

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-350**

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

**PATENT INFORMATION SUBMITTED WITH THE  
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**  
*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and  
Composition) and/or Method of Use*

NDA NUMBER

22-350

NAME OF APPLICANT / NDA HOLDER

Bristol-Myers Squibb Company

*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)

N/A

ACTIVE INGREDIENT(S)

Saxagliptin

STRENGTH(S)

2.5 mg / 5.0 mg

DOSAGE FORM

Tablet

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

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

**FDA will not list patent information if you 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.**

**GENERAL**

a. United States Patent Number

6,395,767

b. Issue Date of Patent

May 28, 2002

c. Expiration Date of Patent

February 16, 2021

d. Name of Patent Owner

Bristol-Myers Squibb Company

Address (of Patent Owner)

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)

patents@bms.com

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

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

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

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

Yes

No

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

Yes

No

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

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

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

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

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

**4. Method of Use**

**Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Patent Claim Number(s) (as listed in the patent) 23, 24	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Saxagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	

**5. No Relevant Patents**

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

**6. Declaration Certification**

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

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

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

Date Signed  
May 28, 2008

*Maurcen P. O'Brien*

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

Check applicable box and provide information below.

NDA Applicant/Holder

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

Patent Owner

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

Name  
Maurcen P. O'Brien

Address  
To the attention of Vice President and Deputy General Counsel, IP  
Route 206 & Province Line Road  
P.O. Box 4000

City/State  
Princeton, New Jersey

ZIP Code  
08543-4000

Telephone Number  
(609)252-5286

FAX Number (if available)  
(609)252-4526

E-Mail Address (if available)  
patents@bms.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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

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

# **Administrative Reviews**

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

Application Information		
NDA # 22-350 BLA# n/a	NDA Supplement #:S- n/a BLA STN # n/a	Efficacy Supplement Type SE- n/a
<b>Proprietary Name: Onglyza</b> Established/Proper Name: saxagliptin Dosage Form: tablet Strengths: 2.5mg, 5mg		
Applicant: Bristol-Myers Squibb Agent for Applicant (if applicable): n/a		
Date of Application: 30Jun08 Date of Receipt: 30Jun08 Date clock started after UN: n/a		
PDUFA Goal Date: 30Apr09		Action Goal Date (if different):
Filing Date: 29Aug08 Date of Filing Meeting: 26Aug08		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed Indication(s): treatment of type 2 diabetes mellitus )		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: n/a		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>Refer to Appendix A for further information.</i>		
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	

b(4)

Collaborative Review Division (if OTC product): n/a	
List referenced IND Number(s): 63,634C )	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Application Integrity Policy</b>	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ora/compliance_ref/aip.html">http://www.fda.gov/ora/compliance_ref/aip.html</a></i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>If yes, explain:</b>	
<b>If yes, has OC/DMPQ been notified of the submission?</b>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
<b>User Fees</b>	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status	<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
<b>Exclusivity</b>	
Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</b>	<input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p><b>Comments:</b></p>	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES # years requested: 5yrs <input type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></b></p>		<input type="checkbox"/> YES <input type="checkbox"/> NO																
<p><b>If yes, please list below:</b></p> <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>			Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration												
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																		
<p><b>Format and Content</b></p>																		
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p><b>Comments:</b></p>		<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)																
<p><b>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</b></p>																		
<p><b>If electronic submission:</b>  <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p><b>Comments:</b></p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO																
<p><b>If electronic submission, does it follow the eCTD guidance?</b>  (<a href="http://www.fda.gov/cder/guidance/7087rev.pdf">http://www.fda.gov/cder/guidance/7087rev.pdf</a>)</p> <p><b>If not, explain (e.g., waiver granted):</b></p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO																

<p><b>Form 356h:</b> Is a signed form 356h included?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible  <input checked="" type="checkbox"/> English (or translated into English)  <input checked="" type="checkbox"/> pagination  <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Controlled substance/Product with abuse potential:</b></p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BLAs/BLA efficacy supplements only:</b></p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<p>n/a</p> <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	
<p>Patent information submitted on form FDA 3542a?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Debarment Certification</b>	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. Agent must</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>sign the certification.</i></p> <p><i>Note: Debarment Certification should use wording in FD&amp;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..."</i></p> <p><b>Comments:</b></p>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Financial Disclosure</b>	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Pediatrics</b>	
<p><b>PREA</b></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p> <p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p> <p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> <li>• <i>If no, request in 74-day letter.</i></li> <li>• <b>If yes</b>, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</li> </ul> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

<b>BPCA (NDAs/NDA efficacy supplements only):</b>	
Is this submission a complete response to a pediatric Written Request?  <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Comments:</b>	
<b>Prescription Labeling</b>	
Check all types of labeling submitted.  <b>Comments:</b>	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format?  <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
Package insert (PI) submitted in PLR format?  If no, was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request?  <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Comments:</b> Will be consulted after label is closer to the final version.	
MedGuide or PPI (plus PI) consulted to OSE/DRISK? ( <i>send WORD version if available</i> )	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b> RCM # 2008-1199	
REMS consulted to OSE/DRISK?	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b> RMP consulted – RCM # 2008-1199	
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b> RCM # 2008-1199	

<b>OTC Labeling</b>	
<p>Check all types of labeling submitted.</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Meeting Minutes/SPA Agreements</b>	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES Date(s): July 28, 2005 <input type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b> pre-NDA</p>	<input checked="" type="checkbox"/> YES Date(s): November 14, 2007 <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** August 26, 2008

**NDA/BLA #:** 22-350

**PROPRIETARY/ESTABLISHED NAMES:** Onglyza (saxagliptin) Tablets, 2.5mg, 5mg

**APPLICANT:** Bristol-Myers Squibb

**BACKGROUND:** NDA 22-350 for Onglyza (saxagliptin) tablets was submitted for review on June 30, 2008. Saxagliptin is a dipeptidyl-peptidase IV (DPP-IV) inhibitor. The proposed indication is for the treatment of type 2 diabetes mellitus in adults as an adjunct to diet and exercise to improve glycemic control.

Onglyza is part of CMC's Quality by Design (QbD) pilot program. The trade name, Onglyza, is currently under review. Saxagliptin was studied under IND 63,634 submitted on November 1, 2001.

On January 11, 2007, Bristol-Myers Squibb and AstraZeneca announced an alliance to develop saxagliptin. Bristol-Myers Squibb will continue to hold the IND and will file the NDA on behalf of the alliance.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Rachel Hartford	Y
	CPMS/TL:	Lina Aljuburi	Y
Cross-Discipline Team Leader (CDTL)	Hylton Joffe		Y
Clinical	Reviewer:	Naomi Lowy	Y
	TL:	Hylton Joffe	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
Labeling Review (for OTC products)	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:		
Clinical Microbiology (for antimicrobial products)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Jayabharathi Vaidyanathan	Y
	TL:	Sally Choe	Y
Biostatistics	Reviewer:	Joy Mele	Y
	TL:	Todd Sahlroot	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Fred Alavi	Y
	TL:	Todd Bourcier	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Su Tran	Y
	TL:	Blair Fraser	Y
Facility (for BLAs/BLA supplements)	Reviewer:		
	TL:		
Microbiology, sterility (for NDAs/NDA efficacy supplements)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Susan Leibenhaut	Y
	TL:		
Other reviewers			

**OTHER ATTENDEES:**

Mary Parks, Director, Division of Metabolism and Endocrinology Products (DMEP)  
 Ilan Irony, Clinical Reviewer, DMEP  
 Julie Marchick, Safety RPM, DMEP  
 Lee Ripper, ADRA, Office of Drug Evaluation II  
 Immo Zdrojewski, Clinical Pharmacology Reviewer  
 Ritesh Jain, Clinical Pharmacology Reviewer

505(b)(2) filing issues?	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
If yes, list issues:	
Per reviewers, are all parts in English or English translation?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
If no, explain:	

<b>Electronic Submission comments</b>  <b>List comments:</b> No comments	<input type="checkbox"/> Not Applicable
<b>CLINICAL</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?   <b>If no, explain:</b></li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?   <b>Comments:</b>   <i>If no, for an original NME or BLA application, include the reason. For example:</i> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul> </li> </ul>	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>• 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?   <b>Comments:</b></li> </ul>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>CLINICAL MICROBIOLOGY</b>  <b>Comments:</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>CLINICAL PHARMACOLOGY</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<b>Comments:</b>	<input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>BIOSTATISTICS</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>PRODUCT QUALITY (CMC)</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Sterile product?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>FACILITY (BLAs only)</b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>REGULATORY PROJECT MANAGEMENT</b></p>	
<p><b>Signatory Authority:</b> Curtis Rosebraugh, Director, Office of Drug Evaluation II</p> <p><b>GRMP Timeline Milestones:</b> n/a</p> <p>Comments:</p>	
<p><b>REGULATORY CONCLUSIONS/DEFICIENCIES</b></p>	
<input type="checkbox"/>	<p>The application is unsuitable for filing. Explain why:</p>
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><b><u>Clinical</u></b></p> <ol style="list-style-type: none"> <li>1. Submit a revised Table 1.2.3A (page 51 of the summary of clinical safety) that outlines exposure to study drug overall and by doses according to the following groups: <math>\geq 24</math> weeks, <math>\geq 52</math> weeks.</li> <li>2. Provide narratives for all Dermatologic adverse events (AEs), including more specific information about the appearance and location (generalized vs. localized) of each AE.</li> <li>3. As discussed in the preNDA meeting, provide narratives for all serious adverse events, not just those you consider treatment-related. As an example, in the Study Report for CV181011 (page 174), it appears that you have only provided subject narratives describing Serious Adverse Events (SAEs) that were reported as related to study drug and SAEs of special interest.</li> <li>4. Explain the criteria used in coding preferred terms used for your cardiovascular adverse events analyses (page 181 of the summary of clinical safety).</li> </ol>

5. Provide narratives for all subjects with potential cardiac preferred terms that may have been classified under other System-Organ Classes (SOCs), such as “chest pain” and preferred terms related to abnormal electrocardiograms.
6. List cardiovascular events by type (e.g., “ischemia-related”, “heart rate/rhythm-related”, “heart failure-related”, and “other”) for your controlled Phase 2/3 database using standardized MedDRA queries (SMQs) for ischemic heart disease. Include a detailed description of the methodology used (e.g., which preferred terms were included).
7. For a composite variable MACE (cardiovascular-death, non-fatal myocardial infarction, and non-fatal stroke) using the controlled Phase 2/3 database, show the number of people with at least one MACE event and provide both the total number of randomized patients and the patient-year exposure for the various treatment groups. Please show these numbers both by individual study and pooled.
8. Submit a summary table of all planned and ongoing studies (including expected completion dates) if this is not included in the NDA already. If the information is in the NDA, please indicate where it is located.
9. Submit a table of exposures broken down by clinical development Phase (1, 2, and 3) with the following variables: total subjects exposed to any dose of saxagliptin, dosage range of saxagliptin, range of days on saxagliptin, and mean number of days on saxagliptin.

