

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205649Orig1s000

OTHER REVIEW(S)

MEMORANDUM

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

DATE: August 26, 2014

TO: Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence I
Office of Generic Drugs

Jean-Marc P. Guettier, M.D.
Director, Division of Metabolism and Endocrinology
Products
Office of New Drugs

FROM: Seongeun Cho, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Recommendation to accept data for (b) (4)
(b) (4) and for NDA 205-649,
Dapagliflozin (BMS-512148)/Metformin Extended Release
Tablets by Bristol-Myers Squibb Co., without on-site
inspection of the analytical site

The Division of Bioequivalence and GLP Compliance (DBGLPC) recommends accepting bioanalytical data for (b) (4) (b) (4) (b) (4) and NDA 205-649 study MB102092, without on-site inspection of the analytical site, (b) (4) (b) (4). This memo provides the rationale for this recommendation and why DBGLPC is declining to inspect (b) (4). Please note that inspections of the requested clinical site for studies (b) (4), and of another bioanalytical site for study MB102092 for dapagliflozin (BMS-512148), have been completed.

[REDACTED]
NDA 205-649, Dapagliflozin (BMS-512148)/Metformin
Extended Release Tablets by Bristol-Myers Squibb Co.

Inspection of the clinical site for study MB102092 is in progress. Separate review memos for these inspections are forthcoming.

Background

The Division of Bioequivalence I (DB1) requested inspections of clinical and analytical sites for the following studies on

[REDACTED] (b) (4).

[REDACTED] (b) (4)

The Division of Metabolism and Endocrinology Products (DMEP) requested inspections of clinical and analytical sites for the following study on 12/16/2013:

MB102092: "Bioequivalence Study of a Fixed-Dose Combination Tablet of 10 mg Dapagliflozin /1000 mg Metformin XR Relative to a Single 10 mg Dapagliflozin Tablet and Two 500 mg Glucophage XR Tablets Co-administered to Healthy Subjects in the Fed and Fasted States and Steady-State Pharmacokinetic Assessment of the Fixed-Dose Combination of 10 mg Dapagliflozin / 1000 mg Metformin XR"

Analytical portions of these three studies were conducted at the following site:

Analytical Site: [REDACTED] (b) (4)

OSI inspected [REDACTED] (b) (4) in the last three years, covering eight applications. The following is a list of

[REDACTED]
 NDA 205-649, Dapagliflozin (BMS-512148)/Metformin
 Extended Release Tablets by Bristol-Myers Squibb Co.

applications with studies audited during those inspections, the dates of bioanalyses for the audited studies, and the analytical methods for the subject sample analyses employed in these studies.

Application	Analytical Method	Bioanalysis Period
NDA [REDACTED] (b) (4)	HPLC-MS/MS	[REDACTED] (b) (4)
NDA	HPLC-MS/MS	[REDACTED]
NDA	HPLC- UV Abs	[REDACTED]

Each inspection included a thorough review of all records associated with the studies and method validations, correspondence with the sponsors and the clinical sites, records of subject sample receipt and storage, notebooks and electronic records, standard operating procedures (SOPs), as well as examination of facilities, and interviews and discussions with the firm's management and staff. No significant adverse observations were identified during these inspections and the inspectional outcomes from all inspections were classified as No Action Indicated (NAI).



The quantification of metformin for study MB102092 was conducted by HPLC with MS/MS detection during [REDACTED] (b) (4). The methodology was representative of most of the audited studies, and conduct was nearly contemporaneous. DBGLPC considers that the inspectional outcomes from previous inspections provide reasonable assurance that [REDACTED] (b) (4) conducted study MB102092 without significant irregularities.

[REDACTED]
NDA 205-649, Dapagliflozin (BMS-512148)/Metformin
Extended Release Tablets by Bristol-Myers Squibb Co.

Conclusion:

Based on five satisfactory inspections in recent years, their final inspectional classifications, and the similarity of the methodologies and processes used to conduct the studies inspected compared with those requested, this reviewer concludes that bioanalytical data from studies [REDACTED] (b) (4), and MB102092 are acceptable for further Agency review without on-site inspection at [REDACTED] (b) (4) [REDACTED].

Seongeun Cho, Ph.D.
BE Branch, DBGLPC, OSI

DARRTS cc:
OSI/Kassim/Taylor/Haidar/Bonapace/Skelly/Choi/Dasgupta/Dejernett
/Nkah/Fenty-Stewart/Johnson
CDER/OGD/DB1/Diana Solana-Sodeinde/ Dale Conner
CDER/OND/DMEP/Jean-Marc Guettier/Elizabeth Chen

Email cc:
ORA/BLT-DO/ORA BLT BIMO

Draft: JC 7/16/2014
Edit: MFS 7/17/2014, AD 7/18/2014; SHH 7/23/2014; WHT 7/23/2014
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program
/Analytical Sites/[REDACTED] (b) (4).

