

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
200678Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

PATIENT LABELING REVIEW

Date: October 14, 2010

To: Mary Parks, M.D., Director
Division of Metabolism and Endocrinology Products (DMEP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)

Barbara Fuller, RN, MSN, CWOCN
Patient Labeling Reviewer
Division of Risk Management

From: Latonia M. Ford, RN, BSN, MBA
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name (established name): TRADENAME (saxagliptin/metformin hydrochloride extended-release) Tablets

Application Type/Number: NDA 200678

Applicant: Bristol-Myers Squibb (BMS) Company

OSE RCM #: 2010-2031

1 INTRODUCTION

This review is written in response to a request by the Division of Metabolic and Endocrine Products (DMEP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME (saxagliptin/metformin HCl extended-release) Tablets.

Bristol-Myers Squibb (BMS) Company submitted a New Drug Application (NDA) for TRADENAME (saxagliptin/metformin HCl extended-release) tablets on December 29, 2009. TRADENAME (saxagliptin/metformin HCl extended-release) tablets is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate.

DRISK conferred with DMEPA and a separate DMEPA review of the PPI has been submitted and placed in DARRTS dated July 2, 2010.

2 MATERIAL REVIEWED

- Draft TRADENAME (saxagliptin/metformin HCL extended-release) Tablets Patient Package Insert (PPI) received on December 29, 2009, revised by the Review Division throughout the current review and sent by the Review Division to DRISK on September 29, 2010.
- Draft TRADENAME (saxagliptin/metformin HCL extended-release) Tablets Prescribing Information (PI) received on December 29, 2009, revised by the Review Division throughout the current review and sent by the Review Division to DRISK on September 29, 2010.
- Approved Janumet (sitagliptin/metformin HCl) Tablets comparator labeling dated, September 24, 2010
- Approved Onglyza (saxagliptin) Tablets comparator labeling dated, July 31, 2009

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible

- removed unnecessary or redundant information
- ensured that the PPI is consistent with the PI
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the PPI are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI

Please let us know if you have any questions.

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immediately following this page

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/s/

LATONIA M FORD

10/15/2010

Saxagliptin and metformin DRISK Final PPI

LASHAWN M GRIFFITHS

10/15/2010

MEMORANDUM

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

DATE: October 7, 2010

TO: Mary H. Parks, M.D.
Director
Division of Metabolic and Endocrine Products

FROM: Gopa Biswas, Ph.D.
Arindam Dasgupta, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. *Martin K. Yau 10/8/10*
Acting Team Leader - Bioequivalence Branch
Division of Scientific Investigations

SUBJECT: Review of EIRs covering NDA 200678, (b)(4)
(Saxagliptin-Metformin HCl extended-release fixed-dose combination) Tablets 5/500 mg, 5/1000 mg, 2.5/1000 mg, sponsored by Bristol-Myers Squibb Company.

At the request of the Division of Metabolic and Endocrine Products (DMEP), the Division of Scientific Investigations (DSI) conducted an audit of the clinical and analytical portions of the following bioequivalence studies:

Study Number: CV181112

Study Title:

"Bioequivalence Study of the Fixed-Dose Combination of 5-mg Saxagliptin/1000-mg Metformin XR (Manufactured in Mt Vernon, IN) Relative to 5 mg of Onglyza and 2 X 500-mg Glucophage XR Co-administered to Healthy Subjects in the Fed State and Steady State Pharmacokinetic Assessment of the Fixed-Dose Combination of 5-mg Saxagliptin/1000-mg Metformin XR"

The clinical portion of the study was conducted at PPD, Inc., Austin, TX. The analytical portions were conducted at (b)(4)

(b)(4) Following the inspections at the clinical site (July 26-29, 2010) and the analytical site at (b)(4)

Page 2 - NDA 200678, (b) (4) (Saxagliptin-Metformin HCl extended-release fixed-dose combination) Tablets 5/500 mg, 5/1000 mg, 2.5/1000 mg

there were no significant findings and no Form FDA-483 was issued.

