

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206073Orig1s000

OTHER REVIEW(S)

**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: January 8, 2015

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)
Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Karen Dowdy, RN, BSN
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): GLYXAMBI (empagliflozin and linagliptin)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 206073

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

1 INTRODUCTION

On January 30, 2014, Boehringer Ingelheim Pharmaceuticals, Inc. submitted for the Agency's review an original New Drug Application (NDA) 206073 for GLYXAMBI (empagliflozin and linagliptin) tablets indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and linagliptin 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 June 23, 2014, and January 6, 2015, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for GLYXAMBI (empagliflozin and linagliptin) tablets.

2 MATERIAL REVIEWED

- Draft GLYXAMBI (empagliflozin and linagliptin) tablets MG received on December 17, 2014, and received by DMPP and OPDP on December 22, 2014.
- Draft GLYXAMBI (empagliflozin and linagliptin) tablets Prescribing Information (PI) received on January 30, 2014, revised by the Review Division and the Applicant throughout the review cycle, and received by DMPP and OPDP on December 22, 2014.
- Approved TRADJENTA (linagliptin) tablets comparator labeling dated May 22, 2014.
- Approved JARDIANCE (empagliflozin) tablets comparator labeling dated August 1, 2014.

3 REVIEW METHODS

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

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

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/

KAREN M DOWDY
01/08/2015

KENDRA Y JONES
01/08/2015

BARBARA A FULLER
01/08/2015

LASHAWN M GRIFFITHS
01/08/2015

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

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

Memorandum

Date: January 7, 2015

To: Callie Cappel-Lynch, 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 206073
OPDP labeling comments for GLYXAMBI® (empagliflozin and linagliptin) tablets, for oral use

OPDP has reviewed the proposed draft prescribing information (PI) and carton container labels for GLYXAMBI® (empagliflozin and linagliptin) tablets, for oral use (Glyxambi) submitted for consult on January 6, 2015.

Prescribing Information

OPDP's comments on the proposed draft PI are based on the version sent from Callie Cappel-Lynch (RPM) on December 22, 2014, and are provided directly on the marked version below.

Carton/Container Labels

We have no further comments on the draft carton and container labeling (provided directly below) at this time.

Medication Guide

OPDP's comments on the proposed draft medication guide will be provided under separate cover in conjunction with Division of Medical Policy Programs (DMPP) at a later date.

Thank you for the opportunity to comment on the proposed draft labeling.

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

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

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/s/

KENDRA Y JONES
01/07/2015

CLINICAL INSPECTION SUMMARY

DATE: October 6, 2014

TO: William H. Chong, M.D., Clinical Reviewer
Richard Chiang, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

FROM: Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 206073

APPLICANT: Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI)

DRUG: Empagliflozin/linagliptin fixed dose combination tablets

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin

and linagliptin is appropriate.

CONSULTATION REQUEST DATE: March 31, 2014

CLINICAL INSPECTION SUMMARY GOAL DATE: October 6, 2014

DIVISION ACTION GOAL DATE: January 30, 2015

PDUFA DATE: January 30, 2015

I. BACKGROUND

Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) is seeking approval of empagliflozin/linagliptin fixed-dose combination (FDC) tablets as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and linagliptin is appropriate. Inspections were requested for the following clinical study:

- Protocol 1275.1 “A Phase III Randomized, Double-Blind, Parallel Group Study to Evaluate the Efficacy and Safety of Once Daily Oral Administration of BI 10773 25 mg/Linagliptin 5 mg and BI 10773 10 mg/Linagliptin 5 mg Fixed Dose Combination Tablets Compared with the Individual Components (BI 10773 25 mg, BI 10773 10 mg, And Linagliptin 5 mg) for 52 Weeks in Treatment Naïve and Metformin Treated Patients with Type 2 Diabetes Mellitus with Insufficient Glycaemic Control”

This multi-center trial was conducted in 212 sites in 22 countries. There were 2504 subjects screened and 1363 subjects enrolled. The first subject was enrolled August 31, 2011 and the last subject visit was September 10, 2013. The primary endpoint was the change from baseline in HbA1c (%) after 24 weeks of treatment.

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of NDA 206073 in accordance with Compliance Program 7348.811. General instructions were also provided with this assignment.

NOTE: During the inspections, it was discovered that BIPI had not obtained any 1572s from the foreign sites. Although the sites were listed in the site selection tool as being conducted under an Investigational New Drug Application (IND), in the application BIPI requested a waiver from certain requirements outlined in 21 CFR 312.120 related to foreign clinical studies not conducted under an IND.