#### **Clinical Pharmacology**

10. Saxagliptin is a chiral molecule with four chiral centers and is an S-isomer. There is no information whether chiral conversion occurs in the body. We recommend you address the chiral conversion using a stereospecific assay for detection of saxagliptin and its isomer.

#### **Biostatistics**

11. Provide Kaplan-Meier curves by treatment group for time to discontinuation for Studies CV181011, CV181013, CV181014, CV181038, CV181039, and CV181040.
12. Provide disposition datasets (xpt files) for Studies CV181011, CV181013, CV181014, CV181038, CV181039, and CV181040 which contain a single record per patient and provide disposition information for the double blind portion of each of these trials. Only patients who were randomized and entered the double-blind segment should be included in the dataset. This

dataset should include both a coded numeric variable (like NNCPRNN on the raw dataset STAT) and a character variable showing the reason for discontinuation. A variable for time on study and a variable for completer status should also be included (these variables should allow FDA to reproduce the Kaplan-Meier curves requested above). Variables for region, country and site should be included along with the usual demographic variables.

**Chemistry, Manufacturing, and Controls**

13. Confirm that the manufacturing and testing facilities listed in Form FDA 356h are all the facilities involved in the manufacture and testing of the commercial drug substance and drug product.
14. Clarify whether the 2.5 mg tablets will be packaged in blisters because this packaging is not in the proposed labeling even though this packaging is listed for this dosage strength in the Container Closure System and Stability sections of the NDA.
15. Provide references to the 21 CFR food additive regulations for the drug-contact components of the container closure systems used to package the drug substance and drug product.
16. Provide the following or their location in the NDA:
  - a) Physical dimensions of the finished tablets.
  - b) Stability information on the potential
  - c) Characterization information on saxagliptin hydrochloride, which is the active ingredient form in the final drug product. The information should include structural and physicochemical characterization, details on manufacturing conditions that
  - d) Stability information on the chirality of the molecule during the drug product manufacture and storage to support
  - e) The characterization report, including data and analysis, on the comparability between metformin and saxagliptin. The information should include, at minimum, structural and physicochemical characterization of the active ingredients, their comparative stability profiles, polymorph/crystal forms, and degradation pathways and products.

b(4)

b(4)

b(4)

f) Data to support your statement that the saxagliptin hydrochloride

b(4)

17. Regarding the pharmaceutical development information:

- a) All data, figures, graphs, and tables provided in section 3.2.P.2 must be identified in their captions as being generated using saxagliptin or metformin.
- b) Was the predictive coating model developed using a design space generated for metformin or saxagliptin?
- c) How much of the process model, used to extend the design space, is based on metformin data?
- d) Indicate which aspects/parameters of the control strategy are based on data generated using metformin.

Standard Review

Priority Review

**ACTIONS ITEMS**

<input type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/> n/a	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/> n/a	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/> n/a	If BLA or priority review NDA, send 60-day letter.
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

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

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

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

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

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

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

for approval on published literature based on data to which the applicant does not have a right of reference).

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

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

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

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Rachel E Hartford  
10/30/2008 12:02:50 PM  
CSO

## EXCLUSIVITY SUMMARY

NDA # 22-350

SUPPL # n/a

HFD # 510

Trade Name: Onglyza

Generic Name: saxagliptin

Dosage Form: tablet

Applicant Name: Bristol Myers Squibb

Approval Date: July 31, 2009

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES  NO

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

505(b)(1)

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

YES  NO

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

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

d) Did the applicant request exclusivity?

YES  NO

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

5 years

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 NDAs AND SUPPLEMENTS**

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

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

YES  NO

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

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials,

such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

YES  NO

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

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

YES  NO

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

YES  NO

If yes, explain:

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

YES  NO

If yes, explain:

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

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

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency

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

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

Investigation #1  
IND #                    YES                     ! NO   
! Explain:

Investigation #2  
IND #                    YES                     ! NO   
! Explain:

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

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

Investigation #1  
IND #                    YES                     ! NO   
! Explain:

Investigation #2  
IND #                    YES                     ! NO   
! Explain:

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

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

Investigation #1  
IND #                    YES                     ! NO   
! Explain:

Investigation #2  
IND #                    YES                     ! NO   
! Explain:

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



Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22350	ORIG 1		SAXAGLIPTIN

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

/s/

RACHEL E HARTFORD  
08/03/2009

MARY H PARKS  
08/03/2009

**PEDIATRIC PAGE**  
**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 22-350 Supplement Number: n/a NDA Supplement Type (e.g. SE5): n/a

Division Name: DMEP PDUFA Goal Date: 30Jul09 Stamp Date: 6/30/2008

Proprietary Name: Onglyza

Established/Generic Name: saxagliptin

Dosage Form: tablet

Applicant/Sponsor: Bristol-Myers Squibb Company

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) \_\_\_\_\_  
(2) \_\_\_\_\_  
(3) \_\_\_\_\_  
(4) \_\_\_\_\_

---

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1  
(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** Treatment of Type 2 diabetes mellitus

**Q1:** Is this application in response to a PREA PMR? Yes  Continue  
No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.  
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

**\* Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

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

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)  
 No: Please check all that apply:  
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)  
 Deferred for some or all pediatric subpopulations (Complete Sections C)  
 Completed for some or all pediatric subpopulations (Complete Sections D)  
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)  
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):  
 Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	0 yr. 0 mo.	9 yr. 11 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief justification):

# Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

\* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):			Reason for Deferral			Applicant Certification †
			Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum				
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/> Other	10 yr. 0 mo.	16 yr. 11 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cdcrpmhs@fda.hhs.gov](mailto:cdcrpmhs@fda.hhs.gov)) OR AT 301-796-0700.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

*{See appended electronic signature page}*

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Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

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

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Rachel E Hartford  
6/10/2009 09:56:58 AM

**NDA NO. 22-350**

**SAXAGLIPTIN NDA**

**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 did not use and will not use in any capacity the services of any person debarred under Section 306 (a) or (b) of the Federal Food, Drug and Cosmetics Act in connection with this Application.

*Pamela J. Smith*

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Pamela J. Smith, M.D.  
Group Director, Global Regulatory Strategy  
Bristol-Myers Squibb Company  
P.O. Box 4000  
Princeton, NJ 08543  
609-252-5228 (office)  
609-252-6000 (fax)

*6/4/08*

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Certification Date

## ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION		
NDA # <b>22-350</b> BLA # <b>N/A</b>	NDA Supplement # <b>N/A</b> BLA STN # <b>N/A</b>	If NDA, Efficacy Supplement Type: <b>N/A</b>
Proprietary Name: <b>Onglyza</b> Established/Proper Name: <b>saxagliptin</b> Dosage Form: <b>tablet</b>		Applicant: <b>Bristol-Myers Squibb</b> Agent for Applicant (if applicable): <b>N/A</b>
RPM: <b>Rachel Hartford</b>		Division: <b>Division of Metabolism and Endocrinology Products</b>
<p><b>NDA Application Type:</b>   <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p><b>Efficacy Supplement:</b>   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		
<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><b>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</b></p> <p><input type="checkbox"/> No changes                      <input type="checkbox"/> Updated Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p> <p><b>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</b></p>		
❖ <b>User Fee Goal Date</b> Action Goal Date (if different)		<b>31Jul2009</b>
❖ <b>Actions</b>		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions ( <i>specify type and date for each action taken</i> )		<input checked="" type="checkbox"/> None
❖ <b>Promotional Materials (<i>accelerated approvals only</i>)</b> Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance <a href="http://www.fda.gov/cder/guidance/2197dft.pdf">www.fda.gov/cder/guidance/2197dft.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received

The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application <sup>2</sup> Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):  <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC  NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies  <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC  Comments: _____	
❖ Date reviewed by PeRC ( <i>required for approvals only</i> ) If PeRC review not necessary, explain: _____	11Mar2009
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM ( <i>approvals only</i> )	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>2</sup> All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic 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.</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-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.)</li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: 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.)</li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric 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.)</li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #                      and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for each paragraph IV certification:

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

Yes  No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

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

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

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
<b>CONTENTS OF ACTION PACKAGE</b>	
<p>❖ Copy of this Action Package Checklist<sup>3</sup></p>	<p>03Aug2009</p>
<b>Officer/Employee List</b>	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input checked="" type="checkbox"/> Included</p>
<b>Action Letters</b>	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>AP - 31Jul2009</p>
<b>Labeling</b>	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	<p>30Jul2009</p>
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	
<p>❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)</p>	<p><input checked="" type="checkbox"/> Medication Guide  <input checked="" type="checkbox"/> Patient Package Insert  <input checked="" type="checkbox"/> Instructions for Use  <input type="checkbox"/> None</p>

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 9/5/08

<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	30Jul2009
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	
❖ Labels (full color carton and immediate-container labels) (write submission/communication date at upper right of first page of each submission)	
<ul style="list-style-type: none"> <li>• Most-recent division proposal for (only if generated after latest applicant submission)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling</li> </ul>	30Jun2008 and 6&17Jul2009
❖ Labeling reviews (indicate dates of reviews and meetings)	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 11Feb2009 & 24Jun09 <input checked="" type="checkbox"/> DRISK 22Jun2009 <input checked="" type="checkbox"/> DDMAC 25Mar2009 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews Safety Team - 30Jul2009 SEALD - 9Jun2009
❖ Proprietary Name	
<ul style="list-style-type: none"> <li>• Review(s) (indicate date(s))</li> </ul>	2Jul09 & 11Feb2009 (DMEPA labeling review)
<ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (indicate date(s))</li> </ul>	11Mar2009
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews (e.g., RPM Filing Review <sup>4</sup> /Memo of Filing Meeting) (indicate date of each review)	RPM Filing Review – 30Oct2008
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ora/compliance_ref/aip_page.html">www.fda.gov/ora/compliance_ref/aip_page.html</a>	
<ul style="list-style-type: none"> <li>• Applicant in on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP           <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (indicate date)</li> <li>○ If yes, OC clearance for approval (indicate date of clearance communication)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatric Page (approvals only, must be reviewed by PERC before finalized)	<input checked="" type="checkbox"/> Included 10Jun2009
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (include certification)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	<input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Outgoing communications (if located elsewhere in package, state where located)</li> </ul>	20Jul2009 (see Outgoing Communication tab)
<ul style="list-style-type: none"> <li>• Incoming submissions/communications</li> </ul>	

