CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208658Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

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

Memorandum

Date: December 5, 2016

To: Michael White, Regulatory Project Manager
Division of Metabolism & Endocrine Products (DMEP)

From: Charuni Shah, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 208658
OPDP labeling comments for SYNJARDY® XR (empagliflozin and metformin hydrochloride extended-release) tablets, for oral use

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On February 15, 2015, OPDP received a consult request from DMEP to review the proposed draft Prescribing Information (PI), Medication Guide, and carton/container for SYNJARDY® XR (empagliflozin and metformin hydrochloride extended-release) tablets, for oral use. OPDP's review of the proposed draft labeling is based on the versions sent by Michael White via email on November 30, 2016 and can be found directly below.

OPDP does not have any comments on the proposed labeling materials at this time.

Comments on the Medication Guide are provided in a collaborative review between DMPP and OPDP under a separate cover.

Thank you for the opportunity to comment on these materials.

If you have any questions, please contact Charuni Shah at 240-402-4997 or Charuni.Shah@fda.hhs.gov.

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/s/

CHARUNI P SHAH
12/05/2016

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:	December 2, 2016
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 Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Charuni Shah, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide
Drug Name (established name):	SYNJARDY XR (empagliflozin and metformin hydrochloride extended-release)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 208658
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.

1 INTRODUCTION

On February 10, 2016, Boehringer Ingelheim Pharmaceuticals submitted for the Agency's review a New Drug Application for SYNJARDY XR (empagliflozin and metformin hydrochloride extended-release) tablets, for oral use. The purpose of the submission is to seek approval for SYNJARDY XR (empagliflozin and metformin hydrochloride extended-release) tablets, for oral use to be used:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)

(b) (4)

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 February 15, 2016, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for SYNDARDY XR (empagliflozin and metformin hydrochloride extended-release) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft SYNDARDY XR (empagliflozin and metformin hydrochloride extended-release) tablets, for oral use MG, received on February 10, 2016, and received by DMPP and OPDP on November 30, 2016.
- Draft SYNDARDY XR (empagliflozin and metformin hydrochloride extended-release) tablets, for oral use, Prescribing Information (PI) received on February 10, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 30, 2016.
- Approved SYNDARDY (empagliflozin and metformin hydrochloride) tablets, for oral use, comparator labeling dated December 4, 2015.

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 APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible

- ensured that the MG is consistent with the Prescribing Information (PI)
- 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 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
12/02/2016

CHARUNI P SHAH
12/02/2016

SHAWNA L HUTCHINS
12/02/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum:	November 21, 2016
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 208658
Product Name and Strength:	Synjardy XR (empagliflozin and metformin ER), tablet 5/1000 mg, 10/1000 mg, 12.5/1000 mg, 25/1000 mg
Submission Date:	November 17, 2016
Applicant/Sponsor Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
OSE RCM #:	2016-373-1
DMEPA Primary Reviewer:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader (Acting):	Hina Mehta, PharmD

1 PURPOSE OF MEMO

Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised container labels for Synjardy XR (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions to the container labels are in response to recommendations that we made during previous label and labeling reviews.[a]

2 CONCLUSION

The revised container labels for Synjardy XR are acceptable from a medication error perspective. We have no further recommendations at this time.

[a]Conrad AO. Label and Labeling Review for Synjardy XR (NDA 208658). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Oct 14. 14 p. OSE RCM No.: 2016-373.

Conrad AO. Review of Revised Label and Labeling Memorandum for Synjardy XR (NDA 208658). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Nov 10. 9 p. OSE RCM No.: 2016-373-1.

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/s/

ARIANE O CONRAD
11/21/2016

HINA S MEHTA
11/21/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum:	November 10, 2016
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 208658
Product Name and Strength:	Synjardy XR (empagliflozin and metformin ER), tablet 5/1000 mg, 10/1000 mg, 12.5/1000 mg, 25/1000 mg
Submission Date:	November 9, 2016
Applicant/Sponsor Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
OSE RCM #:	2016-373-1
DMEPA Primary Reviewer:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader (Acting):	Hina Mehta, PharmD

1 PURPOSE OF MEMO

Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised prescribing information (PI), medication guide, container labels, and carton labeling for Synjardy XR (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions to the container labels and carton labeling are in response to recommendations that we made during a previous label and labeling review.[a] In addition, the sponsor decided to separate the labeling for Synjardy (NDA 206111) and Synjardy XR; thus, they have submitted an updated PI and medication guide for our review.

2 CONCLUSION

We recommend that Boehringer Ingelheim increase the readability and prominence of important information in the proposed labels to clarify information and mitigate any confusion that may interfere with the safe use of Synjardy XR. We have no additional recommendations

[a] Conrad AO. Label and Labeling Review for Synjardy XR (NDA 208658). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Oct 14. 14 p. OSE RCM No.: 2016-373.

for the proposed PI and medication guide. We provide our recommendations for the commercial container labels and sample container labels in section 3.