II. RESULTS (by Site):

Name of CI/ Site #	Protocol 1275.1 / # of Subjects Randomized	Inspection Date	Preliminary Classification
Naresh Aggarwal Site #20001	30	6/09- 6/13/2014	No Action Indicated (NAI)
Diego Aizenberg Site #54005	33	6/09- 6/13/2014	No Action Indicated (NAI)
Georgina Sposetti Site #54004	23	6/16- 6/19/2014	No Action Indicated (NAI)
Lawrence Levinson Site #1088	6	7/14- 7/22/2014	No Action Indicated (NAI)
Mandeep Oberoi Site #1013	7	7/21- 8/01/2014	Voluntary Action Indicated (VAI)
Farid Marquez Site #1063	26 subjects	9/08-pending close out	Official Action Indicated (OAI)

Key to Classifications

NAI = No deviation from regulations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations; data unreliable.

Pending = Preliminary classification based on information in 483, preliminary communication with the field, and review of EIR; final classification is pending letter to site.

1. Naresh Aggarwal, M.D.
490 Bramalea Road
Suite 201
Brampton, ON L6T 0G1
Canada

- a. **What was inspected:** The inspection focused on 100% review of informed consent documents (ICDs), institutional review board (IRB) correspondence, Form FDA 1572, financial disclosures, training records, delegation forms, monitoring reports, inclusion/exclusion criteria checklist, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. There were 26 subject charts reviewed. Source data was verified with data line listings for 16 subjects (15 who completed and one who had withdrawn).

- b. **General observations/commentary:** There were 48 subjects screened at the site and 30 enrolled (three subjects withdrew consent before randomization). Four subjects withdrew consent after randomization. There were 23 subjects that completed the study. The study was overseen by Institutional Review Board Services.

The investigator did not complete an FDA 1572, Statement of Investigator, but did complete the Canadian Qualified Investigator Undertaking.

The primary efficacy endpoint was verifiable. There was no under-reporting of adverse events (only one adverse event of bronchitis found which was not reported for Subject 93130. The antibiotic Zithromax was also not recorded on the concomitant medication log).

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

2. Dr. Diego Aizenberg
Clinical Research Director
Centro Médico Viamonte
Avda Córdoba 2019
Ciudad Autónoma de Buenos Aires
C1120AAC
Argentina

- a. **What was inspected:** The inspection focused on informed consent documents (ICDs), ethics committee (EC) correspondences, investigator agreements,, financial disclosures, protocol deviations, delegation forms, monitoring reports, inclusion/exclusion criteria checklist, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Seven subject's records were reviewed with data line listings compared to source documents.
- b. **General observations/commentary:** There were 37 subjects screened and 33 subjects enrolled. All the documents were organized, complete, and accurate. The records were all hand-written in Spanish and were difficult to read. The Spanish consents had all the elements of informed consent and were very comprehensive. All the subject's records showed they were consented appropriately.

The eligibility criteria were met in all the subject's records that were reviewed. The blinding of the study was followed and maintained throughout the duration of the study, with no unblinding during rescue. The primary efficacy endpoint was verifiable and there was no under-reporting of adverse events.

The logs for the test article accountability were reviewed. There was an isolated incident where the wrong kit was given to a subject (#098474). The incident was thoroughly investigated and corrected by the clinical investigator's personnel and study monitor. There was documentation of the investigation. This issue was brought to the attention of the clinical investigator as a discussion issue.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

Dr. Aizenberg sent an email follow-up on July 17, 2014 to address some of the discussion items of the FDA field investigator. One item was to evaluate the use of electronic or systematized medical charts in order to make them more legible. Dr. Aizenberg stated that he will evaluate the use of computerized systems or electronic medical histories as a substitute for paper records. Based on that evaluation, a final decision will be made, in accordance with the characteristics of the systems available on the market, budget issues, and site infrastructure. Another discussion item was to perform and document a root cause analysis for protocol violations. The site team was re-trained in the use of different tools and how to document the issues and findings on June 23, 2014.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

3. Georgina Sposetti, M.D.
Diabetes and Metabolism Department, Head
Instituto de Investigaciones Clínicas
Av Colon 3364
B7600FZN Mar del Plata, Buenos Aires
Argentina

- a. **What was inspected:** The inspection included review of subjects' medical records, informed consents, laboratory results, case report forms, source documents, monitoring logs, drug accountability and data listings. In addition, the inspection also covered the regulatory binder and ethics committee correspondences. Five subject records were fully reviewed.
- b. **General observations/commentary:** There were 35 subjects screened, 23

subjects enrolled into the study and 20 subjects who completed the study. In the Province of Buenos Aires, it is mandatory that all informed consent forms are witnessed. The informed consents that were reviewed were all witnessed and signed by the subjects and witnesses before any study related procedures were performed.

