CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206111Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 206111 SUPPL # n/a HFD # n/a

Trade Name Synjardy

Generic Name empagliflozin and metformin hydrochloride

Applicant Name Boehringer Ingelheim Pharmaceuticals, Inc.

Approval Date, If Known August 26, 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(2)

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

YES ☒ NO ☐

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

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

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

not stated

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 204629	Jardiance (empagliflozin) tablets
NDA# 206073	Glyxambi (empagliflozin and linagliptin) tablets
NDA# 020357	Glucophage (metformin hydrochloride) tablets
NDA# 201281	Jentadueto (linagliptin and metformin hydrochloride) tablets

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability

studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

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

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

YES ☒ NO ☐

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

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

YES ☐ NO ☒

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

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could

independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

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

Study 1276.10 (completed under IND 102145)- A randomised, double blind, placebo controlled, parallel group efficacy and safety study of oral administration of empagliflozin twice daily versus once daily in two different daily doses over 16 weeks as add-on therapy to a twice daily dosing regimen of metformin in patients with type 2 diabetes mellitus and insufficient glycaemic control.

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

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

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

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

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

b) For each investigation identified as "essential to the approval", does the investigation

duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

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

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

Study 1276.10

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 102145	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor

in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Michael G. White, Ph.D.
Title: Regulatory Project Manager
Date: August 26, 2015

Name of Office/Division Director signing form: Jean-Marc Guettier, M.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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
08/26/2015

JEAN-MARC P GUETTIER
08/26/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 206111 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Synjardy Established/Proper Name: empagliflozin and metformin hydrochloride Dosage Form: tablets		Applicant: Boehringer Ingelheim Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Michael G. White, PhD		Division: Division of Metabolism and Endocrinology Products

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: August 26, 2015

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is September 2, 2015	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR June 4, 2015
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☒ MedGuide w/o REMS
☒ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP: August 26, 2015 CR: June 4, 2015
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Final labeling attached to approval letter.
• Original applicant-proposed labeling	☐ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Final labeling attached to approval letter.
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Final labels attached to approval letter.
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Review: 08/07/2015 10/20/2014
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None 10/10/2014 DMEPA: ☐ None 08/07/2015 03/04/2015 DMPP: ☐ None 05/15/2015 PLT (DRISK): ☒ None OPDP: ☐ None 08/05/2015 05/13/2015 SEALD: ☒ None CSS: ☒ None Product Quality ☐ None see Integrated Quality Assessment (beginning on p.57) 04/14/15 Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ Included 10/10/2014 ☐ Not a (b)(2) 07/21/2015 04/20/2015
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 04/15/2015 If PeRC review not necessary, explain: _____	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	Labeling: 8/19/2015 Labeling: 8/13/2015 Proprietary name grant: 8/11/2015 Ack Class 1 Resub: 07/15/2015 Advice letter: 06/18/2015 Labeling: 06/02/2015 Labeling: 05/27/2015 Advice letter (emails): 05/22/2015 IR request: 05/15/2015 Labeling: 05/15/2015 IR request: 05/04/2015 Labeling: 04/21/2015 IR request: 04/10/2015 Advice letter: 03/05/2015 IR request: 03/04/2015 IR request: 02/24/2015 IR request: 12/30/2014 IR request: 12/15/2014 IR request: 12/04/2014 Proprietary name grant:10/23/2014 No filing issues letter: 10/10/2014 Ack NDA letter: 08/12/2014
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg Meeting cancelled at sponsor's request. Preliminary comments 01/10/2014
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	

❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None See 7/02 CDTL review 06/04/2015
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 07/02/2015 06/04/2015
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review. See CDTL Reviews above
• Clinical review(s) *(indicate date for each review)*	Filing: 09/25/2014
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	06/04/2015 See CDTL Review, page 79
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested Memo 12/09/2014
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None Review: 04/16/2015 Filing: 09/26/2014

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None Review 4/15/2015 Filing: 09/15/2014
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None Review: 4/15/2015 Filing: 09/18/2014
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None Revew 4/14/2015 Filing: 09/22/2014
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☐ None BiopharmReview: 04/15/2015 Microbiology Review: 02/17/2015 Filing: 08/21/2014
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	04/14/2015 See Executive Summary/Chemistry Review, page 65
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable Re-evaluation date: 09/26/15 ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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

/s/

MICHAEL G WHITE
08/26/2015

From: joachim.troost@boehringer-ingelheim.com
To: White, Michael G (CDER)
Subject: RE: NDA206111, Synjardy: 2nd Round, 2nd cycle FDA Draft Labeling
Date: Wednesday, August 19, 2015 4:04:13 PM

Dear Mike,

Thanks, got it. Joachim.

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Wednesday, August 19, 2015 3:59 PM
To: Troost,Dr.,Joachim (DSI) BIP-US-R
Subject: NDA206111, Synjardy: 2nd Round, 2nd cycle FDA Draft Labeling

Dear Dr. Troost,

Attached is the 2nd round of FDA edits of the draft labeling for the second cycle review of NDA 206111, Synjardy (empagliflozin and metformin hydrochloride fixed dose combination tablets). We remind you that these edits do not reflect on the final regulatory decision for this application.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "BI response to FDA change or BI comment."

Because of the tight timeline we ask the you complete your review and return comments *as soon as possible* and no later than the close of business, **Monday, August 24th.**

Please confirm receipt of this email, and let me know if you have any questions.

Regards,

-Mike

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

35 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

MICHAEL G WHITE
08/19/2015

From: joachim.troost@boehringer-ingelheim.com
To: White, Michael G (CDER)
Subject: RE: NDA206111, Synjardy: 1st Round, 2nd cycle FDA DRAFT LABELING
Date: Thursday, August 13, 2015 4:58:01 PM

Dear Mike,

Receipt confirmed – and no questions at the moment. Thanks, Joachim.

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Thursday, August 13, 2015 4:49 PM
To: Troost,Dr.,Joachim (DSI) BIP-US-R
Subject: NDA206111, Synjardy: 1st Round, 2nd cycle FDA DRAFT LABELING

Dear Dr. Troost,

Attached is the 1st round of FDA edits of the draft labeling for the second cycle review of NDA 206111, Synjardy (empagliflozin and metformin hydrochloride fixed dose combination tablets). We remind you that these edits do not reflect on the final regulatory decision for this application.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "BI response to FDA change or BI comment."

Because of the tight timeline we ask the you complete your review and return comments *as soon as possible* and no later than the close of business, **Tuesday, August 18th.**

Please confirm receipt of this email, and let me know if you have any questions.

Regards,

-Mike

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

38 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MICHAEL G WHITE
08/13/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206111

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, CT 06877-0368

ATTENTION: Joachim Troost, M.D.
Senior Associate Director, Regulatory Affairs

Dear Dr. Troost:

Please refer to your New Drug Application (NDA) dated and received July 2, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Empagliflozin and Metformin HCl Tablets, 5 mg/500 mg, 5 mg/1000 mg, 12.5 mg/500 mg, and 12.5 mg/1000 mg.

