Concur:** Katherine A. Laessig, MD, Medical Team Leader, HFD-530  
Linda L. Lewis, M.D., Medical Officer, HFD-530

**Subject:** CLINICAL REVIEW COMMENTS AND RECOMMENDATIONS

The following clinical pharmacology comments are provided on behalf of Kellie Reynolds, Pharm. D., and Derek Zhang, Ph.D:

Based on our preliminary review of the study reports, we do not recommend you repeat the bioequivalence studies (AI463035 and AI463065). However, the results of these studies (very low concentrations from one subject who received the 1.0 mg tablet in 065; no quantifiable concentrations from one subject who received the 0.5 mg tablet in 035) are of concern to us. We need to review the pharmacokinetic data from the bioequivalence studies in the context of all pharmacokinetic data in the NDA. In addition, we may request that the Division of Scientific Investigations inspect the study sites for the two studies. If you have any further information about the investigations you conducted to determine the possible reasons for the unusual concentration data, please submit it with the NDA.

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 at 301-827-2335 if you have any questions regarding the contents of this transmission.

-----  
**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

7/27/04 05:50:09 PM

CSO

This facsimile contains PK BE review comments and was  
sent to BMS 21-Jul-2004.

Kathrine Laessig

7/29/04 03:56:29 PM

MEDICAL OFFICER

**REQUEST FOR CONSULTATION**

O (Division/Office).

**Director, Division of Medication Errors and  
Technical Support (DMETS), HFD-420  
PKLN Rm. 6-34**

FROM:

**Marsha S. Holloman, BS Pharm, JD  
Regulatory Health Project Manager  
Division of Antiviral Drug Products (DAVDP) HFC-530**

DATE December 30, 2004	IND NO. 52,182	NDA NO. NDA 21-797 NDA 21-798	TYPE OF DOCUMENT New NDAs	DATE OF DOCUMENT September 29, 2004
NAME OF DRUG Entecavir 0.5 & 1.0 mg Tablets Entecavir Oral Solution		PRIORITY CONSIDERATION Yes; PDUFA date: March 29, 2994	CLASSIFICATION OF DRUG NME	DESIRED COMPLETION DATE <b>March 18, 2005</b>

NAME OF FIRM: Bristol-Myers Squibb Pharmaceutical Company

**REASON FOR REQUEST**

**I. GENERAL**

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

**II. BIOMETRICS**

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

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

**III. BIOPHARMACEUTICS**

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

**IV. DRUG EXPERIENCE**

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

**V. SCIENTIFIC INVESTIGATIONS**

CLINICAL

PRECLINICAL

**COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:**

I am sending two trade names for the these new entecavir NDAs for the treatment of chronic hepatitis-B virus in adults. The sponsor's 1<sup>st</sup> choice for trade name is "BARACLUDGE". The sponsor's 2<sup>nd</sup> choice for trade name is \_\_\_\_\_  
I informed BMS that the two are so alike, that if one fails approval, the other will probably also fail. I am attaching electronic copies of both names attached to this consult. Please let me know if I should also send paper copies through inter-office mail.

PDUFA DATE: March 29, 2005

ATTACHMENTS: Draft Package Insert, Container and Carton Labels, trade name submissions

CC:

HFD-530/Archival NDA 21-797 & NDA 21798  
HFD-530/Division File  
HFD-530/Marsha S. Holloman, Regulatory Health Project Manager  
HFD-530/Reviewers & Team Leaders

SIGNATURE OF SENDER  
// Marsha S. Holloman 7-2418

METHOD OF DELIVERY (Check one)

MAIL  HAND  ELECTRONIC

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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

/s/

-----  
Marsha Holloman  
1/6/05 09:59:29 AM



-----  
**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

1/28/05 12:57:29 PM

CONSULT ' — BMS 3rd Choice for entecavir

**CONSULTATION RESPONSE**

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT  
OFFICE OF DRUG SAFETY  
(DMETS; HFD-420)**

<b>DATE RECEIVED:</b> 1/6/05 <b>DATE OF DOCUMENT:</b> 9/29/04	<b>DESIRED COMPLETION DATE:</b> 3/18/05 <b>PDUFA DATE:</b> 3/29/05	<b>ODS CONSULT #:</b> 05-0003
---	---	-------------------------------

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

**THROUGH:** Marsha S. Holloman  
Project Manager  
HFD-530

<b>PRODUCT NAME:</b>  Baraclude™ (Entecavir Tablets) 0.5 mg and 1 mg (Entecavir Oral Solution) 0.05 mg/mL  <b>NDA#: 21-797</b> <b>NDA#: 21-798</b>	<b>NDA SPONSOR:</b> Bristol-Myers Squibb Pharmaceutical Company
---	---

**SAFETY EVALUATOR:** Felicia Duffy, RN

**RECOMMENDATIONS:**

1. DMETS has no objections to the use of the proprietary name, Baraclude. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals 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 in order to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name Baraclude acceptable from a promotional perspective.

Carol Holquist, RPh  
Director, Division of Medication Errors and Technical Support  
Office of Drug Safety  
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)  
Office of Drug Safety  
HFD-420; PKLN Rm. 6-34  
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

**DATE OF REVIEW:** January 28, 2005

**NDA#** 21-797  
**NDA#** 21-798

**NAME OF DRUG:** **Baraclude™**  
(Entecavir Tablets)  
0.5 mg and 1 mg  
(Entecavir Oral Solution)  
0.05 mg/mL

**NDA HOLDER:** Bristol-Myers Squibb Pharmaceutical Company

**I. INTRODUCTION:**

This consult was written in response to a request from the Division of Anti-Viral Drug Products (HFD-530), for assessment of the proprietary name, "Baraclude", regarding potential name confusion with other proprietary or established drug names. Container labels, carton labeling and insert labeling were provided for review and comment. Additionally, an independent analysis of the proposed name, conducted by Med-E.R.R.S., was submitted by the sponsor.

PRODUCT INFORMATION

Baraclude (entecavir) is indicated for the treatment of chronic hepatitis B infection in adults with evidence of — . It will be available as 0.5 mg and 1 mg tablets and in an oral solution concentration of 0.05 mg/mL. The usual dose is 0.5 mg to 1 mg once daily. The tablets will be supplied in quantities of 30 and 90. The oral solution will be supplied as a ready-to-use product in a — mL bottle accompanied by a calibrated dosing spoon.

**II. RISK ASSESSMENT:**

The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>1,2</sup>, as well as several FDA databases<sup>3</sup> for existing drug names which sound-alike or look-alike to Baraclude to a degree where potential confusion between drug names could occur under

---

<sup>1</sup> MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

<sup>2</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

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<sup>4</sup>. The Saegis<sup>5</sup> 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 for Baraclude consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care 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 (EPD)**

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Baraclude. Potential concerns regarding drug marketing and promotion related to the proposed names 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 finds the proprietary name Baraclude acceptable from a promotional perspective.
2. The Expert Panel identified one proprietary name that was thought to have the potential for confusion with Baraclude. The product is listed in table 1 (see below), along with the dosage forms available and usual dosage.

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

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Baraclude	Entecavir Tablets: 0.5 mg and 1 mg Oral Solution: 0.05 mg/mL	Tablets: 0.5 mg to 1 mg QD Oral Solution: 10 mL to 20 mL QD (0.5 mg to 1 mg)	
Avalide	Irbesartan and Hydrochlorothiazide Tablets: 150 mg/12.5 mg and 300 mg/12.5 mg	150 mg to 300 mg ibesartan QD.	LA
*Frequently used, not all-inclusive. **LA (look-alike), SA (sound-alike)			

**B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)**

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Baraclude were discussed by the Expert Panel (EPD).

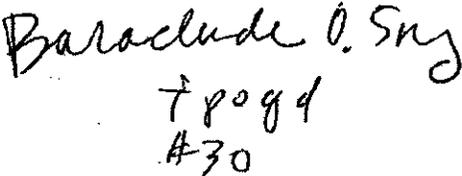
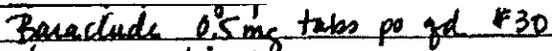
<sup>4</sup> WWW location <http://www.uspto.gov/tmdb/index.html>.

□ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com)

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Baraclude 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 122 health care professionals (pharmacists, physicians, and nurses) for each. 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 Baraclude (see below). 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
<p data-bbox="311 884 472 911"><u>Outpatient RX:</u></p> 	<p data-bbox="1065 1010 1279 1037">Baraclude 0.5 mg</p> <p data-bbox="984 1045 1360 1073">Take 1 tab by mouth once daily</p> <p data-bbox="1097 1081 1247 1108">Dispense 30</p>
<p data-bbox="311 1152 456 1180"><u>Inpatient RX:</u></p> 	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See appendix A for the complete listing of interpretations from the verbal and written studies.

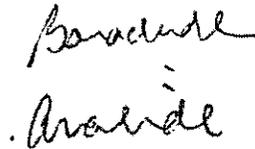
D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Baraclude, the primary concerns related to look-alike and sound-alike confusion with Avalide.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with the aforementioned name. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Baraclude. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size.