3 RECOMMENDATIONS FOR BOEHRINGER INGELHEIM

We recommend the following be implemented prior to approval of this NDA:

A. Container Label-Commercial
    1. For each of the labels for the 30 tablet package size, revise the statement regarding storage, “Store at 25°C (77°F)”, for consistency with the other container labels to read: “Store at 25°C (77°F); excursions permitted to 59°-86°F (15°-30°C) [see USP Controlled Room Temperature].”. Also, consider reducing the font size for the distribution and manufacturing information to accommodate the addition of that information on the label if space is a limitation.

B. Container Label-Professional Sample
    1. For each of the labels, revise the statement regarding storage, “Store at 25°C (77°F)”, for consistency with the commercial container labels to read: “Store at 25°C (77°F); excursions permitted to 59°-86°F (15°-30°C) [see USP Controlled Room Temperature].”. Also, consider reducing the font size for the distribution and manufacturing information to accommodate the addition of that information on the label if space is a limitation.

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/s/

ARIANE O CONRAD
11/10/2016
I noticed that I had the date incorrect as Nov 11

HINA S MEHTA
11/14/2016

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 17, 2016

TO: Jean-Marc Guettier, M.D
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Office of New Drugs

FROM: Mohsen Rajabi, Ph.D.
Pharmacologist
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Directory
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Surveillance Inspection of Boehringer Ingelheim Pharma GmbH & Co. KG. Ingelheim am Rhein, Germany.

Inspection Summary:

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of the clinical portion of bioequivalence study 1276.28 at Boehringer Ingelheim Pharma GmbH & Co. KG. Ingelheim am Rhein, Germany. At the conclusion of the inspection, no deficiencies were observed and no Form FDA 483 was issued. The final classification for this inspection is No Action Indicated (NAI). After reviewing the inspectional findings, I recommend that the data from study 1276.28 be accepted for further agency review.

Inspected Study:

NDA 208658
Study Number: 1276.28
Study Title: "Bioequivalence of a fixed dose combination tablet of empagliflozin/metformin extended release (10 mg/1000 mg) compared with the free combination of empagliflozin and metformin

extended release tablets in healthy subjects following a high-fat, high-caloric meal (an open-label, randomized, single dose, crossover trial).

Study Dates: November 7, 2014 – December 15, 2014

ORA investigator Richard W. Berning (CIN-DO) inspected Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Strasse 65, 88397 Biberach An Der Riss, Germany from August 8-10, 2016. Although the study was conducted at Boehringer Ingelheim's Ingelheim am Rhein site in Germany, the study records were moved to the inspected site after the clinical site closed down its operation. The inspection included a thorough review of the study records, study protocol, subject CRFs, subject selection criteria, informed consent forms, drug accountability and dispensing records, delegation of authority, adverse events reporting, employee training, examination of facilities and equipment, and interviews and discussions with the firm's management and staff.

Conclusion:

After review of the EIR and inspectional findings, I found the data from the audited study to be reliable. Therefore I recommend that the data from the clinical portion of the study 1276.28 be accepted for further agency review.

Mohsen Rajabi, Ph.D.
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

Final Classification:
Clinical
NAI – Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany **(FEI# 3002806518)**

CC:
OTS/OSIS/Kassim/Taylor/Kadavil/Fenty-Stewart/Nkah/Miller/Johnson
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Biswas/Ayala/Rajabi
OTS/OSIS/DGDBE/Cho/Choi/Skelly/Au
CDER/OND/Guettier

Draft: MR 09/11/2016
Edit: GB 10/14/2016 AD 10/17/2016

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/ Clinical Site/ Boehringer Ingelheim Pharma GmbH & Co KG. Germany /NDA 208658/Review (EIR Cover)

BE File #s: 7176
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/s/

MOHSEN RAJABI ABHARI
10/18/2016

ARINDAM DASGUPTA
10/24/2016

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:	October 14, 2016
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 208658
Product Name and Strength:	Synjardy XR (empagliflozin and metformin ER), tablet 5/1000 mg, 10/1000 mg, 12.5/1000 mg, 25/1000 mg
Product Type:	Multi-ingredient
Rx or OTC:	RX
Applicant/Sponsor Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
Submission Date:	February 10, 2016, March 30, 2016, May 27, 2016
OSE RCM #:	2016-373
DMEPA Primary Reviewer:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader (Acting):	Hina Mehta, PharmD

1 REASON FOR REVIEW

Boehringer Ingelheim submitted NDA 208658 for Synjardy XR (empagliflozin and metformin extended release) on February 10, 2016. The Division of Metabolism and Endocrinology Products (DMEP) requested that we evaluate the container labels, carton labels, and prescribing information for vulnerabilities that could lead to medication errors.