Following the inspection at (b) (4), a Form FDA-483 was issued (Attachment 1). Firm's response dated July 13, 2010 was received by DSI (Attachment 2). Our evaluation of the 483 observations and the firm's response follows:

- 1. Analyte interference was not evaluated for BMS-477118, its metabolite BMS-510849 and metformin. The subject samples contained all three analytes at the time of analysis.**

In their written response, (b) (4) acknowledged the observation. They provided additional data to show that there was no interference by metformin in the detection of BMS-477118 (Saxagliptin) and its metabolite BMS-510849. The data is found to be adequate and acceptable.

- 2. Failure to validate sample stability at room temperature during method validation for:**

(b) (4)

(b) (4) subject samples were stored in (b) (4) at room temperature before injection for more than 6 h for runs 1, 2 & 10, (subjects 101-103, 104-106 & 128-130), 11h for run 12 (Per 3-subjects 115, 117, 123, 126, & 128-129) and 14 h for runs 3 & 11 (subjects 107-109 & Per 3-subjects 101, 103, 105, 108-109, 111, & 114).

In response to the observation, (b) (4) provided additional data to demonstrate (b) (4) storage stability at room temperature for 31 hours. The results are adequate and acceptable.

- 3. Freeze thaw stability was not demonstrated in that one aliquot each of low, high and dilution QC was subjected to six F/T cycles and then divided into 6 aliquots before analysis.**

(b) (4) acknowledged this observation and provided additional data for freeze thaw (F/T) stability using 6 aliquots of low, high and dilution QC. The results demonstrate F/T

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stability for 6 cycles and are found acceptable upon review. The firm has also revised the SOP to include minimum of 3 aliquots for each concentration for validation of F/T stability.

4. Failure to apply appropriate acceptance criteria for Incurred Sample Reproducibility (ISR) for metabolite BMS 510849. A (b) (4) acceptance criteria was applied instead of 20% for BMS-510849.

The firm has revised the SOP for ISR and changed the acceptance criteria from (b) (4) to 20% for metabolites. However, 99.99% of the samples exhibited differences <20% between the original and re-assayed data indicating that the assay was robust for BMS-510849. Thus, the above observation is not likely to have significant impact on study outcome.

Conclusion:

Following the above inspections, the Division of Scientific Investigations recommends that the clinical and analytical portions of the Study CV181112 be accepted for Agency review.

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



Arindam Dasgupta, Ph.D.



Gopa Biswas, Ph.D.

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Final Classification:

NAI- PPD, Austin, TX

VAI- (b) (4)

NAI- (b) (4)

CC:

DSI/GLPBB/Ball/Haidar/Biswas/Dasgupta/Rivera-Lopez/CF

OND/ODEII/DMEP/Hai, Mehreen/Parks

CDER/OCP/DCPII/Jain, Ritesh/Sahajwalla, Chandrahas G

HFR-CE350/Jonee Mearns

HFR-CE250/Cynthia Harris

HFR-SW150/Robert Lorenz

Draft: GB AD 10/7/10

Edit: MKY 10/8/10

DSI: 6055

O:\BIOEQUIV\EIRCOVER\200678bms.sax.met.doc

FACTS: 1160674

Email:

CDER DSI PM TRACK

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/s/

GOPA BISWAS
10/08/2010

**DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS
SAFETY TEAM
MEMO TO THE FILE**

NDA#/Submission #/Submission type: 200678/000/N

Product Name: (b) (4) (saxagliptin/metformin HCl extended-release) tablets

Application submission date: 29 December 2009

Safety team reviewer: Amy G. Egan, M.D., M.P.H.

Safety review completion date: 4 October 2010

Action goal date: 29 October 2010

Reason for Review: New PPI

Items Reviewed: PI/PPI/Clinical review

Synopsis of Findings: (b) (4) is a fixed-dose combination of saxagliptin, a DPP-4 inhibitor, and extended-release metformin, a biguanide. There are 3 proposed dosage strengths, 5mg/500mg, 5mg/1000mg, and 2.5mg/1000mg. Saxagliptin was approved July 31, 2009 with a PPI; metformin HCl extended-release was approved October 13, 2000 without a PPI or a Medication Guide; however, Medication Guides are approved with other metformin-containing combination products including Janumet (sitagliptin/metformin HCl), ActoplusMet (pioglitazone/metformin HCl), ActoplusMet XR (pioglitazone/metformin HCl XR), and Avandamet (rosiglitazone/metformin HCl). Metaglip (glipizide and metformin HCl) and Glucovance (glyburide and metformin HCl) have PPIs.