[REDACTED] (b) (4)

File BE6653 (NDA 205-649)
FACTS: [REDACTED] (b) (4)

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/s/

CHASE H BOURKE
08/26/2014

CHARLES R BONAPACE
08/27/2014

WILLIAM H TAYLOR
08/28/2014

MEMORANDUM

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

DATE: August 25, 2014

TO: Director, Investigations Branch
Dallas District Office
4040 N. Central Expressway
Dallas, TX 75204

FROM: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

SUBJECT: **FY 2014, CDER PDUFA, High Priority Pre-Approval Data
Validation Inspection**, Bioresearch Monitoring, Human
Drugs, CP 7348.001

RE: NDA 205-649
DRUG: Dapagliflozin (BMS-512148) and Metformin XR Fixed
Dose Combination Tablet, 10 mg / 1000 mg
SPONSOR: Bristol-Myers Squibb Co., USA

This addendum updates the inspection assignment memo issued on 12/19/2013 that Icon Development Solution's facility in Omaha, NE (clinical site) is no longer in service and that all clinical study records and reserve samples for study MB102092 have been transferred to the Icon Development Solution's facility in San Antonio, TX.

This memo requests that you arrange for an inspection of the clinical portion of the following bioequivalence (BE) study at Icon Development Solution's San Antonio facility listed below.

Background materials will be available in ECMS under the ORA folder. **The inspections should be completed prior to August 29, 2014 to meet PDUFA due date.**

Do not reveal the applicant, application number, study to be inspected, drug name, or the study investigators to the sites prior to the start of the inspections. The sites will receive this information during the inspection opening meeting. The inspections will be conducted under Bioresearch Monitoring

Page 2 - BIMO Assignment Addendum, NDA 205-649, Dapagliflozin (BMS-512148) and Metformin XR Fixed Dose Combination Tablet, 10 mg / 1000 mg, sponsored by Bristol-Myers Squibb Co., USA

Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

At the completion of the inspection, please send a scanned copy of the completed sections A and B of this memo to the DBGLPC POC.

Study: MB102092
Study Title: "Bioequivalence Study of a Fixed-Dose Combination Tablet of 10 mg Dapagliflozin / 1000 mg Metformin XR Relative to a Single 10 mg Dapagliflozin Tablet and Two 500 mg Glucophage XR Tablets Co-administered to Healthy Subjects in the Fed and Fasted States and Steady-State Pharmacokinetic Assessment of the Fixed-Dose Combination of 10 mg Dapagliflozin / 1000 mg Metformin XR"

Clinical Site: ICON Development Solutions
8307 Gault Lane
San Antonio, TX 78209

Investigator: Barbara Newberry
TEL: (210) 283-4500
FAX: (210) 853-0840

SECTION A - RESERVE SAMPLES

Because this bioequivalence study is subject to 21 CFR 320.38 and 320.63, the site conducting the study (i.e., each investigator site) is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided by the Applicant for subject dosing.

The final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) specifically addresses the requirements for bioequivalence studies (<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm>).

Please refer to CDER's "Guidance for Industry, Handling and Retention of BA and BE Testing Samples" (May 2004), which clarifies the requirements for reserve samples (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>).

During the clinical site inspection, please:

- Verify that the site retained reserve samples according to the regulations. If the site did not retain reserve samples or the samples are not adequate in quantity, notify the DBGLPC POC immediately.
- If the reserve samples were stored at a third party site, collect an affidavit to confirm that the third party is independent from the applicant, manufacturer, and packager. Additionally, verify that the site notified the applicant, in writing, of the storage location of the reserve samples.
- Obtain written assurance from the clinical investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific bioequivalence studies, and that samples were stored under conditions specified in accompanying records. Document the signed and dated assurance [21 CFR 320.38(d, e, g)] on the facility's letterhead, or Form FDA 463a Affidavit.
- Obtain confirmation that the sponsor was notified in writing about the name and address of the facility to which the reserve samples were transferred.
- Collect and ship samples of the test and reference drug products **in their original containers** to the following address:

John Kauffman, Ph.D.
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
645 S. Newstead Ave
St. Louis, MO 63110
TEL: 1-314-539-2135

SECTION B - CLINICAL DATA AUDIT

Please remember to collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

During the clinical site inspection, please:

- Confirm the informed consent forms and study records for 100% of subjects enrolled at the site.
- Compare the study report in the NDA submission to the original documents at the site.
- Check for under-reporting of adverse events (AEs).
- Check for evidence of inaccuracy in the electronic data capture system.
- Check reports for the subjects audited.
 - o Number of subject records reviewed during the inspection: _____
 - o Number of subjects screened at the site: _____
 - o Number of subjects enrolled at the site: _____
 - o Number of subjects completing the study: _____
- Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocols.
- Confirm that site personnel followed SOPs during study conduct.
- Examine correspondence files for any applicant or monitor-requested changes to study data or reports.
- Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.
- Other comments:

Additional instructions to the ORA Investigator:

In addition to the compliance program elements, other study specific instructions may be provided by the DBGLPC POC prior to commencement of the inspection. Therefore, we request that the DBGLPC POC be contacted for any further instructions, inspection related questions or clarifications before the inspection and also regarding any data anomalies or questions noted during review of study records on site.

If you issue Form FDA 483, please forward a copy to the DBGLPC POC. If it appears that the observations may warrant an OAI classification, notify the DBGLPC POC as soon as possible.

Remind the inspected site of the 15 business-day timeframe for submission of a written response to the Form FDA 483. In addition, please forward a copy of the written response as soon as it is received to the DBGLPC POC.

DBGLPC POC: Chase Bourke, Ph.D.
Pharmacologist
Office of Scientific Investigations
Tel: 1-240-402-4129
Fax: 1-301-847-8748
E-mail: chase.bourke@fda.hhs.gov

DARRTS cc:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Bonapace/Haidar/Choi/Dasgupta/Skelly/Bourke/
OSI/DBGLPC/Dejernet/Jenty-Stewart/Johnson/Nkah
CDER/OND/Chen

Email cc:
ORA DO/Richard-Math/Harris/Turcovski/Martinez/Bromley/Lopicka

Draft: CHB 8/21/2014
Edit: AD 08/21/2014
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/ICON Development Solutions, San Antonio, TX
OSI file #: BE6653

FACTS: (b) (4)

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/s/

CHASE H BOURKE
08/25/2014

CHARLES R BONAPACE
08/26/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # NDA 205649
Product Name: Xigduo XR

PMR/PMC Description: A study to evaluate whether pediatric patients with type 2 diabetes mellitus or healthy pediatric subjects ages 10 to 17 years (inclusive) can safely swallow Xigduo XR (dapagliflozin and metformin HCl extended-release) tablets. The study should evaluate tablets that are at least as large as the largest Xigduo XR (dapagliflozin and metformin HCl extended-release) tablet. Placebo tablets should be used if the study population consists of healthy subjects.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>October 2015</u>
	Study/Trial Completion:	<u>April 2018</u>
	Final Report Submission:	<u>October 2018</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- 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
- Other

Xigduo XR is ready for approval in adults. Pediatric studies have been deferred until after safety and efficacy were demonstrated in adults.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this study is to assess whether pediatric patients 10 to 17 years (inclusive) will be able to swallow the fixed dose combination (FDC) tablets safely.

The FDC tablets measure 20 mm in diameter. The large size may present a choking hazard for pediatric patients. The PMR addresses this potential risk by requiring the applicant to characterize the swallowability of the FDC tablet.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- 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?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A study to evaluate whether pediatric patients with type 2 diabetes mellitus or healthy pediatric subjects ages 10 to 17 years (inclusive) can safely swallow Xigduo XR tablets. The study should evaluate tablets that are at least as large as the largest Xigduo XR tablet. Placebo tablets should be used if the study population consists of healthy subjects.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Pediatric swallowability study

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) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

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.

(signature line for BLAs)

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/s/

JENNIFER R PIPPINS
10/29/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)**

******Pre-decisional Agency Information******

Memorandum

Date: October 24, 2014

To: Elizabeth Chen, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Kendra Y. Jones, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 205469
OPDP labeling comments for XIGDUO XR (dapagliflozin and metformin HCl extended-release) tablets, for oral use

OPDP has reviewed the proposed draft prescribing information (PI) and carton container labeling for XIGDUO XR (dapagliflozin and metformin HCl extended-release) tablets, for oral use (Xigduo XR) submitted for consult on December 23, 2013.

OPDP's comments regarding the proposed draft medication guide were provided under separate cover with the Division of Medical Policy Programs (DMPP) on October 23, 2014. OPDP's comments on the proposed draft PI are based on the version located in Sharepoint on October 21, 2014 (last revised October 16, 2014).

Thank you for the opportunity to comment on the proposed draft PI and carton container labeling at this time.

If you have any questions, please contact Kendra Jones at 301.796.3917 or Kendra.jones@fda.hhs.gov.