1.1 REGULATORY HISTORY

Immediate release Synjardy (empagliflozin and metformin) tablets were approved August 26, 2015 under NDA 206111. The same Applicant has submitted this NDA for an extended release formulation of Synjardy.

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)*	B
Labels and Labeling	C

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container labels, carton labeling, prescribing information, and medication guide to identify deficiencies that may lead to medication errors and other areas of improvement. In addition, we reviewed the approved labels and labeling for Synjardy (NDA 206111), so that comparisons could be made with the immediate release formulation. We also searched FAERS to identify whether medication errors occurred with Synjardy so that comparisons can be made. Our search of FAERS did not identify any relevant cases.

Our review identified deficiencies in the labels and labeling. We provide recommendations in sections 4.1 and 4.2 and recommend their implementation prior to approval of this application.

4 CONCLUSION & RECOMMENDATIONS

We recommend that Boehringer Ingelheim increase the readability and prominence of important information in the proposed labeling to clarify information and mitigate any confusion that may interfere with the safe use of Synjardy XR.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI)

1. Highlights of Prescribing Information: Dosage and Administration
    a. Separate the dosing information in the statement "take with a meal, with gradual dose escalation to reduce the gastrointestinal side effects due to metformin." to clearly indicate the differences between Synjardy and Synjardy XR as follows: "Take Synjardy twice daily with meals or take Synjardy XR once daily with the morning meal, with gradual dose escalation to reduce the gastrointestinal side effects due to metformin."
2. Full Prescribing Information: Section 2.1 Recommended Dosage
    a. Revise the section heading "(b) (4)" with "Synjardy" below as follows for improved readability and clarity: "Synjardy Recommended Starting Dose:". In addition, revise the section heading noted as "(b) (4)" as follows: "Synjardy XR Recommended Starting Dose:".

    b. Revise the statement "(b) (4)" to include the phrase "1 tablet" as follows for improved clarity: "(b) (4) ."

    c. Under Synjardy XR, we recommend moving the information in the bullet starting "(b) (4) to immediately follow the bullet "Take Synjardy XR once daily with a meal in the morning." In addition, consider separating the sentences in this bullet into two sub-bullets to improve visibility of these statements as follows:

    - "Take Synjardy XR once daily with a meal in the morning:
        - (b) (4) 10 mg/1000 mg and 25 mg/1000 mg (b) (4) tablets should be taken as a single tablet once daily.
        - (b) (4) 5 mg/1000 mg and 12.5 mg/1000 mg (b) (4) tablets should be taken as a two tablets taken together once daily."
3. Full Prescribing Information: Section 16 How Supplied/Storage and Handling
    a. Under Storage, revise the statement "Store at 25°C (77°F);" for consistency with the information provided in the Medication Guide as follows: "Store between 68°F to 77°F (20°C to 25°C);".

4.2 RECOMMENDATIONS FOR BOEHRINGER INGELHEIM

We recommend the following be implemented prior to approval of this NDA:

A. Container Label-Commercial

1. For each of the labels, revise the statement regarding storage, “Store at 25°C (77°F)”, for consistency with the other container labels to read: “Store between 68°F to 77°F (20°C to 25°C); excursions permitted to 59°-86°F (15°-30°C) [see USP Controlled Room Temperature].”. Also, consider reducing the font size for the distribution and manufacturing information to accommodate the addition of that information on the label if space is a limitation.

B. Carton Labeling and Container Label-Professional Sample
    1. For each of the sample labeling and labels, revise the statement regarding storage, “Store at 25°C (77°F)”, for consistency with the trade container labels to read: “Store between 68°F to 77°F (20°C to 25°C); excursions permitted to 59°-86°F (15°-30°C) [see USP Controlled Room Temperature].”. Also, consider reducing the font size for the distribution and manufacturing information to accommodate the addition of that information on the label if space is a limitation.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Synjardy XR that Boehringer Ingelheim submitted on March 30, 2016, and the listed drug (LD).

Table 2. Relevant Product Information for Synjardy XR and Synjardy		
Product Name	Synjardy XR	Synjardy
Initial Approval Date	N/A	August 26, 2015
Active Ingredient	empagliflozin and metformin hydrochloride extended-release	empagliflozin and metformin immediate-release
Indication	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4) both empagliflozin and metformin is appropriate
Route of Administration	Oral	Oral
Dosage Form	Tablets	Tablets
Strength	5 mg /1000 mg, 10 mg/1000 mg, 12.5 mg/1000 mg, 25 mg/1000 mg	5mg/500 mg, 5 mg/1000 mg, 12.5 mg/500 mg, 12.5 mg/1000 mg
Dose and Frequency	Once daily	Twice daily
How Supplied	Bottles of 60 or 180 tablets (5 mg /1000 mg, 12.5 mg/1000 mg) Bottles of 30 or 90 tablets (10 mg/1000 mg, 25 mg/1000 mg)	Bottles of 60 or 180 tablets
Storage	(b) (4)	Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F)