Avalide may look similar to Baraclude when scripted. Avalide is a combination anti-hypertension medication containing irbesartan and hydrochlorothiazide. The letters “ara” in Baraclude may look similar to the letters “ava” in Avalide. In addition, the ending of each name can look similar when scripted (“lude” vs. “lide”). Despite some orthographic similarities, the first letter of Baraclude (“B”) helps to distinguish it from Avalide, which begins with the letter “A”. Furthermore, the letter “c” in the middle of Baraclude helps to further differentiate between the two names. The name Baraclude also appears longer than Avalide when scripted. Overlapping product characteristics include route of administration (oral), frequency of administration (once daily), and dosage form (tablet). Baraclude and Avalide differ in strength (0.5 mg, 1 mg, 0.05 mg/mL vs. 150 mg/12.5 mg and 300 mg/12.5 mg), indication for use (hepatitis vs. hypertension), and usual dosage (0.5 mg to 1 mg vs. 150 mg to 300 mg). Although there are some overlapping product characteristics, the lack of convincing orthographic similarities along with the differentiating product characteristics help to minimize the potential for medication errors between Baraclude and Avalide.

Baraclude/Avalide



E. INDEPENDENT NAME ANALYSIS (Med-E.R.R.S.)

The analysis conducted by Medical Error Recognition and Revision Strategies (Med-E.R.R.S.) discussed the proprietary name Avalide as having potential look-alike similarities to Baraclude. The slight look-alike similarity was noted especially if the “B” of Baraclude was misinterpreted as indicating the second medication in an order set (i.e. B. Avalide). Med-E.R.R.S. concluded Baraclude could safely exist in the market. DMETS performed a risk assessment of Avalide and Baraclude in section II (D). DMETS concurs that the aforementioned name does not pose a significant safety risk. Thus, we concur with the overall finding of the study.

**III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:**

In the review of the container labels, carton and insert labeling of Baraclude, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL (Oral solution- 210 mL)



2.

B. CONTAINER LABEL (30 and 90 count)

C. CARTON LABELING

No comment.

D. INSERT LABELING

Dosage and Administration

1. The information about administering the medication on an empty stomach should appear after the recommended dosage to ensure proper usage of the medication. Relocate the sentence beginning with line 610 to immediately follow the end of the sentence of line 607.
2. Include a — tatement about diluting or mixing the oral solution: "Diluting or mixing TRADEMARK with water or any other solvent or liquid products is not recommended."
- 3.

How Supplied

4.

E. PATIENT PACKAGE INSERT

How Should I Take TRADEMARK?

1. See comment D2.
- 2.

IV. RECOMMENDATIONS:

- A. DMETS has no objections to the use of the proprietary name Baraclude.
- B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with this use of this product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.
- C. DDMAC finds the proprietary name Baraclude 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 Sammie Beam, project manager, at 301-827-3242.

---

Felicia Duffy, RN  
Safety Evaluator  
Division of Medication Errors and Technical Support  
Office of Drug Safety

Concur:

---

Alina Mahmud, RPh, MS  
Team Leader  
Division of Medication Errors and Technical Support  
Office of Drug Safety

Appendix A. Baraclude Prescription Study Results

<b>Written Inpatient</b>	<b>Written Outpatient</b>	<b>Verbal</b>
Baraclude	Baraclude	Baraclude
Baraclude	Baraclude	Baracude
Baraclude	Baraclude	Bariclude
Baraclude	Baraclude	Bariclude
Baraclude	Baraclude	Bariclude
Baraclude	Baraclude	Barocclude
Baraclude	Baraclude	Baroccluz
Baraclude	Baraclude	Barraclude
Baraclude	Baraclude	Varaclude
Baraclude	Baraclude	
	Baraclude	
	Baraclude	
	Baroclude	

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

/s/

-----  
Felicia Duffy  
3/1/05 09:43:15 AM  
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud  
3/3/05 10:12:01 AM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
3/3/05 03:52:26 PM  
DRUG SAFETY OFFICE REVIEWER

**REQUEST FOR CONSULTATION**

TO (Division/Office):

**ODS (Room 15B-08, PKLN Bldg.)  
ATTN: DDRE**

FROM:

Marsha S. Holloman, BS Pharm, JD  
Regulatory Health Project Manager  
Division of Antiviral Drug Products HFC-530  
CORP2/Rm 432 PHONE: 301-827-2418

DATE January 27, 2005	IND NO. 52,196	NDA NO. 21-797 & 21-798	TYPE OF DOCUMENT Concept Sheet for Pharmacovigilance Study	DATE OF DOCUMENT December 22, 2004
NAME OF DRUG Entecavir (ETV; BMS-475)		PRIORITY CONSIDERATION Yes	CLASSIFICATION OF DRUG 7030242	DESIRED COMPLETION DATE <b>February 02, 2005</b>

NAME OF FIRM **Bristol-Myers Squibb Pharmaceutical Company**

**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"/> <b>OTHER (SPECIFY BELOW)</b><br><b>Review Of Pharmacovigilance Protocol</b> |
| <input type="checkbox"/> MEETING PLANNED BY            |  |   |

**III. BIOPHARMACEUTICS**

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

**IV. DRUG EXPERIENCE**

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

**V. SCIENTIFIC INVESTIGATIONS**

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

**COMMENTS/SPECIAL INSTRUCTIONS:**

Entecavir is a guanosine nucleoside analogue proposed as a new treatment for patients with chronic hepatitis B infection with evidence of ongoing hepatic inflammation. NDA 21-797 (tablet) and NDA 21-798 (liquid) are undergoing priority review with an Advisory Committee meeting planned for March 11, 2005, and a planned action date of March 29, 2005. Bristol-Myers Squibb has submitted a proposal for a pharmacovigilance plan for entecavir intended to evaluate events of special interest identified during the drug development program: post-treatment exacerbation of hepatitis, rates of development of hepatocellular carcinoma, and possible drug-related carcinogenicity. The pharmacovigilance proposal includes a draft synopsis of a proposed Phase-4 study, a large simple study to detect long-term outcomes of chronic hepatitis B in patients randomized to receive either entecavir or other nucleoside/nucleotide therapy to be conducted over 5 to 8 years.

Please advise as to the appropriateness of the general study design to provide useful information regarding potential human cancer risk and potential for detection of decreases in hepatocellular carcinoma in the study population. Please include considerations of the strengths and limitations of such a study. Examples of successfully implemented programs for other drugs at raised similar concerns would be helpful.

SIGNATURE OF REQUESTER // <i>Marsha S. Holloman</i>	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> e-doc per DFS <input checked="" type="checkbox"/> Hand
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

---

DATE:            March 1, 2005

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

THROUGH:      Mark Avigan, M.D., C.M., Director  
                    Division of Drug Risk Evaluation, HFD-430

FROM:            Kate Gelperin, M.D., M.P.H., Medical Officer  
                    Division of Drug Risk Evaluation, HFD-430

SUBJECT:        Consult: Evaluation of proposed pharmacovigilance study to assess cancer risk  
                    Drug: Entecavir (BMS-475) IND 52,196; NDA 21-797 and 21-798  
                    Issue: Assess risk of cancer based on positive animal carcinogenicity studies  
                    PID #D050051

**Executive summary**

This memorandum is in response to a consult request from DAVDP to review the draft protocol entitled "Protocol AI463080: International Randomized Study of the Long Term Outcomes of Chronic HBV Patients Treated with Nucleosides or Nucleotides". This has been submitted by the sponsor as part of a program to assess the unknown risk of cancer in humans treated with entecavir, intended for the treatment of chronic hepatitis B (HBV) infection with evidence of ongoing hepatic inflammation. In pre-approval animal carcinogenicity studies, increased incidences of various tumors were observed. These findings were generally noted at high exposure multiples [ $\geq 40$  times (in mice) and  $\geq 24$  times (in rats)] the exposures in humans at therapeutic doses. The Carcinogenicity Assessment Committee has determined that these findings are of unknown relevance to human cancer risk.

The sponsor proposes to conduct a large simple randomized international cohort study aimed at comparing rates of mortality, the progression of liver disease, and development of cancers in patients with chronic HBV infection treated with entecavir compared with other nucleosides / nucleotides. After the initial randomization, the study will be observational; treatments may be switched or terminated during the study by the physician. Over the course of the study, follow-up will be conducted annually through \_\_\_\_\_

\_\_\_\_\_ . Follow-up, unblinded, is currently planned to continue  
annually for \_\_\_\_\_

The proposed study, along with the Sponsor's proposed pharmacovigilance plan, have the potential to provide valuable information about the balance of risks and benefits of entecavir therapy in patients with chronic HBV infection during actual use of this drug in a geographically diverse population. However, the ability to detect an adverse effect which may have a very long latency, such as cancer, is limited by the duration of follow-up of the study cohort, misclassification due to switching treatments over time, heterogeneity of patient population, especially with regard to pre-existing HCC risk, as well as the unknown nature of the specific risks.

