CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206111Orig1s000

CHEMISTRY REVIEW(S)

NDA 206111

Synjardy™
(Empagliflozin and Metformin Hydrochloride) Tablet

Boehringer Ingelheim Pharmaceuticals, Inc.

Joseph Leginus, PhD
Office of New Drug Quality Assessment
Division III, Branch VII

For the Division of
Metabolism and Endocrinology Products

CHEMISTRY REVIEW #1

Table of Contents

Chemistry Review Data Sheet

1. NDA 206111

2. REVIEW #: 1

3. REVIEW DATE: 16-Dec-2014

4. REVIEWER: Joseph Leginus, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA	04-Aug-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
Address:	900 Ridgebury Road, PO Box 368 Ridgefield, CT 06877
Representative:	Joachim Trost, MD Sr. Associate Director, Regulatory Affairs
Telephone:	203-798-5155

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Synjardy™
b) Non-Proprietary Name (INN): Empagliflozin/Metformin Hydrochloride
c) Code Name/# (ONDC only): Empagliflozin/Metformin HCl
d) Type/Submission Priority (ONDC only):

- Chem. Type: 4 (New combination)
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: This NDA is submitted as a 505(b)(2) application.

10. PHARMACOL. CATEGORY:

Empagliflozin is an inhibitor of the sodium-dependent glucose cotransporter 2 (SGLT-2), the major transporter responsible for renal glucose reabsorption; metformin is an antihyperglycemic agent in the biguanide class which acts by decreasing endogenous hepatic output of glucose by inhibition of gluconeogenesis.

11. DOSAGE FORM: Fixed Dose Tablet, Film Coated

12. STRENGTH/POTENCY:

Empagliflozin/metformin hydrochloride tablets are manufactured [redacted] (b) (4) represented as empagliflozin mg/metformin hydrochloride mg: 5 mg/500 mg, [redacted] (b) (4) [redacted] (b) (4) 5 mg/1000 mg, 12.5 mg/500 mg, [redacted] (b) (4) and 12.5 mg/1000 mg.

13. ROUTE OF ADMINISTRATION: Oral

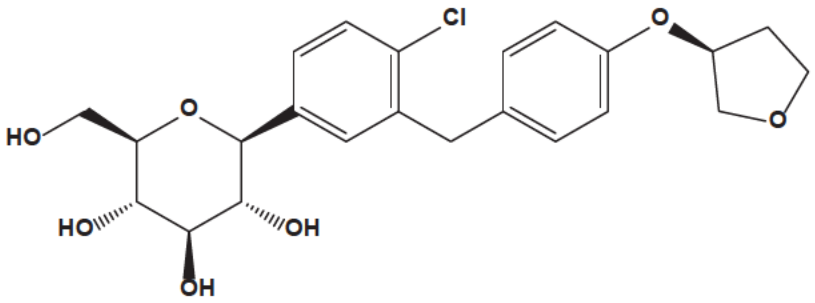
14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
__x___Not a SPOTS product

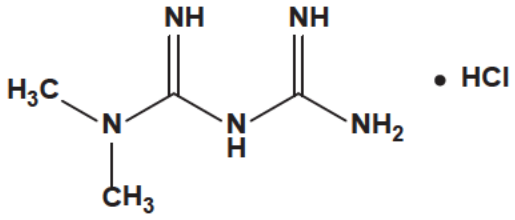
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

A. Empagliflozin
Chemical Name: D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S)
Structural Formula:



Molecular Formula: $C_{23}H_{27}ClO_7$
Molecular Weight: 450.91 g/mol

B. Metformin Hydrochloride
Chemical Name: N,N-Dimethylimidodicarbonimidic diamide hydrochloride
Structural Formula:



Molecular Formula: $C_4H_{11}N_5$ •HCl
Molecular Weight: 165.6

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed
(b) (4)	II	(b) (4)		1	Adequate	19-Aug-2014
	III			3	Adequate	14-Dec-2012
	III			3	Adequate	15-Jun-2012
	III			3	Adequate	10-Sep-2012
	III			3	Adequate	12-Mar-2013
	III			3	Adequate	17-Apr-2012
	III			3	Adequate	24-Oct-2012
	III			3	Adequate	5-Feb-2007
	III			3	Adequate	4-Sep-2013
	III			1	Adequate	12-Mar-2009