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on October 6, 2016 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[a]

Table 3: FAERS Search Strategy	
Date Range	**August 26, 2015 to October 1, 2016**
Product	**Empagliflozin and metformin** [active ingredient] **Synjardy** [product name]
Event (MedDRA Terms)	**DMEPA Official FBIS Search Terms Event List:** Contraindicated Drug Administered (PT) Drug Administered to Patient of Inappropriate Age (PT) Inadequate Aseptic Technique in Use of Product (PT) Medication Errors (HLGT) Overdose (PT) Prescribed Overdose (PT) Prescribed Underdose (PT) Product Adhesion Issue (PT) Product Compounding Quality Issue (PT) Product Formulation Issue (PT) Product Label Issues (HLT) Product Packaging Issues (HLT) Product Use Issue (PT) Underdose (PT)
Country (Derived)	**USA**

B.2 Results

Our search identified zero cases.

B.3 Description of FAERS

[a] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX C. LABELS AND LABELING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Synjardy XR labels and labeling submitted by Boehringer Ingelheim on February 10, 2016.

- Container Label
- Professional Sample Container Label
- Professional Sample Carton Labeling
- Medication Guide

C.2 Label and Labeling Images

Container Label-Commercial

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

ARIANE O CONRAD
10/14/2016

HINA S MEHTA
10/14/2016

M E M O R A N D U M

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

DATE: July 8, 2016

TO: Jean-Marc Guettier, MD
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Office of New Drugs

FROM: Sripal R. Mada, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

THROUGH: Seongeun Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

SUBJECT: Review of EIR for an analytical inspection conducted at [redacted] (b) (4) covering NDA 208658, sponsored by Boehringer Ingelheim Pharmaceuticals, Inc., USA

Recommendation:

At the request of the Division of Metabolism and Endocrinology Products (DMEP), OND, Sripal R. Mada, Ph.D. from the Office of Study Integrity and Surveillance (OSIS), Office of Translational Sciences audited the analytical portions of studies 1276.15 and 1276.28 that were submitted to NDA 208658. Based on the inspectional findings, this reviewer recommends that the data from the analytical portions of studies 1276.15 and 1276.28 be accepted for further agency (FDA) review.

Application	Study	Drug Product	Sponsor	Recommendation
NDA 208658	1276.15 and 1276.28	empagliflozin / metformin ER tablets (25 mg/1000 mg and 10 mg/1000 mg)	Boehringer Ingelheim Pharmaceuticals, Inc., USA	Acceptable

1276.15: "Bioequivalence of a fixed dose combination tablet of empagliflozin / metformin extended release (25 mg/1000 mg) compared with the free combination of empagliflozin and metformin extended release tablets in healthy subjects following a high-fat, high caloric meal (an open-label, randomized, single dose, crossover trial)"

Dates of sample analysis: November 5, 2014 - December 3, 2014

1276.28: "Bioequivalence of a fixed dose combination tablet of empagliflozin / metformin extended release (10 mg/1000 mg) compared with the free combination of empagliflozin and metformin extended release tablets in healthy subjects following a high-fat, high caloric meal (an open-label, randomized, single dose, crossover trial)"

Dates of sample analysis: January 13, 2015 – January 26, 2015

The inspection of the analytical portion of studies 1276.15 and 1276.28 was conducted at [redacted] from [redacted].

The audit included a thorough review of method validation and study records, examination of the electronic laboratory notebook system, [redacted] facility and equipment, and interviews and discussions with the firm's management and staff. During the inspection, no objectionable issues were found. At the conclusion of the inspection, Form FDA 483 was not issued.

Conclusion:

After reviewing the inspectional findings, this reviewer concludes that the analytical portions of the audited studies are reliable and recommends accepting the data for further agency (FDA) review.

Sripal R. Mada, Ph.D.
OSIS, DGDBE

Final Site Classification:

NAI – [redacted]
FEI: [redacted]

cc:
OSIS/Kassim/Taylor/Kadavil/CDER-OSIS-BEQ@fda.hhs.gov
OSIS/DGDBE/Cho/Choi/Skelly/Au/Mada
OSIS/DNDBE/Bonapace/Dasgupta/Biswas/Ayala
OND/ODEII/DMEP/Guettier/White

Draft: SRM 07/5/2016
Edit: SA 07/06/2016; YMC 07/08/2016

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/ANALYTICAL [redacted] (b) (4)

NDA 208658_Empagliflozin / Metformin ER Tablets

OSI file# BE7176

FACTS: [redacted] (b) (4)

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/s/

SRIPAL R MADA
07/08/2016

YOUNG M CHOI
07/08/2016
Signed on behalf of Dr. Seongeun (Julia) Cho

M E M O R A N D U M

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

DATE: 5/17/2016

TO: Division of Metabolism and Endcrinology Products
Office of Drug Evaluation II