Due to the important effects of duration of HBV infection and previous treatment on cancer risk (especially HCC), consideration should be given to conducting separate analyses for treatment naïve and previously treated groups, including patients with lamivudine resistance, with separate sample size requirements for each group. Consideration should also be given to increasing the duration of study follow-up to ten years. After the initial three year subject accrual period, and five year observation period, investigators should continue to report on patients who reached pre-specified study endpoints as they become aware of this (passive surveillance). In addition, study design should include

## Background

Entecavir is a guanosine nucleoside analogue proposed as a new treatment for patients with chronic HBV infection with evidence of ongoing hepatic inflammation. NDA 21-797 (tablet) and NDA 21-798 (liquid) are undergoing priority review with an Advisory Committee meeting planned for March 11, 2005, and a planned action date of March 29, 2005.

In pre-approval animal carcinogenicity studies, increased incidences of various tumors were observed.<sup>1</sup> Tumors observed in mice with statistically significant increases relative to controls included lung adenoma, lung carcinoma, liver carcinoma, vascular tumors (primarily ovarian and uterine hemangiosarcoma), and ductal adenoacanthoma of the salivary gland. Tumors observed with increased incidence in rats included malignant mesenchymal cell tumors of the kidney, liver carcinoma, Zymbal gland carcinoma, and brain gliomas. With the exception of lung adenomas in male mice, which were seen at three times the recommended human dose, these rodent findings were noted at relatively high multiples [ $\geq 40$  times (in mice) and  $\geq 24$  times (in rats)] compared to the corresponding exposure in humans at therapeutic doses.

The sponsor has submitted a proposal for a pharmacovigilance plan for entecavir intended to evaluate events of special interest identified during the drug development program: post-treatment exacerbation of hepatitis, rates of development of hepatocellular carcinoma, and

---

<sup>1</sup> New Drug Application Entecavir NDA 21-797 (tablet) and 21-798 (oral solution): Pharmacovigilance Plan and Draft Protocol, submitted by BMS December 22, 2004.

possible drug-related carcinogenicity. The pharmacovigilance proposal includes a draft synopsis of a proposed Phase 4 study, a large simple study to detect long-term outcomes of chronic HBV in patients randomized to receive either entecavir or other nucleoside / nucleotide therapy to be conducted over 5 to —

As noted by the sponsor, it is estimated that 350 million people worldwide are chronically infected with HBV and that over one million people die each year from HBV-associated complications of cirrhosis and primary hepatocellular carcinoma (HCC). Currently, there are three approved therapies for the treatment of chronic HBV infection: alpha interferon, lamivudine, and adefovir dipivoxil. Each of these drugs has potential therapeutic limitations in patients with HBV. Lamivudine is associated with a high rate of viral resistance, rising from 15 – 30% during the first year of treatment to 50% during the third year. Despite recent improvements in HBV treatment, complete and sustained response rates have remained low.

DAVDP has requested DDRE consultation regarding the appropriateness of the general study design to provide useful information regarding potential human cancer risk and potential for detection of decreases in hepatocellular carcinoma in the study population, with an assessment of the strengths and limitations of such a study. DAVDP has also requested examples of successfully implemented programs for other drugs that raised similar concerns.

### **Draft Protocol Summary**

The sponsor proposes to conduct a large simple randomized international cohort study aimed at comparing rates of mortality, the progression of liver disease, and development of cancers in patients with chronic HBV infection treated with entecavir compared with other nucleosides / nucleotides. Approximately 12,500 patients will be randomized from a central location on a 1:1 basis into either an entecavir treated group or a standard of care including lamivudine. Patients will be enrolled through their physician. About ten patients are expected to be recruited per physician; thus approximately 1,250 physicians are expected to participate in this study. The study population will include patients with confirmed chronic HBV infection (HBsAg positive on at least two occasions at least six months apart) who are initiating or, because of virologic failure, switching nucleoside/nucleotide treatment. Virologic failure must be documented by PCR ( $\geq 10^5$  copies/mL) or HBV DNA ( $\geq 0.7$  mEq/mL). Patients with cancer or decompensated liver disease will be excluded from the study. The study will be conducted in the US, Europe, Asia, North and South America. Randomization will be stratified based on treatment experience (treatment-naïve and previously treated). Dosing will be determined by the patient's physician.

After the initial randomization, the study will be observational; treatments may be switched or terminated during the study by the physician. Patients will be followed up for a minimum of 5 years as two unblinded treatment cohorts. Over the course of the study, follow-up will be conducted annually through r

ollow-up, unblinded, is currently planned to continue annually for —

Follow-up will be maintained regardless of discontinuation of treatment or switch to alternative therapy.

Study endpoints include:

- All-cause and cause specific mortality
- Cancer, with a separate analysis for
  - All cancers combined (excluding non-melanoma skin)
  - Hepatocellular carcinoma (HCC)
  - Non-HCC (including non-HCC liver)
- Liver transplantation

Descriptive statistics of baseline and follow-up patient characteristics (demographics, medical and behavioral health history, HBV clinical and laboratory data and treatments) will be generated annually. An analysis of the incidence of endpoints is planned once

As secondary analyses, incidence rates will be stratified by treatment history, extent of liver disease (no cirrhosis, compensated cirrhosis, decompensated cirrhosis) at baseline, region, gender, and age. Secondary analyses will also be conducted to examine the effects of initial treatment duration and dose, and other treatments subsequent to study start on the endpoints of interest. All statistical tests will be two-tailed.

### *Sample Size Considerations*

Sample size considerations were targeted to ascertain total tumors and were based on background cancer incidence rates determined by the sponsor in two studies of patients with chronic HBV: a retrospective observational study conducted in the US, and a prospective cohort study conducted in Taiwan with up to 11 years of follow-up. Combined, these studies covered 3 million subjects in integrated health systems. Approximately 70% of subjects were in the respective system for eight years or more.

Both the US and the Taiwan studies showed significant increases in cancer risk among patients infected with chronic HBV compared to a population not infected with HBV. For the US study, the overall incidence rate of malignancy in the confirmed chronic HBV cohort was 970 per 100,000 person-years (95% CI: 825-1131). The Taiwan study showed an overall malignancy incidence rate in the HBsAg+ cohort of 653 per 100,000 person-years (95% CI: 579-734). The increased overall cancer risk was mainly due to the increase in liver cancer, which contributed approximately one half of all the cancer cases in both studies.

The combined results of these studies were used to provide an expected background incidence rate of all cancers in the proposed study population of 800 per 100,000 person-years, half contributed by hepatocellular carcinoma, and half from all other tumor types. Based on these expected rates, the sponsor calculated that, for the primary analysis, a sample size of 6,250 patients in the entecavir group and 6,250 in the comparison group with alpha (two-tailed) = 0.05 and power = 0.80, will provide a minimum detectable relative risk for all tumors of 1.3, for

hepatocellular carcinoma of 0.7, and for non-hepatocellular carcinoma of 1.4. This calculation assumes an attrition rate of 20% over five years, based on the sponsor's previous experience studying this patient population. The sponsor proposes to use incentives to reduce patient attrition from the study.

## Discussion

### *Regulatory Perspective*

Positive results of animal carcinogenicity studies are described in approved product labeling for many drugs, including some drugs administered for prolonged periods of time (see tabular summary on next page).

Examples of indications for such drugs include lipid lowering (lovastatin, simvastatin, pravastatin, and atorvastatin), antiepileptic drugs (phenobarbital and phenytoin), ADHD (methylphenidate), oral hypoglycemic agents (pioglitazone), benign prostatic hypertrophy (finasteride), HIV infection (zidovudine, abacavir), osteoporosis with high risk of fracture (teriparatide), atopic dermatitis (tacrolimus), and gastroesophageal reflux disease (pantoprazole).

*Please note, this list is meant to be illustrative, but is not comprehensive.*

Many of the drugs included in this tabular summary can cause malignant tumors in one or more animal models at low multiples (<10) of the recommended human dose.

### *Special Problems of Cancer Epidemiology Studies*

Examples of drugs for which Phase 4 study commitments or other types of risk assessment or risk management plans have been requested by FDA include pantoprazole (Protonix<sup>®</sup>), omalizumab (Xolair<sup>®</sup>), tacrolimus (Protopic<sup>®</sup>) ointment, teriparatide (Forteo<sup>®</sup>), and pioglitazone (Actos<sup>®</sup>).

For one of these drugs (tacrolimus), positive data already exist for increased cancer risk in humans. Systemic exposure to tacrolimus (previously approved in 1994 as Prograf<sup>®</sup> capsules and injection for use as an immunosuppressant in organ rejection prophylaxis after organ transplant) is known to increase the risk of skin cancer and lymphoma in human patients who receive this treatment.<sup>2</sup>

---

<sup>2</sup> Jonas S, Rayes N, Neumann U, et al. De Novo malignancies after liver transplantation using tacrolimus-based protocols or cyclosporine-based quadruple immunosuppression with an interleukin-2 receptor antibody or antithymocyte globulin. *Cancer* 1997; 80(6):1141-50.