We also refer to your correspondence, dated and received July 2, 2015, requesting review of your proposed proprietary name, Synjardy.

We have completed our review of the proposed proprietary name, Synjardy, and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your July 2, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Michael White, Regulatory Project Manager in the Office of New Drugs, at 240-402-6149.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
08/11/2015

From:	Holovac, Mary Ann
To:	White, Michael G (CDER)
Cc:	Stradley, Sara; Duvall, Beth A; Holovac, Mary Ann
Subject:	NDA 206111, Synjardy (empa/met FDC) - cleared for action
Date:	Tuesday, July 21, 2015 2:27:30 PM

Mike,

We discussed this application at Monday's 505(b)(2) clearance meeting. This application is cleared for action from a 505(b)(2) perspective.

Please make the changes to the draft assessment (as conveyed to you on 4//16/15, see below) before archiving in DARRTS, assuming you are heading towards an approval. If you are not approving this cycle, please make the changes below but defer archiving in DARRTS until you are headed towards approval (in which case you would need to have the application cleared again). If that's the case, please let us know when the RS arrives so that we can add it anew to our clearance queue.

Please let me know if you have any questions.

Mary Ann

From: White, Michael G (CDER)
Sent: Wednesday, July 15, 2015 11:44 AM
To: Holovac, Mary Ann
Subject: RE: 505(b)(2) Re-review for Resubmitted (class 1) NDA 206111, Synjardy (empa/met FDC)

Hi Mary Ann,

We just got word from ORP that NDA 206111 (Synjardy) will be considered a pending application and thus its resubmission following the CR will not be required to conform to the PLLR.

This means that we will, as originally intentioned, classify the resubmission as a class 1 on the 2-month clock with a PDUFA date of September 2nd.

Thank you for bearing with us and please let me know if you need anything!

-Mike
Michael G. White, PhD
Regulatory Project Manager, DMEP; WO22 - Room 3389, phone 240-402-6149

From: Holovac, Mary Ann
Sent: Tuesday, July 07, 2015 1:39 PM
To: White, Michael G (CDER)
Subject: RE: 505(b)(2) Re-review for Resubmitted (class 1) NDA 206111, Synjardy (empa/met FDC)

Ok, not a problem. I have it in queue but will wait until you provide me with updates. Thank you.

The July 2, 2015, resubmission of NDA 206111, in response to our June 4, 2015, Complete Response letter, induced no changes to the 505(b)(2) Assessment that was filed in DARRTS on 04/20/2015. For convenience, a copy of the 04/20/2015 assessment follows.

-Michael G. White, PhD
Regulatory Project Manager

8 Pages have been Withheld in Full as duplicate copy of the 505(b)(2) Assessment located in OtherR, dated 04/20/2015, immediately following this page

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/s/

MICHAEL G WHITE
07/21/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206111

ACKNOWLEDGE -
CLASS 1 COMPLETE RESPONSE

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Joachim Troost, M.D.
Senior Associate Director, Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Troost:

We acknowledge receipt on July 2, 2015, of your July 2, 2015, resubmission to your supplemental new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for empagliflozin and metformin hydrochloride tablets.

We consider this resubmission a complete, class 1 response to our action letter. Therefore, the user fee goal date is **September 2, 2015**.

If you have any questions, call me at (240) 402-6149.

Sincerely,

{See appended electronic signature page}

Michael G. White, Ph.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MICHAEL G WHITE
07/15/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206111

GENERAL ADVICE

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Joachim Troost, M.D.
Senior Associate Director, Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Troost:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for empagliflozin and metformin hydrochloride tablets.

We also refer to your June 10, 2015, email containing a request for clarification on requirements for the resubmission of your application that were contained in the Complete Response letter dated June 4, 2015.

We have the following responses to your questions contained in your June 10, 2015, email:

Prescribing Information (PI)
BI proposes to cross-reference the previously submitted in the planned Synjardy resubmission, and not resubmit this documentation. Does the Agency concur with BI's proposal?

> **FDA Response: In your resubmission, it is sufficient for you to cross reference data and documentation that was previously submitted to your application in order to support labeling. However, in your resubmission, please include an updated PI which contains your response to our last draft labeling for NDA 206111 emailed on June 2, 2015.**

Carton and Container Labeling
BI proposes to cross-reference the previously submitted carton and container labeling in the planned Synjardy resubmission (SEQ 0018, submitted May 21, 2015), and not resubmit this documentation. BI considers these final, pending any further comments from FDA. Does the Agency concur with BI's proposal?

> **FDA Response: We agree, so long as no changes are made to the last submitted carton & container labeling dated May 21, 2015.**

Proprietary Name

BI proposes to cross-reference the previously submitted proprietary name request in the planned Synjardy resubmission, and not resubmit this documentation. Does the Agency concur with BI's proposal?

> **FDA Response: We do not agree. For administrative purposes, you will need to submit the proprietary name request as a separate submission from the Complete Response. In the separate submission of the proprietary name request, you may reference your previously submitted proprietary name request dated August 8, 2014.**

If you have any questions, call Michael G. White, Ph.D., Regulatory Project Manager, at (240) 402-6149.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JEAN-MARC P GUETTIER
06/18/2015

From:	White, Michael G (CDER)
To:	"joachim.troost@boehringer-ingelheim.com"
Subject:	NDA206111, Synjardy: 4th Round FDA DRAFT LABELING
Date:	Tuesday, June 02, 2015 7:49:00 PM
Attachments:	4th Rnd Empagliflozin Metformin BI response to FDA 2June2015.doc

Dear Dr. Troost,

Attached is the fourth round of FDA edits of the draft labeling for NDA 206111, Synjardy (empagliflozin and metformin hydrochloride fixed dose combination tablets). We remind you that these edits do not reflect on the final regulatory decision for this application.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "BI response to FDA change or BI comment."

Because of the tight timeline we ask the you complete your review and return comments *as soon as possible* and no later than **noon, Wednesday, June 3rd.**

Please note the following comments regarding the Clinical Studies section that are included on the draft labeling:

(b) (4)

We view the 52-week efficacy data (b) (4) *reliable, robust and as sufficient to inform the safe and effective use of the product in this setting. Replace labeling language with language in the current empagliflozin label. The Agency is continuing to evaluate the multiple imputation approach for the Week-52 analysis and may have be additional edits to relay before final agreement."*

Please confirm receipt of this email, and let me know if you have any questions.

Regards,

-Mike

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

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/s/

MICHAEL G WHITE
06/02/2015

From: joachim.troost@boehringer-ingelheim.com
To: White, Michael G (CDER)
Subject: RE: NDA206111, Synjardy: 3rd Round FDA DRAFT LABELING
Date: Wednesday, May 27, 2015 6:49:29 PM

Dear Mike,

Thanks a lot. Got it and I will get back to you as soon as possible.

Thanks, Joachim.