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/s/

KENDRA Y JONES
10/24/2014

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

PATIENT LABELING REVIEW

Date: October 23, 2014

To: Jean-Marc Guettier, MD
Director
**Division of Metabolism and Endocrinology Products
(DMEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Kendra Y. Jones
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): XIGDUO XR (dapagliflozin and metformin hydrochloride extended-release)

Dosage Form and Route: Tablets, for oral use

Application Type/Number: NDA 205649

Applicant: Bristol-Myers Squibb Company

1 INTRODUCTION

On October 30, 2013, Bristol-Myers Squibb Company submitted for the Agency's review an Original New Drug Application for XIGDUO XR (dapagliflozin and metformin HCl extended-release) tablets for oral use, a combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on December 23, 2013, and December 23, 2013, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for XIGDUO XR (dapagliflozin and metformin HCl extended-release) tablets.

2 MATERIAL REVIEWED

- Draft XIGDUO XR (dapagliflozin and metformin HCl extended-release) MG received on October 30, 2013, and received by DMPP on July 25, 2014.
- Draft XIGDUO XR (dapagliflozin and metformin HCl extended-release) MG received on October 30, 2013, and received by OPDP on July 25, 2014.
- Draft XIGDUO XR (dapagliflozin and metformin HCl extended-release) Prescribing Information (PI) received on October 30, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on October 17, 2014.
- Draft XIGDUO XR (dapagliflozin and metformin HCl extended-release) Prescribing Information (PI) received on October 30, 2013, revised by the Review Division throughout the review cycle, and received by OPDP on October 16, 2014.
- Approved FARXIGA (dapagliflozin) comparator labeling dated August 8, 2014.
- Approved INVOKAMET (canagliflozin and metformin hydrochloride) comparator dated August 8, 2014.

3 REVIEW METHODS

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.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
10/23/2014

SHAWNA L HUTCHINS
10/23/2014

LASHAWN M GRIFFITHS
10/23/2014

MEMORANDUM

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

DATE: October 17, 2014

TO: Jean-Marc P. Guettier, M.D.
Director, Division of Metabolism and Endocrinology
Products (DMEP)
Office of New Drugs

FROM: Arindam Dasgupta, Ph.D.
Pharmacologist, GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

Chase Bourke, Ph.D.
Pharmacologist, GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Charles Bonapace, Pharm.D.
Chief (acting), GLP Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D.
Director,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIR covering NDA 205-649, Dapagliflozin
(BMS-512148) and Metformin XR Fixed Dose Combination
Tablet, 10 mg / 1000 mg, sponsored by Bristol-Myers
Squibb Co., USA

At the request of the Division of Metabolism and Endocrinology Products (DMEP), the Division of Bioequivalence and GLP Compliance (DBGLPC) arranged inspections of the clinical and analytical portions of the following bioequivalence study:

Study #1: MB102092
Study Title: "Bioequivalence Study of a Fixed-Dose
Combination Tablet of 10 mg Dapagliflozin /
1000 mg Metformin XR Relative to a Single 10 mg
Dapagliflozin Tablet and Two 500 mg Glucophage

XR Tablets Co-administered to Healthy Subjects in the Fed and Fasted States and Steady-State Pharmacokinetic Assessment of the Fixed-Dose Combination of 10 mg Dapagliflozin / 1000 mg Metformin XR"

Clinical Site: ICON Development Solutions, San Antonio, TX

DBGLPC arranged the audit of the clinical portion of the study at ICON Development Solutions, San Antonio, TX after the records were transferred to ICON's San Antonio facility following closure of ICON's Omaha, NE facility. The clinical portion of the study was audited by ORA Investigator Joel Martinez between October 6-8, 2014. Following the audit of the study records, no objectionable conditions were observed and no Form FDA 483 was issued.

Analytical Site: (b) (4) (Metformin analysis)

Based on (b) (4) satisfactory inspections in recent years, their final inspectional classifications, and the similarity of the methodologies and processes used to conduct the studies inspected compared with the requested study for audit, DBGLPC reviewers Dr. Seongeun Cho and Dr. Chase Bourke concluded that the analytical portion of the study data generated at (b) (4) are acceptable for further Agency review without an on-site inspection.

Analytical Site: (b) (4) (Dapagliflozin analysis)

The analytical portion of the study (dapagliflozin analysis) was audited at (b) (4) by Leighton Ngai (ORA), Arindam Dasgupta, Ph.D. (OSI), and Chase H. Bourke, Ph.D. (OSI) between (b) (4). The audits included a thorough examination of facilities and equipment; examination of study records, including communications between sponsor and laboratory staff; and interviews and discussions with (b) (4)'s management and staff. Following the inspection of the analytical site, no objectionable conditions were observed and no Form FDA 483 was issued.