According to the medical review, no new safety issues were identified with co-administration of saxagliptin and metformin XR. The known safety issues with saxagliptin include: hypersensitivity, and lymphopenia; dosage adjustment is required for moderate or severe renal impairment. The known safety issues with metformin XR include: lactic acidosis due to metformin accumulation, especially in the setting of compromised renal function, and a decrease in Vitamin B12 levels.

Unlike sitagliptin, saxagliptin remains unlabeled with respect to the occurrence of pancreatitis. At the time of approval, there were 6 (0.2%) cases of pancreatitis in patients treated with saxagliptin versus 2 (0.2%) cases in patients treated with comparator. An OSE review of AERS was conducted in May 2010 that revealed two reports of acute pancreatitis associated with saxagliptin use. In the last PSUR (dated January 31, 2010 to April 30, 2010), there were 7 cases of pancreatitis reported. The sponsor has been asked to provide a summary/analysis of all postmarketing pancreatitis cases along with drug

utilization data, and to provide a cumulative summary of the data on pancreatitis in future PSURs. Additionally, saxagliptin will undergo a 915 review beginning 31 January 2011 at which time a more comprehensive approach to this safety issue will be undertaken to determine if the saxagliptin label should be revised to include language regarding acute pancreatitis and whether a Medication Guide-only REMS should be required.

At this time, I do not recommend that the PPI be converted to a Medication Guide or that a REMS be required.

Determination:

REMS triggered: Y N I

If yes (Y) or indeterminate (I), was submission referred to the SRT?: Y N

Date submitted:

Date response received:

SRT response:

If no (N), why not?:

If no (N), please check one (or more) of the following reasons below:

No significant safety issue identified

Only editorial changes made

Changes pertain only to proper use of a device

Other:

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

/s/

AMY G EGAN
10/07/2010

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

Application Information	
NDA # 200678 BLA# N/A	NDA Supplement #:S- N/A BLA STN # N/A
Efficacy Supplement Type SE- N/A	
Proprietary Name: (b) (4) (rejected), (b) (4) (rejected), (b) (4) (under review)	
Established/Proper Name: Saxagliptin-Metformin HCl extended release	
Dosage Form: Tablets	
Strengths: 5/500 mg, 5/1000 mg, 2.5/1000 mg	
Applicant: Bristol-Myers Squibb	
Agent for Applicant (if applicable): N/A	
Date of Application: December 29, 2009	
Date of Receipt: December 29, 2009	
Date clock started after UN: N/A	
PDUFA Goal Date: October 29, 2010	Action Goal Date (if different): October 29, 2010
Filing Date: February 27, 2010	
Date of Filing Meeting: February 16, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only): 4	
Proposed Indication(s): Treatment of Type 2 Diabetes Mellitus	
Type of Original NDA: AND (if applicable)	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Type of NDA Supplement: N/A <i>Refer to Appendix A for further information.</i>	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
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"/> N/A	
Resubmission after refuse to file? <input type="checkbox"/> N/A	
Part 3 Combination Product? <input type="checkbox"/> N/A	<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: N/A	<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)

Collaborative Review Division (if OTC product): N/A	
List referenced IND Number(s): IND 063634 and IND 076500	
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
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ora/compliance_ref/aip.html If yes, explain: N/A If yes, has OC/DMPQ been notified of the submission? Comments: N/A	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status Comments: None	<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>	
Exclusivity	
Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at:</i> http://www.fda.gov/cder/ob/default.htm 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)]?	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <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>Comments: N/A</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>Comments: N/A</p>	<p><input type="checkbox"/> YES # years requested: N/A</p> <p><input checked="" 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>
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
<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)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</p> <p>If yes, please list below: N/A</p>		<input type="checkbox"/> YES <input type="checkbox"/> NO	
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>			
Format and Content			
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p>Comments: N/A</p>		<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)	
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>		<p>N/A</p>	
<p>If electronic submission: <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>Comments: N/A</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<p>If electronic submission, does it follow the eCTD guidance? (http://www.fda.gov/cder/guidance/7087rev.pdf)</p> <p>If not, explain (e.g., waiver granted): N/A</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	