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Wednesday, May 27, 2015 6:49 PM
To: Troost,Dr.,Joachim (DSI) BIP-US-R
Subject: NDA206111, Synjardy: 3rd Round FDA DRAFT LABELING

Dear Dr. Troost,

Attached is the third round of FDA edits of the draft labeling for NDA 206111, Synjardy (empagliflozin and metformin hydrochloride fixed dose combination tablets). We remind you that these edits do not reflect on the final regulatory decision for this application.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "BI response to FDA change or BI comment."

Because of the tight timelines we ask the you complete your review and return comments *as soon as possible* and no later than **noon, Friday, May 29th.**

Please confirm receipt of this email, and let me know if you have any questions.

Regards,

-Mike

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

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/s/

MICHAEL G WHITE
05/27/2015

From: joachim.troost@boehringer-ingelheim.com
To: White, Michael G (CDER)
Subject: RE: NDA206111, Synjardy: Statistics team teleconference follow-up
Date: Friday, May 22, 2015 11:51:55 AM

Dear Mike,

Thanks to you and FDA statistics team as well.

I will send you a response by today, but won't get it through the eCTD gateway in time. I will work on submitting the official response on Tuesday. In case that there would be any change (besides formatting of the written response document), I will outline these.

Thanks and have a nice extended weekend,

Joachim.

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Friday, May 22, 2015 11:36 AM
To: Troost,Dr.,Joachim (DSI) BIP-US-R
Subject: NDA206111, Synjardy: Statistics team teleconference follow-up

Hi Joachim,

It was a pleasure talking to you at the teleconference on Friday May 22, 2015, at 11am.

From the conversation, our statics review team has concluded that the statistical approach provided in your prior email, in which you now incorporate the sampling of the 'off-treatment' regression coefficients from the multivariate normal distribution, is reasonable.

We requested and look forward to receiving a detailed description of your methodology, as well as the analysis code and corresponding results with which we will consider providing additional feedback.

Please let me know if you any further questions.

Kind regards,

-Mike

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research

U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

From: joachim.troost@boehringer-ingelheim.com [mailto:joachim.troost@boehringer-ingelheim.com]
Sent: Friday, May 22, 2015 10:44 AM
To: White, Michael G (CDER)
Subject: FW: structure of sampling

Dear Mike,

Please find below an outline prepared by my statistical colleagues for our discussion at 11 am.

Could you please share the information with your colleagues?

I also would like to provide an updated BI participation list

- Michael Shear (statistics)
- Dr Stefan Hantel (statistics)
- Dr Dacheng Liu (statistics)
- Dr Erich Bluhmki (statistics)
- Dr Afshin Salsali (medical)
- me

Thanks and kind regards,

Joachim.

Dear Dr. White,
We have prepared an update to the statistical handling of missing data at week 52/104 previously submitted to FDA (Monday, 18 May) [please see below for reference to previous email communication] whereby we additionally now incorporate sampling of the 'off-treatment' regression coefficients from the multivariate normal distribution. We would like to discuss this approach and confirm whether this would be acceptable to the authority.

Previous email communication
'Per FDA request (dated 15 May 2015), we plan to perform the following missing value imputation strategy at week 52 (and subsequently at week 104). Does the FDA agree with this approach??
1: Estimate variability of the overall HbA1c data, including both on- and off-treatment measurements, at week 52, on FAS (OC-AD), via ANCOVA conditioning on baseline eGFR, baseline HbA1c, and treatment.
2: Estimate mean(s) of the 'off-treatment' data at week 52 using ANCOVA (per

conditioning on variables listed in [1.] above).
3: Impute missing patient data at week 52, for RS, assuming normal distribution with mean and variability estimates from [2.] and [1.] above, conditioning on the aforementioned variables of the patient.
4: Analyze treatment effect at week 52, for RS (OC-AD), via ANCOVA (per conditioning on variables listed in [1.] above).
5: Repeat [3.] and [4.] by 100 times
6: Calculate overall estimate of treatment effect
Please note that, for analysis of the week 104 data only, the 'region' effect is also included as a conditioning variable in all of the above-specified analyses. This effect is excluded from analysis of the week 52 data because of technical non-convergence of the ANCOVA 'imputation' model on 'off-treatment' data at this same time-point (only 14 HbA1c 'off-treatment' values available). Consequently, region is also excluded from the treatment effect analysis model at week 52 in order to avoid issues with uncongeniality (Meng, 1994). Region was selected for exclusion from the week 52 analyses because not all regions were populated with 'off-treatment' data.'

From: White, Michael G (CDER)
To: "joachim.troost@boehringer-ingelheim com"
Subject: RE: NDA206111, Synjardy: INFORMATION REQUEST / TCon 11:00 am to 11:30 am
Date: Thursday, May 21, 2015 4:08:00 PM
Attachments: image001.png

Thanks Joachim,

FYI, we expect the following participants:

Gregory Levin (stats)
Susie Sinks (stats)
Bradley McEvoy (stats)
me
and tentatively, Bill Chong (clinical)

Let me know if you need anything else,

-Mike

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

From: joachim.troost@boehringer-ingelheim.com [mailto:joachim.troost@boehringer-ingelheim.com]
Sent: Thursday, May 21, 2015 3:52 PM
To: White, Michael G (CDER)
Subject: NDA206111, Synjardy: INFORMATION REQUEST / TCon 11:00 am to 11:30 am

Dear Mike,

Thanks for being available at such a short notice. Please find below the phone number and the conference ID for the dial-in.

Day/Date/Time: Friday/ May 22, 2015/ 11:00 am to 11:30 am.

BI participants:

- Michael Shear (statistics)
- Dr Stefan Hantel (statistics)
- Dr Dacheng Liu (statistics)
- me

Join by Phone
(b) (4) English (United States - Ridgefield)
(b) (4) English (United States - Ridgefield)

Conference ID: 572334128

Thanks and BR, Joachim.

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Thursday, May 21, 2015 3:41 PM
To: Troost,Dr.,Joachim (DSI) BIP-US-R
Subject: RE: NDA206111, Synjardy: INFORMATION REQUEST

Hi Joachim,

11am tomorrow (Friday the 22nd) works for a t-con. Send along a call-in number.

-Mike

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

From: joachim.troost@boehringer-ingelheim.com [mailto:joachim.troost@boehringer-ingelheim.com]
Sent: Thursday, May 21, 2015 10:07 AM
To: White, Michael G (CDER)
Subject: RE: NDA206111, Synjardy: INFORMATION REQUEST

Dear Mike,

Thanks for the email. I am collecting feedback from my statistical colleagues.

One question: should I still submit the response that we prepared for today (May 21, 2015)? It's currently made ready for submission. Or would you prefer to receive only the updated response?

Once I have feedback whether the statistical colleagues would like to have a TC, I will get back with times and a call-in number.

Thanks, Joachim.

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Thursday, May 21, 2015 9:49 AM
To: Troost,Dr.,Joachim (DSI) BIP-US-R
Subject: RE: NDA206111, Synjardy: INFORMATION REQUEST

Hi Joachim,

I have the following response to your question.