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	117670	Empagliflozin/Metformin Tablet[1]
NDA	204629	Empagliflozin Tablet[1]

[1]Applicant/Sponsor is Boehringer Ingelheim

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Facilities	Acceptable.	7-Jan-2015	N/A
Pharm/Tox	N/A. Impurity degradants are below ICH qualification thresholds.		
Biopharm	A recommendation for approval was provided.	14-Apr-2015	K. Kitchens
Methods Validation	Not required. No novel methods.		
EA	Conducted by CMC reviewer. Granting the categorical exclusion as per 21 CFR 25.31.	16-Dec-2014	Joseph Leginus
Microbiology	Recommended for approval from the standpoint of product quality microbiology.	17-Feb-2015	John Metcalfe

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 206111

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 206111 is recommended for Approval from the standpoint of chemistry, manufacturing and controls.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

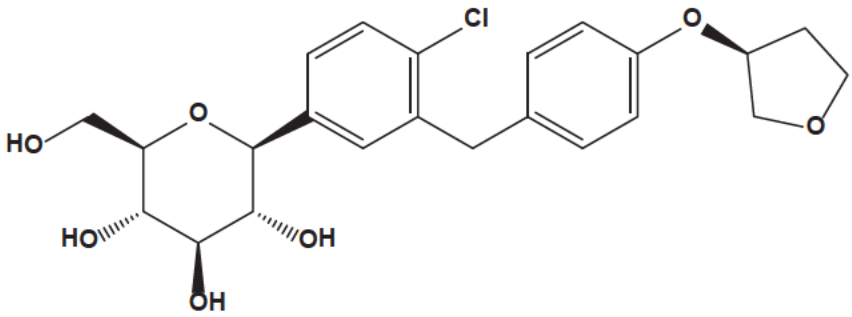
DRUG SUBSTANCES

Synjardy™ is a fixed dose combination product containing two drug substances: empagliflozin and metformin hydrochloride.

Empagliflozin

Empagliflozin is an inhibitor of the sodium-dependent glucose cotransporter 2 (SGLT-2). SGLT-2 accounts for about 90 percent of glucose reabsorption into the blood. Therefore, an SGLT-2 inhibitor such as empagliflozin may be effective at reducing blood glucose levels by blocking glucose reabsorption in the kidney and allowing glucose to be excreted in the urine.

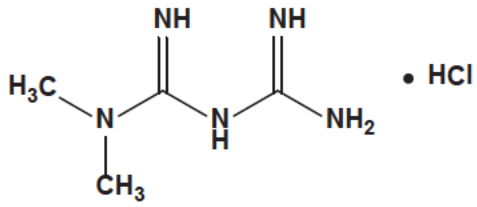
Empagliflozin is a non-hygroscopic white to yellowish powder. The molecular structure of empagliflozin is shown below.



Information for empagliflozin drug substance is provided in the Applicant's NDA 204629 for Jardiance (empagliflozin) tablet which was approved on Aug 1, 2014 and is incorporated by reference herein.

Metformin Hydrochloride

Metformin hydrochloride (HCl) is an antihyperglycemic agent in the biguanide class which acts by decreasing endogenous hepatic output of glucose by inhibition of gluconeogenesis. It is a white to off-white crystalline solid that is freely soluble in water. The structural formula of metformin HCl is:



Information for metformin HCl has been provided in [redacted] (b) (4) Type II DMF [redacted] (b) (4) and is incorporated by reference herein. DMF [redacted] (b) (4) was reviewed on Aug 19, 2014 and found to be Adequate. A Letter of Authorization to allow the Agency to refer to DMF [redacted] (b) (4) has been provided by the manufacturer and is included in the NDA.