Selected Examples of Drugs with Positive Animal Carcinogenicity Studies in USPI<sup>3</sup>

Drug	Species	Multiple of human dose <sup>4</sup>	Tumor type
Lovastatin	Mice	3	Hepatocellular carcinoma
	Mice	4	Pulmonary adenoma
	Mice	1	Papilloma stomach
	Rats	2	Hepatocellular carcinoma
Pravastatin	Rats	4	Hepatocellular carcinoma
	Mice	15	Hepatocellular carcinoma
	Mice	15	Lung adenoma
Simvastatin	Mice	4	Liver carcinoma
	Mice	4	Lung adenoma
	Mice	8	Harderian gland
	Rats	11	Thyroid follicular adenoma
	Rats	7	Hepatocellular carcinoma
	Rats	25	Thyroid follicular cell carcinoma
Atorvastatin	Rats	16	Rhabdomyosarcoma, fibrosarcoma
	Mice	6	Liver carcinoma
Methylphenidate	Mice	2.5	Hepatocellular adenoma
	Mice	2.5	Hepatoblastoma
Zidovudine	Mice	3	Vaginal neoplasms
	Rats	24	Vaginal carcinoma
Abacavir	Mice	6	Malignant tumors male preputial gland, female clitoral gland
	Rats	6	Malignant tumor of liver
	Rats	6	Malignant tumors male preputial gland, female clitoral gland
	Rats	6	Non-malignant thyroid tumors
Teriparatide	Rats	3	Osteosarcoma
Finasteride	Mice	228	Testicular Leydig cell adenoma
Tacrolimus	Mice	26	Lymphoma
Pantoprazole	Rats	0.1	Malignant gastric neuroendocrine cell tumors
	Rats	10	Adenocarcinoma of the duodenum and gastric fundus
	Mice	15	Hepatocellular carcinoma
Pioglitazone	Rats	1	Malignant urinary bladder transitional cell carcinoma

<sup>3</sup> PDR Electronic Library™ Online: © 2002-2005. Thomson PDR. Available from: <http://pdrel.thomsonhc.com/pdrel/librarian>. Accessed: February 9, 2005.

<sup>4</sup> Positive result in animal carcinogenicity studies were observed at this multiple of the recommended human dose. When label refers to mg/kg and mg/m<sup>2</sup> basis for comparison, or a range of values, the more conservative value is included in this table. Bolded values indicate the occurrence of tumors in animal models at multiples less than ten times the human dose.

Except for omalizumab, positive results in animal carcinogenicity studies were noted for each of these drugs. In the case of omalizumab, a recombinant DNA-derived monoclonal antibody for the treatment of patients with moderate to severe persistent asthma and whose symptoms are inadequately controlled with inhaled corticosteroids, no animal carcinogenicity studies were performed. However, as noted in the Xolair<sup>®</sup> USPI, in clinical trials of less than one year duration, malignant neoplasms were observed in 0.5% omalizumab-treated patients, compared with 0.2% of controls. The observed malignancies were a variety of types. A Warning in the USPI states: "the impact of longer exposure to Xolair or use in patients at higher risk of malignancy (e.g., elderly, current smokers) is not known."

Proposed study designs<sup>5</sup> for these drugs include:

---

<sup>5</sup> As described in Office of Drug Safety (ODS) reviews or other FDA documents available to this reviewer.

<sup>6</sup> McCloskey CA. ODS Consult – Evaluation of Phase 4 protocol revision on Protonix (pantoprazole) for a postmarketing long-term study on incidence and risk of cancer among pantoprazole users compared to other proton pump inhibitor users, February 6, 2003.

<sup>7</sup> Biologics License Application for omalizumab. Product Approval Information - Licensing Action (June 20, 2003). Available from <http://www.fda.gov/cder/foi/applletter/2003/omalgen062003L.htm>. Accessed: February 9, 2005.

<sup>8</sup> La Grenade L. ODS Consult – Review of protocol entitled "APPLES: A Prospective Pediatric Longitudinal Evaluation to assess the long-term safety of tacrolimus ointment for the treatment of atopic dermatitis", January 13, 2005.

<sup>9</sup> La Grenade L. ODS Consult – Evaluation of draft post-approval surveillance case series study submitted by the sponsor, with special emphasis on appropriateness of design. Forteo (teriparatide), February 15, 2002.

<sup>10</sup> Ouellet-Hellstrom R. ODS Consult – Review of the proposed epidemiological study to ascertain the relative risk of bladder cancer in Actos (pioglitazone) users, February 25, 2003.

Limitations exist for each of these proposed study designs, and in several cases, have been previously discussed in ODS consults, as referenced. This experience is illustrative of the challenges involved in studying human cancer risk, and the dilemma presented by potentially useful drugs with positive animal carcinogenicity findings.<sup>11 12</sup>

The Women's Health Initiative (WHI) trial<sup>13</sup> is an example of a placebo-controlled randomized trial that conclusively answered a question about cancer risk. The study sample size (16,608 women enrolled) was based on the estimated influence of hormone replacement therapy (HRT) on coronary heart disease; however, a pre-specified global index of benefit and risk was assessed including heart disease, stroke, colorectal cancer, endometrial cancer, pulmonary embolus, hip fracture, and death due to other causes, as well as invasive breast cancer. The trial was stopped early after a mean (SD) follow-up of 5.2 years (1.3), based on the breast cancer risk exceeding the pre-defined stopping boundary, and overall risks exceeding benefits based on the global index. According to the WHI Investigators<sup>14</sup>, the increased risk of breast cancer identified in the WHI trial was consistent with findings in observational studies, but the cancers developed in a shorter than predicted interval, suggesting an effect on growth of established breast cancers. After one year, the percentage of women with abnormal mammograms was significantly greater in the active treatment group; however, an increased hazard ratio for overall invasive breast cancers was not observed until year three of the study, and was not statistically significant until year five. Prior to year three, hazard ratios for invasive breast cancer in the active treatment group were less than one.

Although latency periods for cancer can be 20 years or more, this duration of follow-up may not be feasible in many cases. It is clearly desirable for proposed studies to ascertain cancer outcomes for as long a period of time as possible. The results of the WHI trial provide an example where meaningful information about breast cancer was obtained after a mean follow-up period of 5.2 years. This finding suggests that drugs which have an effect on established cancers (i.e., promoters) may be identified in a relatively short time frame (less than ten years).

### ***Appropriateness of Sponsor's Proposed Study Design***

The sponsor proposes to conduct a large simple randomized international cohort study aimed at comparing rates of mortality, the progression of liver disease, and development of cancers in patients with chronic HBV infection treated with entecavir compared with other nucleosides / nucleotides.

---

<sup>11</sup> Maronpot RR, Flake G, Huff J. Relevance of animal carcinogenesis findings to human cancer predictions and prevention. *Toxicologic Pathology* 2004; 32(Suppl.1):40-48.

<sup>12</sup> Singh G, Driever PH, Sander JW. Review - Cancer risk in people with epilepsy: the role of antiepileptic drugs. *Brain* 2005; 128:7-17.

<sup>13</sup> Rossouw JE, Anderson GL, Prentice RL, et al, for Writing Group for the Women's Health Initiative. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative. *JAMA* 2002; 288:321-333.

<sup>14</sup> Chlebowski RT, Hendrix SL, Langer RD, Stefanick ML, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative randomized trial. *N Engl J Med.* 2003; 289:3243-3253.

Strengths of the proposed study design include:

- Randomized study design with active control group;
- Subjects are identified and started on study medication by their own physician;
- International experience;
- 1,250 physician / investigators will each follow ten subjects to ascertain endpoints;
- Annual follow-up using medical records, patient interview, or death indexes;
- Incentives to reduce premature dropout are planned;
- Complete ascertainment of baseline patient characteristics is planned including demographics, medical and behavioral health history, HBV clinical and laboratory data and treatments;
- Study endpoints and planned analyses are pertinent;
- Secondary analyses will examine the effects of initial treatment duration and dose, and other treatments subsequent to study start on the endpoints of interest;
- An adjustment for drug exposure incorporated into the multivariate analysis of incidence rates for endpoints is planned at pre-specified time intervals;
- Subgroup analyses are planned to include patients with HCV, HIV, or cirrhosis at baseline, as well as for treatment naïve, previously treated, and lamivudine resistant patients;
- Planned statistical tests are two-tailed;
- The sponsor has conducted studies in the US and Taiwan characterizing the natural history of disease and risk of cancer in the patient population of interest with up to eleven years follow-up.

Potential limitations include:

- Planned follow-up may not be adequate to detect adverse effects with very long latency such as cancer, depending on time-course of possible increased cancer risk, currently unknown;
- Subjects assigned at randomization to the comparison group may switch to entecavir therapy later in the study (and vice versa), or subjects randomized to entecavir may discontinue study therapy, decreasing the likelihood of detecting an effect (misclassification);
- Attrition rates may exceed the assumed rate of 20% over five years;
- Inability to prospectively identify a specific tumor type of concern decreases the likelihood that an effect will be detected, since study endpoint includes all tumor types; it is highly unlikely that a drug would have an effect on all tumor types;
- Potential confounders include effects of duration of HBV infection and differences in:
  - levels of necroinflammatory liver disease / fibrosis,
  - sequential or concomitant treatment with other antiviral agents,
  - HBeAg status, and serum HBV DNA levels at the time of randomization;
- Geographic differences and heterogeneity of patient populations (vertical HBV transmission vs recent onset HBV infection) are associated with marked differences in underlying risk of HCC;
- May need separate analyses for treatment naïve and previous treatment groups, with separate sample size requirements for each group;

## Conclusions and Recommendations

Based on review of currently available information, we conclude that the proposed study, along with the Sponsor's proposed pharmacovigilance plan, have the potential to provide valuable information about the balance of risks and benefits of entecavir therapy during actual use of this drug in geographically diverse populations. However, the ability to detect an adverse effect which may have a very long latency, such as cancer, is limited by the duration of follow-up of the study cohort, heterogeneity of patient population with regard to pre-existing HCC risk, differences in healthcare environments pertinent to the proposed multinational patient recruitment, misclassification due to switching treatments over time, as well as the unknown nature of the specific risk. Because of these limitations, failure to detect an adverse effect does not necessarily imply that there is none, although it may provide some reassurance about the magnitude of any potential adverse effect, as well as information about the overall balance of benefit and risk. Further discussion of study design issues that may hinder detection of a potential adverse effect is recommended. Please note that further biostatistical review is planned when the full protocol is submitted by the sponsor.