> Your proposal will not adequately address our request. Your algorithm is similar to the approach described here [redacted] (b) (4) [redacted] We recommend that your imputation in Step 3 incorporates both the variability estimated in Step 1 (as you have already proposed) *and* the uncertainty in the estimates of the ANCOVA parameters used to estimate the off-treatment means in

Step 2. Please outline the algorithm you implemented in your response to the IR. We are available for a t-con if there are any outstanding issues.

If you'd like to have a t-con, please send me a few suggested times and a call-in number.

Regards,

-Mike

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

From: joachim.troost@boehringer-ingelheim.com [mailto:joachim.troost@boehringer-ingelheim.com]
Sent: Monday, May 18, 2015 1:32 PM
To: White, Michael G (CDER)
Subject: FW: NDA206111, Synjardy: INFORMATION REQUEST

Dear Dr White,

In response to FDA's information request below, my statistical colleagues are preparing to respond as outlined below. We would like to ensure, that this will appropriately address FDA's request. If not, would it be possible to schedule a TC for tomorrow so that FDA and BI statisticians could clarify open topics?

Could you please propose a time, when FDA statisticians would be available:

Thanks and kind regards,

Joachim.

Per FDA request (dated 15 May 2015), we plan to perform the following missing value imputation strategy at week 52 (and subsequently at week 104). Does the FDA agree with this approach?

(b) (4)

[redacted] (b) (4)

Boehringer Ingelheim

Dr Joachim Troost
Regulatory Affairs
Boehringer Ingelheim Pharmaceut cals, Inc.
Ridgefield, Connect cut
P: 203 798 5155 :: C: [redacted] (b) (6)
joachim.troost@boehringer-ingelheim.com

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Friday, May 15, 2015 3:26 PM
To: Troost,Dr.,Joachim (DSI) BIP-US-R
Subject: NDA206111, Synjardy: INFORMATION REQUEST

Dear Dr. Troost,

In reference to NDA 206111, Synjardy (empagliflozin and metformin hydrochloride) FDC tablets, we have the following request for information from the statistics review team:

> "**Reference is made to the May 12, 2015 BI response to the FDA IR submitted May 4, 2015.**
>
> We have read your response and have the following comments. We do not agree [redacted] (b) (4)
>
> We also do not agree [redacted] (b) (4)
>
> We have some comments on your approach [redacted] (b) (4) We agree in principle with your approach, but understand your concern [redacted] (b) (4) We recommend a multiple imputation approach that continues to sample missing data based on the means of the available off-treatment measurements but uses an imputation variance that more reasonably approximates the variance observed based on the overall HbA1C data. The approach should be implemented to estimate mean differences between treatment groups at both week 52 and week 104. Please submit the results of your analysis, a description of the methodology, and the programming code used."

Provide this information *as soon as possible* or by the close of business **close of business, Thursday, May 21st**.

Let me know if you have any questions and please confirm receipt of this request. Please email me a copy as well as officially submitting the information to your application.

Regards,

-Mike

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

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/s/

MICHAEL G WHITE
05/22/2015

From: joachim.troost@boehringer-ingelheim.com
To: White, Michael G (CDER)
Subject: RE: NDA206111, Synjardy: INFORMATION REQUEST
Date: Friday, May 15, 2015 3:28:48 PM

Dear Dr White,

I confirm receipt of your information request and I will get back to you as soon as possible.

Thanks and have a nice weekend,

Joachim.

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Friday, May 15, 2015 3:26 PM
To: Troost,Dr.,Joachim (DSI) BIP-US-R
Subject: NDA206111, Synjardy: INFORMATION REQUEST

Dear Dr. Troost,

In reference to NDA 206111, Synjardy (empagliflozin and metformin hydrochloride) FDC tablets, we have the following request for information from the statistics review team:

"**Reference is made to the May 12, 2015 BI response to the FDA IR submitted May 4, 2015.**

We have read your response and have the following comments. We do not agree (b) (4) [redacted]

We also do not agree (b) (4) [redacted]

We have some comments on your approach (b) (4) [redacted] We agree in principle with your approach, but understand your concern (b) (4) [redacted] We recommend a multiple imputation

approach that continues to sample missing data based on the means of the available off-treatment measurements but uses an imputation variance that more reasonably approximates the variance observed based on the overall HbA1C data. The approach should be implemented to estimate mean differences between treatment groups at both week 52 and week 104. Please submit the results of your analysis, a description of the methodology, and the programming code used."

Provide this information *as soon as possible* or by the close of business **close of business, Thursday, May 21st**.

Let me know if you have any questions and please confirm receipt of this request. Please email me a copy as well as officially submitting the information to your application.

Regards,

-Mike

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

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/s/

MICHAEL G WHITE
05/15/2015

From: joachim.troost@boehringer-ingelheim.com
To: White, Michael G (CDER)
Subject: RE: NDA206111, Synjardy: 2nd Round FDA DRAFT LABELING
Date: Friday, May 15, 2015 3:18:26 PM
Attachments: image001.png

Dear Dr White,

Thanks for your email with FDA's edits of the draft labeling. I will get back to you as soon as possible.

Have a nice weekend,

Joachim

Boehringer Ingelheim

Dr Joachim Troost
Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5155 :: C: (b) (6)
joachim.troost@boehringer-ingelheim.com

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Friday, May 15, 2015 3:12 PM
To: Troost,Dr.,Joachim (DSI) BIP-US-R
Subject: NDA206111, Synjardy: 2nd Round FDA DRAFT LABELING

Dear Dr. Troost,

Attached is the second round of FDA edits of the draft labeling for NDA 206111, Synjardy (empagliflozin and metformin hydrochloride fixed dose combination tablets). We remind you that these edits do not reflect on the final regulatory decision for this application.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "BI response to FDA change or BI comment."

Because of the tight timelines we ask the you complete your review and return comments *as soon as possible* and no later than **the close of business, Thursday, May 21st.**

Please confirm receipt of this email, and let me know if you have any questions.

Regards,

-Mike

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

34 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MICHAEL G WHITE
05/15/2015

From: joachim.troost@boehringer-ingelheim.com
To: White, Michael G (CDER)
Subject: RE: NDA206111, Synjardy: INFORMATION REQUEST
Date: Monday, May 04, 2015 4:23:37 PM

Dear Mike,

Thanks for your email. I will get back to you as soon as possible.