<sup>4</sup> Filing reviews for other disciplines should be filed behind the discipline tab.  
Version: 9/5/08

❖ Postmarketing Commitment (PMC) Studies	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>)</li> <li>• Incoming submission documenting commitment</li> </ul>	
❖ Outgoing communications ( <i>letters (except previous action letters), emails, faxes, telecons</i> )	included
❖ Internal memoranda, telecons, etc.	n/a
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>• PeRC (<i>indicate date; approvals only</i>)</li> <li>• Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)</li> <li>• Regulatory Briefing (<i>indicate date</i>)</li> <li>• Pre-NDA/BLA meeting (<i>indicate date</i>)</li> <li>• EOP2 meeting (<i>indicate date</i>)</li> <li>• Other (e.g., EOP2a, CMC pilot programs)</li> </ul>	<input checked="" type="checkbox"/> Pending <input type="checkbox"/> 30Jul2009 <input checked="" type="checkbox"/> No mtg <input type="checkbox"/> 14Dec2007 <input type="checkbox"/> 23Aug2005 QbD CMC Pilot program 25May2007
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> <li>• 48-hour alert or minutes, if available</li> </ul>	1Apr2009 Official Transcript
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 31Jul2009
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 29Jul2009
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 28Jul2009
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> <li>• Clinical review(s) (<i>indicate date for each review</i>)</li> <li>• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	See CDTL review 6Jul2009 <input checked="" type="checkbox"/> None
❖ Safety update review(s) ( <i>indicate location/date if incorporated into another review</i> )	Pg 121 of 6Jul2009 Clinical Review
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	Pg 21 of 6Jul2009 Clinical Review
❖ Clinical reviews from other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None 15Jul2009
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not needed
❖ Risk Management <ul style="list-style-type: none"> <li>• Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> <li>• REMS Memo (<i>indicate date</i>)</li> <li>• REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> </ul>	<input checked="" type="checkbox"/> None

<sup>5</sup> Filing reviews should be filed with the discipline reviews.

❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input type="checkbox"/> None requested 6Apr2009
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 4May2009 and 25Jun2009
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 7May2009 & 8Sep2009
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> None 23Jul2009
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 13May2009 & 1Jun2009
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 1Jun2009 & 8Sep2008
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input type="checkbox"/> No carc 24Feb2009
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 5Mar2009 & 1Jun2009 Included in P/T review
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None requested
<b>CMC/Quality</b> <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None 17Apr2009
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• CMC/product quality review(s) (indicate date for each review)	<input type="checkbox"/> None 27Aug2008, 29Oct2008, 25Nov2008, 9Dec2008, 25Mar2009 (3), 3Apr2009, & 25Jun2009
• BLAs only: Facility information review(s) (indicate dates)	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	<input checked="" type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology (indicate date of each review)	

❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input type="checkbox"/> None 23Jan2009 (statistical review – manufacturing process development)
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	25Jun2009
<input type="checkbox"/> Review & FONSI (indicate date of review)	
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> <li>• NDAs: Facilities inspections (include EER printout) (date completed must be within 2 years of action date)</li> </ul>	Date completed: 26Feb2009 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> <li>• BLAs:               <ul style="list-style-type: none"> <li>○ TBP-EER</li> <li>○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) (date completed must be within 60 days prior to AP)</li> </ul> </li> </ul>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold

The following Contents of Action Package Tabs were removed: they are not applicable:

Labeling – Medication Guide and Instructions for Use

Labeling Reviews – RPM and Controlled Substance Staff

Administrative/Regulatory Documents – Postmarketing Commitment Studies, Internal Memoranda, and Minutes of Meetings (PeRC and Regulatory Briefing)

Clinical Microbiology

Clinical Pharmacology – DSI Clinical Pharmacology Inspection Review Summary

Nonclinical – Consult Reviews, DSI NonClinical Inspection Review Summary

CMC/Quality – Microbiology Reviews

The following Contents of Action Package Tabs were removed: the information is presented in other locations:

Clinical Information – Financial Disclosure, Controlled Substance Staff Review, and Risk Management

## Appendix A to Action Package Checklist

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

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

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

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

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

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

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

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

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

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22350	ORIG 1		SAXAGLIPTIN

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/s/

RACHEL E HARTFORD  
08/03/2009

**Hartford, Rachel**

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**From:** Hartford, Rachel  
**Sent:** Monday, August 25, 2008 2:41 PM  
**To:** 'M. D. Pamela J Smith (pamela.smith@bms.com)'  
**Subject:** NDA 22-350

**Follow Up Flag:** Follow up  
**Flag Status:** Purple

Dr. Smith,

As you requested, I'm following up my verbal request with an email. Were the raw carci data files (SAS) submitted for Saxagliptin NDA 22-350? If yes, where in the submission are they located?

Thanks,

Rachel

*Rachel E. Hartford*  
**Regulatory Project Manager**  
**Division of Metabolism and Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food and Drug Administration**  
**[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)**  
**301-796-0331 (phone)**  
**301-796-9712 (fax)**

**Attachment B: Sample PMR/PMC Development Template**

This template should be completed by review management and included for each PMR/PMC in the Action Package.

---

PMR/PMC Title: A randomized, double-blind, controlled trial evaluating the effect of saxagliptin on the incidence of major adverse cardiovascular events in patients with type 2 diabetes mellitus.

---

PMR/PMC Schedule Milestones: Protocol Submission Date: 11/30/2009  
Study Initiation Date: NA  
Study Completion Date: C >  
Final Study Report Submission Date: 01/31/2016  
Other: \_\_\_\_\_ NA

b(4)

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

There have been signals of a serious risk of cardiovascular events with some medications developed for the treatment of type 2 diabetes and available data have not definitively excluded the potential for this serious risk with saxagliptin. We have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of cardiovascular events with anti-diabetic medication, including saxagliptin, to definitively exclude unacceptable cardiovascular toxicity. Such a trial will likely involve at least 10,000 patients followed for 3-5 years. Although such a trial can be conducted preapproval when warranted, the premarketing data with saxagliptin do not support such an approach (see below).

2. If required, characterize the PMR. Check all that apply and add text where indicated.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated approval
- Animal efficacy confirmatory studies
- Pediatric requirement
- FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

To support approvability and continued marketing, sponsors of unapproved drugs and biologics developed for the treatment of type 2 diabetes mellitus should provide evidence that these therapies do not result in an unacceptable increase in cardiovascular risk as recommended in the December 2008 Guidance to Industry, entitled Diabetes Mellitus: Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes.

The sponsor has already provided sufficient evidence that saxagliptin does not unacceptably increase cardiovascular risk to support marketing, but has not definitively excluded unacceptable cardiovascular risk. Therefore, consistent with the above guidance, the primary objective of the required postmarketing trial is to establish that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events observed with saxagliptin to that observed in the control group is less than 1.3. Secondary objectives will include an assessment of the long-term effects of saxagliptin on lymphocyte counts, infections, hypersensitivity reactions, liver, bone fracture, pancreatitis, skin reactions, and renal safety. These are adverse events of interest based on data from the saxagliptin trials or on data from pharmacologically-related products.

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

Risk of ischemic cardiovascular events.

- **If the PMR is a FDAAA safety study/clinical trial, does it:**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

- Clinical trial:** any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this **PMC**

5. What type of study or clinical trial is required or agreed upon (describe)?

Large, randomized, double-blind, controlled cardiovascular safety trial.

Required

- Pharmacoepidemiologic study (list risk to be evaluated)

---

- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)  
Risk of ischemic cardiovascular events

---

- Subpopulation (list type)

---

- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)

---

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety

Other (provide explanation)

---

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

---

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

---

**CDTL or PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22350	ORIG 1	BRISTOL MYERS SQUIBB CO	SAXAGLIPTIN

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/s/

AMY G EGAN  
07/31/2009

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

---

PMR/PMC Title: An epidemiologic study to compare the risk of severe hepatic events among patients with type 2 diabetes exposed to saxagliptin to the risk in patients exposed to other antidiabetic medications.

---

PMR/PMC Schedule Milestones:

Protocol Submission Date:	<u>01/31/2010</u>
Study Initiation Date:	<u>NA</u>
Study Completion Date:	<u>05/30/2015</u>
Final Study Report Submission Date:	<u>11/30/2015</u>
Other: _____	<u>NA</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Saxagliptin is a dipeptidyl peptidase (DPP)-4 inhibitor. Potential hepatotoxicity has been associated with another DPP-4 inhibitor in development. There were no cases of Hy's Law in the saxagliptin development program, which enrolled thousands of patients. Therefore, the incidence of severe drug-induced hepatic injury with saxagliptin (if such an association exists) will be rare.

2. If required, characterize the PMR. Check all that apply and add text where indicated.  
*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated approval  
 Animal efficacy confirmatory studies  
 Pediatric requirement  
 FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

A handful of saxagliptin- and comparator-treated patients developed serum transaminases greater than 10-times above the upper limit of the reference range. No Hy's Law cases have been associated with saxagliptin, although there has been a Hy's Law case with another DPP-4 inhibitor. Therefore, the goal of the proposed epidemiological study is to assess whether saxagliptin itself carries a low risk for severe hepatotoxicity.

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

Risk of hepatotoxicity.

- **If the PMR is a FDAAA safety study/clinical trial, does it:**
  - Assess a known serious risk related to the use of the drug?
  - Assess signals of serious risk related to the use of the drug?
  - Identify an unexpected serious risk when available data indicate the potential for a serious risk?
  
- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
  
  - Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  
  - Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
  
  - Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this PMC

5. What type of study or clinical trial is required or agreed upon (describe)?

An epidemiologic study to compare the risk of severe hepatic events among patients with type 2 diabetes exposed to saxagliptin to those patients exposed to other antidiabetic medications.

Required

- Pharmacoeconomic study (list risk to be evaluated)  
Risk of hepatotoxicity
- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)
- Subpopulation (list type)
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)
- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoeconomic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)
- Other

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

---

**CDTL or PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22350	ORIG 1	BRISTOL MYERS SQUIBB CO	SAXAGLIPTIN

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/s/

AMY G EGAN  
07/31/2009

## Attachment B: Sample PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

PMR/PMC Title: An epidemiologic study to compare severe hypersensitivity and severe cutaneous reactions among patients with type 2 diabetes exposed to saxagliptin to the risk in patients exposed to other antidiabetic medications.

PMR/PMC Schedule Milestones:

Protocol Submission Date:	<u>01/31/2010</u>
Study Initiation Date:	<u>NA</u>
Study Completion Date:	<u>11/30/2016</u>
Final Study Report Submission Date:	<u>06/30/2017</u>
Other: _____	<u>NA</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

Saxagliptin is a dipeptidyl peptidase (DPP)-4 inhibitor. Severe hypersensitivity reactions have been reported in the postmarketing setting for Januvia, which is the only FDA-approved DPP-4 inhibitor. Some hypersensitivity reactions occurred in the saxagliptin development program but no severe cases (e.g., angioedema) occurred among the thousands of patients studied in the saxagliptin premarketing application. Therefore, the incidence of severe hypersensitivity reactions with saxagliptin (if such an association exists) will be rare.

With regard to cutaneous lesions, saxagliptin causes skin lesions in distal body parts of monkeys at high exposures (approximately 20-fold above the maximum recommended human dose) with necrosis at exposures approximately 60-fold above the maximum recommended human dose. Other DPP-4 inhibitors cause similar cutaneous lesions in monkeys at or near clinical exposures. No clinical correlate was identified in the saxagliptin premarketing application, but rare events cannot be definitively excluded.

2. If required, characterize the PMR. Check all that apply and add text where indicated.  
*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated approval  
 Animal efficacy confirmatory studies  
 Pediatric requirement  
 FDAAA required safety study/clinical trial

- **Describe the particular review issue leading to the PMR**

See response under Question 1. The goal of the epidemiological study is to compare the risk of severe hypersensitivity reactions and severe cutaneous reactions among patients with type 2 diabetes exposed to saxagliptin to those exposed to other antidiabetic medications.

- If the PMR is a FDAAA safety study/clinical trial, describe the risk

Risk of severe hypersensitivity reactions and severe cutaneous reactions.

- If the PMR is a FDAAA safety study/clinical trial, does it:

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

4. If not required by regulation, characterize the review issue leading to this PMC

5. What type of study or clinical trial is required or agreed upon (describe)?

An epidemiologic study to compare the risk of severe hypersensitivity and severe cutaneous reactions among patients with type 2 diabetes exposed to saxagliptin to those patients exposed to other antidiabetic medications.

Required

- Pharmacoeconomic study (list risk to be evaluated)  
Risk of severe hypersensitivity reactions and severe cutaneous reactions.
- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)
- Subpopulation (list type)
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)
- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoeconomic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)
- Other

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

---

**CDTL or PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22350	ORIG 1	BRISTOL MYERS SQUIBB CO	SAXAGLIPTIN

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/s/

AMY G EGAN  
07/31/2009

**Hartford, Rachel**

---

**From:** Hartford, Rachel  
**Sent:** Friday, July 24, 2009 7:16 PM  
**To:** 'Smith, Pamela'  
**Subject:** Fracture Information Request

**Attachments:** Fractures.pdf

Hello Pam,

Please relook at the fracture cases to see which ones were associated with major trauma (e.g., car accidents). Your response (attached) states only 1 saxa fracture has been identified in the setting of a car accident. However, there are three serious adverse events of fracture among saxa patients that were reported to occur in the setting of car accidents.

Thank you,

Rachel



Fractures.pdf (131  
KB)

*Rachel E. Hartford*

**Regulatory Project Manager**

**Division of Metabolism and Endocrinology Products**

**Center for Drug Evaluation and Research**

**Food and Drug Administration**

[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)

**301-796-0331 (phone)**

**301-796-9712 (fax)**

## Hartford, Rachel

---

**From:** Hartford, Rachel  
**nt:** Wednesday, July 22, 2009 2:57 PM  
**o:** 'Smith, Pamela'  
**Subject:** Request earlier today

Hello Pam,

As per the conversation earlier today between Dr. Parks and Dr. Lamendola, we are requesting case narratives for those 18 cases of hypersensitivity. Specifically, we need information to determine if any of these cases coded as hypersensitivity reactions had signs/symptoms of anaphylaxis.

Please provide in these narratives comments on whether any of the following were present/absent in these cases:

- involvement of the skin, mucosal tissue or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
- respiratory compromise (e.g., dyspnea, wheezing-bronchospasm, stridor, reduced PEF, hypoxemia)
- reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

Please also provide:

- outcome
- the timing of the event with respect to dosing of drug and Study Day
- interventions (study drug discontinued or not, what happened with any such action, any rechallenge)

Thanks,

Rachel

*Rachel E. Hartford*  
**Regulatory Project Manager**  
**Division of Metabolism and Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food and Drug Administration**  
**[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)**  
**301-796-0331 (phone)**  
**301-796-9712 (fax)**

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/s/

-----  
Rachel E Hartford  
7/22/2009 03:00:37 PM  
CSO



NDA 22-350

PMR PROTOCOL COMMENTS

Bristol-Myers Squibb Company  
Attention: Pamela Smith, M.D.  
Group Director, Global Regulatory Strategy  
P.O. Box 4000  
Princeton, NJ 08543-4000

7/20/09

Dear Dr. Smith:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Onglyza (saxagliptin) tablet, 2.5 mg and 5 mg.

We also refer to your June 17, 2009 submission, containing two protocols: DN09018 "*Saxagliptin (BMS-477118) and Metformin (BMS-207150): Oral Combination Study of Embryo-Fetal Development in Rats (II)*" and DN09020 "*Saxagliptin (BMS-477118) and Metformin (BMS-207150): Oral Combination Study of Embryo-Fetal Development in Rabbits.*"

We have reviewed these two protocols and have the following comment:

The intent of our request for repeating the rat embryofetal study was to assess the reproducibility of the neural tube malformation observed with the metformin/saxagliptin combination along with an evaluation of each component alone. The proposed 600 mg/kg dose of metformin selected for the rat study is 3-fold greater than the metformin dose evaluated in the original rat study. Increasing the metformin dose to 600 mg/kg may confound interpretation of the repeat study due to several factors, including unexpected maternal/fetal toxicity when combined with saxagliptin and laparotomy data that differs from the original study. Not including the dose combination associated with the neural tube malformation in the original study is also a deficiency of the current protocol. In the event that the results of these studies, as currently designed, yield uninterpretable results, additional studies would be required to assess this signal of a serious risk of neural tube malformation associated with the combined use of saxagliptin and metformin. To proactively address the possibility that additional studies would be required, we request that you submit new study protocols that incorporate the following design elements:

- Include a 25/200 mg/kg saxagliptin/metformin combination group plus separate arms for saxagliptin and metformin in the rat embryofetal study. Additional combination groups at doses that bracket the 25/200 mg/kg group are acceptable. Signs of maternal toxicity at the highest dose combination group is desirable. Doses of the separate saxagliptin and metformin arms should equal those in the highest combination dose group.
- Evaluate at least two combination dose levels in the rabbit study that enable identification of a no-observed-adverse-effect-level (NOAEL) and a maternally toxic dose. Separate

arms for metformin and saxagliptin should also be incorporated (at doses equivalent to those used in the highest dose combination group).

- Monitor blood glucose, folate and vitamin B12 levels in both rat and rabbit studies to assess the potential role of metformin in neural tube malformations observed in rats.

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

*{See appended electronic signature page}*

Mary H. Parks, M.D.

Director

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

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

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Todd Bourcier  
7/20/2009 05:21:16 PM  
Signing for Dr. Parks

**Hartford, Rachel**

---

**From:** Hartford, Rachel  
**Sent:** Monday, July 20, 2009 9:38 AM  
**To:** 'Smith, Pamela'  
**Subject:** Urgent Request

Hello Pam,

Please submit the case report forms for the 18 hypersensitivity cases.

I'll contact you about the labeling this afternoon.

Thanks,

Rachel

*Rachel E. Hartford*  
**Regulatory Project Manager**  
**Division of Metabolism and Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food and Drug Administration**  
[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)  
**301-796-0331 (phone)**  
**301-796-9712 (fax)**

**Hartford, Rachel**

---

**From:** Hartford, Rachel  
**nt:** Friday, July 10, 2009 1:41 PM  
**From:** 'Smith, Pamela'  
**Subject:** Request to change the CV Final Protocol Submission date

Hello Pam,

We propose changing the CV Final Protocol Submission date from 31Oct09 to 30Nov09.

Please indicate if you agree with revised timeline:

Final Protocol Submission:	by November 30, 2009
Study Completion:	by July 31, 2015
Final Report Submission:	by January 31, 2016

Thank you,

Rachel

*Rachel E. Hartford*

**Regulatory Project Manager**

**Division of Metabolism and Endocrinology Products**

**Center for Drug Evaluation and Research**

**Food and Drug Administration**

[chel.hartford@fda.hhs.gov](mailto:chel.hartford@fda.hhs.gov)

1-796-0331 (phone)

301-796-9712 (fax)

**Hartford, Rachel**

---

**From:** Hartford, Rachel  
**nt:** Friday, July 10, 2009 8:24 AM  
**To:** 'Smith, Pamela'  
**Subject:** Information Request

Hello Pam,

Have there been any more cases of ALT >10x ULN or any cases of Hy's Law (ALT >3x ULN and total bilirubin >2x ULN) in the saxagliptin clinical trials since the database lock for the 120-day safety update? If yes, submit narratives for these patients.