DRUG PRODUCT

Synjardy (empagliflozin and metformin hydrochloride) tablet is formulated as a fixed-dose combination, immediate-release, film-coated tablet for oral administration containing two drug substances, empagliflozin and metformin hydrochloride (HCl) [redacted] (b) (4) tablets have been developed containing two amounts of empagliflozin (5 mg or 12.5 mg) and [redacted] (b) (4) metformin HCl (500 mg, [redacted] (b) (4) or 1000 mg). Tablets are identical in shape (oval, biconvex) but are distinguished by size, color of the film-coat and debossing.

[redacted] (b) (4) No novel excipients are used to manufacture empagliflozin/metformin HCl tablets. All excipients have compendial references and are identified in FDA's Inactive Ingredients Database as inactive ingredients found in other oral tablet products at levels higher than those described above for empagliflozin/linagliptin tablets.

Empagliflozin/metformin HCl tablets are manufactured [redacted] (b) (4)

The proposed release specifications include description (visual), identification (HPLC and UV), degradation products (HPLC), assay (HPLC), content uniformity, dissolution, and microbiological quality. Batch analysis data from 28 clinical and stability lots manufactured at commercial scale at the proposed site for commercial supply show that the drug products meet the specifications proposed.

Results from stability studies show that empagliflozin/metformin HCl tablets packaged in either HDPE bottles (b) (4) remain stable through a) 18 months for the 5 mg empagliflozin series and 24 months for the 12.5 mg empagliflozin series at the long-term storage condition of 25°C/60% RH, and b) 6 months at the accelerated condition of 40°C/75% RH. The drug product also demonstrates good stability when exposed to ambient and high humidity conditions for longer than its intended in-use period. Photostability studies indicate no effect on the product due to exposure to light. Based on these data, and following the recommendations outlined in ICH QE1 Evaluation of Stability Data, a shelf-life of 30 months is granted for empagliflozin/metformin HCl tablets 5 mg/500 mg, (b) (4) and 5 mg/1000 mg and 36 months for empagliflozin/metformin HCl tablets 12.5 mg/500 mg, (b) (4) and 12.5 mg/1000 mg when maintained at 25°C/60% RH in the proposed container closure systems. This is in agreement with the Applicant's proposed expiry period for the drug product.

Boehringer Ingelheim requested a categorical exclusion from submitting an environmental assessment for the drug product empagliflozin/metformin HCl tablets based on the regulations in 21 CFR, part 25, section 25.31(b). The request is granted.

B. Description of How the Drug Product is Intended to be Used

Synjardy combines two antihyperglycemic agents (empagliflozin and metformin hydrochloride) with complementary mechanisms of action to improve glycemic control in patients with type 2 diabetes.

Empagliflozin is an inhibitor of the sodium-dependent glucose cotransporter 2 (SGLT-2). SGLT-2 accounts for about 90 percent of glucose reabsorption into the blood. Therefore, an SGLT-2 inhibitor such as empagliflozin may be effective at reducing blood glucose levels by blocking glucose reabsorption in the kidney and allowing glucose to be excreted in the urine. The approved doses of empagliflozin alone are 10 and 25 mg once a day.

Metformin hydrochloride (HCl) is an antihyperglycemic agent in the biguanide class which acts by decreasing endogenous hepatic output of glucose by inhibition of

gluconeogenesis. Metformin hydrochloride has been approved in dose strengths of 500 mg, (b) (4) and 1000 mg for twice-daily administration.

Synjardy (empagliflozin/metformin hydrochloride) tablet is formulated as an immediate-release tablet for twice-daily oral administration. In order to adhere to its approved daily dosages, the approved levels of empagliflozin were halved to allow two doses of 5 mg and 12.5 mg each to be combined with approved daily dose levels of metformin HCl.

C. Basis for Approvability or Not-Approval Recommendation

This is a 505(b)(2) application where both empagliflozin and metformin hydrochloride, are drug substances in approved drug products. Information for empagliflozin drug substance is provided in the Applicant's NDA 204629 for Jardiance (empagliflozin) tablet and information for metformin HCl has been provided in (b) (4) Type II DMF (b) (4) which was reviewed (Aug 19, 2014) and found to be Adequate.