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 208658

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	Boehringer Ingelheim Pharma GmbH & Co. KG	Department of Translational Medicine and Clinical Pharmacology, Human Pharmacology Centre, Birkendorfer Str. 65, Biberach/Riß, (Riss), Germany

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/s/

SHILA S NKAH
05/27/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

BIMO Inspection Assignment - General Information Section

Memorandum of NDA - Initiated Bioequivalence Inspection Assignment

Date: May 17, 2016

From: Arindam Dasgupta
Deputy Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

To: ORAHQDFFIIOBBIMO@fda.hhs.gov

Subject: Premarket Original BIMO Inspection Assignment

Preannounce: No

Compliance Program: 7348.001 (BE)
PAC Code: 48001A (NDA)
Priority: High
Operation Code: 11 (Foreign Inspection), 31 (Sample Collection), 41 (Sample Analysis)

Application Number: NDA 208658
Product Name: Empagliflozin/Metformin
Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

Study/Protocol Number:

Application Number	Study/Protocol Number
NDA 208658	1276.28

Inspection Due Date**: 8/10/2016**
EIR Due Date**: 9/10/2016**
Center Participation**:** No
Joint Regulatory Agency Participation**:** No

Establishment(s) for inspection	FEI Number	FACTS Number
Clinical Site: Boehringer Ingelheim Pharma GmbH & Co. KG, Department of Translational Medicine & Clinical Pharmacology Human Pharmacology Centre Binger Straße 173, Ingelheim am Rhein, Germany **POC:** Regina Sennewald Phone: +49 (0)7351 54-94762 Fax: +49 (0)7351 83-94762 Email: regina.sennewald@boehringer-ingelheim.com	Refer to ORA	**11640835**

Note	**Please contact the Arindam Dasgupta prior to the beginning of the inspection at arindam.dasgupta@fda.hhs.gov or (301) 796-3326 to verify the focus and intent of the inspection. We frequently receive real-time information from the review team that may change the focus of the inspection.** Please follow the compliance program with emphasis on the specific instructions in the memorandum. If significant deviations are found during the inspection that may have impact on the safety of study subjects or accuracy and reliability of the data, we request that you expand the scope of your inspection as necessary and contact me immediately. **At the end of the inspection, send an e-mail to arindam.dasgupta@fda.hhs.gov and CDER-OSIS-BEQ@fda.hhs.gov with any inspection findings.** **If a form FDA-483 is issued, send to CDER-OSIS-BEQ@fda.hhs.gov or fax it to the OSIS Project Specialist at (301) 847-8748.** **If the endorsed EIR and exhibits are in OSAR (or in another electronic format), send the email notification regarding the availability of the documents in OSAR to CDER-OSIS-BEQ@fda.hhs.gov and cc Dinah Miller, OSIS Project Manager.** **If the endorsed EIR and exhibits are paper, send the documents to Angel Johnson, OSIS Project Specialist.** **Ms. Angel Johnson** **Project Specialist** **FDA/CDER/OTS/OSIS** **WO51 RM5331** **10903 New Hampshire Ave.** **Silver Spring, MD 20993-0002** **Important:** Forward any post-inspection correspondence from the establishment to CDER-OSIS-BEQ@fda.hhs.gov if electronic, or to the OSIS Project Specialist, if paper, as soon as possible. All post-inspection correspondence must be reviewed prior to issuing any post-inspection notification of compliance status.

BACKGROUND INFORMATION

This inspection memo provides pertinent information to conduct inspections of the clinical portion of the following bioequivalence (BE) study. Background materials are available in ECMS under the ORA folder.

Do not reveal the study to be inspected, drug names, or the study investigator to the site when scheduling the inspection. You should provide this information during the inspection opening meeting. Please note that the inspection 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 OSIS POC.

Study to be audited

NDA 208658

Study #: 1276.28
Study Title: "Bioequivalence of a fixed dose combination tablet of empagliflozin/metformin extended release (10 mg/1000 mg) compared with the free combination of empagliflozin and metformin extended release tablets in healthy subjects following a high-fat, high-caloric meal (an open-label, randomised, single dose, crossover trial)

Investigator: Dr. Klaus Kammerer
Subject #: 30

Please collect a list of bioequivalence studies performed at the site in the last 5 years. The list should also include information on test and reference reserve samples retained at the site or at a third party for the bioequivalence studies. Refer to Table 1 for an example. Please do spot checks to verify that the lot number(s) listed in the table match the reserve samples in the clinical site storage.