Thank you,

Rachel

*Rachel E. Hartford*

**Regulatory Project Manager**

**Division of Metabolism and Endocrinology Products**

**Center for Drug Evaluation and Research**

**Food and Drug Administration**

[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)

**301-796-0331 (phone)**

**301-796-9712 (fax)**

MEMORANDUM

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

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**CLINICAL INSPECTION SUMMARY**

DATE: April 6, 2009

TO: Rachel Hartford, Regulatory Project Manager  
Naomi Lowy, M.D., Medical Officer  
Division of Metabolic and Endocrine Products

FROM: Susan Leibenhaut, M.D.  
Good Clinical Practice Branch I  
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Branch I  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: #22-350

APPLICANT: Bristol Meyers Squibb Company

DRUG: Onglyza (saxigliptin)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Adjunct to diet and exercise to improve glycemic control in adults with  
type 2 diabetes mellitus (DM)

CONSULTATION REQUEST DATE: October 10, 2009

DIVISION ACTION GOAL DATE: April 30, 2009

PDUFA DATE: April 30, 2009

## **I. BACKGROUND:**

Bristol Meyers Squibb has submitted an NDA for a new molecular entity saxagliptin, a dipeptidyl peptidase 4 (DPP4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 Diabetes Mellitus (DM).

The goals of the inspections were to assess adherence to FDA regulatory requirements concerning investigator oversight, protocol compliance, validity of primary efficacy endpoint data, and protection of subjects' rights, safety, and welfare. The number of subjects randomized was taken into account in selecting sites for auditing. Clinical sites were chosen based on number of subjects randomized and discontinued at a particular site and the number of Phase 3 studies conducted for this product. Inspectional history and number of clinical studies listed in the DSI database were also taken into account in choosing sites. Inspection was requested for Dr. William Jacks site, but the clinical investigator at this site was actually Dr. Rubin Saavedra.

The clinical sites were blinded to the primary endpoint Hemoglobin A1C (HA1C). Because the efficacy data were not located at the clinical sites, the data was audited at the clinical laboratories.

The protocols inspected were:

- A. Protocol CV181011 entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial to Evaluate the Efficacy and Safety of Saxagliptin (BMS-477118) as Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control with Diet and Exercise"
- B. Protocol CV181014 entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial to Evaluate the Efficacy and Safety of Saxagliptin (BMS-477118) in Combination with Metformin in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Alone"
- C. Protocol CV181039 entitled "A Multicenter, Randomized, Double-Blind, Active-Controlled, Phase 3 Trial to Evaluate the Efficacy and Safety of Saxagliptin in Combination with Metformin IR as Initial Therapy Compared to Saxagliptin Monotherapy and to Metformin IR Monotherapy in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control"
- D. Protocol CV181040 entitled "A Multicenter, Randomized, Double-blind, Placebo-controlled Phase 3 Trial to Evaluate the Efficacy and Safety of Saxagliptin in Combination with Glyburide in Subjects with Type 2 Diabetes Who Have Inadequate Glycemic Control on Glyburide Alone"

**II. RESULTS (by Site):**

Name of Clinical Investigator (CI), Clinical Laboratory (CL), or Sponsor, and Location	Protocol # and # of Subjects:	Inspection Date	Final Classification
CI: Ernie Riffer, M.D. Central Phoenix Medical Clinic 7600 N. 15 <sup>th</sup> Street, Suite 190 Phoenix, AZ 85020	Protocol CV181011 16 enrolled	December 8 to 18, 2008	NAI
CI: Rubin Saavedra, M.D. Nevada Alliance Against Diabetes 1440 North Eastern Ave North Las Vegas, NV 89030	Protocol CV181011 14 randomized  CV181039 17 enrolled	March 9 to 25, 2009	Pending (Preliminary classification VAI)
CI: Ronald Goldberg, MD Univ. Of Miami Diabetes Research. Institute 1450 NW 10th Ave. #1060 Miami, FL 33136	Protocol CV181014 8 randomized	March 16 to 19, 2009	VAI
CI: Danny Sugimoto, MD Cedar-Crosse Research Center 800 South Wells St., Suite M 15 Chicago, IL 60607	Protocol CV181039 5 enrolled/  Protocol CV181040 11 enrolled/	February 4 to 23, 2009	Pending (Preliminary classification VAI)
CL: J	Protocol CV181039 21 randomized  Protocol CV181040 9 randomized	March 9, 2009	NAI
CL: {	Protocol CV181011 24 randomized  Protocol CV181014 8 randomized	March 30 and 31, 2009	Pending (Preliminary classification NAI)
Sponsor: Bristol-Meyers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000		January 12 to 30, 2009	VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

b(4)

1. Ernie Riffer, M.D.  
7600 N. 15<sup>th</sup> Street, Suite 190  
Phoenix, AZ 85020

- a. **What was inspected:** At this site, 16 subjects were screened, 10 subjects were randomized, and 10 subjects completed the study. There were no deaths or serious adverse events reported. An audit of all subjects' records was conducted.
- b. **General observations/commentary:** There was no under-reporting of adverse events. No regulatory violations were noted. Due to the fact that the sites were blinded to the HA1C values, the efficacy data were verified by inspection of the laboratory, C
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

b(4)

2. Rubin Saavedra, M.D.  
Nevada Alliance Against Diabetes  
1440 North Eastern Ave.  
North Las Vegas, NV 89030

**Note:** Observations noted for this site are based on communications with the FDA investigator and review of the FDA Form 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

- a. **What was inspected:** For Protocol 181011, this site enrolled 17 subjects and randomized 13 subjects. Seven subjects completed the study, two subjects withdrew consent, three subjects discontinued due to lack of efficacy, and one subject was not compliant. Eight subject records were reviewed. For Protocol 181039 this site screened 32 subjects and 13 subjects completed the study. Six subject records were reviewed for completeness.
- b. **General observations/commentary:** There was no under-reporting of adverse events. Due to the fact that the sites were blinded to the HA1C values, the efficacy data were verified by inspection of the clinical laboratories for the respective studies. The following regulatory violations were noted:
  - 1. For study Protocol CV 181011, the following adverse events were recorded in the source documents but not reported to the sponsor by the clinical investigator:
    - i. Subject 00029 morning sickness and vaginal spotting
    - ii. Subject 01021 tooth pain
    - iii. Subject 00185 common cold

2. The CI did not maintain adequate and accurate records concerning reason for discontinuation in the trial for study Protocol CV 181011.

- i. Subjects 00028, 00029, and 00267 were listed on the case report form (CRF) as being discontinued because of lack of efficacy, but source documents indicated that Subject 00028 had no document to indicate early termination, Subject 00029 was withdrawn because of pregnancy, and Subject 00267 withdrew consent.
- ii. Subject 00185 was listed on the CRF as having withdrawn consent, but no source document was completed.
- iii. Subject 00905 was listed on the CRF as having withdrawn because of a withdrawn consent, but source document indicates that there was an adverse event.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. Ronald Goldberg, MD  
University of Miami Diabetes Research Institute  
1450 NW 10th Ave. #1060  
Miami, FL 33136

- a. **What was inspected:** This site screened 15 subjects and randomized 11 subjects. Eight subjects completed the study. All of the records for the randomized subjects were reviewed.
- b. **General observations/commentary:** The finding of mild edema of the lower extremities in subject 00131 that was listed in the adverse event log on March 19, 2006, was not reported to the sponsor. Due to the fact that the sites were blinded to the HA1C values, the efficacy data were verified by inspection of the

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

4. Danny Sugimoto, MD  
Cedar-Crosse Research Center  
800 South Wells St., Suite M 15  
Chicago, IL 60607

**Note:** Observations noted for this site are based on communications with the FDA investigator and review of the FDA Form 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

b(4)

- a. **What was inspected:** For Protocol CV18039 at this site, 6 subjects were screened, 4 subjects enrolled and 2 subjects were lost to follow-up. For Protocol CV18040, 15 subjects were screened, 9 subjects were enrolled, 1 subject was discontinued due to an adverse event, and 2 subjects were lost to follow-up. All subject records were reviewed.
- b. **General observations/commentary:** Due to the fact that the sites were blinded to the HA1C values, the efficacy data were verified by inspection of the  
C ) The following regulatory violations were noted: **b(4)**
1. Adverse events were recorded in the source documents but not reported to the sponsor by the clinical investigator:
    - i. Subject 00771: Week 4- disruption in sleep and Week 10- dizziness and constipation.
    - ii. Subjects 01151: Lead-in Phase-headache and decrease in appetite
  2. Accurate records were not maintained for the body mass index (BMI) calculations of two enrolled subjects, leading to enrollment of potentially ineligible subjects. A BMI of less than or equal to  $40\text{kg/m}^2$  was required to be eligible for the study.
    - i. The height and weight of Subject 01769 documented in the source records should have resulted in a BMI calculation of  $40.3\text{kg/m}^2$ . The BMI value was reported as  $39.6\text{kg/m}^2$  in the source records and the case report form.
    - ii. The height and weight of Subject 0021 documented in the source records resulted in a BMI calculation of  $40.6\text{kg/m}^2$ . The BMI value was changed to  $40.00\text{kg/m}^2$  in the source record.
  3. There is no documentation that the serious adverse event of gastroenteritis/dehydration for subject 00109 was reported to the sponsor within 24 hours as required by the protocol. The event was not reported to the sponsor until 4 days after the event.
  4. There was no pregnancy test on file for Subject 00109 at Week 4 as required by the protocol.
  5. Subject 00039 was enrolled and dispensed lead-in medication on 6/19/06 prior to the receipt of the hepatitis screening test results which were positive and resulted in exclusion of the subject from the study.

The clinical investigator provided an adequate response to the Form 483 observations in written correspondence on February 27, 2009.

- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

5.

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b(4)

- a. **What was inspected:** To verify the endpoint data, the inspection reviewed baseline HA1C results and either Week 24 or the last week of testing/listed result for each of the protocols. For Protocol CV181039, HA1C results were reviewed for 4 subjects at the Sugimoto site and 13 subjects for the Saavedra site. For Protocol CV181040, HA1C results were reviewed for all 9 randomized subjects at the Sugimoto site.
- b. **General observations/commentary:** There were no discrepancies of the collection dates, subject numbers and HA1C values between the laboratory source data and the data submitted in the NDA.
- c. **Assessment of data integrity:** Data from this site appear acceptable in support of the application.

6.