The drug product will be manufactured as immediate-release tablets manufactured at the Boehringer Ingelheim Pharma facility in Ingelheim am Rhein, Germany. Drug product specifications include attributes standard for this type of dosage form. Limits on degradation products are within applicable ICH thresholds. 28 clinical and stability lots have been manufactured at commercial scale at the proposed site for commercial supply with each lot meeting the specifications proposed. Stability of the drug product has been adequately established in the two container closure systems, HDPE bottles (b) (4) to grant a minimum shelf-life of 30 months when stored at controlled room temperature.

A recommendation for approval has been provided by the Biopharmaceutics Reviewer.

An acceptable recommendation has been provided by the Facilities team.

The risk from a safety perspective for this combination drug product is anticipated to be low since both drug substances in empagliflozin/metformin HCl are active ingredients in approved drug products at similar strengths: NDA 204629 for empagliflozin tablets and NDA 20357 for metformin hydrochloride tablets, respectively.

ONDQA Risk Assessment

From Initial Quality Assessment			Review Assessment		
Product Attribute/ CQA	**Factors That Can Impact the CQA**	**Risk Ranking***	**Risk Mitigation Approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****

Assay, Stability	• Formulation • Container Closure • Raw Materials • Process • Parameters • Scale/Equipment • Site	L	Empagliflozin- and metformin-related impurities in accordance with the ICH Q3B(R2).	Acceptable	None
Physical Stability (solid state)	• Formulation • Container Closure • Raw Materials • Process • Parameters • Scale/Equipment • Site	L	(b) (4)	Acceptable	(b) (4)
Content Uniformity	• Formulation • Container Closure • Raw Materials • Parameters • Scale/Equipment • Site	L		Acceptable	

Content Uniformity	(b) (4)	L	(b) (4)	Acceptable	
Microbial Limits	See Risk Assessment by the Microbiology reviewer.				
Dissolution	See Risk Assessment by the Biopharmaceutics reviewer.				
Other CQAs	--	--	--	--	--

*Risk ranking applies to product attribute/CQA
**For example, post marketing commitment, knowledge management post approval, etc.

At this time, recommendations from Biopharmaceutics regarding adequacy of dissolution testing of the drug product are pending.

III. Administrative

A. Reviewer's Signature: in Panorama

B. Endorsement Block: in Panorama

C. CC Block: in Panorama

Chemistry Assessment

I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data

S DRUG SUBSTANCES

Empagliflozin
Information for empagliflozin drug substance is provided in the Applicant's NDA 204629 for Jardiance (empagliflozin) tablet which was approved on Aug 1, 2014 and is incorporated by reference herein.

Metformin HCl
Information for metformin HCl has been provided in (b) (4) Type II DMF (b) (4) and is incorporated by reference herein. DMF (b) (4) was reviewed on Aug 19, 2014 and found to be Adequate. A Letter of Authorization to allow the Agency to refer to DMF (b) (4) has been provided by the manufacturer and is included in the NDA.

Note: (b) (4)

P DRUG PRODUCT

P.1 Description and Composition of the Drug Product

Note: The fixed dose combination formulation of empagliflozin and metformin HCl has not been used in Phase 3 clinical trials. However, bioequivalence of the fixed dose combination formulation and the combination of empagliflozin tablets in both strengths (supplied by Boehringer Ingelheim) with metformin HCl tablets (Glucophage® commercial product) has been evaluated for all strengths (see pivotal bioequivalence studies 1276.6 [5 mg / 500 mg and 12.5 mg / 500 mg], (b) (4) and 1276.8 [5 mg / 1000 mg and 12.5 mg / 1000 mg]). The Biopharmaceutics team will determine the acceptability of the pivotal bioequivalence studies.

Synjardy (empagliflozin and metformin hydrochloride) tablet is formulated as a fixed-dose combination, immediate-release, film-coated tablet for oral administration containing two drug substances, empagliflozin and metformin hydrochloride (HCl). Two (b) (4) strengths each have been developed containing two amounts of empagliflozin (5 mg or 12.5 mg) and (b) (4) metformin HCl (500 mg, (b) (4) 1000 mg). Tablet strengths are expressed as empagliflozin mg and metformin HCl mg. Tablets are identical in shape (oval, biconvex) but are distinguished by size, color of the film-coat and debossing. The (b) (4) drug products containing 5 mg of empagliflozin are presented in yellowish colors while the (b) (4) drug products containing 12.5 mg of empagliflozin are (b) (4) purple in color.