All the documents were in Spanish. They were well organized, accurate, and complete. Part of the source documents were printed from a database that was at the investigational center. Some other documents were written by hand, such as the Drug Accountability Log, the Delegation Log, Subject Enrollment Logs, and the Training Logs. A review of the study records revealed that all inclusion criteria were met and none of the exclusion criteria was met by the study subjects. In some of the records it was briefly mentioned that the exercise and dietary counseling had taken place.

The primary and secondary efficacy endpoints were verifiable. There was no under-reporting of adverse events.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

During the close out meeting, the FDA field investigator stressed the importance of detailed documentation of all the procedures of the protocol, instructions and events related to the subject visits. For example, it could be inferred that the food intake diary was given to the subjects from other information consigned in the subject notes but it was not specifically documented that the diaries were given to them.

Dr. Sposetti responded to the discussion items via an email dated July 15, 2014. His site has implemented a check list describing the procedures to be performed as well as the materials to be used in each protocol visit. After the visit completion, the coordinator will check with the patient whether or not the required materials were given to him/her. If necessary, other useful tools will be implemented, including alert signs in the appointment book, flowcharts describing the procedures, etc. There is also a new staff member in charge of Quality Control tasks, especially focused on protocol critical procedures, trainings, preventive measures and corrective actions.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

4. Lawrence S. Levinson, M.D.
Tipton Medical & Diagnostic Center
4371 East Pleasant Valley Boulevard
Tipton, PA 16684

- a. **What was inspected:** Records reviewed included the investigator agreements, 1572s, financial disclosures, drug accountability logs, study enrollment/screening logs, consent forms, case report forms, source documents, sponsor correspondence, monitoring visit correspondence, ethics committee correspondence, and training records. All six enrolled subjects' records were reviewed.
- b. **General observations/commentary:** There were 13 subjects screened and 6 subjects enrolled at the site. All subjects completed the study. Some subjects had initially signed the incorrect version of consent. This was caught by the sponsor, corrected by the firm and reported to the IRB.

The primary efficacy endpoint was verifiable and there was no under-reporting of adverse events.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

5. Mandeep S. Oberoi, M.D.
240 Williamson Street
Suite 305
Elizabeth, NJ 07202

- a. **What was inspected:** The inspection focused on 100% review of informed consent documents (ICDs), IRB correspondence, training, 1572s, financial disclosures, delegation forms, randomization, monitoring reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Eleven subject records were reviewed.
- b. **General observations/commentary:** Eleven subjects were screened, seven subjects were randomized, and six completed the study. Study was overseen by [REDACTED] ^{(b) (4)}. The informed consent was approved for an English and Spanish version. The Regulatory Binder was neat

and organized with all documents present. During the course of the inspection, it was found that several worksheets provided by the sponsor did not have the study subject's initials or subject study number. The primary efficacy endpoint was verifiable. There were no issues with randomization or drug accountability. It was noted that several adverse events (AEs) failed to be recorded into the case report forms. These AEs were not discovered by the monitor.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiency:

1. An investigation was not conducted in accordance with the investigational plan.

Specifically, not all adverse events and concomitant medications were entered into the electronic data capture system for four out of the seven randomized subjects (#90442, #90444, #90446, #90447).

- Subject 90442 sustained a motor vehicle accident with pain to multiple extremities requiring Relafen and Zoloft. No AE or medications were reported.
- Subject 90444 was diagnosed with a urinary tract infection and prescribed ciprofloxacin. No AE or medications were reported.
- Subject 90446 sustained a motor vehicle accident with pain to multiple extremities requiring Motrin and Flexeril. No AE or medications were reported. The subject later complained of mild dizziness and occasional headaches. No AEs were reported. The subject was prescribed Mobic for joint pains and Cozaar. No AE or medications were reported.
- Subject 90447 was diagnosed with urinary tract infection and prescribed ciprofloxacin. No AE or medication was reported. Subject also had a complaint of gastro-esophageal reflux and bloating. No AEs were reported.