( )

b(4)

**Note:** Observations noted for this site are based on communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

- a. **What was inspected:** To verify the endpoint data, the inspection reviewed baseline HA1C results and either Week 24 or the last week of testing/listed result for each of the protocols. For Protocol CV181011, HA1C results were reviewed for eleven subjects at the Riffer site and 14 subjects at the Saavedra site. For Protocol CV181014 HA1C results were reviewed for eleven subjects at the Goldberg site.
- b. **General observations/commentary:** There were no discrepancies of the collection dates, subject numbers and HA1C values between the laboratory source data and the data submitted in the NDA.
- c. **Assessment of data integrity:** Data from this site appear acceptable in support of the application.

7. Bristol Meyers Squibb  
P.O. Box 4000  
Princeton, NJ 08543-4000

- a. **What was inspected:** The inspection reviewed the following sponsor responsibilities: monitoring, test article accountability, financial disclosures, Form FDA 1572, monitoring plans, qualifications of investigators and site monitors, transfer of obligations and adverse events. The inspection audited Protocols CV181011, CV181014, CV181039, and CV181040 and focused on the following clinical investigators: Dr. Danny Sugimoto, Dr. Ruben Saavedra, Dr. Ernie Riffer, and Dr. Ronald Goldberg.
- b. **General observations/commentary:** Minor deficiencies concerning clinical trial conduct monitoring and test article shipping and test article accountability were noted. Bristol-Myers Squibb Company responded adequately to the items listed on the Form 483 in a letter dated February 11, 2009.
- c. **Assessment of data integrity:** Data from the sponsor appear acceptable in support of the application.

The sponsor provided an adequate response to the Form 483 observations in written correspondence on February 11, 2009.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspections of Drs. Saavedra, Goldberg, Sugimoto and of Bristol-Meyers Squibb Company showed regulatory violations noted above. All other inspections did not note regulatory violations.

The studies appear to have been conducted adequately, and the data generated by the clinical sites may be used in support of the respective indication.

An addendum to this clinical inspection summary will be forwarded to the review division should there be a change in the final classification or additional observations of clinical and regulatory significance are discovered after reviewing the EIRs for Drs. Saavedra, Sugimoto, and C

b(4)

*{See appended electronic signature page}*

Susan Leibenhaut, M. D.  
Good Clinical Practice Branch I  
Division of Scientific Investigations

#### CONCURRENCE:

*{See appended electronic signature page}*

Constance Lewin, M.D., M.P.H  
Branch Chief  
Good Clinical Practice Branch I  
Division of Scientific Investigations

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/s/

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Susan Leibenhaut  
4/6/2009 12:31:04 PM  
MEDICAL OFFICER

Constance Lewin  
4/6/2009 01:32:29 PM  
MEDICAL OFFICER

**Hartford, Rachel**

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**From:** Hartford, Rachel  
**Sent:** Thursday, July 09, 2009 4:16 PM  
**To:** 'Smith, Pamela'  
**Subject:** PI - Clinical Pharmacology  
**Attachments:** Saxaglitpin-Response to sponsor.doc

Hello Pam,

The attachment contains the Clinical Pharmacology PI comments.

Thank you,

Rachel



Saxaglitpin-Response to sponso...

*Rachel E. Hartford*  
**Regulatory Project Manager**  
**Division of Metabolism and Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food and Drug Administration**  
[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)  
**301-796-0331 (phone)**  
**301-796-9712 (fax)**

**Response to sponsor:**

**Comments on section 7, DRUG INTERACTIONS**

**7.1 Inducers of CYP3A4/5 enzyme**

Ideally, AUC<sub>0-t</sub> is more accurate parameter as compared to the extrapolated AUC<sub>inf</sub>. However, in this case as the value is within 20% of AUC<sub>0-t</sub>, the use of AUC<sub>inf</sub> value is acceptable as a representative of the exposure data.

**7.2 Inhibitors of CYP3A4/5 enzyme**

We consider that a dose reduction to 2.5 mg QD when saxagliptin is co-administered with strong CYP3A4/5 inhibitors is required.

The sponsor's rationale that the extent of interaction between ketoconazole and saxagliptin is best represented by study CV181005 is not acceptable. Typically, clinical pharmacology studies are not designed to have power but to detect any signal of PK changes (eg, special population studies like renal or hepatic impairment PK study have about 6 subjects/group).

Although, study CV181022 was designed as a pharmacodynamic study, there were enough number of subjects (N= 11 as compared to N=15 in Study CV181005) to provide adequate interpretation of the interaction with ketoconazole. Both studies used similar bioanalytical methods; saxagliptin in saxagliptin alone treatment arm was quantifiable up to 12 h in all 15 subjects in study CV181005, while it was quantifiable up to 10 h in 9(out of 11) subjects in study CV181005. Sponsor's statement that saxagliptin was quantifiable to up to 18 h in study CV181005 is applicable to only 3 samples (Reference sponsor Table S.11.2.1A from study reports of CV181005 and CV181022).

Characterization of the saxagliptin systemic exposure in terms of the total active moiety is applicable when impact on efficacy is being addressed, for example effect of CYP inducers on saxagliptin PK or exposure-response relationships. This is not an accurate parameter when addressing the effect of CYP inhibition and the effect on parent moiety has to be considered separately. Based on the 3.79-fold increase in AUC and 2.44-fold increase in C<sub>max</sub> of saxagliptin (20 mg dose) when administered with ketoconazole, the saxagliptin dose need to be reduced to 2.5 mg QD in presence of strong CYP3A4/5 inhibitors.

Please incorporate the labeling language that was sent earlier by the Agency regarding this dose adjustment in appropriate sections of the label.

We agree to remove statements regarding C

b(4)

### **Comments on section 12.3, PHARMACOKINETICS**

Text format for drug interaction findings is acceptable. The language detailing the extrapolations of the saxagliptin drug-drug interaction findings to other compounds should be as follows:

#### Effect of saxagliptin on other drugs:

Metformin: The DDI study can conclude that saxagliptin is not an OCT-2 inhibitor but not regarding OCT 1 inhibition, since this study did not address effect on the pharmacodynamics of metformin. Therefore, the statement should exclude extrapolation to other OCT1 substrates.

Glyburide: proposed language acceptable.

Pioglitazone: Extrapolation to all 2C8 substrates is not acceptable, since pioglitazone is metabolized by multiple enzymes.

Digoxin: proposed language acceptable.

Simvastatin: proposed language acceptable.

Diltiazem: Extrapolation cannot be done to include other moderate CYP3A4/5 inhibitors.

Ketoconazole: Extrapolation cannot be done to include other strong CYP3A4/5 and P-gp inhibitors.

#### Effect of other drugs on saxagliptin:

Remove first paragraph under this. Also, extrapolation to other compounds is not applicable in this section and such language should be removed.

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

-----  
Rachel E Hartford  
7/15/2009 05:48:11 PM  
CSO

## Hartford, Rachel

---

**From:** Hartford, Rachel  
**Sent:** Wednesday, July 08, 2009 12:51 PM  
**To:** 'Smith, Pamela'  
**Subject:** Information Request

Hello Pam,

We have two more information requests:

1. Regarding that liver case with ALT ~2,300 U/L:

(a) The narrative of the MedWatch form states that study medication was temporarily stopped. Was saxagliptin restarted? If yes, what were the liver tests after restarting?

(b) Are there any bilirubin measurements available for other days besides the bilirubin measurement on April 16, 2008? Was jaundice reported? Were International Normalized Ratios (INRs) obtained?

2. Renal analyses in the ISS and 120-day safety update will not detect small changes in renal function with saxagliptin. Please perform the following renal analyses on the 120-day safety update database (combined short-term and long-term, including rescue). If you present data separately for the "Pooled Safety" population and for the initial combination with metformin trial, then please also conduct an additional analysis that pools data from the 2 monotherapy trials, the 3 add-on combination therapy trials, and the initial combination with metformin trial. For each saxagliptin treatment group, for the combined saxagliptin group and for comparator, show:

(a) Change from baseline in serum creatinine at Months 6, 12, 18, 24, and 30.

(b) Number and proportion of patients developing treatment-emergent serum creatinine >1.5x baseline.

(c) Number and proportion of patients developing treatment-emergent serum creatinine >1.5x baseline and exceeding the upper limit of the reference range.

Thank you,

Rachel

*Rachel E. Hartford*

**Regulatory Project Manager**

**Division of Metabolism and Endocrinology Products**

**Center for Drug Evaluation and Research**

**Food and Drug Administration**

[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)

**301-796-0331 (phone)**

**301-796-9712 (fax)**

## Hartford, Rachel

---

**From:** Hartford, Rachel  
**Sent:** Thursday, July 09, 2009 1:41 PM  
**To:** 'Smith, Pamela'  
**Subject:** 5mg Labels

Hello Pam,

We have an additional label revision for the 5mg strength:

**The size of the 5 mg strength designation on the physician sample pack is small and should be increased and should be similarly displayed as the strength on the trade container labels.**

Please send a label for each revised 5mg presentation via email.

Thank you,

Rachel

*Rachel E. Hartford*  
**Regulatory Project Manager**  
**Division of Metabolism and Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food and Drug Administration**  
[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)  
791-796-0331 (phone)  
1-796-9712 (fax)

**Hartford, Rachel**

---

**From:** Hartford, Rachel  
**Sent:** Wednesday, July 08, 2009 6:12 PM  
**To:** 'Smith, Pamela'  
**Subject:** Labeling Comments

Hello Pam,

We have two additional labeling comments.

1- Remove the *The data from a single study is insufficient to demonstrate the effect is sustained. All of the five other Phase 3 trials had fewer than 50% of the saxagliptin 5 mg patients completing 50 weeks; in one trial the rate was only 10%. One cannot argue that the treatment effect is sustained and is durable when rescue rates for insufficient response are 50% and higher after one year of treatment. Also the extensions were primarily designed to assess safety although data on HbA1c levels continued to be collected with an intention to report mean values. The assessment of HbA1c beyond Week 24 is potentially biased by the study designs in which eligibility for the extension was determined differentially between the treatment groups by an outcome variable, namely the need for rescue during the first 24 weeks. There was also no statistical plan to perform analyses of long-term HbA1c levels conditional on a patient being a responder during the initial 24-week period.*

b(4)

2- In the combined short-term and long-term periods of the pooled phase 3 trials including the initial combination with metformin trial but excluding the small mechanism-of-action trial (120-day safety update database), the incidence of fracture is 1.2% in the saxagliptin group and 0.6% in the comparator group without evidence of a relationship to saxagliptin dose. When corrected for patient exposure, the incidence of fracture is 1.0 per 100 patient-years for saxagliptin and 0.6 per 100 patient-years for comparator. Nineteen (0.6%) saxagliptin patients (eight on 2.5 mg, six on 5 mg, and five on 10 mg) and all 7 (0.6%) comparator patients had fractures within the first 6 months of treatment with study medication. There were an additional 9 saxagliptin patients with fracture occurring between 6 months and 1 year of treatment and another 7 saxagliptin patients with fracture after 1 year of treatment.