- 5 mg/500 mg (empagliflozin mg/metformin HCl mg)
  Orange-yellow; one side debossed with "S5" and the other side debossed with "500".
  (b) (4)
- 5 mg/1000 mg (empagliflozin mg/metformin HCl mg)
  Brownish yellow; one side debossed with "S5" and the other side debossed with "1000".
- 12.5 mg/500 mg (empagliflozin mg/metformin HCl mg)
  Pale brownish purple; one side debossed with "S12" and the other side debossed with "500".
  (b) (4)
- 12.5 mg/1000 mg (empagliflozin mg/metformin HCl mg)
  Dark brownish purple; one side debossed with "S12" and the other side debossed with "1000".

Empagliflozin/metformin HCl tablets are manufactured (b) (4)

The compositions of empagliflozin/metformin HCl tablets for each of the two empagliflozin series strengths (5 mg and 12.5 mg) are shown below.

Composition of Film-Coated Empagliflozin/Metformin HCl Tablets – 5 mg Empagliflozin Series

Empagliflozin/Metformin HCl Tablet Composition. 5 mg Empagliflozin Series.				
Component	Function	Reference to Standards	Strength (empagliflozin/metformin HCl)	
			5 mg/500 mg	5 mg/1000 mg
Empagliflozin	Active	Internal	5.000	5.000
Metformin HCl	Active	Internal	500.000	1000.000
Corn Starch	(b) (4)	NF		(b) (4)
Copovidone		NF		
Colloidal Silicon Dioxide		NF		
Magnesium Stearate[1]		NF		
Film Coating				
Component	Function	Reference to Standards	Strength (empagliflozin/metformin HCl)	
			5 mg/500 mg	5 mg/1000 mg
			mg/tablet	
(b) (4)	Film-Coat	N/A		(b) (4)
Total Coated Tablet Weight (mg)				(b) (4)

[1] (b) (4) [2] See Film Coat composition in table below. (b) (4)

Film Coating Composition – 5 mg Empagliflozin Series

Film Coating Agents – (b) (4) for 5 mg Empagliflozin Series				
Ingredient	Strength (empagliflozin/metformin HCl)		Function	Reference to Standard
	5 mg/ 500 mg	5 mg/ 1000 mg (b) (4)		
Hypromellose (b) (4)			(b) (4)	USP
Polyethylene Glycol 400				NF
Titanium Dioxide				USP
Ferric Oxide Yellow				NF
Talc				USP
Total Weight				

Composition of Film-Coated Empagliflozin/Metformin HCl Tablets – 12.5 mg Empagliflozin Series

Empagliflozin/Metformin HCl Tablet Composition. 12.5 mg Empagliflozin Series.				
Component	Function	Reference to Standards	Strength (empagliflozin/metformin HCl)	
			12.5 mg/ 500 mg	12.5 mg/ 1000 mg
Empagliflozin	Active	Internal	12.500	12.500
Metformin HCl	Active	Internal	500.000	1000.000
Corn Starch	(b) (4)	NF	(b) (4)	(b) (4)
Copovidone		NF		
Colloidal Silicon Dioxide		NF		
Magnesium Stearate[1]		NF		
Film Coating				
Component	Function	Reference to Standards	Strength (empagliflozin/metformin HCl)	
			12.5 mg/ 500 mg	12.5 mg/ 1000 mg
(b) (4)	Film-Coat	N/A		(b) (4)
Total Coated Tablet Weight (mg)				

[1] (b) (4) [2] See Film Coat composition in table below. (b) (4).