Thanks and KR, Joachim

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Monday, May 04, 2015 3:27 PM
To: Troost,Dr.,Joachim (DSI) BIP-US-R
Subject: NDA206111, Synjardy: INFORMATION REQUEST

Dear Dr. Troost,

In reference to NDA 206111, Synjardy (empagliflozin and metformin hydrochloride) FDC tablets, we have the following request for information from the statistics review team:

> **"Reference is made to the BI response to the April 15, 2015 FDA IR submitted April 17, 2015.**
>
> **We have read your response and have the following comments. We do not believe the mixed model for repeated measures (MMRM) reliably estimates the difference in average HbA1c change at week 104. To clarify, we are referring to an estimate of the average difference in HbA1c change at week 104 regardless of treatment adherence.**
>
> **For your MMRM we question the appropriateness of representing HbA1c change for those with missing data by the HbA1c change from those with data since patients with data appear to be systematically different than those without data. For example, in trial 1245.28 about 4% of those with data at week 104 were off-treatment, whereas about 90% of those without data stopped treatment prior to (the beginning of the analysis window for) week 104. Moreover, of those with data at week 104, those that were off-treatment tended to have not as favorable HbA1c values as those that were on-treatment. Given these considerations, your MMRM may overstate the HbA1c change at week 104, possibly resulting in an upwardly biased estimate of the treatment effect.**
>
> **We request you fit alternative model(s) that addresses the concerns raised above. Please provide results from an analysis where you impute, using a multiple imputation approach, HbA1c change at week 104 for those without data using information from those with data at week 104 that were off-treatment, accounting for baseline HbA1c, assigned treatment and possibly other effect modifiers (e.g., baseline eGFR). You can also provide results from additional alternative models accompanied with a description of the approach and underlying assumptions being made. Please provide the requested**

information by May 12, 2015."

Provide this information as soon as possible or by the close of business Tuesday, May 12, 2015.

Let me know if you have any questions and please confirm receipt of this request. Please email me a copy as well as officially submitting the information to your application.

Regards,

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

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/s/

MICHAEL G WHITE
05/04/2015

PeRC Meeting Minutes
April 15, 2015

PeRC Members Attending:
Lynne Yao
Robert "Skip" Nelson
Wiley Chambers
Rosemary Addy
George Greeley
Ruthanna Davi Non-responsive
Tom Smith
Karen Davis-Bruno
Daiva Shetty
Andrew Mulberg Non-responsive
Greg Reaman Non-responsive
Adrienne Hornatko-Munoz
Andrew Mosholder
Hari Cheryl Sachs
Julia Pinto Non-responsive
Lily Mulugeta
Kevin Krudys
Rachel Witten
Dianne Murphy
Maura O'Leary
Olivia Ziolkowski

Agenda

9:00	Non-responsive			
9:20				
9:40				
10:00				
	NDA	*206111*	*Synjardy (empagliflozin/metformin hydrochloride) tablets, fixed dose combination (Full Waiver)*	*An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus* (b) (4)
	Non-responsive			

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Non-responsive

Synjardy (empagliflozin/metformin) FDC Partial Waiver/Deferral

- Proposed Indication: An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)
- The Division noted that the Agreed iPSP did not include a plan for full waivers for this combination product. However, there are outstanding PREA requirement for empagliflozin that are in progress. These studies are being conducted with metformin. Therefore, the PREA studies being conducted currently would fulfill the requirements for this product. (b) (4)

(b) (4)

- The current paradigm of studying the single ingredient in combination with metformin should provide sufficient information to label both the single ingredient as well as the combination products. However, the PeRC acknowledge certain situations in which this policy could fall short in providing adequate labeling for pediatric patients:
    - If the single agent product NDA was withdrawn before PREA studies were completed and the combination product was available, then there would be no ability to require studies of the single agent. However, one potential strategy to address this would be to invoke the marketed drugs provision under PREA and require studies under PREA that were previously waived for the combination product. Before this provision could be invoked, the Division and the PeRC would need to reevaluate the public health benefit and the need for pediatric studies of the combination product. PeRC notes that the marketed drug provision has not been invoked to date.
    - If the single agent PREA requirements are not completed at the time of the NDA submission for a combination product that includes the single agent then studies under PREA for the combination product could not be waived because the grounds for waiver would not have been met (i.e., studies in the combination product could not be waived because there was no meaningful benefit over existing therapies since the single agent has not yet been approved in pediatric patients).
- If the empagliflozin pediatric studies had been completed, the combination product could potentially be labeled for pediatric use and/or pediatric studies could be waived (see bullet above). However, the empagliflozin pediatric studies are still outstanding and therefore, there is no adequate grounds for waiver under PREA for this combination product.
- PeRC Recommendations:
    - See comments above. Additionally, the due dates for the PREA PMRs for this product should be consistent with the PREA PMR due dates for empagliflozin NDA.
    - The PeRC also recommends (b) (4)
    - The PeRC agreed with the Division to grant a partial waiver in pediatric patients less than 10 years because the product would not offer a meaningful benefit because in pediatric patients.

Non-responsive

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/s/

GEORGE E GREELEY
04/29/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206111

LABELING DISCUSSION COMMENTS

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Joachim Troost, M.D.
Senior Associate Director, Regulatory Affairs
900 Ridgebury Road
PO Box 368
Ridgefield, CT 06877

Dear Dr. Troost:

Please refer to your New Drug Application (NDA) dated August 4, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Synjardy (empagliflozin and metformin hydrochloride) fixed dose combination tablets.

We also refer to our October 10, 2014, letter in which we notified you of our target date of May 4, 2015, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017."

On March 11, 2015, we received your most recent proposed PI labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by April 28, 2015. The resubmitted labeling will be used for further labeling discussions.

Your proposed prescribing information (PI) must conform to the content and format regulations found at CFR 201.56(a) and (d) and 201.57. Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

These revisions have been reviewed and cleared to the level of Cross Discipline Team Leader.

If you have any questions, call me at (301) 240-402-6149.

Sincerely,

{See appended electronic signature page}

Michael G. White, Ph.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE: Round 1 FDA Draft Labeling for NDA206111

36 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

White, Michael G (CDER)

To: joachim.troost@boehringer-ingelheim.com
Subject: NDA206111, Syjardy: 1st Round FDA DRAFT LABELING

Dear Dr. Troost,

Attached are the first round of FDA edits of the draft labeling for NDA 206111, Synjardy (empagliflozin and metformin hydrochloride fixed dose combination tablets). We remind you that these edits do not reflect on the final regulatory decision for this application.

Please accept all FDA edits that you agree with. The document that you return to us should only show in tracked changes (1) any new edits you have made to our prior edits and (2) any new edits from you unrelated to our prior edits. To help avoid confusion, please delete outdated comments and formatting bubbles, and leave only comment and formatting bubbles relevant to this round of labeling negotiations in the label. When you add a comment bubble, please state "BI response to FDA change or BI comment."

Because of the tight timelines we ask the you complete your review and return comments by the **close of business, Tuesday, April 28th.**

Please confirm receipt of this email, and let me know if you have any questions.

Regards,

-Mike

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

Reference ID: 3736669

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/s/

MICHAEL G WHITE
04/21/2015

From: joachim.troost@boehringer-ingelheim.com
To: White, Michael G (CDER)
Subject: RE: NDA206111, Synjardy: INFORMATION REQUEST
Date: Friday, April 10, 2015 10:06:59 AM

Dear Mike,

Thanks for your email – receipt confirmed.

I will get back to you as soon as possible.