Based on the above, the sponsor should include language on fracture in the label unless the sponsor can show that the incidence of fracture is comparable between groups after fractures in the setting of car accidents have been excluded.

The Clinical Pharmacology comments should be available by the end of the week.

Thank you,

Rachel

*Rachel E. Hartford*  
**Regulatory Project Manager**  
**Division of Metabolism and Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food and Drug Administration**  
[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)  
301-796-0331 (phone)  
301-796-9712 (fax)

**Hartford, Rachel**

---

**From:** Hartford, Rachel  
**Sent:** Tuesday, July 07, 2009 9:29 AM  
**To:** 'joseph.lamendola@bms.com'  
**Subject:** Case 14162028 follow-up question  
**Attachments:** 14162028 Unblinded 3500A.pdf

Hello Joe,

Regarding the patient with marked ALT elevation in the ongoing renal impairment trial (attached Form 3500A):

1. The narrative mentions that the patient was on 3 concomitant medications. Were any of these medications discontinued when the marked ALT elevation occurred? If yes, on what date were these medications discontinued?
2. The narrative states: "The investigator stated that the case was discussed with the chief of hemodialysis unit and it was found that there were similar problem at the same time with the other patients in the same period and they did not receive any study medication from any other trials." Please provide as much information about these other cases as possible.
3. The narrative also mentions that the investigator attributed the liver test abnormalities possibly to a problem with the hemodialysis machine. Please provide any additional information on this, including published literature that supports such an association.

Thank you,

Rachel



14162028  
Unblinded 3500A.pdf

*Rachel E. Hartford*  
**Regulatory Project Manager**  
**Division of Metabolism and Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food and Drug Administration**  
[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)  
**301-796-0331 (phone)**  
**301-796-9712 (fax)**

**Hartford, Rachel**

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**From:** Hartford, Rachel  
**Sent:** Saturday, July 04, 2009 1:01 PM  
**To:** 'Smith, Pamela'  
**Subject:** Onglyza PI and PPI  
**Attachments:** Onglyza PI 04Jul2009.doc; Onglyza PPI 04Jul09.doc

Hello Pam,

Please accept all FDA changes and comments you agree with in the Onglyza PI and PPI and return via email. We request that you use track changes for edits and comment bubbles for additional comments. As discussed, I will send you the Clinical Pharmacology section of the PI next week.

Thank you,

Rachel



Onglyza PI  
04Jul2009.doc (1 MB)



Onglyza PPI  
04Jul09.doc (126 K..)

*Rachel E. Hartford*

**Regulatory Project Manager**

**Division of Metabolism and Endocrinology Products**

**Center for Drug Evaluation and Research**

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[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)

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**301-796-9712 (fax)**

## Hartford, Rachel

---

**From:** Hartford, Rachel  
**Date:** Tuesday, June 30, 2009 9:59 AM  
**To:** 'Smith, Pamela'  
**Subject:** FW: saxagliptin

Pam,

We agree with your first proposal. As for item two, there are other PTs reported that may also be relevant - e.g. Depressed mood, mood altered, dysthymic disorder. Review all such cases and include in the depression analysis or provide an adequate rationale as to why some of these PTs should not be included.

Thank you,

Rachel

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**From:** Smith, Pamela [mailto:pamela.smith@bms.com]  
**Sent:** Sunday, June 28, 2009 11:10 PM  
**To:** Hartford, Rachel  
**Subject:** RE: saxagliptin

Dear Rachel,

We have a clarification request and proposal regarding the Information Request you sent June 26:

1. Clarification re Questions 3, 4, 5, and 7. We propose to base our responses to these questions on the 120 day Safety Update R database (for the placebo pool of monotherapy and add-on studies and for study 039) including rescue, i.e., the most comprehensive Saxagliptin clinical database. Does the Agency agree? (Please note that Question 5 requested that the 120 day SUR database be used but did not specify rescue status).

2. Clarification re Question 4 regarding AEs of depression. We propose to base our analyses on the two PTs "depression" and "major depression." Does the Agency agree?

The BMS & AZ Team has already begun preparing the Responses and therefore we would very much appreciate a rapid clarification!

Thanks, and I hope you had a lovely weekend,

Pam

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**From:** Hartford, Rachel [mailto:Rachel.Hartford@fda.hhs.gov]  
**Sent:** Friday, June 26, 2009 7:07 AM  
**To:** Smith, Pamela  
**Subject:** FW: saxagliptin

Hello Pam,

Just wanted to follow-up on the status of your response to the email below. We have a few more information requests:

**1. In Study CV181062, there is a report of marked ALT elevation (2375 U/L) in subject D1680C00007-2106-2106007. Please unblind this patient and inform FDA whether the patient was receiving saxagliptin or placebo. If the patient was randomized to saxagliptin, (1) are any other liver test data available for this patient (e.g., total bilirubin, alkaline phosphatase), (2) besides testing for hepatitis**

B and C, did the patient undergo any additional tests to evaluate the cause for the liver test abnormalities, (3) what was the patient's severity of renal impairment, and (4) are there saxagliptin pharmacokinetic exposure data available for this patient?

2. On page 251 of the integrated summary of safety, you provide a narrative for subject CV1810F 40-805, stating that this patient had ALT and/or AST >10x ULN. However, the highest ALT in the narrative is 8x ULN and the highest AST is 5x ULN. Please clarify if this patient indeed had ALT >10x ULN.

3. Please perform an analysis of fracture adverse events occurring in the pooled phase 3 dataset (the 2 monotherapy trials and the 3 add-on combination trials) and in the initial combination with metformin trial.

4. Please perform an analysis of depression adverse events occurring in the pooled phase 3 dataset (the 2 monotherapy trials and the 3 add-on combination trials) and in the initial combination with metformin trial.

5. Please place the narratives for all of the following events in one document, sorted by preferred term.

<b>Discontinuations due to adverse events in the short-term and long-term periods of the pooled phase 3 monotherapy and add-on combination trials (up to cutoff date for 120-day safety update)</b>					
<b>System Organ Class</b>	<b>Saxa 2.5 mg</b>	<b>Saxa 5 mg</b>	<b>Saxa 10 mg</b>	<b>All Saxa</b>	<b>Placebo</b>
<b>Preferred term</b>	<b>N=882</b>	<b>N=882</b>	<b>N=279</b>	<b>N=2043</b>	<b>N=799</b>
	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>
Alanine aminotransferase increased	3 (0.3)	3 (0.3)	0	6 (0.3)	1 (0.1)
Blood creatinine increased	7 (0.8)	2 (0.2)	2 (0.7)	11 (0.5)	2 (0.3)
Lymphopenia	2 (0.2)	4 (0.5)	1 (0.4)	7 (0.3)	1 (0.1)
Eye pain	0	1 (0.1)	1 (0.4)	2 (<0.1)	0
Renal failure	1 (0.1)	1 (0.1)	0	2 (<0.1)	0
Thrombocytopenia	0	1 (0.1)	1 (0.4)	2 (<0.1)	0
Hematology test abnormal	0	1 (0.1)	0	1 (<0.1)	0
Liver function test abnormal	0	1 (0.1)	0	1 (<0.1)	0
Lymphocyte count decreased	0	1 (0.1)	0	1 (<0.1)	0
Neutropenia	0	1 (0.1)	0	1 (<0.1)	0
Leukopenia	1 (0.1)	0	0	1 (<0.1)	0

6. For study -039, please provide narratives for withdrawals due to adverse events in one document for patients with hepatic function abnormal, lymphopenia, pancytopenia, thrombocytopenia, blood creatinine increased, alanine aminotransferase increased, hepatic enzyme increased, blood bilirubin

increased, lymphocyte count decreased, and platelet count decreased. Sort narratives by preferred term.

7. In the pooled phase 3 dataset (the 2 monotherapy trials and the 3 add-on combination trials) and the initial combination with metformin trial, what proportion of patients in each treatment group had an adverse event of cholecystitis (i.e., reported to have either "cholecystitis" or "cholecystitis acute").

---

**From:** Hartford, Rachel  
**Sent:** Monday, June 22, 2009 1:46 PM  
**To:** 'Smith, Pamela'  
**Subject:** FW: saxagliptin

Pam.

We have reviewed the clarification below and are still unclear.

It is stated that 80 patients in Study -039 and 22 patients in Study -038 had a frozen A1c sample used in the calculation of change from baseline to Week 24 (LOCF). This seems to be at odds with the statement below that only 8 patients were excluded from -039 and no patients were excluded from -038 for calculating the change from baseline in HbA1c.

Are you stating in the last paragraph that frozen A1c samples from these 102 patients would be classified as "missing" for calculating the primary efficacy endpoint of change from baseline in HbA1c?

F

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**From:** Smith, Pamela [mailto:pamela.smith@bms.com]  
**Sent:** Tuesday, June 09, 2009 12:13 AM  
**To:** Hartford, Rachel  
**Subject:** RE: saxagliptin

Dear Rachel,

Please see below for our clarification Response regarding your query regarding the number patients/samples used in the calculation of the primary endpoint in the studies in which patients from Russia were enrolled and for which samples were frozen:

Appendix 1.1 and Appendix 2.1 of the response to Question 2 of May 11 reports the number of subjects with at least one sample that was frozen as a result of the Russian export suspension and subsequently used in the calculation of change from baseline to Week 24 (LOCF). A total of 80 subjects from study CV181039 had at least one frozen sample and 22 subjects from study CV181038 had at least one frozen sample.

Tables 1 and 2 of the response to Question 3 of May 11 reports the change from baseline in A1C including all data (top panel) and excluding data from the frozen samples (bottom panel) to illustrate the impact on excluding the frozen samples. The number of subjects data that were totally excluded from the analysis of A1C change from baseline due to the exclusion of the frozen samples was 8 from study CV181039, and no subject data were totally excluded from study CV181038. The analysis of A1C change from baseline (LOCF) excluding the frozen samples applied the same rules as in the Clinical Study Reports, ie, the last value prior to Week 24, prior to rescue, was used. Thus, the majority of subjects who had at least one frozen sample had / data from other (non frozen) samples that were used in the LOCF analysis.