Film Coating Composition – 12.5 mg Empagliflozin Series

Film Coating Agents – (b) (4) for 12.5 mg Empagliflozin Series				
Ingredient	Strength (empagliflozin/metformin HCl)		Function	Reference to Standard
	12.5 mg/ 500 mg	12.5 mg/ 1000 mg		
		(b) (4)		
Hypromellose (b) (4)			(b) (4)	USP
Polyethylene Glycol 400				NF
Titanium Dioxide				USP
Ferrosoferric Oxide Black				NF
Ferric Oxide Red				NF
Talc				USP
Total Weight				

38 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

A APPENDICES

A.1 Facilities and Equipment (biotech only)

Not applicable

A.2 Adventitious Agents Safety Evaluation

There are no components in this drug product that are of human or animal origin. The magnesium stearate used in the manufacture of this product is of vegetable origin.

A.3 Novel Excipients

No novel excipients were used in the drug product formulation.

R REGIONAL INFORMATION

R1 Executed Batch Records

As agreed in a Type B meeting communication with the Agency (FDA response to PIND 117670 of April 8, 2013), the applicant has submitted copies of executed (and translated) batch records for empagliflozin/metformin HCl tablets [redacted] (b) (4) 5 mg/1000 mg (batch 202570), 12.5 mg/500 mg (batch 105938) [redacted] (b) (4) Certificates of Analysis for the drug substances and excipient batches used in the manufacture of these drug products are also provided.

These are acceptable.

R2 Comparability Protocols

No comparability protocol has been submitted.

R3 Methods Validation Package

As per 21 CFR 314.50(e), four identical sets of samples have been set aside for method validation purposes. Details of the drug product samples for method validation are provided in the table below.

Sample Identity	Batch Number	Date of Manufacture	Package Type	Quantity
Empagliflozin / Metformin Hydrochloride Film-coated Tablets, 5 mg / 500 mg	303804	(b) (4)		4 x 3 bottles 12 bottles total
(b) (4)				4 x 3 bottles 12 bottles total
Empagliflozin / Metformin Hydrochloride Film-coated Tablets, 5 mg / 1000 mg	402975			4 x 3 bottles 12 bottles total
Empagliflozin / Metformin Hydrochloride Film-coated Tablets, 12.5 mg / 500 mg	303808			4 x 3 bottles 12 bottles total
(b) (4)				4 x 3 bottles 12 bottles total
Empagliflozin / Metformin Hydrochloride Film-coated Tablets, 12.5 mg / 1000 mg	402976			4 x 3 bottles 12 bottles total

The drug product batches are representative of the to-be-marketed drug product.

Included are samples of the drug product empagliflozin/metformin HCl tablets of each dosage strengths and all reference materials required to perform testing according to the proposed specifications. A sufficient amount for three replications of the testing is provided in each set of samples. The samples will be provided to FDA laboratories upon request, along with the test results obtained on each batch (Certificate of Analysis).

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

This CMC labeling review assesses the technical information found on the labels. Refer to the DMEPA review for the evaluation of the proprietary name, colors, graphics and prominence of text.

Note: (b) (4)