Due to the important effects of duration of HBV infection, levels of inflammation and fibrosis, and previous treatment on cancer risk (especially HCC), additional consideration is recommended with regard to separate analyses for treatment naïve and previously treated groups, including patients with lamivudine resistance, with separate sample size requirements for each group. We note that the sponsor plans several secondary analyses involving specific subgroups of patients.

Consideration should also be given to increasing the duration of study follow-up to ten years.

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

/s/

-----  
Kate Gelperin  
3/1/05 09:59:05 AM  
DRUG SAFETY OFFICE REVIEWER

Mark Avigan  
3/1/05 02:35:35 PM  
DRUG SAFETY OFFICE REVIEWER

# REQUEST FOR CONSULTATION

Division/Office):

: ODS (Room 15B-08, PKLN Bldg.)

**DSRCS**

FROM:

Marsha S. Holloman, BS Pharm, JD  
Division of Antiviral Drug Products (DAVDP)  
HFD-530, 9201 Corporate Blvd, N432  
Rockville, MD 20850

DATE March 18, 2005	IND NO. 52,196	NDA NO. 21-797 & 21-798	TYPE OF DOCUMENT Package Insert & Patient Package Insert	DATE OF DOCUMENT March 18, 2005
NAME OF DRUG BARACLUDE 05mg & 1mg Tabs BARACLUDE 0.05mg/ml Soln		PRIORITY CONSIDERATION Yes	CLASSIFICATION OF DRUG Antiviral (to treat HBVI)	DESIRED COMPLETION DATE ASAP (PDUFA Date: 3/29/2005)

NAME OF FIRM: Bristol-Myers Squibb Pharmaceutical Company

### 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"/> <b>OTHER (SPECIFY BELOW):</b> |
| <input type="checkbox"/> MEETING PLANNED BY            |  | <b>PI &amp; PPI LABELING REVIEWS</b>                              |

#### II. BIOMETRICS

##### STATISTICAL EVALUATION BRANCH

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

##### STATISTICAL APPLICATION BRANCH

- CHEMISTRY REVIEW  
 PHARMACOLOGY  
 BIOPHARMACEUTICS  
 OTHER (SPECIFY BELOW):

#### III. BIOPHARMACEUTICS

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

#### IV. DRUG EXPERIENCE

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

#### V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

#### COMMENTS/SPECIAL INSTRUCTIONS:

Please see original labeling and draft revised labeling as both PDF and WORD docs sent to Karen Young via email on March 21, 2005.

TITLE OF REQUESTER  
Marsha S. Holloman, BS Pharm, JD

METHOD OF DELIVERY (Check one)

E MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

**MEMORANDUM**

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

**DATE:** March 22, 2005

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

**VIA:** Marsha S. Holloman, B.S. Pharm, J.D. Regulatory Project  
Manager, Division of Antiviral Drug Products  
HFD-530

**FROM:** Jeanine Best, M.S.N., R.N., P.N.P.  
Patient Product Information Specialist  
Division of Surveillance, Research, and Communication Support  
(DSRCS), HFD-410

**THROUGH:** Gerald Dal Pan, M.D., M.H.S., Director  
Division of Surveillance, Research, and Communication  
Support (DSRCS), HFD-410

**SUBJECT:** DSRCS Review of Patient Information (PPI) for Baraclude  
(entecavir) Tablets and Oral Suspension,  
NDAs 21-797 and 21-798

**Background and Summary**

The attached labeling represents the revised Patient Information (PPI) for Baraclude (entecavir) Tablets and Oral Suspension, NDAs 21-797 and 21-798. We have simplified the wording, made it consistent with the Prescribing Information (PI), removed unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

These revisions are based on revised draft labeling dated February 25, 2005. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

We also have the following Comment:

The PI, PRECAUTIONS section, Information for patients subsection states: "A patient package insert (PPI) for TRADEMARK is available for patient information." The sponsor needs to state how the PPI will be made available for patients, since distribution of a PPI for this product would be voluntary. The sponsor appears to be packaging the product in unit-of-use packages. The sponsor should indicate whether the PPI would be packaged with this unit-of-use packaging, which would ensure that patients receive the PPI.

Comments to the review division are bolded, underlined and italicized. We can provide Word Copies (clean and marked) of the PPI if requested by the review division. Please call us if you have any questions.

**APPEARS THIS WAY  
ON ORIGINAL**

5 Page(s) Withheld

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

       § 552(b)(5) Deliberative Process

✓ § 552(b)(5) 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/  
-----

Jeanine Best  
3/22/05 03:02:32 PM  
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp  
3/22/05 05:08:01 PM  
DRUG SAFETY OFFICE REVIEWER  
for Gerald Dal Pan

12 Page(s) Withheld

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

✓  
\_\_\_\_\_ § 552(b)(5) Deliberative Process

\_\_\_\_\_ § 552(b)(5) Draft Labeling

# REQUEST FOR CONSULTATION

TO (Office/Division):

DMAC: Attn: Suzanne Berkman HFD-040

FROM (Name, Office/Division, and Phone Number of Requestor):

Marsha S. Holloman, BS Pharm, JD  
ODEIV/DAVDP HFD-530  
301-827-2418 - Phone  
hollomanm@cdcr.fda.gov

DATE 03/21/2005	IND NO. 52,196	NDA NO. 21-797 and 21-798	TYPE OF DOCUMENT Labeling (PI and PPI)	DATE OF DOCUMENT 09/30/2004 03/18/2005
NAME OF DRUG BARACLUDE 0.5 AND 1.0 mg Tabs and BARACLUDE 0.05mg/ml Soln		PRIORITY CONSIDERATION Yes	CLASSIFICATION OF DRUG NME antiviral (anti- HBVI)	DESIRED COMPLETION DATE ASAP

NAME OF FIRM: Bristol-Myers Squibb Pharmaceutical Company

### 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 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<br>MEETING PLANNED BY | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
|  | <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: New NDA PI and PPI (1) emailed to Susanne Berkman (2) Please let me know if BMS sent you the new drug marketing and advertising materials.

NATURE OF REQUESTOR

Marsha S. Holloman, BS Pharm, JD

METHOD OF DELIVERY (Check one)

- DFS     EMAIL     MAIL     HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

4 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

6 Page(s) Withheld

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

       § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** April 27, 2004  
**TIME:** 9 - 11 AM  
**LOCATION:** Conference Room S400, 9201 Corporate Blvd, Rockville, MD  
**APPLICATION:** IND 52,196/SN-241  
**DRUG NAME:** Entecavir (BMS-200475; ETV)  
**TYPE OF MEETING:** Pre-NDA  
**MEETING CHAIR:** Linda L. Lewis, MD, Medical Officer  
**MEETING RECORDER:** Marsha S. Holloman, BS Pharm, JD

### **FDA ATTENDEES: Division of Antiviral Drug Products**

Virginia Behr, Chief, Project Management Staff  
Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager  
Katherine A. Laessig, MD, Medical Team Leader  
Linda L. Lewis, MD, Medical Officer  
Kendall Marcus, MD, Medical Officer  
Jeffery S. Murray, MD, MPH, Deputy Director  
Jeff O'Neill, ACRN, Regulatory Project Manager  
Jules J. O'Rear, PhD, Microbiology Team Leader  
Kellie S. Reynolds, Pharm D, Pharmacokinetics Team Leader  
David Roeder, Associate Director, Regulatory Affairs  
Kenny Shade, RN, JD, Regulatory Project Manager  
Lincy Thomas, Pharmacokinetics PhD Fellow  
Kuei-Meng Wu, PhD, Pharmacologist  
Derek Zhang, PhD, Pharmacokinetics Reviewer

### **EXTERNAL CONSTITUENT ATTENDEES: Bristol-Myers Squibb, Inc (BMS)**

David Apelian, MD, PhD; Medical Co-Lead, Entecavir Team  
Helena Brett-Smith, MD; Medical Co-Lead, Entecavir Team  
Michael Brady, PhD; Director, Global Regulatory Science  
Renzo Canetta, MD; Vice President, Clinical Design & Evaluation, Oncology  
Rich Colonno, PhD; Vice President, Preclinical Virology & Resistance  
Joseph Costa, PhD; Executive Director, Drug Safety Evaluation  
Anne Cross, PhD; Director, Clinical Biostatistics  
Dennis Grasela, PharmD, PhD; Executive Director, Clinical Pharmacology  
Dominic Labriola, PhD; Executive Director, Clinical Biostatistics  
Frank LaCreta, PhD; Director, Clinical Pharmacology-Infectious Diseases

Phil Pierce, MD; Executive Director, Global Pharmacovigilance  
Donna Morgan Murray, PhD; Executive Director, Global Regulatory Science  
Lois Sechler, PhD, Associate Director, Global Regulatory Science - CMC

Elliott Sigal, MD, PhD; Senior Vice President, Global Development  
Kathy Takaki, PhD; Director, Project Planning & Management  
Dominique Tersago; Associate Director, Regulatory Affairs-Europe  
Richard Wilber, MD; Executive Director, Clinical Research

**BACKGROUND:**

Reference is made to Investigational New Drug (IND) application 52,196 dated December 26, 1996, for BMS-200475 (entecavir, ETV) (SQ 34,676) for the treatment of hepatitis B virus (HBV). Also, reference is made to SN-233 dated February 13, 2004, containing a pre-NDA meeting request. Additionally, reference is made to an email message dated March 15, 2004 and a meeting letter from the Agency confirming a meeting between the Agency and BMS scheduled for April 27, 2004. Finally, reference is made to SN-241 containing the pre-NDA meeting package.