Table 1:

Study Number	Drug Name	Study Title	Sponsor	Submission Agency	Study Conduct Dates	Location of Reserve Samples	Quantity	Lot# for Test and Reference Samples
xxxx	Aspirin+Dipyridamole Capsules		xxxx	US-FDA	Dec 24-Dec 31, 2014	On site	300 for Test, 200 for Reference	xxxx and xxxx
xxxx	Montelukast Tablets		xxxx	Unknown	xx xx-xx, xxxx	Third Party		xxxx and xxxx
xxxx	xxxx		xxxx	Pilot	xx xx-xx, xxxx	Not Retained		xxxx and xxxx

SECTION A – RESERVE SAMPLES

Reserve samples must be collected for study 1276.28. In addition, verify that the lot numbers on the reserve sample containers match those in the study report for the study mentioned above.

The recommended quantity of reserve samples (test and reference product) to be collected from each shipment is based on the dosage formulation and is shown below:

Dosage formulation	# of units to collect
Oral solid dosage forms (e.g., tablets, capsules)	30 units each test and reference
Topical creams, ointments, and gels	3 units each test and reference
Inhalers, pumps, and vials for injection	3 units each test and reference
Any dosage form in block design	1 Block (containing Kits of test and reference)

Collect a convenient quantity that has at least the amount specified above. For example, if tablets are kept in bottles of 100, collect one bottle. If tablets are kept in bottles of 10, collect three bottles. **Do not open and subsample bottles.**

Because theses bioequivalence studies are 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 OSIS POC immediately.

☐ If the reserve samples were stored at a third party site, (1) collect an affidavit to confirm that the third party is independent from the applicant, manufacturer, and packager; and (2) request the reserve samples to be shipped back to the site so that the samples can be collected during the inspection. 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
John.kauffman@fda.hhs.gov

SECTION B – CLINICAL DATA AUDIT

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

Data Audit Checklist:

☐ Confirm that informed consent was obtained prior to the study procedures for all subjects enrolled in the study.

☐ Randomly select and audit the study records for at least 20 subjects enrolled in the study.

☐ Compare the study reports submitted to FDA with 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.

☐ Confirm that adequate corrective actions were implemented for observations cited during the last inspection (if applicable).

☐ 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 OSIS scientific POC prior to commencement of the inspection. Therefore, we request that the OSIS scientific 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 CDER-OSIS-BEQ@fda.hhs.gov, if electronic or please forward a copy to the OSIS Project Specialist contact at the address below, if paper. If it appears that the observations may warrant an OAI classification, send notification to Arindam Dasgupta at arindam.dasgupta@fda.hhs.gov and CDER-OSIS-BEQ@fda.hhs.gov, 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 CDER-OSIS-BEQ@fda.hhs.gov, if electronic or if paper, forward a copy to the OSIS Project Specialist contact at the address below.

If the endorsed EIR and exhibits are in OSAR (or in another electronic format), send the email notification regarding the availability of the documents in OSAR to CDER-OSIS-BEQ@fda.hhs.gov and cc Ms. Angle Johnson, OSIS Project Manager.

If endorsed EIR and exhibits are paper, send to the OSIS Project Specialist at the address below.

OSIS Project Specialist: Ms. Angel Johnson
Project Specialist
FDA/CDER/OTS/OSIS
WO51 RM5331
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
Tel: 301-796-3374
Fax: 1-301-847-8748

OSIS Scientific POC: Arindam Dasgupta, Ph.D.
Deputy Director
Division of New Drug
Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and
Surveillance (OSIS)
Tel: 1-301-796-3326
Fax: 1-301-847-8748
E-mail:
arindam.dasgupta@fda.hhs.gov

Email cc:
ORAHQ/OMPTO/DMPTI/BIMO/Bukowczyk/Arline/Montemurro/Colon
OSIS/Kassim/Taylor/Haidar/Kadavil/CDER-OSIS-BEQ@fda.hhs.gov
OSIS/DNDBE/Bonapace/Dasgupta
OSIS/DGDBE/Cho/Skelly/Choi

Draft: MR 05/13/16
Edit: GB 05/16/2016 AD 05/17/2016
ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/Boehringer Ingelheim, Germany/NDA 208658 Empagliflozin/Metformin

OSI file #: 7176
FACTS: 11640835

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/s/

MOHSEN RAJABI ABHARI
05/17/2016

ARINDAM DASGUPTA
05/17/2016

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

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

Application: NDA 208658

Application Type: New NDA

Drug Name(s)/Dosage Form(s): Synjardy XR [proposed proprietary name, under review] (empagliflozin and metformin hydrochloride extended-release) tablets

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

Receipt Date: February 10, 2016

Goal Date: December 10, 2016

1. Regulatory History and Applicant's Main Proposals

Boehringer Ingelheim Pharmaceuticals, Inc. (BI) has been developing various strengths of fixed-dose combination (FDC) tablets for empagliflozin plus extended release (XR) metformin hydrochloride (HCl). BI originally submitted a combined Pre-IND meeting request for PIND 111919 (empagliflozin/metformin HCl XR FDC tablets) and PIND 111970 (linagliptin/metformin hydrochloride XR FDC) on May 25, 2011, with preliminary comments provided on October 11, 2011. After a period of inactivity resulting in administrative withdrawal of PIND 111919, it was reinstated on January 28, 2013, at the request of the sponsor.