1. Labeling

HDPE Bottle

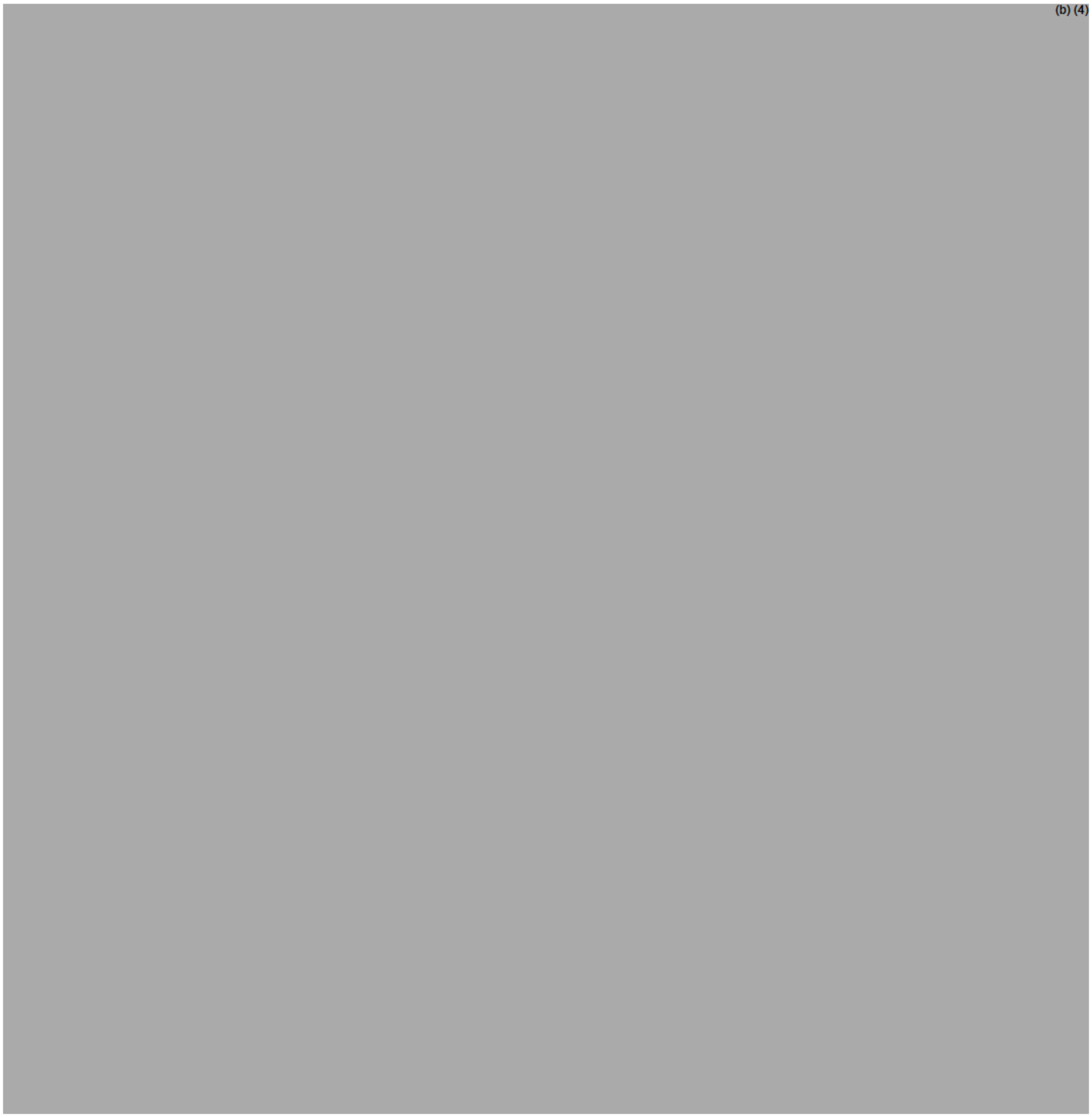
The differences on the labels of Synjardy™ (empagliflozin/metformin hydrochloride) tablets in HDPE bottles are a) strength (tablets 5 mg/500 mg, (b) (4) 5 mg/1000 mg, 12.5 mg/500 mg, (b) (4) (b) (4) and 12.5 mg/1000 mg), b) number of tablets per bottle ((b) (4) 60 or 180), c) color (corresponding to strength), and d) NDC numbers. As a representative example of empagliflozin/metformin HCl tablets in HDPE bottles, the proposed label for Synjardy™ (empagliflozin/metformin hydrochloride) tablet 5 mg/500 mg, 60 count is reproduced below.

(b) (4)

Item	Information Provided	Recommended Changes
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Synjardy™ (empagliflozin and metformin hydrochloride) Tablets	None
Dosage strength	5 mg/500 mg	None
Net contents	60 tablets	None
"Rx only" displayed prominently on the main panel	Rx only	None
NDC number (21 CFR 207.35(b)(3)(i))	0597-0159-60	None
Lot number and expiration date (21 CFR 201.17)	Lot Exp.	None

Storage conditions	Store at 25°C (77°F); excursions permitted to 15°- 30°C (59°C-86°F) [see USP Controlled Room Temperature].	None
Bar code (21CFR 201.25)	Acceptable	None
Name of manufacturer/distributor	Boehringer Ingelheim and Lilly	None

(b) (4)



(b) (4)

[redacted]

c. Labeling Text

CMC-Relevant Sections of the Package Insert.