**MEETING OBJECTIVES:**

To discuss of the entecavir NDA development plan. Specifically, BMS submitted questions in the pre-NDA meeting package.

**DISCUSSION POINTS & DECISIONS MADE:**

1. *Is the proposed submission package sufficient in scope to support the filing of the NDAs for the treatment of chronic hepatitis B virus (HBV) infection in adults?*

The proposed package appears to be adequate to support filing the NDAs. Exactly what will be contained in the package is still somewhat unclear. In the opening question, the sponsor notes that 19 clinical pharmacology studies and 20 Phase II/III studies including 3 pivotal studies will be submitted. In the Efficacy section, Tables 7.1 and 7.2 identify 11 studies being submitted for evaluation of efficacy. The Safety section identifies 12 studies to be submitted in the safety database with two additional studies to be presented separately. Six on-going studies are noted to contribute "limited safety" [only serious adverse events (SAEs) and deaths or targeted events]. Will the last six studies remain blinded (for those that are blinded)? Will the amount of data available be sufficient to make inclusion helpful to the review?

2. *Is this proposal for submission of ongoing studies acceptable to the FDA?*

The sponsor proposes to include a significant amount of data in the safety update. This includes the analysis of 24-week follow-up efficacy and safety data for Study 027, one of the three large pivotal trials. These data will be important to determine the durability of response in patients who are HBeAg-negative. The sponsor also plans to submit the final study report of Study 038, the evaluation of HIV/HBV co-infected patients, in the safety update (submitting Week 24 data in the original NDA). The sponsor also plans to submit Week 24

data on a small cohort of patients enrolled in Study 048, the evaluation of patients with decompensated liver disease (Appendix 5B lists 23 patients enrolled) in the original NDA with further data to be submitted with the safety update. These data will be important to characterize the patient populations who may benefit from ETV and the safety profile in different groups. If the number of patients available for submission in Study 048 is very small, it would be preferable to collect as much data as possible and submit it only once at the time of the safety update. Will any other safety data be included in the safety update? The proposed data cut-off is 4/04, how much additional safety data will be available after an additional 2-4 months?

3. *Will the proposed NDAs provide adequate information to evaluate the efficacy and safety of entecavir? Are the data cohorts and displays adequate, including special safety and ongoing studies?*

It would be preferable to present the data for Study 015 separately since this small group of post-transplant patients may be significantly different than other "lamivudine-refractory" patients (Cohort D) because of surgical procedures and immunosuppressive medications. This group should be included as another special population.

Please include a subgroup analysis of efficacy by age (already proposed for the safety analysis). For both efficacy and safety analyses, please restructure the age groups to include: 16 to < 21 years, 21 to < 65 years, and > 65 years. We are particularly interested in the adolescent population for whom there is very little data regarding treatment of HBV. In at least one large pediatric HBV treatment study, it appeared that adolescents responded less well to treatment. Since it is likely that many patients in this age group may have perinatally-acquired HBV, it is certainly possible that they may respond differently to treatment or have a different course of illness than older patients.

Please clarify how the duration of hepatic serious adverse events (SAEs) will be calculated in patients with missing resolution documentation. The draft NDA states that the duration will be measured from the onset date to the resolution date, noting that "the onset date will be used if the resolution date is missing."

Since it appears that several of the "on-going" studies will contribute relatively little safety data to the submission, these studies should have SAEs and deaths or targeted events reported through the latest possible cut-off. Please include summary demographic data for all of these studies. Deaths, malignancies, and SAEs attributed to study drug in any study should also be updated in the safety update.

The proposed safety analyses using several cohorts of patients grouping different studies together is very complex. The presentation of these data and analyses will need to be very well organized.

4. *Are the PIDs in clinical pharmacology study reports acceptable to the FDA?*

This proposal is acceptable.

5. *Does the FDA concur with BMS' rationale that the outliers can be removed?*

Since this is a review issue, you must include statistical analyses of data sets both with and without outliers in the NDA. Also, we may ask for submission of these BE study reports prior to the NDA submission so we can evaluate whether these studies need to be repeated. We may ask the Division of Scientific Investigation to inspect the study sites for the bioequivalence studies.

6. *Will the FDA grant Fast Track status for entecavir? Assuming Fast Track status, will entecavir be a candidate for a priority review? (It is understood that a final decision on this request will be rendered at the filling meeting post-submission.) At what point in the review cycle would the FDA require the safety update?*

There are currently three available treatments for chronic HBV infection in adults: alpha-interferon, lamivudine, and adefovir. Entecavir represents a fourth potential treatment option (third oral therapy). Summary conclusions from two of the pivotal trials presented in this pre-NDA background information suggest that ETV may be superior to lamivudine in some measures of efficacy and some populations. Results of other studies are not available at this time and assumptions regarding efficacy in different patient populations cannot be made. To date, the ETV drug development program has not been directed at proving efficacy in the subpopulation of patients intolerant or resistant to all other therapies who might represent the population with an unmet medical need.

The Review Team has also been in communication with the sponsor regarding the results of the rodent carcinogenicity studies previously submitted. The FDA Carcinogenicity Advisory Committee has reviewed these studies and determined that ETV is a potential carcinogen in humans. As previously discussed, the determination of risks and benefits after full review of the efficacy and safety data from the drug development program will determine whether ETV is a viable treatment option. It is very likely that a DAVDP Advisory Committee will be convened in order to reach a risk/benefit judgment. In this setting, ETV is not considered a candidate for Fast Track development since there is no assurance that it will fulfill an unmet medical need. At this late stage of drug development, significant evidence of superiority of ETV to all alternative therapies (lamivudine and adefovir) and a consensus that the benefits of the drug outweigh the potential risk of carcinogenicity would be required for Fast Track status to be granted.

Entecavir may be a candidate for priority review. The decision to grant Fast Track status and the decision to conduct a priority review are independent. In order to be considered for priority review, a drug product should provide a significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease. At this time ETV does not seem to fulfill this criterion, but a final decision will be made at the time of filing the NDA. Given the amount of data planned for this submission, the plan to submit significant data at the time of the safety update, and the necessity of conducting an Advisory Committee meeting to independently assess the risk/benefit of ETV, it is unlikely that a priority review will be granted. The safety update should be submitted so that there is adequate time to review the material. Since this data will include both safety and efficacy

data it should be submitted at least 4 months before the action date so that pertinent findings may be presented to the Advisory Committee if necessary.

7. *Are the proposed format and content acceptable to the FDA?*

Electronic submission of this NDA is acceptable. We have previously discussed with BMS staff our suggestions for the format of electronic datasets. For convenience, we would like to have desk copies of Module 1 (containing administrative information and proposed labeling) and Module 2 (technical summaries) in addition to the electronic submission.

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

There were no unresolved issues.

**ACTION ITEMS:**

There were no action items.