BI opened IND 111919 for empagliflozin/metformin HCl XR FDC on September 18, 2013. On December 23, 2013, BI submitted a request for a Type C guidance meeting in order to obtain FDA input related to the proposed Phase 1 clinical development program, CMC development and stability requirements, and tablet differentiation strategy for this drug product. Written responses were provided by the Agency on March 10, 2014.

The marketing application for the empagliflozin monotherapy (NDA 204629, proprietary name Jardiance) was approved on August 1, 2014.

On May 18, 2015, BI submitted a request for a written-response, pre-NDA meeting to IND 111919 in order to obtain FDA comment on the proposed format and content of a complete new drug application for empagliflozin/metformin HCl XR FDC tablets. Written responses for this pre-NDA meeting were issued on July 16, 2015.

The NDA for the immediate release fixed dose combination product of empagliflozin/metformin HCl (NDA 206111, proprietary name Synjardy) was approved on August 26, 2015.

An Agreed Initial Pediatric Study Plan (Agreed iPSP) for empagliflozin/metformin HCl XR was issued on December 22, 2015, under IND 111919.

RPM PLR Format Review of the Prescribing Information

The new marketing application (NDA 208658) for empagliflozin/metformin HCl XR tablets (proposed proprietary name "Synjardy XR", under review) was received on February 10, 2016. This NDA relies on two pivotal bioequivalence studies comparing the XR version of empagliflozin/metformin HCl with free combinations of empagliflozin and metformin XR. This application also references previously reviewed information on safety and efficacy for the previously approved BI products Jardiance (NDA 204629), Synjardy (NDA 206111), and Jentadueto (NDA 201281, linagliptin and metformin HCl). BI also references data from previously approved Glumetza (NDA 021748, metformin HCl XR), for which it has obtained the right of reference from Valeant Pharmaceuticals North America, LLC.

(b) (4) indication (b) (4) for NDA 208658 (empagliflozin/metformin HCl XR):

- As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)

(b) (4)

(b) (4)

Updated draft labeling for NDA 208658 (empagliflozin/metformin HCl XR) was received on March 30, 2016. (b) (4)

(b) (4)

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/s/

MICHAEL G WHITE
04/15/2016

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 # 208658 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Synjardy XR (proposed, under review) Established/Proper Name: empagliflozin and metformin hydrochloride extended-release Dosage Form: tablets Strengths: 5 mg empagliflozin/1000 mg metformin hydrochloride extended-release 10 mg empagliflozin/1000 mg metformin hydrochloride extended-release 12.5 mg empagliflozin/1000 mg metformin hydrochloride extended-release 25 mg empagliflozin/1000 mg metformin hydrochloride extended-release		
Applicant: Boehringer Ingelheim Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: February 10, 2016 Date of Receipt: February 10, 2016 Date clock started after UN: n/a		
PDUFA/BsUFA Goal Date: December 10, 2016	Action Goal Date (if different): December 9, 2016	
Filing Date: April 10, 2016	Date of Filing Meeting: March 22, 2016	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☒ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): • As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)		

Type of Original NDA: AND (if applicable)	☒ 505(b)(1) ☐ 505(b)(2)
Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☐ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 111919	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***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.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***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*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***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.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
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.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☐	☒		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• 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)].**	☐	☐		
• 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)]?** ***If you answered yes to any of the above bulleted 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 for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, 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.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug 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)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it;*	☐	☒	☐	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
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)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ 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).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications				
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 (3397/3792), 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.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
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)?	☒	☐	☐	
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)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☐	☒		All investigators who conducted clinical studies included in the application are full-time employees of the applicant (Boehringer Ingelheim). Therefore, no forms FDA 3454 or 3455 were provided. A list of the applicant's full-time employees who conducted

				clinical trials in the application was provided. Only BE studies were conducted.
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***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…"*	☒	☐	☐	
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? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
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)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		PeRC review schedule on September 28, 2016
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	Agreed iPSP (partial waiver and deferral) under IND111919 for the glycemic control indication dated 12/22/2015 (b) (4)
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)[3]***	☐	☒		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

[3]

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	Submitted separately on March 2, 2016 (eCTD # 0001, supporting doc number 2)
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		
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? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5] Has a review of the available pregnancy and lactation data been included?	☒ ☒	☐ ☐	☐ ☐	 Via cross-reference to NDA206111/S-001 (Supp Doc 75, Nov 12, 2015)
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or	☐	☐	☒	

http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837 htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	consulted on 2/15/2016
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☒	no REMS, no IFU
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	consulted on 2/15/2016
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:*** Patient Labeling (DMPP) consulted on 2/15/2016	☒	☐	☐	Pediatric & Maternal Health was consulted under NDA206111/ S-001 on 9/16/2015 for the first PLLR conversion of Synjardy
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** July 16, 2015 ***If yes, distribute minutes before filing meeting***	☒	☐		Meeting conducted as Written Responses
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 22, 2016

BACKGROUND:
Under the corresponding IND11919, Pre-IND, Type C, and Pre-NDA meeting written responses were issued on October 11, 2011, March 10, 2014, and July 16, 2015, respectively. An Agreed iPSP for empagliflozin and metformin extended-release was subsequently issued on December 23, 2015.