<p>Form 356h: Is a signed form 356h included?</p> <p><i>If foreign applicant, both 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>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Index: Does the submission contain an accurate comprehensive index?</p> <p>Comments:</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 type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Controlled substance/Product with abuse potential:</p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BLAs/BLA efficacy supplements only:</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
Patent Information (NDAs/NDA efficacy supplements only)	
<p>Patent information submitted on form FDA 3542a?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Debarment Certification	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, both the applicant and the U.S. Agent must</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>sign the certification.</p> <p><i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p> <p>Comments:</p>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
<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>
Financial Disclosure	
<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>Comments:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Pediatrics	
PREA	
<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 & 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><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</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"> • <i>If no, request in 74-day letter.</i> • If yes, 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) 	<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>
Comments:	

<p><u>BPCA (NDAs/NDA efficacy supplements only):</u></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i></p> <p>Comments:</p>	<p>N/A</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
Prescription Labeling	
<p>Check all types of labeling submitted.</p> <p>Comments:</p>	<p><input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input 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)</p>
<p>Is electronic Content of Labeling submitted in SPL format?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Package insert (PI) submitted in PLR format?</p> <p>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?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>REMS consulted to OSE/DRISK?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

OTC Labeling	
<p>Check all types of labeling submitted.</p> <p>Comments: N/A</p>	<input checked="" type="checkbox"/> Not Applicable <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>Comments: N/A</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>Comments: N/A</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>Comments: N/A</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>Comments: N/A</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Meeting Minutes/SPA Agreements	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES Date(s): <input checked="" 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>Comments:</p>	<input checked="" type="checkbox"/> YES Date(s): OCTOBER 15, 2009 <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>Comments:</p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT
MEMO OF FILING MEETING

DATE: FEBRUARY 16, 2010

NDA/BLA #: 200678

PROPRIETARY/ESTABLISHED NAMES: Saxagliptin-Metformin HCl extended-release fixed-dose combination

APPLICANT: Bristol-Myers Squibb

BACKGROUND: Saxagliptin (Trade name: Onglyza) is an inhibitor of dipeptidyl peptidase-4 (DPP-4) and was approved by the FDA as an anti-diabetic drug on July 31, 2009, under NDA 022350. Metformin XR (Trade name: Glucophage XR) is an anti-diabetic drug of the biguanide class and was approved by the FDA on October 13, 2000, under NDA 021202. Both drug products are marketed by BMS.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Mehreen Hai	Y
	CPMS/TL:	Lina AlJuburi	Y
Cross-Discipline Team Leader (CDTL)	Hylton Joffe		Y
Clinical	Reviewer:	Arlet Nedeltcheva-Peneva	Y
	TL:	Hylton Joffe	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	None needed	
	TL:	None needed	
Labeling Review (<i>for OTC products</i>)	Reviewer:	None needed	
	TL:	None needed	
OSE	Reviewer:	None needed	
	TL:	None needed	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	None needed	
	TL:	None needed	

Clinical Pharmacology	Reviewer:	Weili Huang, changed to Ritesh Jain on 07-21-10	Y
	TL:	Sally Choe	Y
Biostatistics	Reviewer:	Wei Liu	Y
	TL:	Todd Sahlroot	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Lauren Murphree Mihalcik	Y
	TL:	Todd Bourcier	Y
Statistics, carcinogenicity	Reviewer:	None needed	
	TL:	None needed	
Product Quality (CMC)	Reviewer:	Elsbeth Chikhale	Y
	TL:	Suong Tran	Y
Facility (<i>for BLAs/BLA supplements</i>)	Reviewer:	None needed	
	TL:	None needed	
Microbiology, sterility (<i>for NDAs/NDA efficacy supplements</i>)	Reviewer:	Jessica Cole	Y
	TL:	James McVey	N
Bioresearch Monitoring (DSI)	Reviewer:	Susan Leibenhaut	
	TL:		
Other reviewers	Houda Mahayni (Biopharm)		Y

OTHER ATTENDEES:

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

<p>Electronic Submission comments</p> <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<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
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: Clinical studies were previously reviewed for Onglyza NDA 022350</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <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> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: N/A
<ul style="list-style-type: none"> 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? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<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
<p>CLINICAL PHARMACOLOGY</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<p>Comments: Study Reports for Study CV181111 and CV 181112 must be submitted within 90 days. DSI inspection requested for Study CV181112.</p>	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments: Could not open some data files, but problem was resolved before filing date.</p>	<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
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<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
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<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"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<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"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<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"> Sterile product? 	<input type="checkbox"/> YES