Conclusions:

Following the above inspections, these reviewers recommend that the data for the clinical and analytical portions of study MB102092 be accepted for agency review.

Arindam Dasgupta, Ph.D.
GLP Branch, DBGLPC, OSI

Chase H. Bourke, Ph.D.
GLP Branch, DBGLPC, OSI

Final Classification:

NAI - Icon Development Solutions, San Antonio, TX

FEI: 3007158681

NAI - (b) (4)

FEI: (b) (4)

CC:

CDER OSI PM TRACK

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Draft: AD 10/16/2014

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Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/Analytical Sites (b) (4)

NDA 205-649 Dapagliflozin (BMS-512148) and Metformin XR Fixed
Dose Combination Tablet

File: BE 6653; O:\BE\EIRCOVER\205649bri.dap.met.doc

FACTS: (b) (4)

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/s/

ARINDAM DASGUPTA
10/17/2014

CHASE H BOURKE
10/17/2014

CHARLES R BONAPACE
10/17/2014

WILLIAM H TAYLOR
10/17/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 6, 2014
Requesting Office or Division:	Division of Metabolic and Endocrinology Products (DMEP)
Application Type and Number:	NDA 205649
Product Name and Strength:	Xigduo XR (dapagliflozin and metformin HCl extended-release) tablets, 5 mg/500 mg, 5 mg/1000 mg, 10 mg/500 mg, 10 mg/1000 mg
Product Type:	Multi-ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Bristol-Myers Squibb and AstraZeneca
Submission Date:	October 30, 2013
OSE RCM #:	2013-2529
DMEPA Primary Reviewer:	Sarah K. Vee, PharmD
DMEPA Team Leader:	Yelena Maslov, PharmD

1 REASON FOR REVIEW

The Division of Metabolic and Endocrinology Products (DMEP) requested DMEPA evaluate the container label, carton labeling, and package insert for areas of vulnerability that could lead to medication errors for Xigduo XR.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	N/A
Previous DMEPA Reviews	N/A
Human Factors Study	N/A
ISMP Newsletters	N/A
Other	N/A
Labels and Labeling	B

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We conclude that minor revisions are recommended to the proposed container label, carton and insert labeling as outlined in section 4.1.

4 CONCLUSION & RECOMMENDATIONS

The proposed container label, sample blister card, sample carton labeling can be improved to increase the readability and prominence of important information to promote the safe use of the product, to mitigate any confusion, and to clarify information.

4.1 RECOMMENDATIONS FOR THE APPLICANT

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. CONTAINER LABEL

1. Remove the statement [REDACTED] (b) (4). We do not believe this to be critical information that warrants prominent placement on the carton and container.
2. Revise the storage statement to regular text (i.e. not bold) since this statement is common to most solid oral dosage forms and does not provide important safety information.

B. PROFESSIONAL SAMPLE BLISTER CARDS

1. See A.1
2. We recommend that bar code and manufacturer appear over each blister cell so that this important information remains available to the end user up to the point at which the last dose is removed.¹
3. Differentiate the product strengths with color, boxing, or some other means.¹

C. PROFESSIONAL SAMPLE CARTON

1. See A.1
2. See A.2
3. Consider removing the [REDACTED] (b) (4) color on the bottom of the principle display panel and revise the font color to black. The [REDACTED] (b) (4) color is the [REDACTED] (b) (4) [REDACTED] (b) (4).

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Xigduo XR that Bristol-Myers Squibb and AstraZeneca submitted on October 30, 2013.

Table 2. Relevant Product Information for Xigduo XR				
Active Ingredient	Dapagliflozin and metformin HCl			
Indication	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate.			
Route of Administration	Oral			
Dosage Form	Extended-release tablets			
Strength	<ul style="list-style-type: none"> • 10 mg dapagliflozin/500 mg metformin HCl extended-release • 10 mg dapagliflozin/1000 mg metformin HCl extended-release • 5 mg dapagliflozin/500 mg metformin HCl extended-release • 5 mg dapagliflozin/1000 mg metformin HCl extended-release 			
Dose and Frequency	Once daily (b) (4)			
How Supplied	Tablet Strength	Film-Coated Tablet Color/Shape	Tablet Markings	Pack Size
	10/500 mg	pink, biconvex, capsule-shaped	"1072" and "10/500" debossed on one side and plain on the reverse side.	Bottle of 30 Bottle of 500
	10/1000 mg	yellow to dark yellow, biconvex, oval-shaped	"1073" and "10/1000" debossed on one side and plain on the reverse side	Bottle of 30 Bottle of 90 Bottle of 400
	5/500 mg	orange, biconvex, capsule-shaped	"1070" and "5/500" debossed on one side and plain on the reverse side.	Bottle of 30 Bottle of 500
	5/1000 mg	pink to dark pink, biconvex, oval-shaped	"1071" and "5/1000" debossed on one side and plain on the reverse side.	Bottle of 30 Bottle of 60 Bottle of 90 Bottle of 400
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].			
Container Closure	High density polyethylene (HDPE) bottle with a (b) (4) closure, desiccant, and a heat induction-seal liner or HDPE bottle with (b) (4) closure, desiccant, and a heat induction-seal liner.			