BR and nice WE, Joachim

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Thursday, April 09, 2015 9:17 PM
To: Troost,Dr.,Joachim (DSI) BIP-US-R
Subject: NDA206111, Synjardy: INFORMATION REQUEST

Dear Dr. Troost,

In reference to NDA 206111, Synjardy (empagliflozin and metformin hydrochloride) FDC tablets, we have the following request for information from the statistics review team:

> **"The primary analysis population should include both on-treatment and off-treatment measurements. In the proposed labelling, your imputation for study 1245.28 and 1245.49 were all based on the observed cases where patients were on-treatment using LOCF method.**
>
> **Please provide the statistical analyses performed on all patients regardless of early discontinuation."**

Provide this information as soon as possible or by the close of business Friday, April 17, 2015.

Let me know if you have any questions and please confirm receipt of this request. Please email me a copy as well as officially submitting the information to your application.

Regards,

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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/s/

MICHAEL G WHITE
04/10/2015

From: joachim.troost@boehringer-ingelheim.com
To: White, Michael G (CDER)
Subject: RE: NDA206111, Synjardy: CARTON & CONTAINER LABELING
Date: Thursday, March 05, 2015 1:28:09 PM

Dear Dr White,

Thanks for your email, receipt confirmed.

Thanks and kind regards,

Joachim Troost.

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Thursday, March 05, 2015 1:15 PM
To: Troost,Dr.,Joachim (DSI) BIP-US-R
Subject: NDA206111, Synjardy: CARTON & CONTAINER LABELING

Dear Dr. Troost,

We have the following comments and recommendations from the Division of Medication Error Prevention and Analysis (DMEPA) pertaining to your carton and container labels for NDA 206111, Synjardy, submitted on January 22, 2015.

Please note that we may have further comments later on but wanted to send what we have as of now.

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. DMEPA recommends the following be implemented prior to the approval of this NDA:

A. Container Label and Carton Labeling

a. **The established name is ½ the size of the proprietary name, but lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).**

b. **Consider stating numbers greater than or equal to 1,000 with a comma to prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000".[1,2]**

B. Container Label and Carton Labeling

a. **Revise the box colors of the strengths 5 mg/500 mg and 12.5 mg/500 mg.** (b) (4) [redacted]

b. **Revise the box colors of the strengths 5 mg/1000 mg and 12.5 mg/1000 mg.** (b) (4) [redacted]

[1] **Food and Drug Administration. Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf .**

[2] **ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations**

Please resubmit any updated labeling with applicable changes. Let me know if you have any questions and please confirm receipt of this email.

Regards,
-Mike

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

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/s/

MICHAEL G WHITE
03/05/2015

From: joachim.troost@boehringer-ingelheim.com
To: White, Michael G (CDER)
Subject: RE: NDA206111, Synjardy: INFORMATION REQUEST
Date: Wednesday, March 04, 2015 4:13:47 PM

Dear Dr White,

Thanks for your email and we will get back to you as soon as possible.

Kind regards,

Joachim Troost.

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Wednesday, March 04, 2015 3:18 PM
To: Troost,Dr.,Joachim (DSI) BIP-US-R
Subject: NDA206111, Synjardy: INFORMATION REQUEST

Dear Dr. Troost,

In reference to NDA 206111, Synjardy (empagliflozin and metformin hydrochloride) FDC tablets, we have the following request for information from the statistics review team:

> **"Please submit the sas program on analysis of the occurrence of confirmed hypoglycaemic AE for study 1245.28."**

Provide this information by close of business Wednesday, March 11, 2015.

Let me know if you have any questions and please confirm receipt of this request. Please email me a copy as well as officially submitting the information to your application.

Regards,

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

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/s/

MICHAEL G WHITE
03/04/2015

From: joachim.troost@boehringer-ingelheim.com
To: White, Michael G (CDER)
Subject: RE: NDA206111, Synjardy: INFORMATION REQUEST
Date: Tuesday, February 24, 2015 2:41:38 PM

Dear Dr White,

Thanks for your email. We will get back to you as soon as possible.

Thanks and kind regards,

Joachim Troost.

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Tuesday, February 24, 2015 2:24 PM
To: Troost,Dr.,Joachim (DSI) BIP-US-R
Subject: NDA206111, Synjardy: INFORMATION REQUEST

Dear Dr. Troost,

In reference to NDA 206111, Synjardy (empagliflozin and metformin hydrochloride) FDC tablets, we have the following request for information from the review team:

> **"Regarding your revised carton labeling and container label for Synjardy, there was no indication** [redacted] (b) (4) **for which you submitted labeling with the original submission.**
>
> **The revised C&C labeling did not include** [redacted] (b) (4) **"**

Provide this information by close of business Monday, March 2, 2015.

Let me know if you have any questions and please confirm receipt of this request. Please email me a copy as well as officially submitting the information to your application.

Regards,

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

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/s/

MICHAEL G WHITE
02/24/2015

From: joachim.troost@boehringer-ingelheim.com
To: White, Michael G (CDER)
Subject: RE: NDA206111, Empa+met FDC: Clinical INFORMATION REQUEST
Date: Tuesday, December 30, 2014 11:00:14 AM

Dear Dr White,

We received your request and will get back to you as soon as possible.

Thanks and kind regards,

Joachim Troost.

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Tuesday, December 30, 2014 9:44 AM
To: Troost,Dr.,Joachim (DSI) BIP-US-R
Subject: NDA206111, Empa+met FDC: Clinical INFORMATION REQUEST

Dear Dr. Troost,

In reference to NDA 206111, empagliflozin and metformin hydrochloride FDC tablets, we have the following request for information from the clinical review team:

> **"We note that the presentation of adverse events by renal function for SAF-C2 in section 5.1.6 of the Summary of Clinical Safety does not include all patients from this safety population. We request that you provide additional information on the safety of the proposed FDC product in patients with renal impairment. Specifically, we request that you present results in a similar format to Table 5.1.6: 1 of the Summary of Clinical Safety based on the following eGFR categories: > 90 ml/min/1.73 m2, 60 to < 90 ml/min/1.73 m2, < 60 ml/min/1.73 m2, 30 to < 45 ml/min/1.73 m2, and 45 to < 60 ml/min/1.73 m2."**

Provide this information by close of business **Friday, January 16, 2015**.

Let me know if you have any questions and please confirm receipt of this request. Please email me a copy as well as officially submitting the information to your application.

Regards,

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

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/s/

MICHAEL G WHITE
12/30/2014

From: joachim.troost@boehringer-ingelheim.com
To: White, Michael G (CDER)
Subject: RE: NDA206111, Empa+met FDC: Microbiology INFORMATION REQUEST
Date: Sunday, December 14, 2014 11:06:59 AM

Dear Mike,

Thanks for your email – receipt confirmed. I will get back to you as soon as possible.

Thanks and kind regards,

Joachim.