<p>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</p>	<input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>FACILITY (BLAs only)</p> <p>Comments:</p>	<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
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Mary Parks, M.D., Division Director</p> <p>GRMP Timeline Milestones: Primary Reviews due in DARRTS: September 24, 2010 Secondary Reviews due in DARRTS: October 1, 2010 Get labeling to company: October 1, 2010</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> 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"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	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"/>	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.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200678

ORIG-1

BRISTOL MYERS
SQUIBB

 (b) (4) (saxagliptin +
metformin XR) Tablets

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/s/

MEHREEN HAI
09/02/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: July 1, 2010

To: Mary Parks, MD, Director
Division of Metabolic and Endocrinology Products

Through: Kristina A. Toliver, PharmD, Team Leader
Carol A. Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Loretta Holmes, BSN, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): (b) (4)
(Saxagliptin and Metformin HCl Extended-release) Tablets
5 mg/500 mg, 5 mg/1000 mg, and 2.5 mg/1000 mg

Application Type/Number: NDA 200678

Applicant: Bristol-Myers Squibb Company

OSE RCM #: 2010-389

1 INTRODUCTION

This review responds to a request from the Division of Metabolic and Endocrinology Products for assessment of the container labels, carton and insert labeling for (b) (4) (Saxagliptin and Metformin HCl Extended-release) Tablets, 5 mg/500 mg, 5 mg/1000 mg, and 2.5 mg/1000 mg.

2 METHODS AND MATERIALS

DMEPA used Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels, carton, and insert labeling submitted as part of the December 29, 2009 (container labels and insert labeling) and April 28, 2010 submission (blister labels and carton labeling), see Appendices A, B, and C.

- Container Labels (Trade)
 - 5 mg/500 mg and 5 mg/1000 mg (30, 90, and 500-count)
 - 2.5 mg/1000 mg (60 and 500-count)
- Blister Card Labels (Professional Sample)
 - 5 mg/500 mg and 5 mg/1000 mg (7-count)
 - 2.5 mg/1000 mg (6-count)
- Carton Labeling (Professional Sample)
 - 5 mg/500 mg and 5 mg/1000 mg (7-count)
 - 2.5 mg/1000 mg (6-count)
- Insert Labeling (no image)

3 RECOMMENDATIONS

Our evaluation noted areas where information on the container labels, blister labels, and carton labeling can be improved to minimize the potential for medication errors. Section 3.1 *Comments to the Applicant* contains our recommendations for the container labels, blister labels, and carton labeling. We request the recommendations in Section 3.1 be communicated to the Applicant prior to approval.

Additionally, DMEPA notes the container labels, blister labels, and carton labeling are imprinted with the proposed proprietary name (b) (4). This proposed name has been found unacceptable. Therefore, we recommend that when an alternate name is found acceptable that the Applicant submit revised labels and labeling with the new name for our review and comment.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Margarita Tossa, at 301-796-4053.

3.1 COMMENTS TO THE APPLICANT

- A. General Comments on the Container Labels, Professional Sample Blister Labels, and Professional Sample Carton Labeling
 1. The (b) (4) portions of the name are presented in two different colors and fonts on the container labels and professional sample carton labeling.

The (b) (4) portion of the name is highlighted and more prominent since it is in a darker color and heavier font than the remaining portion of the name. This may make product selection from a shelf more difficult. Therefore, we request you present the entire name in the same color and font in a manner that gives equal prominence to all the letters in the name.

2. The established name has a (b) (4) that separates the two ingredients (i.e., (b) (4)). Replace the (b) (4) with the word “and” so that the established name reads as: (Saxagliptin and Metformin HCl Extended-release) Tablets.
3. The dosage form statement “tablets” is part of the established name but appears smaller in size as compared to the established name and is difficult to read. Increase the size of the dosage form statement so that it is commensurate with the size of the active ingredients.
4. Include instructions that state the product “must be swallowed whole and never crushed, cut or chewed”. Place this information on the principal display panel.