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,² along with postmarket medication error data, we reviewed the following Xigduo XR labels and labeling submitted by Bristol-Myers Squibb and AstraZeneca on October 30, 2013.

- Container label
- Professional Sample Blister Cards
- Professional Sample Carton Labeling

B.2 Label and Labeling Images



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

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/s/

SARAH K VEE
06/06/2014

YELENA L MASLOV
06/06/2014

**REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 205649

Application Type: Original NDA

Name of Drug/Dosage Form: Xigduo XR (dapagliflozin and metformin hydrochloride extended release) tablets

Applicant: Bristol-Myers Squibb

Receipt Date: October 29, 2013

Goal Date: October 29, 2014

1. Regulatory History and Applicant's Main Proposals

Dapagliflozin and metformin HCl extended release is a sodium-glucose cotransporter (SGLT2) inhibitor intended as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The proposed doses are 5/500, 10/500, 5/1000, 10/1000 mg. Bristol-Myers Squibb submitted the NDA on October 29, 2013. This is an NME, type 4 NDA. The PDUFA goal date is October 29, 2014.

The NDA references NDA 202293 for dapagliflozin as a single agent, which is currently under review after a resubmission, with a goal date of January 11, 2014 (date of original NDA submission: December 27, 2010).

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- NO** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment: *Waiver has been submitted by the applicant.*

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between

Selected Requirements of Prescribing Information

the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Selected Requirements of Prescribing Information

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.

Comment:

- YES** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- YES** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- YES** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES

Selected Requirements of Prescribing Information

19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- YES** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- YES** 36. In the BW, all text should be **bolded**.

Comment:

- YES** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

ELIZABETH R CHEN
01/22/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information	
NDA # 205649	
Proprietary Name: Xigduo XR Established/Proper Name: dapagliflozin and metformin HCl extended release Dosage Form: tablets Strengths: 5/500, 5/1000, 10/500, 10/1000 mg	
Applicant: Bristol-Myers Squibb	
Date of Application: October 29, 2013 Date of Receipt: October 29, 2013	
PDUFA Goal Date: October 29, 2014	Action Goal Date (if different):
Filing Date: December 28, 2013	Date of Filing Meeting: December 10, 2013
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1 (NME) and 4 (new combination)	
Proposed indication(s)/Proposed change(s): type 2 diabetes mellitus	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<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>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and 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 is 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"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <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)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): IND 106890 and IND 068652				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><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</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only) N/A</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>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 is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>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>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1619"> <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													<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	
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 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 5 years <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes , 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)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<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)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<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)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	eCTD submission
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <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</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Meeting will be held September 3, 2014

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Submitted separately on October 31, 2013
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Risk management plan submitted
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (RMP)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

format?				
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<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)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 10, 2013

BLA/NDA/Supp #: 205649

PROPRIETARY NAME: Xigduo XR

ESTABLISHED/PROPER NAME: dapagliflozin and metformin HCl extended release

DOSAGE FORM/STRENGTH: tablets

APPLICANT: Bristol-Myers Squibb

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Type 2 diabetes mellitus

BACKGROUND: Dapagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Metformin is a biguanide with anti-hyperglycemic effects that has been in use as a first-line antidiabetic agent since 1995. This fixed dose combination tablet will contain both drugs, reducing daily pill burden for patients. Dosage form and strengths: 5mg dapagliflozin/500mg metformin; 5 mg dapagliflozin/1000mg metformin; 10 mg dapagliflozin/500 mg metformin; 10 mg dapagliflozin/1000 mg metformin tablets.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Elizabeth Chen	Y
	CPMS/TL:	Pamela Lucarelli	Y
Cross-Discipline Team Leader (CDTL)	Ali Mohamadi		Y
Clinical	Reviewer:	Kaveeta Vasisht	N
	TL:	Ali Mohamadi	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		

Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Sury Sista	Y
	TL:	Lokesh Jain	N; Jaya Vaidyanathan
Biostatistics	Reviewer:	Wei Liu	Y
	TL:	Mark Rothmann	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Mukesh Summan	Y
	TL:	Todd Bourcier	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Joseph Leginus	N
	TL:	Suong Tran	Y; Danae Christodoulou
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		