I hope this is helpful. Please let me know if we should formally submit this clarification response to the NDA.

Thanks,

Pam

---

**From:** Hartford, Rachel [mailto:Rachel.Hartford@fda.hhs.gov]  
**Sent:** Thursday, June 04, 2009 5:27 PM  
**To:** Smith, Pamela  
**Subject:** RE: saxagliptin

Good Afternoon Pam,

Please clarify the "n" in Tables 1 and 2 under Response 3. These "n" do not appear consistent with the Response to question 1, where it states that 80 patients in CV181039 had a frozen A1c sample used in the calculation of the primary endpoint and that 22 patients in CV181038 had a frozen A1c sample used in the calculation of the primary endpoint.

Thank you,

Rachel

---

**From:** Smith, Pamela [mailto:pamela.smith@bms.com]  
**Sent:** Tuesday, June 02, 2009 10:25 AM  
**To:** Hartford, Rachel  
**Subject:** RE: saxagliptin

Hi Rachel,

Attached please find Responses to Question 1, 2, and 3 of the May 11 query about lab samples involved in the suspension of shipment of samples from Russia. We will formally submit the Responses to all 3 questions this week.

Pam

---

**From:** Hartford, Rachel [mailto:Rachel.Hartford@fda.hhs.gov]  
**Sent:** Monday, May 11, 2009 9:40 AM  
**To:** Smith, Pamela  
**Subject:** saxagliptin

Good Morning Pam,

We have a few additional information requests regarding the suspension of samples from Russia:

1. Is there evidence to show that the freezing and thawing of samples did not affect reliability of the data?
2. How many samples (total and by study) used for the efficacy analyses were affected as a result of the suspension?
3. If the affected samples were excluded, would the efficacy results be consistent?

Thanks,

Rachel

*Rachel E. Hartford*  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)  
301-796-0331 (phone)

301-796-9712 (fax)

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/s/

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Rachel E Hartford  
7/15/2009 05:50:58 PM  
CSO

**Hartford, Rachel**

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**From:** Hartford, Rachel  
**Sent:** Sunday, June 28, 2009 8:36 PM  
**To:** 'Smith, Pamela'  
**Subject:** Additional Request

Hello Pam,

We have an additional request:

Up to the cut-off date for the 120-day safety update, there are a total of 9 reports of "lymphadenopathy" with saxagliptin vs. 0 cases with comparator in the phase 3 program. Please provide additional information on these 9 cases - e.g., did all 9 reports reflect regional metastasis of a known tumor?

Thanks,

Rachel

*Rachel E. Hartford*  
**Regulatory Project Manager**  
**Division of Metabolism and Endocrinology Products**  
**Center for Drug Evaluation and Research**  
**Food and Drug Administration**  
[rachel.hartford@fda.hhs.gov](mailto:rachel.hartford@fda.hhs.gov)  
**301-796-0331 (phone)**  
**301-796-9712 (fax)**

**Hartford, Rachel**

**From:** Hartford, Rachel  
**nt:** Friday, June 26, 2009 7:07 AM  
**o:** 'Smith, Pamela'  
**Subject:** FW: saxagliptin

Hello Pam,

Just wanted to follow-up on the status of your response to the email below. We have a few more information requests:

1. In Study CV181062, there is a report of marked ALT elevation (2375 U/L) in subject D1680C00007-2106-2106007. Please unblind this patient and inform FDA whether the patient was receiving saxagliptin or placebo. If the patient was randomized to saxagliptin, (1) are any other liver test data available for this patient (e.g., total bilirubin, alkaline phosphatase), (2) besides testing for hepatitis B and C, did the patient undergo any additional tests to evaluate the cause for the liver test abnormalities, (3) what was the patient's severity of renal impairment, and (4) are there saxagliptin pharmacokinetic exposure data available for this patient?

2. On page 251 of the integrated summary of safety, you provide a narrative for subject CV181008-40-805, stating that this patient had ALT and/or AST >10x ULN. However, the highest ALT in the narrative is 8x ULN and the highest AST is 5x ULN. Please clarify if this patient indeed had ALT >10x ULN.

3. Please perform an analysis of fracture adverse events occurring in the pooled phase 3 dataset (the 2 monotherapy trials and the 3 add-on combination trials) and in the initial combination with metformin trial.

4. Please perform an analysis of depression adverse events occurring in the pooled phase 3 dataset (the 2 monotherapy trials and the 3 add-on combination trials) and in the initial combination with metformin trial.

5. Please place the narratives for all of the following events in one document, sorted by preferred term.

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<b>System Organ Class</b>	<b>Saxa 2.5 mg</b>	<b>Saxa 5 mg</b>	<b>Saxa 10 mg</b>	<b>All Saxa</b>	<b>Placebo</b>
<b>Preferred term</b>	<b>N=882</b>	<b>N=882</b>	<b>N=279</b>	<b>N=2043</b>	<b>N=799</b>
	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>
Alanine aminotransferase increased	3 (0.3)	3 (0.3)	0	6 (0.3)	1 (0.1)
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Eye pain	0	1 (0.1)	1 (0.4)	2 (<0.1)	0
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Thrombocytopenia	0	1 (0.1)	1 (0.4)	2 (<0.1)	0
Hematology test abnormal	0	1 (0.1)	0	1 (<0.1)	0
Liver function test abnormal	0	1 (0.1)	0	1 (<0.1)	0
Lymphocyte count decreased	0	1 (0.1)	0	1 (<0.1)	0
Neutropenia	0	1 (0.1)	0	1 (<0.1)	0
Leukopenia	1 (0.1)	0	0	1 (<0.1)	0

6. For study -039, please provide narratives for withdrawals due to adverse events in one document for patients with hepatic function abnormal, lymphopenia, pancytopenia, thrombocytopenia, blood creatinine increased, alanine aminotransferase increased, hepatic enzyme increased, blood bilirubin increased, lymphocyte count decreased, and platelet count decreased. Sort narratives by preferred term.

7. In the pooled phase 3 dataset (the 2 monotherapy trials and the 3 add-on combination trials) and in the initial combination with metformin trial, what proportion of patients in each treatment group had an adverse event of cholecystitis (i.e., reported to have either "cholecystitis" or "cholecystitis acute").

---

**From:** Hartford, Rachel  
**Sent:** Monday, June 22, 2009 1:46 PM  
**To:** 'Smith, Pamela'  
**Subject:** FW: saxagliptin

Pam.

We have reviewed the clarification below and are still unclear.

It is stated that 80 patients in Study -039 and 22 patients in Study -038 had a frozen A1c sample used in the calculation of change from baseline to Week 24 (LOCF). This seems to be at odds with the statement below that only 8 patients were excluded from -039 and no patients were excluded from -038 for calculating the change from baseline in HbA1c.

Are you stating in the last paragraph that frozen A1c samples from these 102 patients would be classified as "missing" for calculating the primary efficacy endpoint of change from baseline in HbA1c?

Rachel

---

**From:** Smith, Pamela [mailto:pamela.smith@bms.com]  
**Sent:** Tuesday, June 09, 2009 12:13 AM  
**To:** Hartford, Rachel  
**Subject:** RE: saxagliptin

Dear Rachel,

Please see below for our clarification Response regarding your query regarding the number patients/samples used in the

6/29/2009

calculation of the primary endpoint in the studies in which patients from Russia were enrolled and for which samples were frozen:

Appendix 1.1 and Appendix 2.1 of the response to Question 2 of May 11 reports the number of subjects with at least one sample was frozen as a result of the Russian export suspension and subsequently used in the calculation of change from baseline to Week 24 (LOCF). A total of 80 subjects from study CV181039 had at least one frozen sample and 22 subjects from study CV181038 had at least one frozen sample.

Tables 1 and 2 of the response to Question 3 of May 11 reports the change from baseline in A1C including all data (top panel) and excluding data from the frozen samples (bottom panel) to illustrate the impact on excluding the frozen samples. The number of subjects data that were totally excluded from the analysis of A1C change from baseline due to the exclusion of the frozen samples was 8 from study CV181039, and no subject data were totally excluded from study CV181038. The analysis of A1C change from baseline (LOCF) excluding the frozen samples applied the same rules as in the Clinical Study Reports, ie, the last value prior to Week 24, prior to rescue, was used. Thus, the majority of subjects who had at least one frozen sample had A1C data from other (non frozen) samples that were used in the LOCF analysis.

I hope this is helpful. Please let me know if we should formally submit this clarification response to the NDA.

Thanks,

Pam

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**From:** Hartford, Rachel [mailto:Rachel.Hartford@fda.hhs.gov]  
**Sent:** Thursday, June 04, 2009 5:27 PM  
**To:** Smith, Pamela  
**Subject:** RE: saxagliptin

Good Afternoon Pam,

Please clarify the "n" in Tables 1 and 2 under Response 3. These "n" do not appear consistent with the Response to question 1, where it states that 80 patients in CV181039 had a frozen A1c sample used in the calculation of the primary endpoint and that 22 patients in CV181038 had a frozen A1c sample used in the calculation of the primary endpoint.

Thank you,

Rachel

---

**From:** Smith, Pamela [mailto:pamela.smith@bms.com]  
**Sent:** Tuesday, June 02, 2009 10:25 AM  
**To:** Hartford, Rachel  
**Subject:** RE: saxagliptin

Hi Rachel,

Attached please find Responses to Question 1, 2, and 3 of the May 11 query about lab samples involved in the suspension of shipment of samples from Russia. We will formally submit the Responses to all 3 questions this week.

Pam

---

**From:** Hartford, Rachel [mailto:Rachel.Hartford@fda.hhs.gov]  
**Sent:** Monday, May 11, 2009 9:40 AM  
**To:** Smith, Pamela  
**Subject:** saxagliptin

6/29/2009

Good Morning Pam,

We have a few additional information requests regarding the suspension of samples from Russia:

1. Is there evidence to show that the freezing and thawing of samples did not affect reliability of the data?
2. How many samples (total and by study) used for the efficacy analyses were affected as a result of the suspension?
3. If the affected samples were excluded, would the efficacy results be consistent?

Thanks,

Rachel

*Rachel E. Hartford*

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/s/

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CSO