B. Container Labels and Professional Sample Carton Labeling

1. Each strength is presented in a color block. However, the color blocks used for each strength are green, purple or blue. Green and purple are also the colors used in the trade dress and blue is a color that can look similar to green and purple. This use of color minimizes the effectiveness of color to differentiate the strengths. In order to better differentiate the strengths, present the strength in color blocks that are not the same or similar in color to those colors used in the trade dress.
2. The statement of strength is located at the very top of the labels and labeling, above the net quantity statement and NDC number. This is not the usual location of the statement of strength. Relocate the statement of strength to appear on the line below the established name and dosage form so that patients and healthcare providers can easily find this information.
3. Specify the location for the lot number and expiration date on the labels and labeling.

C. Bulk Container Label (500-count)

On the 500-count bulk bottle, place instructions to the pharmacist concerning the type of container in which the tablets should be dispensed.

D. Professional Sample Blister Labels

1. Each blister card contains either 6 or 7 tablets and there is one label that covers the blister. Thus, as the tablets are used the label can be torn, ripped, or punched out. This can interfere with the product identifying information on the label such as the proprietary name, established name, dosage form and strength and render it unreadable. We recommend that each tablet be packaged in its own blister with its own label such that as the tablets are used the product identifying information for the remaining tablets stays intact. Alternatively, at a minimum, repeat the product information over and over so that as the tablets are removed there is product identifying information that remains intact on the label.
2. Include instructions on the label that instruct patients on how to remove the tablets from the blister.

E. Professional Sample Carton Labeling

On each carton there is a round color graphic that contains the strength. Delete the graphic. Relocate the statement of strength from the top of the carton labeling to appear on the line below the established name. See comment B-2, above.

6 Page(s) of Draft Labeling
have been Withheld in Full
as b4 (CCI/TS) immediately
following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200678	ORIG-1	BRISTOL MYERS SQUIBB	(b) (4) (saxagliptin + metformin XR) Tablets

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

/s/

LORETTA HOLMES
07/01/2010

KRISTINA C ARNWINE
07/02/2010

CAROL A HOLQUIST
07/02/2010

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: March 16, 2010

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: (Required for international inspections)
Director, Review Division, HFD-510 or

Director, Division of Pharmaceutical Evaluation, HFD-###

FROM: Mehreen Hai, Regulatory Project Manager, Division of Metabolism and Endocrinology Products, HFD-510

SUBJECT: Request for Biopharmaceutical Inspections
NDA 200678
(b) (4) (Saxagliptin-Metformin HCl extended-release fixed-dose combination) Tablets 5/500 mg, 5/1000 mg and 2.5/1000 mg
Bristol-Myers Squibb

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
<p>Protocol CV181-111: Bioequivalence Study of the Fixed-Dose Combination of 5-mg Saxagliptin and 500-mg Metformin XR Tablet (Manufactured in Mt Vernon, IN) Relative to 5-mg Saxagliptin Tablet and 500-mg Metformin XR Tablet (Manufactured in Evansville, IN) Coadministered to Healthy Subjects in a Fed Condition</p> <p>Protocol CV181-112: Bioequivalence Study of the Fixed-Dose Combination of 5-mg Saxagliptin/1000-mg Metformin XR (Manufactured in Mt Vernon, IN)</p>	<p>Matthew M. Medlock, MD, Principal Investigator PPD Development, LP 7551 Metro Center Drive Suite 200 Austin, TX 78744 Ph: (512) 447-2985</p>	<p>(b) (4)</p>

Relative to 5 mg of Onglyza and 2 × 500-mg Glucophage XR Coadministered to Healthy Subjects in the Fed State and Steady-State Pharmacokinetic Assessment of the Fixed-Dose Combination of 5-mg Saxagliptin/1000-mg Metformin XR		(b) (4)

International Inspections:

(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)

We have requested an international inspection because:

There is a lack of domestic data that solely supports approval;

Other (please explain):

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **SEPTEMBER 15, 2010**. We intend to issue an action letter on this application by **OCTOBER 29, 2010**.

Should you require any additional information, please contact **Mehreen Hai, Regulatory Project Manager, 301-796-5073**.

Concurrence: (Optional)

Name Medical Team Leader Biopharm Team Leader

Name Medical Reviewer Biopharm Reviewer

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-200678

ORIG-1

BRISTOL MYERS
SQUIBB

 (b) (4) (saxagliptin +
metformin XR) Tablets

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/s/

MEHREEN HAI
03/16/2010