Dr. Oberoi responded to the Form FDA-483 in a letter dated August 14, 2014. The response was acceptable.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

6. Farid Marquez, M.D.
Palm Springs Research Institute, Inc.
1490 West 49 Place
Suite 205
Hialeah, Florida 33012

- a. **What was inspected:** The inspection focused on informed consent documents (ICDs), the regulatory binder, medical chart review for all subjects, and verifying the authenticity of the medical records used by the site to support the inclusion of subjects into the clinical trial.
- b. **General observations/commentary:** Enrollment at this site took place between 10/5/2011 thru 2/3/2012. There were 38 subjects screened and 26 subjects enrolled. There were 22 subjects active at the time of the site's termination. It was identified during a routine monitoring visit and noted in the monitoring report that six subjects' medical charts contained very similar documents from different physicians (#92450, #92451, #92452, #92467, #92468, #92462). Fraudulent activity was suspected and then confirmed by an independent auditor. The findings of this investigation led to the sponsor's decision to end the site's participation in the 1275.1 trial. All data was excluded from all analyses. The site closure letter for Dr. Marquez was submitted to the FDA on April 9, 2012 to IND 108388. BIPI submitted a follow-up letter to the Agency on May 7, 2012. In closing this site, BIPI also discontinued the site's participation in Study 1275.25 being conducted under IND (b) (4).

The current inspection disclosed that medical notes and medical records supposedly from the subjects' private physicians contained false information such as physicians' signatures, letter heads, patient names, and outpatient clinics' visit dates. Because past medical records needed to be obtained as required by the protocol, this documentation was used in part by the site's staff to confirm a type 2 diabetes mellitus diagnosis and treatment of various subjects enrolled in the study. Furthermore, some of the referenced medical notes supposedly written by the private physician to confirm eligibility after subjects were enrolled into the trial are dated with dates preceding subjects' consenting date. The referenced documentation pertains to Subjects 92450, 92451, 92452, 92455, 92462, and 92468.

As part of the inspection, the FDA field investigators interviewed Dr. Marquez and his study staff. The site claimed the fraudulent records were brought by the patients to the site. The FDA field investigators interviewed the outside physicians who confirmed the medical records in question were not signed by them and/or were not generated at their corresponding clinics. The FDA field investigators were able to locate a subject who was able to confirm that she did not bring the medical records and medical notes to the site. The FDA field investigators also went to addresses listed in the medical records and could not find the subjects at those addresses.

Additionally, the inspection disclosed that the site notified some of the subjects' physicians of their participation in the study against the subjects' expressed will. The form used by the research site to request medical records from the subjects' physician states, "Your patient is undergoing an Investigational Trial in our Facility." This statement is not in agreement with the directive expressed at the

time of consenting by Subjects 92459, 92464, 92469, 92470, 92471, 92474, 92477, 92475, 92476, 92462, 92468, 92478.

On the initial submission dated 7/26/2011 made to the IRB requesting study approval, the site failed to disclose the occurrence of the FDA audit conducted on 6/6-7/5/2011 and findings listed on the Form FDA-483.

Further affidavits are being gathered. The investigation is still pending close-out. A Form FDA-483, Inspectional Observations, will be issued for the following deficiencies:

1. Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.
 2. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.
 3. Failure to assure that an IRB was responsible for the initial and continuing review and approval of a clinical study.
- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator. The audit indicates serious deviations/findings that would impact the validity and reliability of the submitted data. OSI is in agreement with the sponsor that data from this site are considered not reliable.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA consisted of three domestic and three foreign clinical sites.

Observations noted above for Drs. Aggarwal and Oberoi are based on the preliminary review of the Establishment Inspection Reports. Observations noted above for Drs. Aizenberg, Sposetti and Levinson are based on communications from the field investigator. Observations noted above for Dr. Marquez are based on communications from the field investigator and review of the Form FDA-483. An inspection summary addendum will be generated if conclusions change upon OSI final classification.

One site, Dr. Marquez will be issued a Form FDA-483 citing inspectional observations and pending classification is Official Action Indicated (OAI). The sponsor had closed this site and has determined not to use the data in any of the analyses. OSI was able to confirm the unreliability of the data.

One site, Dr. Oberoi was issued a Form FDA-483, citing inspectional observations and classification is Voluntary Action Indicated (VAI). Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Reliability of data from this site is acceptable for use in support of the indication for this application.

Drs. Aggarwal, Aizenberg, Levinson, and Sposetti were not issued a Form FDA 483; the classifications are all NAI (No Action Indicated). Data from these sites are considered reliable based on the available information.