**NDA REGULATORY FILING REVIEW**  
(Including Memo of Filing Meeting)

NDA # 21-797 Supplement # Efficacy Supplement Type SE-  
21-798

Trade Name: BARACLUDE  
Established Name: entecavir  
Strengths: 0.5 and 1.0 mg oral tablets

Applicant: Bristol-Myers Squibb Company  
Agent for Applicant: Joan C. Fung-Tome, PhD, ABMM

Date of Application: 09/29/2004  
Date of Receipt: 09/29/2004  
Date clock started after UN: N/A  
Date of Filing Meeting: 10/25/2004  
Filing Date: 11/05/2004  
Action Goal Date (optional): User Fee Goal Date: 03/29/2005

Indication(s) requested: Treatment of chronic hepatitis B infection in adults with evidence of active liver inflammation

Type of Original NDA: (b)(1)  (b)(2)   
OR  
Type of Supplement: (b)(1)  (b)(2)

**NOTE:**

- (1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.
- (2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

NDA is a (b)(1) application OR  NDA is a (b)(2) application

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

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

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

**NOTE:** If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES  NO   
If yes, explain:
- Does another drug have orphan drug exclusivity for the same indication? YES  NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES  NO   
If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).
- Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES  NO
- Does the submission contain an accurate comprehensive index? YES  NO
- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**
- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A  YES  NO   
**If an electronic NDA, all forms and certifications must be in paper and require a signature.**  
Which parts of the application were submitted in electronic format? All  
Additional comments: Answers pending reply from EDR staff
- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A  YES  NO
- Is it an electronic CTD (eCTD)? N/A  YES  NO   
**If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.**  
Additional comments: Answers pending reply from EDR staff
- Patent information submitted on form FDA 3542a? YES  NO
- Exclusivity requested? YES,  Years NO   
**NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.**
- Correctly worded Debarment Certification included with authorized signature? YES  NO

**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

*NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."*

- Financial Disclosure forms included with authorized signature? YES  NO   
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)  
*NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y  NO
- PDUFA and Action Goal dates correct in COMIS? YES  NO   
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. YES  NO
- List referenced IND numbers: 52,196
- End-of-Phase 2 Meeting(s)? Date(s) 12/13/2002 NO   
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 04/27/2004 NO   
If yes, distribute minutes before filing meeting.

**Project Management**

- Was electronic "Content of Labeling" submitted? YES  NO   
If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES  NO
- Risk Management Plan consulted to ODS/IO? N/A  YES  NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y  NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A  YES  NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A  YES  NO

**If Rx-to-OTC Switch application:**

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A  YES  NO
- Has DOTCDP been notified of the OTC switch application? YES  NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?  
YES  NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES  NO   
If no, did applicant submit a complete environmental assessment? YES  NO   
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES  NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES  NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES  NO

Appears This Way  
On Original

ATTACHMENT

**MEMO OF FILING MEETING**

DATE: October 25, 2004

**BACKGROUND:** Reference is made to the Bristol-Myers Squibb's (BMS) Investigational New Drug Application (IND) 52,196 for entecavir (ETV; BMS-200475; SQ 34,676) dated December 26, 1996 for the treatment of hepatitis B virus (HBV). Also, reference is made to BMS' September 29, 2004 new drug applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Entecavir (BMS-20075) 0.5 mg and 1 mg Oral Tablets and Solution.

Additionally, reference is made to BMS' pre-submissions dated: June 17, 2004, July 2, 2004, July 14, 2004, July 27, 2004, August 2, 2004, August 6, 2004, August 23, 2004, September 3, 2004, September 9, 2004, and September 10, 2004.

**ATTENDEES:**

Virginia Behr, Chief, Project Management Staff  
Kimberly Bergman, Pharm D, Clinical Pharmacologist  
Debra B. Birnkrant, MD, Division Director  
Edward M. Cox, MD, ODE IV Deputy Director  
Antoine N. El Hage, DSI  
Thomas S. Hammerstrom, PhD, Mathematical Statistician  
Katherine A. Laessig, MD, Medical Team Leader  
Linda L. Lewis, MD, Medical Officer  
Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager  
Stephen P. Miller, PhD, CMC Team Leader  
Yoshi Murata, MD, PhD, Medical Officer  
Jeffrey S. Murray, MD, MPH, Deputy Director  
Lisa Naeger, PhD, Microbiologist  
Julian J. O'Rear, PhD, Microbiology Team Leader  
Kellie S. Reynolds, Pharm D, Clinical Pharmacology Team Leader  
Lorenzo A. Rocca, PhD, Chemist  
David L. Roeder, ODE IV ADRA  
Guoxing (Greg) Soon, PhD, Biometrics Team Leader

**MEETING OBJECTIVES:**

To decide if these NDAs are acceptable for filing and protocol is safe to proceed

**DISCUSSION POINTS:**

1. Clinical: No filing issues identified.
2. Chemistry, Manufacturing and Controls: No filing issues identified. Send review comment in 74-day filing letter.
3. Pharmacology: No filing issues identified.
4. Microbiology: No filing issues identified. Send review comments in 74-day filing letter.

5. Clinical Pharmacology: No issues identified. Send review comments in 74-day filing letter.
6. Statistical: No issues identified.

**DECISIONS (AGREEMENTS) REACHED:**

NDA 21-797 and NDA 21-798 are acceptable for filing.

**ACTION ITEMS:**

The following review comments will be included in the 74-day filing letter:

1. We notice that you failed to enroll any significant numbers of African Americans or other black minorities in your clinical trials. This deficiency may need to be addressed at a later time.
2. Please explain what role, if any, \_\_\_\_\_ will play in the testing of commercial entecavir drug substance and drug product.
3. Please modify the clinical resistance dataset so that amino acids are in numerical order rather than alphabetical order. The template is not usable in the current format. In addition to the official submission of these data to the NDA, please attach the same information to an email and send it to Marsha Holloman by November 10, 2004.
4. Please examine the activity of entecavir against the adefovir-resistant mutations rtN236T and rtA181V.
5. Please determine the *in vitro* combination activity relationship of entecavir and adefovir dipivoxil.
6. Please explain why there are two different PCR assay limits ( — 300) in your database.
7. Please submit the assay performance characteristics for the PCR assay.
8. Attach the Template for Submitting Resistance to the 74-day filing letter.

Regulatory Project Management:  
Other Consults:

Marsha S. Holloman, BS Pharm, JD  
Antoine El Hage, PhD  
ODS/DDRE  
ODS/DMETS  
ODS/DSRCS

Per reviewers, are all parts in English or English translation? YES  NO   
If no, explain:

CLINICAL FILE  REFUSE TO FILE

- Clinical site inspection needed? YES  NO
- Advisory Committee Meeting needed? YES, date if known 03/11/2005 NO

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A  YES  NO

CLINICAL MICROBIOLOGY      N/A       FILE       REFUSE TO FILE

STATISTICS      N/A       FILE       REFUSE TO FILE

BIOPHARMACEUTICS      FILE       REFUSE TO FILE

- Biopharm. inspection needed?      YES       NO

PHARMACOLOGY      N/A       FILE       REFUSE TO FILE

- GLP inspection needed?      YES       NO

CHEMISTRY      FILE       REFUSE TO FILE

- Establishment(s) ready for inspection?      YES       NO
- Microbiology      YES       NO

**ELECTRONIC SUBMISSION:**

Any comments: Answers pending reply from EDR staff

**REGULATORY CONCLUSIONS/DEFICIENCIES:**

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- No filing issues have been identified.
- Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1.  If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2.  If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3.  Convey document filing issues/no filing issues to applicant by Day 74.

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

### Appendix A to NDA Regulatory Filing Review

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).

Appears to be  
On Original

**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES  NO

*If "No," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES  NO

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

*If "No," skip to question 4. Otherwise, answer part (b).*

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES  NO   
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

*If "Yes," skip to question 6. Otherwise, answer part (c).*

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES  NO

*If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES  NO

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*If "No," skip to question 5. Otherwise, answer part (b).*

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES  NO   
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

**NOTE:** *If there is more than one pharmaceutical alternative approved, consult the Director, Division of*

*Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "Yes," skip to question 6. Otherwise, answer part (c).*

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES  NO

*If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES  NO

*If "No," skip to question 6.*

*If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.*

- (b) Is the approved drug product cited as the listed drug? YES  NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").
7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES  NO
8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES  NO
9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES  NO
10. Are there certifications for each of the patents listed for the listed drug(s)? YES  NO
11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)  
Patent number(s):
  - 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)  
Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)  
Patent number(s):

**NOTE:** *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must subsequently submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)  
Patent number(s):
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).  
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.  
Patent number(s):

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?  
YES  NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?  
YES  NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?  
N/A  YES  NO
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?  
N/A  YES  NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a). YES  NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval. YES  NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND# \_\_\_\_\_ NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES  NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES  NO

-----  
**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  
2/17/05 03:30:48 PM  
CSO  
NDA Regulatory Filing Review (Including Memo of Filing Meeting)

Tony DeCicco  
2/18/05 03:57:28 PM  
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 52,196

Gilead Sciences, Inc  
Attn: Michael E. Brady, PhD  
Director, Global Regulatory Sciences  
Bristol-Myers Squibb  
5 Research Parkway  
Signature 91 Bldg, 3SIG-503  
Wallingford, CT 06492

Dear Dr. Brady:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for entecavir (BMS-200475; ETV).

We also refer to the pre-NDA meeting between representatives of your firm and the FDA on April 27, 2004. The purpose of the meeting was to discuss the ETV development plan.

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 Marsha Holloman, Regulatory Health Project Manager, at (301) 827-2335.

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

Enclosure

## MEMORANDUM OF TELECONFERENCE

**DATE:** January 31, 2003

**APPLICATION NUMBER:** IND 52,196/SN-132 BMS-200475 (Entecavir) tablets

### **FDA PARTICIPANTS:**

James G. Farrelly, Pharmacology Team Leader  
Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager  
Katherine A. Laessig, MD, Medical Team Leader  
Linda L. Lewis, MD, Medical Officer  
Pritam Verma, PhD, Pharmacologist

### **BMS PARTICIPANTS:**

Michael E. Brady, PhD, Director, Regulatory Affairs  
Joseph Costa, PhD, Executive Director, Drug Safety Evaluation  
Deborah DeHertogh, Vice President, Global Development  
Kathy Takaki, PhD, Associate Director, Project Planning

**SUBJECT:** Discussion of Carcinogenicity Issues

### **BACKGROUND:**

BMS requested this TCON for an update from the Division on the status of the ETV carcinogenicity review. Several foreign countries, including China, require BMS to send them periodic updates on the Division's ETV review.