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Friday, December 12, 2014 7:59 PM
To: Troost,Dr.,Joachim (DSI) BIP-US-R
Subject: NDA206111, Empa+met FDC: Microbiology INFORMATION REQUEST

Dear Dr. Troost,

In reference to NDA 206111, empagliflozin and metformin hydrochloride FDC tablets, we have the following request for microbiology information from the review team:

You propose to perform (b) (4)

Address the following points.

1. **Identify and justify critical control points in the manufacturing process that could affect microbial load of the drug product.**

   a. Define (b) (4)

   b. Define (b) (4)

2. Describe microbiological monitoring and acceptance criteria for the critical control points that you have identified. Verify the suitability of your testing methods for your drug product. Conformance to the acceptance criteria

established for each critical control point should be documented in the batch record in accordance with 21 CFR 211.188.

3. Describe activities taken when microbiological acceptance criteria are not met at control points.

In addition to these points, address the following:

1. You should minimally perform microbial limits testing at the initial stability testing time point. Provide an updated stability schedule to reflect this testing.

If you choose to omit microbial limits testing for release, then remove the microbial limits tests and acceptance criteria from the drug product release specification. Alternatively, you may retain a microbial limits specification for product release, but testing must be performed on every lot of drug product produced.

Please submit a revised drug product release specification for whichever microbial limits testing alternative that you select.

Provide this information by close of business **Wednesday, December 30, 2014**.

Let me know if you have any questions and please confirm receipt of this request. Please email me a copy as well as officially submitting the information to your application.

Regards,

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

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/s/

MICHAEL G WHITE
12/15/2014

From: joachim.troost@boehringer-ingelheim.com
To: White, Michael G (CDER)
Subject: RE: NDA206111, Empa+met FDC: INFORMATION REQUEST
Date: Thursday, December 04, 2014 5:22:14 PM

Dear Michael,

Thanks for your email – and receipt confirmed.

I will get to you as soon as possible.

Thanks and kind regards,

Joachim.

From: White, Michael G (CDER) [mailto:Michael.White1@fda.hhs.gov]
Sent: Thursday, December 04, 2014 5:17 PM
To: Troost,Dr.,Joachim (DSI) BIP-US-R
Subject: NDA206111, Empa+met FDC: INFORMATION REQUEST

Dear Dr. Troost,

In reference to NDA 206111, empagliflozin and metformin hydrochloride FDC tablets, we have the following request for information from the review team.

"Provide SAS code utilized to create inferential analyses of the primary and key secondary efficacy endpoints for study 1245.28."

Provide this information by close of business **Wednesday, December 10, 2014**.

Let me know if you have any questions and please confirm receipt of this request. Please email me a copy as well as officially submitting the information to your application.

Regards,

Michael G. White, PhD
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6149
Fax: 301-796-9712
michael.white1@fda.hhs.gov

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/s/

MICHAEL G WHITE
12/04/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206111

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

ATTENTION: Joachim Troost, M.D.
Sr. Associate Director, Regulatory Affairs

Dear Dr. Troost:

Please refer to your New Drug Application (NDA) dated and received August 4, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Empagliflozin/Metformin Tablets, 5 mg/500 mg, [redacted] (b) (4) 5 mg/1000 mg, 12.5 mg/500 mg, [redacted] (b) (4) and 12.5 mg/1000 mg.

We also refer to:

- your correspondence, dated and received August 8, 2014, requesting review of your proposed proprietary name, Synjardy
- your October 3, 2014, amendment, received October 3, 2014, to your request for name review

We have completed our review of the proposed proprietary name, Synjardy and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your August 8, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Lyle Canida, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-1637. For any other information regarding this application, contact Patricia Madara, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
10/23/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206111

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Boehringer Ingelheim Pharmaceuticals, Inc.
Joachim Troost, M.D.
Senior Associate Director, Regulatory Affairs
900 Ridgebury Road / P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Troost:

Please refer to your New Drug Application (NDA) dated and received August 4, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for empagliflozin and metformin hydrochloride tablets.

We also refer to your amendments dated August 8 and October 3, 8, and 9, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**.

Therefore, the user fee goal date is June 4, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by approximately May 4, 2015.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

We acknowledge your request for a waiver of the requirement that the Highlights of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Patricia Madara, Regulatory Project Manager, at 301-796-1249.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PATRICIA J MADARA
10/10/2014
Signing for Dr. Guettier, Division Director

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206111

NDA ACKNOWLEDGMENT

Boehringer Ingelheim Pharmaceuticals, Inc.
Joachim Troost, M.D.
Senior Associate Director, Regulatory Affairs
900 Ridgebury Road / P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Troost:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: empagliflozin / metformin hydrochloride tablets, fixed dose combination (FDC)

Date of Application: August 4, 2014

Date of Receipt: August 4, 2014

Our Reference Number: NDA 206111

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 3, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PATRICIA J MADARA
08/12/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 117670

MEETING PRELIMINARY COMMENTS

Boehringer Ingelheim Pharmaceuticals, Inc.
Joachim Troost, M.D.
Senior Associate Director, Regulatory Affairs
PO Box 368
Ridgefield, CT 06877

Dear Dr. Troost:

Please refer to your Pre-Investigational New Drug Application (PIND) file for empagliflozin / metformin fixed dose combination (FDC) tablet.

We also refer to your November 15, 2013, correspondence, received November 15, 2013, requesting a meeting to discuss submission of a new drug application (NDA) for the empagliflozin / metformin fixed dose combination (FDC) tablet.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	PreNDA
Meeting Date and Time:	January 13, 2014
Meeting Location:	teleconference
Application Number:	PIND 117670
Product Name:	empagliflozin / metformin fixed dose combination (FDC) tablet
Indication:	as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes (b) (4)
Sponsor/Applicant Name:	Boehringer Ingelheim Pharmaceuticals

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for January 13, 2014, at between Boehringer Ingelheim Pharmaceuticals and the Division of Metabolism and Endocrinology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 Background

On February 5, 2013, Boehringer Ingelheim Pharmaceuticals opened a pre-Investigational New Drug (IND) file for empagliflozin / metformin fixed dose combination (FDC) tablets. Empagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor and is a new molecular entity (NME). Metformin hydrochloride (N,N-dimethylimidodicarbonimidic diamide hydrochloride) is a member of the biguanide class of oral antihyperglycemics and is not chemically or pharmacologically related to any other class of oral antihyperglycemic agents.

All Phase IIb/III studies of the clinical program for development of the empagliflozin / metformin FDC tablets have been performed with free combination of the individual products

and bioequivalence studies for all six intended dose strengths of the E/M FDC have been performed for bridging purposes (Studies 1276.6, (b) (4) and 1276.8). All studies were conducted under IND 102145 (empagliflozin).

Now the company is requesting a preNDA meeting to be held as a teleconference. The meeting is scheduled for January 13, 2014.

2. Discussion

2.1. Chemistry, Manufacturing and Controls

Question 1

The chemistry, manufacturing, and controls information will be organized in the ICH Common Technical Document (CTD) format in Module 3 of the NDA. An overview of the planned CMC documentation and proposed table of contents to be submitted in the NDA is provided in [Section 10.1] and in [Annex 1]. Does the Division have any comments about the general organization and/or proposed content to be included in Module 3 of the NDA?