In general, based on the inspections of the six clinical sites, the inspectional findings of these sites, excluding the Marquez site, support validity of data as reported by the Sponsor under this NDA.

{See appended electronic signature page}

Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
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/s/

CYNTHIA F KLEPPINGER
10/06/2014

JANICE K POHLMAN
10/06/2014

KASSA AYALEW
10/06/2014

MEMORANDUM

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

DATE: October 3, 2014

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

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

Sripal R. Mada, 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 (DBGLPC)
Office of Scientific Investigations (OSI)

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

SUBJECT: Review of EIR covering NDA 206-073, Glyxambi
(Empagliflozin / Linagliptin Fixed Dose Combination
Tablets) from Boehringer Ingelheim Pharmaceuticals

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

Study 1275.003: Relative bioavailability investigations of a 25 mg BI 10773/ 5 mg Linagliptin fixed dose combination (FDC) tablet (formulation A1) including the comparison with its mono-components, the comparison with a second FDC tablet (formulation A3), and the

investigation of food (an open-label,
randomized, single dose, crossover, Phase I
trial in healthy male and female
volunteers)“

Clinical Site: Boehringer Ingelheim Pharma GmbH & Co.
Human Pharmacology Centre
Biberach an der Riss, Germany

Analytical Site #1:

(b) (4)

Analytical Site #2:

Inspection of the clinical portion of the study was
conducted by Kate Swat (ORA) at Boehringer Ingelheim,
Biberach, Germany, from 9/22/2014 to 9/26/2014. The audit
reviewed informed consent, study records for enrolled
subjects, drug accountability and dosing records,
correspondence with the sponsor and IRB, and adverse event
reporting. Inspection of the analytical portion of the
study at (b) (4) was

conducted by (b) (4) Seongeun Julia Cho, Ph.D.
(OSI) from (b) (4). I p o
analytical (b) (4) at (b) (4)

was conducted by Robert M. Barbosa (ORA) and Sripal R.
Mada, Ph.D. (OSI) from (b) (4) The audits
at both sites reviewed study records, examination of
facilities and equipment, and interviews and discussions
with the firms' management and staff. Reserve samples were
collected at Boehringer Ingelheim, Biberach, Germany.

At the conclusion of the inspections, no Form FDA-483 was issued
at any of the above sites.

Conclusion:

Based on the inspectional outcomes, these reviewers conclude
that the clinical and analytical portions of the Study 1275.003
are acceptable for further Agency review.

Seongeun (Julia) Cho, Ph.D.
Bioequivalence Branch, DBGCC, OSI

Sripal R. Mada, Ph.D.
Bioequivalence Branch, DBGCC, OSI

Final Classifications:

NAI: Boehringer Ingelheim Pharma GmbH & Co., Biberach, Germany

NAI: [REDACTED] (b) (4)

NAI: [REDACTED]

CC:
OSI/Kassim
OSI/DBGLPC/Taylor/Dejernet/Nkah/Fenty-Stewart/Johnson
OSI/DBGLPC/GLPB/Dasgupta/Bonapace
OSI/DBGLPC/BB/Mada/Cho/Choi/Skelly/Haidar
OND/DMEP/Chiang/Guettier
ORA/DET-DO/Barbosa/Swat

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/Boehringer Ingelheim, Biberach, Germany
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laborat [REDACTED] /INSPECTIONS/BE Program/Analytical
Sites/ [REDACTED] (b) (4)
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laborat [REDACTED] INSPECTIONS/BE Program/Analytical
Sites/ [REDACTED] (b) (4)

Draft: SC 9/30/2014; SRM 9/30/2014
Edit: YMC 10/1/2014; MFS 10/2/2014; WHT 10/3/2014
OSI: BE6696; O:\Bioequiv\EIRCover\206073.boe.gly.doc

FACTS: [REDACTED] (b) (4)

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/s/

SRIPAL R MADA
10/03/2014

SEONGEUN CHO
10/03/2014

WILLIAM H TAYLOR
10/03/2014

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: June 18, 2014
Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number: NDA 206073
Product Name and Strength: Glyxambi (Empagliflozin and Linagliptin) Tablets,
10 mg / 5 mg
25 mg / 5 mg
Submission Date: January 29, 2014
Applicant/Sponsor Name: Boehringer Ingelheim
OSE RCM #: 2014-525
DMEPA Primary Reviewer: Neil Vora, PharmD, MBA
DMEPA Team Leader: Yelena Maslov, PharmD

1 PURPOSE OF MEMO

The Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised container labeling, carton labeling and blister labeling (Appendix A) to determine if it is acceptable from a medication error perspective.