### **DISCUSSION:**

The overall genotoxicity studies establish entecavir as nongenotoxic. A number of different tumor types were seen at greater incidences in mice and rats than in the controls. In mice, lung neoplasms were directly related to drug exposure. These findings could be predictive of cancer hazard to humans. Other tumors (*i.e.*, liver tumors in male mice and female rats, vascular tumors in female mice, brain neoplasms in male and female rats, and skin neoplasms in female rats) were significant by the Peto analysis. However, the relationship to entecavir exposure was not clear. For the tumor types with incidences greater than the controls, there may be a relationship to the entecavir administration in mice and rats.

For the reasons mentioned above, entecavir is considered to represent a cancer hazard to patients under the intended conditions of use, which are one to two years for the treatment of HBV infection.

### **ACTION ITEMS:**

1. The Division requested, and BMS will submit, the individual animal study reports used in the historic controls for review.

2. Mathematical Statistician Tom Hammerstrom will produce the statistical analysis of the carcinogenicity data as soon as possible. The final pharmacology review will be presented to the Executive Carcinogenicity Advisory Committee (CAC) for evaluation and concurrence.
3. The Division will share the Exec CAC final evaluation with BMS.

*{See appended electronic signature page}*

---

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

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** December 13, 2002

**TIME:** 9:00 - 10:30 AM

**LOCATION:** 9401 Corporate Blvd, Conference Room S300

**APPLICATION:** BMS -200475 (Entecavir)

**TYPE OF MEETING:** Face-to-Face Meeting with Industry

**MEETING CHAIR:** Stephen P. Miller, PhD, Chemistry Team Leader

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

### FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division Name &amp; HFD#</u>
1. Marsha S. Holloman, BS Pharm, JD	Regulatory Health Project Manager	Division of Antiviral Drug Products (DAVDP) HFD-530
2. Katherine A. Laessig, MD	Medical Team Leader	DAVDP
3. Ko-yu Lo, PhD	Chemistry Reviewer	DAVDP
4. Stephen P. Miller, PhD	Chemistry Team Leader	DAVDP
5. Jeffrey S. Murray, MD, MPH	Deputy Director	DAVDP
6. Kellie S. Reynolds, Pharm D	Pharmacokinetics Team Leader	DAVDP
7. Derek Zhang, PhD	Pharmacokinetics Reviewer	DAVDP

### EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
1. Michael Burnett	Director, Global Regulatory Sciences, CMC	Bristol-Myers Squibb (BMS)
2. Daniel Carney	Director, Analytical R&D	BMS
3. Divyakant Desai	Associate Director, Pharmaceuticals R&D	BMS
4. William Fiske	Director, Clinical Discovery	BMS
5. Rachel Mathew	Documentation Resources Manager	BMS
6. Sandeep Modi	Director, Pharmaceutical Development S Operations	BMS
7. Pia Mountford	Development Chemist, Technical Ops	BMS
8. Daniel Pedota	Associate Director, Technical Ops	BMS
9. Yadagiri Pendri	Associate Director, Process R&D	BMS
10. Ambarish Singh	Associate Director, Process R&D	BMS
11. Poonam V. Tuliani	Senior Regulatory Affairs Associate Global Regulatory Sciences - CMC	BMS

## BACKGROUND:

Reference is made to IND 52,196 BMS-200475 (Entecavir) for the treatment of hepatitis B virus (HBV) dated December 20, 1996. Also, reference is made to SN-137 containing CMC information and dated August 15, 2002. Finally, reference is made to SN-148 dated October 11, 2002, containing a request for an End-of-Phase 2 (EOP2) meeting with the Division and the background document for the meeting. BMS requested a face-to-face meeting with the Division in order to discuss the EOP2 chemistry, manufacturing, and controls, and bioequivalence issues.

## MEETING OBJECTIVES:

1. Discussion of EOP2 chemistry, manufacturing, and controls (CMC) issues.
2. Discussion of EOP2 bioequivalence (BE) issues.

## QUESTIONS AND DISCUSSION POINTS

1. *BMS intends to use \_\_\_\_\_ and \_\_\_\_\_, as starting materials for the synthesis of entecavir drug substance. Is this proposal acceptable to the FDA?*

FDA considers that additional information on the starting materials is necessary before a decision on this issue can be made. Critical information to be amended includes the following: (i) Synthesis of the proposed starting materials, (ii) purification details for all synthesis steps, (iii) fate of impurities, (iv) tracking of vendor's changes (vendor qualification and control change), (v) whether a significant nonpharmaceutical market exists for any of the proposed starting materials. FDA recommended that (i) BMS provides this information in an IND amendment and follow up by a teleconference with the FDA to discuss the starting material issue, and (ii) that BMS decides which synthetic steps are appropriate to be performed under GMP until an agreement on starting materials is reached.

2. *The quality of entecavir drug substance manufactured by the current and commercial process is equivalent. BMS will provide \_\_\_\_\_ of long term stability data for the drug substance manufactured from the current process to support the NDA filing. In addition, BMS also plans to include the release data for the first \_\_\_\_\_ commercial batches prepared at the commercial manufacturing site, Swords, Ireland. Is this proposal acceptable to the FDA?*

The FDA considered the changes between the current and commercial manufacturing processes as minor \_\_\_\_\_

\_\_\_\_\_. Based on the analytical data provided (p.14), the quality of the entecavir drug substance produced by the two processes is equivalent. FDA agreed with the firm's proposal: (i) To provide \_\_\_\_\_ long term stability data for the drug substance prepared by the current process at the NDA filing and (ii) to include release data for the first \_\_\_\_\_ commercial lots (prepared by the commercial process) in the NDA.

3. Please comment on the proposed registration stability programs for the DS and DP.

For DS -- Stability protocols for drug substance prepared by the current process (pp. 18-19) and by the commercial process (p. 20) are acceptable.

For Entecavir Tablets -- Stability protocol and matrix design for entecavir tablets are acceptable. BMS indicated that \_\_\_\_\_ on long-term stability as a worst case scenario. The FDA agreed with this approach.

For Entecavir Oral Solution -- Stability protocol is acceptable

4. BMS intends to provide \_\_\_\_\_ of stability data for the drug products. However, in the event of an early filing, would the FDA accept a minimum of \_\_\_\_\_ of stability data for the Oral Solution product? If so, BMS would provide \_\_\_\_\_ stability data for the Oral Solution as an NDA amendment during the review period.

- For Entecavir Tablets -- BMS indicated in the meeting that the firm will provide stability data at the NDA filing and \_\_\_\_\_ update during the review period. FDA agreed with this approach.
- For Entecavir Oral Solution -- If the clinical division considers that this dosage form has an urgent medical need, the chemistry division would consider \_\_\_\_\_ data at the NDA filing acceptable. Otherwise, FDA recommends that \_\_\_\_\_ of data on the primary stability batches be available at filing of the NDA. BMS indicated in the meeting that the firm will provide \_\_\_\_\_ stability update during the review period. The firm should clarify whether a \_\_\_\_\_ update will be provided during the review period.

5. \_\_\_\_\_ degradants observed in the entecavir oral solution are predicted to reach \_\_\_\_\_ each at the end of shelf-life. These levels are in compliance with ICH Q3B. Therefore, no additional toxicology studies are planned. Is this proposal acceptable to the FDA?

Based on ICH Q3B Impurities in New Drug Products, the threshold for qualification is 1.0% or 50 mg TDI, whichever is lower, for a maximum of daily dose of <10 mg. The dose used in Phase II trials was 0.5 mg or less. The FDA pharmacologist agreed that no additional toxicology studies need be conducted.

6. Other Key Discussion Points:

Drug Substance (DS):

Starting Materials -- see Q1 above:

Please address the following in the NDA

Entecavir Tablets: Source of magnesium stearate: Vegetable or BSE-free animal origin. Dissolution method (USP II, \_\_\_\_\_) is justifiable based on pH-solubility profile (p. 35). See additional comments from the Division of Pharmaceutical Evaluation 3 (See Decision 2 below).

Entecavir Oral Solution \_\_\_\_\_ test at the \_\_\_\_\_ time point in the event of early filing.

**DECISIONS (AGREEMENTS) REACHED:**

1. BMS will provide an IND amendment to the Division with additional information on starting materials as described above.
2. BMS will provide individual dissolution data for '1' \_\_\_\_\_ media studied \_\_\_\_\_

*{See appended electronic signature page}*  
**Minutes Preparer:** \_\_\_\_\_ 08/06/2003  
Marsha S. Holloman, BS Pharm, JD Date  
Regulatory Health Project Manager

*{See appended electronic signature page}*  
**Chair Concurrence:** \_\_\_\_\_ 08/05/2003  
Stephen P. Miller, PhD Date  
CMC Team Leader