	TL:		
Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees	Jean-Marc Guettier		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input 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:</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 NME NDA or original BLA , 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: There were no additional safety concerns raised by the combination that were not already raised with the single agent (dapagliflozin) in a recent AC; as of January 8, 2014, this drug is no longer the first in its class.
<ul style="list-style-type: none"> Abuse Liability/Potential <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
<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 type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</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 pharmacology study site(s) inspections(s) needed? (Consult sent out) 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</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>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <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>	<p><input checked="" 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><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <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><u>Facility/Microbiology Review (BLAs only)</u></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
<p><u>CMC Labeling Review</u></p> <p>Comments: None</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	<p>None</p>
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Office Level - Curtis Rosebraugh

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): April 3, 2014

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

- a. **Mid-Cycle Meeting:** March 28, 2014
- b. **Wrap Up Meeting:** September 10, 2014
- c. **Team and Labeling Meetings:** TBD
- d. **Complete Primary Reviews:** July 3, 2014
- e. **Complete Secondary Reviews:** July 10, 2014
- f. **Send labeling and PMC/PMR to sponsor:** July 11, 2014
- g. **Complete CDTL Review:** September 23, 2014
- h. **Complete Division Director Review:** October 7, 2014
- i. **Complete Office Director Review:** October 28, 2014
- j. **PDUFA Action Date:** October 29, 2014

Comments: May be Division-level sign off after approval of the single agent.

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>

ACTIONS ITEMS

<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are
-------------------------------------	--

	entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to 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"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<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.

/s/

ELIZABETH R CHEN
01/17/2014

MEMORANDUM

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

DATE: December 19, 2013

TO: Director, Investigations Branch
Baltimore District Office
6000 Metro Dr., Suite 101
Baltimore, MD 21215

Director, Investigations Branch
Dallas District Office
4040 N. Central Expressway
Dallas, TX 75204

Director, Investigations Branch
Kansas District Office
11630 W. 80th St.
Lenexa, KS 66214

FROM: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

SUBJECT: **FY 2014, CDER PDUFA, High Priority Pre-Approval Data
Validation Inspection**, Bioresearch Monitoring, Human
Drugs, CP 7348.001

RE: NDA 205-649
DRUG: Dapagliflozin (BMS-512148) and Metformin XR Fixed
Dose Combination Tablet, 10 mg / 1000 mg
SPONSOR: Bristol-Myers Squibb Co., USA

This memo requests that you arrange for inspections of the clinical and analytical portions of the following bioequivalence (BE) study.

Once you identify an ORA investigator, please contact the DBGLPC point of contact (POC) listed at the end of this assignment memo to schedule the inspection of the analytical site. A DBGLPC scientist will participate in the inspection of the analytical site to provide scientific and technical expertise.

Page 2 - BIMO Assignment, NDA 205-649, Dapagliflozin (BMS-512148) and Metformin XR Fixed Dose Combination Tablet, 10 mg / 1000 mg, sponsored by Bristol-Myers Squibb Co., USA

Background materials will be available in ECMS under the ORA folder. **The inspections should be completed prior to August 29, 2014 to meet PDUFA due date.**

Do not reveal the applicant, application number, study to be inspected, drug name, or the study investigators to the sites prior to the start of the inspections. The sites will receive this information during the inspection opening meeting. The inspections will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

At the completion of the inspection, please send a scanned copy of the completed sections A and B of this memo to the DBGLPC POC.

Study: MB102092
Study Title: "Bioequivalence Study of a Fixed-Dose Combination Tablet of 10 mg Dapagliflozin / 1000 mg Metformin XR Relative to a Single 10 mg Dapagliflozin Tablet and Two 500 mg Glucophage XR Tablets Co-administered to Healthy Subjects in the Fed and Fasted States and Steady-State Pharmacokinetic Assessment of the Fixed-Dose Combination of 10 mg Dapagliflozin / 1000 mg Metformin XR"

Clinical Site: ICON Clinical Pharmacology, Omaha
10845 Harney St
Omaha, NE 68154

Investigator: Karl Roth, MD
TEL: (402) 996-2600
FAX: (402) 403-1441

SECTION A - RESERVE SAMPLES

Because this bioequivalence study is subject to 21 CFR 320.38 and 320.63, the site conducting the study (i.e., each investigator site) is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided by the Applicant for subject dosing.

The final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) specifically addresses the

requirements for bioequivalence studies

(<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm>).

Please refer to CDER's "Guidance for Industry, Handling and Retention of BA and BE Testing Samples" (May 2004), which clarifies the requirements for reserve samples

(<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>).