2 CONCLUSIONS

DMEPA concludes that the revised container label, carton label and blister label is acceptable from a medication error perspective. We have no additional comments at this time.

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

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/s/

NEIL H VORA
06/19/2014

LUBNA A MERCHANT
06/19/2014

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: May 23, 2014

Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)

Application Type and Number: NDA 206073

Product Name and Strength: Glyxambi (Empagliflozin and Linagliptin) Tablets,
10 mg / 5 mg
25 mg / 5 mg

Product Type: Multi-Ingredient Product

Rx or OTC: Rx

Applicant/Sponsor Name: Boehringer Ingelheim

Submission Date: January 29, 2014

OSE RCM #: 2014-525

DMEPA Primary Reviewer: Neil Vora, PharmD, MBA

DMEPA Team Leader: Yelena Maslov, PharmD

REASON FOR REVIEW

This review is written to review of proposed container labels, blister labels, carton as well as prescribing information labeling of Glyxambi tablets (NDA 206073) for the areas of vulnerability that could lead to medication errors. This review is performed as part of the review of the original Application. This NDA was submitted by Boehringer Ingelheim on January 29, 2014.

1 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 – N/A
Previous DMEPA Reviews	C
Human Factors Study	D – N/A
ISMP Newsletters	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

2 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We did not identify any areas of vulnerability to medication errors on the container labels, carton labeling, or in prescribing information labeling.

However, the blister label does not clearly indicate the strength per tablet. Identifying the strength per tablet on the blister may prevent dosing errors where consumers may misinterpret the dose to mean that the entire blister contains that particular strength of the product.

3 CONCLUSION

We conclude the container labels, carton labeling, or in prescribing information labeling are acceptable from the medication error perspective.

However, blister label can be improved to clarify the strength of the product per blister cell on the blister label. We provide our recommendations regarding blister label in Section 5, Recommendations.

4 RECOMMENDATIONS

Blister Card Label:

We recommend adding a phrase of “per tablet” on the blister label to clarify that each blister cell contains one dosage unit per blister¹.

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 Glyxambi (Empagliflozin and Linagliptin) that Boehringer Ingelheim submitted on January 30, 2014.

Table 2. Relevant Product Information for Glyxambi	
Active Ingredient	Empagliflozin and Linagliptin
Indication	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and linagliptin is appropriate.
Route of Administration	Oral
Dosage Form	Tablets
Strength(s)	10 mg empagliflozin and 5 mg linagliptin 25 mg empagliflozin and 5 mg linagliptin
Dose and Frequency	One tablet by mouth once daily
How Supplied	Tablets are available in 10 mg/5 mg and 25 mg/5 mg strengths as follows: <u>10 mg/5 mg tablets:</u> <ul style="list-style-type: none"> • Bottles of 30 tablets • Bottles of 90 tablets • Bottles of 1000 tablets • Cartons containing 3 blister cards of 10 tablets each (3 x 10) <u>25 mg/ 5 mg tablets:</u> <ul style="list-style-type: none"> • Bottles of 30 tablets • Bottles of 90 tablets • Bottles of 1000 tablets • Cartons containing 3 blister cards of 10 tablets each (3 x 10)
Storage	Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Store in safe place out of reach of children.

APPENDIX B. Not Applicable

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L: DRIVE on May 27, 2014 using the terms, Glyxambi to identify reviews previously performed by DMEPA.

C.2 Results

Our search identified the following previous proprietary name reviews relevant to this Glyxambi review;

- 2014-17064 Glyxambi (empagliflozin linagliptin) Proprietary Name Review (NDA 206073), dated May 7, 2014. In this review, we conducted an analysis of the proposed name Glyxambi and concluded the name is acceptable for use.

APPENDIX D. Not Applicable

APPENDIX E. Not Applicable

APPENDIX F. Not Applicable

APPENDIX G. LABELS AND LABELING

G.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 Glyxambi labels and labeling submitted by Boehringer Ingelheim on January 30, 2014.