FDA Response

We have no comment on your proposal.

2.2. Nonclinical Pharmacology

Question 2

As previously communicated, BI plans to refer to NDA 204629 for nonclinical information specifically related to empagliflozin, and to approved US labeling for relevant nonclinical information for metformin.

The nonclinical information specifically supporting concomitant administration of empagliflozin and metformin will be organized in the ICH Common Technical Document (CTD) format in Module 4 of the NDA. A proposed table of contents for Module 4 is provided in [Annex 2]. Does the Division have any comments about the general organization and/or proposed content to be included in Module 4 of the NDA?

FDA Response

In your NDA submission, please also include a Nonclinical Overview (CTD module 2.4) and a Nonclinical Summary (CTD module 2.6) applicable to the new nonclinical information supporting the empagliflozin and metformin FDC.

2.3 Clinical Pharmacology

Question 3

Does the Division concur with the proposed approach (reference briefing document) for clinical pharmacology information to be provided in the E/M FDC NDA?

Reference ID: 3434547

FDA Response

Yes, we concur with your proposed approach. Please include all relevant PK datasets and program codes along with study reports.

Question 4

Does the Division concur with the proposed approach for bridging the clinical trial formulations in efficacy/safety studies to be included in the E/M FDC NDA with the to-be-commercialized fixed dose combination tablets?

FDA Response

Yes, we concur with your proposed approach.

2.4 Clinical

Question 5

Does the Division concur that the proposed clinical data package as outlined in Table 3 is adequate to support an assessment of the efficacy and safety of concomitant administration of empagliflozin and metformin in patients with type 2 diabetes?

FDA Response

The proposed clinical data package appears to be adequate for an assessment of efficacy and safety.

Question 6

The groupings of studies to be presented in Module 2.7.3, Summary of Clinical Efficacy (SCE) as well as in the SCE Appendix for the Integrated Summary of Efficacy (ISE) are outlined in the Statistical Analysis Plan for the ISE, provided in [Annex 4]. Does the Division have any comments regarding the proposed groupings of studies proposed for the SCE/ISE and the provided Statistical Analysis Plan?

FDA Response

We do not have any comment on the proposed groupings at this time.

Question 7

The groupings of studies to be presented in Module 2.7.4, Summary of Clinical Safety (SCS) as well as in the SCS Appendix for the Integrated Summary of Safety (ISS) are outlined in the Statistical Analysis Plan for the ISS, provided in [Annex 5]. Does the Division have any comments regarding the proposed groupings of studies proposed for the SCS/ISS and the provided Statistical Analysis Plan?

FDA Response

We do not have any comment regarding the proposed safety groupings at this time. Analysis of adverse events relative to dosing time (i.e. morning vs. evening) should be performed. In addition to an overall analysis of malignancies, analysis of bladder cancer, lung cancer, and melanoma events should be performed. Additional frequency tables

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similar to what is proposed for the analysis of urinary tract infection and genital infection would be informative for other adverse events of special interest. In particular, evaluation of decreased renal function and volume depletion events by age, gender, baseline renal function, and concomitant diuretic use would be of interest.

Question 8

BI proposes to include case report forms (CRFs) and narratives for all clinical efficacy/safety study reports (Table 3) included in the E/M FDC NDA for:

- Patients who died or experienced a serious adverse event
- Patients who experienced the following adverse events of special interest
  - Biochemical cases of Hy's Law (ALT or AST ≥3x ULN with total bilirubin ≥2x ULN) and cases of ALT or AST ≥5x ULN
  - Renal failure (creatinine >/= 2x baseline and above ULN)
  - Urosepsis or acute pyelonephritis
- Patients who permanently discontinued study medication due to an adverse event.

Does the Division agree with this proposal?

FDA Response

In addition to the CRFs and narratives that you propose to include, also include CRFs and narratives for cases of bladder cancer, lung cancer, and melanoma. Additional CRFs and narratives may be requested as a result of safety concerns that may arise during our review.

Question 9

BI proposes to submit datasets as outlined below, in STDM or ADaM format, as appropriate:

- Pharmacokinetic datasets for the BA/BE studies 1276.5, .6, .7, .8, and .9 will be submitted as STDM. The following domains will be provided: DM-Demographics, EX-Exposure, DS-Disposition, PC-Pharmacokinetic Concentrations, PP- Pharmacokinetic Parameters, CO-Comment and the supplemental domains that go with these domains.
- Data tabulation datasets and analysis datasets for the clinical efficacy/safety studies included in the E/M FDC NDA (rf to Table 3) will be submitted as STDM.
- Integrated analyses for Phase 2/3 studies (rf to Table 3) will be provided as ADaM format including MedDRA version 16.1, WhoDD version 13.SEP. The ADaM datasets will contain the US laboratory units as defined in [Annex 6].

Does the Division concur with this proposal?

FDA Response

In addition to your proposed dataset format, please also submit your analysis datasets as SAS transport files (.xpt). Submit the plasma concentration dataset which includes the following variables:

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Subject, Sequence, Period, Treatment, Concentration (C1, C2, C3,…Cn), KE_FIRST, KE_LAST, Time point (T1, T2, T3,…Tn)

where KE_FIRST and KE_LAST are the first and last time points, respectively, used to estimate the elimination constant (Kel) for each subject/period. Also submit the pharmacokinetic dataset which includes the following variables:

Subject, Sequence, Period, Treatment, AUC_{0-t}, AUC_{0-inf}, Cmax, Tmax, Kel, T½.

Question 10

Does FDA have any comments to the proposed safety package proposed to be submitted as the 4-month safety update?

FDA Response

We do not have any comments on the proposed 4-month safety update at this time.

2.5 Additional FDA Comments:

For new trials, please note that the LOCF method for dealing with data missing in the primary analysis is no longer recommended by the Division since the publication of the National Academy of Sciences (NAS) 2010 report *The Prevention and Treatment of Missing Data in Clinical Trials*. The method for handling missing data in the primary analysis should discuss what assumptions went into the choice of method. The reasonableness of the assumptions should be assessed statistically. You should also define the estimand of your primary analysis. For further advice on missing data, see the National Academies of Sciences report on The Prevention and Treatment of Missing Data in Clinical Trials (NAS, 2010).

3.0 Discussion of the Content of a Complete Application

As stated in our December 6, 2013, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission. In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

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Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

4. Additional Important Information

4.1. PREA Requirements

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

4.2. Prescribing Information

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements of Prescribing Information* website including the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, regulations, related guidance documents, a sample tool illustrating the format for Highlights and Contents , and the Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

4.3. Manufacturing Facilities

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

4.4. 505(b)(2) Regulatory Pathway

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's

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interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

Reference ID: 3434547

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

Reference ID: 3434547

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/s/

PATRICIA J MADARA
01/10/2014