This is a New Drug Application (NDA) from Boehringer Ingelheim Pharmaceuticals, Inc. (BI) submitted under section 505(b)(1) for empagliflozin and metformin hydrochloride extended-release tablets (proposed proprietary name "Synjardy XR", under review by DMEPA). This Type 3 NDA proposes a new dosage form of Synjardy that includes an extended-release version of metformin.

The application cross-references clinical and non-clinical data in NDA 204629 (Jardiance), NDA 206111 (Synjardy), and NDA 021748 (Glumetza). BI has obtained the right of reference for Glumetza (metformin hydrochloride extended-release tablets) from Salix Pharmaceuticals. BI also cross-references NDA 204629 and NDA 201281 (Jentadueto) for drug substance information.

There are two proposed indications:

- As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)

(b) (4)

(b) (4)

The PLLR language for section 8.1-8.3 is being reviewed by Maternal Heath under NDA206111 S-001.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Michael White	Y
	CPMS/TL:	Pam Lucarelli	Y

Cross-Discipline Team Leader (CDTL)	William Chong		Y
Division Director/Deputy	Jean-Marc Guettier		N
Office Director/Deputy			
Clinical	Reviewer:	Andreea Ondina Lungu	Y
	TL:	William Chong	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Ritesh Jain	Y
	TL:	Manoj Khurana	N
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Susie Sinks	N
	TL:	Mark Rothmann	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Dave Carlson	Y
	TL:	Todd Bourcier	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Su Tran	Y
	RBPM:	Anika Lalmansingh	Y
• Drug Substance	Reviewer:	Debasis Ghosh	N
• Drug Product	Reviewer:	John Amartey	N
• Process	Reviewer:	Tarun Mehta	N
• Microbiology	Reviewer:	Tarun Mehta	N
• Facility	Reviewer:	Sherry (Xiaohui) Shen	N
• Biopharmaceutics	Reviewer:	Peng Duan	N
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Sharon Williams	Y
	TL:	Shawna Hutchins	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Charuni Shah	Y
	TL:	Melinda McLawhorn	N
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Ariane Conrad	N
	TL:	Yelena Maslov	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Cynthia Kleppinger	N
	TL:	Kassa Ayalew	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• DPV	Reviewer:	Christine Chamberlain	N
	TL:	Christian Cao	N
• DEPI	Reviewer:	Yangdong Qiang	Y
	TL:	Patricia Bright	N
• DMEP Safety	Safety RPM:	Elisabeth Hanan	Y
	Dep Dir Safety:	Jenn Pippins	N
Other attendees	Monika Houstoun, Assoc Dir Labeling		Y
	Terrolyn Thomas, Sr Drug Safety Mgr		Y

FILING MEETING DISCUSSION:

GENERAL • 505 b)(2) filing issues:	☒ Not Applicable
o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☐ NO
o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☐ YES ☐ NO
Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	
• Per reviewers, are all parts in English or English translation?	☒ YES ☐ NO

If no, explain:	
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: Application only contains BE studies	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***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***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• 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? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**: Will request OSI inspection for the 2 pivotal BE studies	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	☐ YES ☒ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • 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?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO

• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Jean-Marc Guettier, Division Director **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): n/a **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): Stamp Date: February 10, 2016 Filing/Planning Meeting: March 22, 2016 Filing Date: April 10, 2016 Day 74 Letter Date: **April 22, 2016** Mid-Cycle Meeting: July 7, 2016 @ 3pm Labeling Planning Meeting: July 20, 2016 @ 2pm PeRC review: September 28, 2016 Labeling meeting #1: October 27, 2016 @ 3pm Review Completion Goal Date according to GRMP: **Fri, November 4, 2016** Wrap-Up Meeting: November 7, 2016 @ 11am Labeling meeting #2 (if necessary): November 14, 2016 @ noon Secondary Reviews due: November 11, 2016 Send proposed labeling to applicant: November 11, 2016 CDTL Review Due: November 18, 2016 Action Date: Friday, **December 9, 2016** PDUFA Date: Saturday, December 10, 2016 **Comments**:

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
	ACTION ITEMS
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM

☐	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.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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

/s/

MICHAEL G WHITE
03/25/2016