- Container label (Appendix G.2.1)
- Professional Sample Carton Labeling (Appendix G.2.2)
- Professional Sample Blister Cards (Appendix G.2.3)
- Professional Sample Blister Cards Carton Labeling (Appendix G.2.4)
- Professional Blister Cards Carton Labeling (Appendix G.2.5)
- Full Prescribing Information (No Image)

G.2 Label and Labeling Images

G.2.1 Container Labeling



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

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

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/s/

NEIL H VORA
06/16/2014

YELENA L MASLOV
06/16/2014

MEMORANDUM

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

DATE: April 11, 2014

TO: Chief,
Medical Products & Tobacco Trip Planning Branch
Division of Medical Products and Tobacco Inspections
Office of Medical Products and Tobacco Operations

Director, Investigations Branch
300 River Place, Suite #5900
Detroit, MI 48207

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 206-073
DRUG: Glyxambi (Empagliflozin/Linagliptin fixed-dose
combination Tablets)
SPONSOR: Boehringer Ingelheim Pharmaceuticals, 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 inspections of the analytical sites. A DBGLPC scientist will participate in the inspections of the analytical sites to provide scientific and technical expertise.

Background materials will be available in ECMS under the ORA folders. **The inspections should be completed prior to November 30, 2014.**

Do not reveal the applicant, application number, studies 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 Number: 1275.0003
Study Title: "Relative bioavailability investigations of a 25 mg BI 10773/5 mg Linagliptin fixed dose combination (FDC) tablet (formulation A1) including the comparison with its mono-components, the comparison with a second FDC tablet (formulation A3), and the investigation of food (an open-label, randomized, single-dose, crossover, Phase I trial in healthy male and female volunteers)"

Clinical Site: Boehringer Ingelheim Pharma GmbH & Co. KG
Human Pharmacology Centre
Birkendorfer Strasse 65
88397 Biberach an der Riss
Germany

Clinical Investigator: Dr. Mario Iovino

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 study, 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)

Analyte Analyzed: BI 1356 BS (Linagliptin)

Analytical

Investigator:

(b) (4)

Methodology: LC-MS/MS

Analytical Site #2:

(b) (4)

Analyte Analyzed: BI 10773 (Empagliflozin)

Analytical

Investigator:

(b) (4)

Methodology: LC-MS/MS

During the analytical site inspection, please:

- Examine all pertinent items related to the analytical method used for the determination of empagliflozin (b) (4) linagliptin (b) (4) concentrations in human plasma at respective sites.
- 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 subject 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

(For Domestic):

Gajendiran Mahadevan, Ph.D.
Office of Scientific Investigations
Tel: 1-240-402-0507
Fax: 1-301-847-8748
E-mail: gajendiran.mahadevan@fda.hhs.gov

DBGLPC POC

(For Foreign): Arindam Dasgupta, Ph.D.
Pharmacologist
Office of Scientific Investigations
Tel: 1-301-796-3326
Fax: 1-301-847-8748
E-mail: arindam.dasgupta@fda.hhs.gov

DARRTS cc:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Bonapace/Haidar/Mada/Mahadevan/Dejernet
CDER/OND/DMEP/Riviere/Chiang

Email cc:
ORAHQ/OMPTO/DMPTI/BIMO/Turner/Arline/Oliver/Colon
ORA/DET-DO/ORA DET BIMO

Draft: GM 04/04/2014
Edit: SRM 04/09/2014
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical
Sites/ (b) (4)
OSI file # BE6696

FACTS: (b) (4)

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/s/

GAJENDIRAN MAHADEVAN
04/11/2014

CHARLES R BONAPACE
04/11/2014

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 # 206073 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: (empagliflozin and linagliptin) Dosage Form: tablets Strengths: 10 mg empagliflozin/5 mg linagliptin; 25 mg empagliflozin/5 mg linagliptin		
Applicant: Boehringer Ingelheim Pharmaceuticals Inc. Agent for Applicant (if applicable):		
Date of Application: January 30, 2014 Date of Receipt: January 30, 2014 Date clock started after UN:		
PDUFA Goal Date: January 30, 2015		Action Goal Date (if different):
Filing Date: March 31, 2014		Date of Filing Meeting: March 25, 2014 (moved to this later date due to a snowstorm)
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Adjunct to diet and exercise to improve glycemic control in adults with 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)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 </i>	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Type of BLA <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	<input type="checkbox"/> 351(a) N/A <input type="checkbox"/> 351(k)	
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 or pediatric rare 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 <input type="checkbox"/> Pediatric Rare 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)
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<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>): N/A				
List referenced IND Number(s): IND 108388				
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"/>	Standard review
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: No specific number of years requested <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 the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>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.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	N/A