During the clinical site inspection, please:

- Verify that the site retained reserve samples according to the regulations. If the site did not retain reserve samples or the samples are not adequate in quantity, notify the DBGLPC POC immediately.
- If the reserve samples were stored at a third party site, collect an affidavit to confirm that the third party is independent from the applicant, manufacturer, and packager. Additionally, verify that the site notified the applicant, in writing, of the storage location of the reserve samples.
- Obtain written assurance from the clinical investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific bioequivalence studies, and that samples were stored under conditions specified in accompanying records. Document the signed and dated assurance [21 CFR 320.38(d, e, g)] on the facility's letterhead, or Form FDA 463a Affidavit.
- Collect and ship samples of the test and reference drug products **in their original containers** to the following address:

John Kauffman, Ph.D.
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
645 S. Newstead Ave
St. Louis, MO 63110
TEL: 1-314-539-2135

SECTION B - CLINICAL DATA AUDIT

Please remember to collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

During the clinical site inspection, please:

- Confirm the informed consent forms and study records for 100% of subjects enrolled at the site.
- Compare the study report in the NDA submission to the original documents at the site.
- Check for under-reporting of adverse events (AEs).
- Check for evidence of inaccuracy in the electronic data capture system.
- Check reports for the subjects audited.
 - o Number of subject records reviewed during the inspection: _____
 - o Number of subjects screened at the site: _____
 - o Number of subjects enrolled at the site: _____
 - o Number of subjects completing the study: _____
- Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocols.
- Confirm that site personnel followed SOPs during study conduct.
- Examine correspondence files for any applicant or monitor-requested changes to study data or reports.
- Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.
- Other comments:

SECTION C - AUDIT OF ANALYTICAL DATA

Analytical Site #1:

(b) (4)

Contact person:

Methodology:

LC-MS/MS

Analytical Site #2:

(b) (4)

Contact person:

Methodology:

LC-MS/MS

During the analytical site inspection, please:

- Examine all pertinent items related to the analytical method used for the measurement of dapagliflozin or metformin concentrations in human plasma.
- Compare the accuracy of the analytical data in the NDA submission against the original documents at the site.
- Determine if the site employed a validated analytical method to analyze the subject samples.
- Compare the assay parameters (such as variability between and within runs, accuracy and precision, etc.) observed during the study sample analysis with those obtained during method validation.
- Confirm that the accuracy and precision in matrix were determined using standards and QCs prepared from separate stock solutions.
- Determine if the subject samples were analyzed within the conditions and times of demonstrated stability.

- Confirm that freshly made calibrators and/or freshly made QCs were used for stability evaluations during method validation.
- Scrutinize the number of repeat assays of the subject plasma samples, the reason for such repetitions, the SOP(s) for repeat assays, and if relevant stability criteria (e.g., number of freeze-thaw cycles) sufficiently covered the stability of reanalyzed subject samples.
- Examine correspondence files between the analytical site and the Applicant for their content.

Additional instructions to the ORA Investigator:

In addition to the compliance program elements, other study specific instructions may be provided by the DBGLPC POC prior to commencement of the inspection. Therefore, we request that the DBGLPC POC be contacted for any further instructions, inspection related questions or clarifications before the inspection and also regarding any data anomalies or questions noted during review of study records on site.

If you issue Form FDA 483, please forward a copy to the DBGLPC POC. If it appears that the observations may warrant an OAI classification, notify the DBGLPC POC as soon as possible.

Remind the inspected site of the 15 business-day timeframe for submission of a written response to the Form FDA 483. In addition, please forward a copy of the written response as soon as it is received to the DBGLPC POC.

DBGLPC POC: Chase Bourke, Ph.D.
Pharmacologist
Office of Scientific Investigations
Tel: 1-240-402-4129
Fax: 1-301-847-8748
E-mail: chase.bourke@fda.hhs.gov

DARRTS cc:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Bonapace/Haidar/Mada/Bourke/Dejernet
CDER/OND/Chen

Email cc:
ORA DO/Richard-Math/Harris/Turcovski/Martinez/Bromley/Lopicka

Page 7 - BIMO Assignment, NDA 205-649, Dapagliflozin (BMS-512148) and Metformin XR Fixed Dose Combination Tablet, 10 mg / 1000 mg, sponsored by Bristol-Myers Squibb Co., USA

Draft: CHB 12/18/2013

Edit: SRM 12/18/2013

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical Sites/ (b) (4)

Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical Sites/ (b) (4)

Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/ICON Clinical Pharmacology, Omaha, NE

OSI file #: BE6653

FACTS: (b) (4)

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

/s/

CHASE H BOURKE
12/19/2013

CHARLES R BONAPACE
12/19/2013