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	

Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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, <u>both</u> 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"/>	
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 checked="" type="checkbox"/>	<input 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 reviewed by PeRC prior to approval of the application/supplement.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		PeRC already scheduled for December 3, 2014.
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 type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<u>BPCA</u> (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"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

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

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

<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
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 (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	They will be consulted
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	They will be consulted
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"/>	They will be consulted
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"/>		

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

<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 checked="" type="checkbox"/>	<input type="checkbox"/>	More consults may be needed as review progresses
<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): 8.14.13	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Comments sent to sponsor on 8.14.13 in lieu of meeting
<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: March 25, 2014 (rescheduled to this later date due to snow storm)

BLA/NDA/Supp #: NDA 206073

PROPRIETARY NAME: N/A

ESTABLISHED/PROPER NAME: empagliflozin and linagliptin

DOSAGE FORM/STRENGTH: 10 mg empagliflozin/5 mg linagliptin
25 mg empagliflozin/5 mg linagliptin

APPLICANT: Boehringer Ingelheim Pharmaceuticals, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when both empagliflozin and linagliptin is appropriate.

BACKGROUND: The two individual components of this proposed new fixed-dose combination product were each previously developed by Boehringer Ingelheim for treatment of type 2 diabetes. Linagliptin is available in the US as Tradjenta® (linagliptin) tablets (NDA 201280 approved May 2, 2011), and empagliflozin is the subject of pending NDA 204629 submitted on March 5, 2013.

Empagliflozin/linagliptin FDC tablets have been studied in treatment-naïve patients and in patients on metformin background. The Phase III study evaluated two doses of the empagliflozin/linagliptin FDC tablets (25 mg empagliflozin/5 mg linagliptin and 10 mg empagliflozin/5 mg linagliptin) for 52 weeks.

The chemistry, manufacturing, and controls information for both empagliflozin and linagliptin drug substance are fully cross-referenced to section 3.2.S of NDA 204629 and NDA 201280, respectively. This NDA cross-references nonclinical and clinical information for each of the individual components to Modules 4 and 5 of NDA 201280 and NDA 204629, respectively.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Raymond Chiang	Y
	CPMS/TL:	Pamela Lucerelli	Y
Cross-Discipline Team Leader (CDTL)	William Chong		Y
Clinical	Reviewer:	William Chong	Y

	TL:	William Chong	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:		

Clinical Pharmacology	Reviewer:	Sury Sista	Y
	TL:	Lokesh Jain	Y
Biostatistics	Reviewer:	Jennifer Clark	Y
	TL:	Mark Rothmann	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	David Carlson	Y
	TL:	Todd Bourcier	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Joseph Leginus/Su Tran (filing)	Y
	TL:		
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Erika Pfeiler	Y
	TL:		
CMC Labeling Review	Reviewer:	Joseph Leginus	N
	TL:		
Facility Review/Inspection	Reviewer:	pending	
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Mishale Mistry	Y
	TL:	Yelena Maslov	N
OSE/DRISK (REMS)	Reviewer:	Amarilys Vega	Y
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Cynthia Kleppinger	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers	Karen Riviere (biopharmaceutics) – team leader is Tapash Ghosh		Y
Other attendees			

FILING MEETING DISCUSSION:

GENERAL	
<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? If no, explain: 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments List comments: No comments 	<input type="checkbox"/> Not Applicable
CLINICAL	<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? If no, explain: 	<input checked="" type="checkbox"/> YES <input 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: the application did not raise significant safety or efficacy issues
<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 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>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? 	<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 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? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO If no, was a complete EA submitted? <input type="checkbox"/> YES <input type="checkbox"/> NO If EA submitted, consulted to EA officer (OPS)? <input type="checkbox"/> YES <input type="checkbox"/> NO <p>Comments: EA was not submitted</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: They have comments for 74-day letter</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" 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? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <p>Comments: ONDQA submitted consult to OC/OMPQ</p>	<p><input type="checkbox"/> Not Applicable</p>

<p>for possible inspection. ONDQA still waiting to hear back from OC/OMPQ</p>	
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<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>
<p><u>CMC Labeling Review</u></p> <p>Comments: Joseph Leginus will review label</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<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? 	<p><input type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	<p>N/A</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? 	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<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	
<p>Signatory Authority: Dr. Curt Rosebraugh</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): To be scheduled around June 29, 2014</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
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"/>	
<input type="checkbox"/>	<p>If priority review:</p> <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"/>	<p>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://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

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

/s/

RAYMOND S CHIANG
03/27/2014

PAMELA LUCARELLI
03/27/2014