Text	Recommended Changes
HIGHLIGHTS OF PRESCRIBING INFORMATION	
TRADENAME (empagliflozin and metformin hydrochloride) tablets, for oral use	None
DOSAGE FORMS AND STRENGTHS	
Tablets: 5 mg empagliflozin/500 mg metformin hydrochloride (b) (4) [redacted] 5 mg empagliflozin/1000 mg metformin hydrochloride 12.5 mg empagliflozin/500 mg metformin hydrochloride (b) (4) [redacted] 12.5 mg empagliflozin/1000 mg metformin hydrochloride (3)	None
FULL PRESCRIBING INFORMATION	
3. DOSAGE FORMS AND STRENGTHS	
TRADENAME is a combination of empagliflozin and metformin hydrochloride. TRADENAME is available in the following dosage forms and strengths: • 5 mg empagliflozin/500 mg metformin hydrochloride tablets are orange yellow, oval, biconvex, film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol and "S5"; the other side is debossed with "500". (b) (4) [redacted] • 5 mg empagliflozin/1000 mg metformin hydrochloride tablets are brownish yellow, oval, biconvex, film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol and "S5"; the other side is debossed with "1000".	None

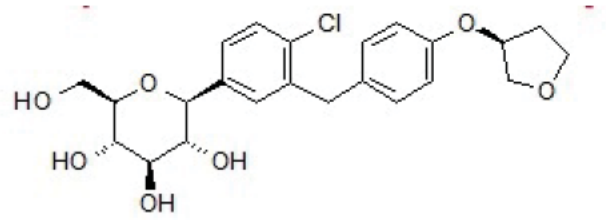
• 12.5 mg empagliflozin/500 mg metformin hydrochloride tablets are pale brownish purple, oval, biconvex, film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol and "S12"; the other side is debossed with "500".	
(b) (4)	
• 12.5 mg empagliflozin/1000 mg metformin hydrochloride tablets are dark brownish purple, oval, biconvex, film-coated tablets. One side is debossed with the Boehringer Ingelheim company symbol and "S12"; the other side is debossed with "1000".	
11. DESCRIPTION	

TRADENAME tablets contain two oral antihyperglycemic drugs used in the management of type 2 diabetes: empagliflozin and metformin hydrochloride.

Empagliflozin
Empagliflozin is an orally-active selective inhibitor of the sodium glucose co-transporter 2 (SGLT2).

The chemical name of empagliflozin is D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S)

Its molecular formula is $C_{23}H_{27}ClO_7$ and the molecular weight is 450.91 g/mol. The structural formula is:

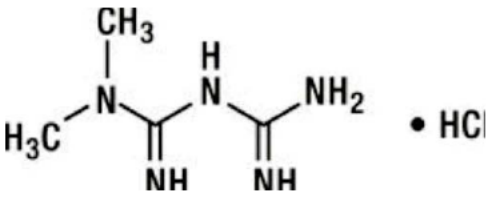


Empagliflozin is a white to yellowish, non-hygroscopic powder. It is very slightly soluble in water, sparingly soluble in methanol, slightly soluble in ethanol and acetonitrile; soluble in 50% acetonitrile/water; and practically insoluble in toluene.

Metformin hydrochloride

(b) (4)

Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is:



Metformin hydrochloride

(b) (4)

Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $C_4H_{11}N_5$•HCl and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is:

TRADENAME (b) (4)  Each film-coated tablet of TRADENAME contains the following inactive ingredients: copovidone, corn starch, colloidal silicon dioxide, magnesium stearate. Film-coating: hypromellose, titanium dioxide, polyethylene glycol 400, and yellow ferric oxide (5 mg/500 mg, (b) (4) 5 mg/1000 mg) or red ferric oxide and black ferrosoferric oxide (12.5 mg/500 mg, (b) (4) 12.5 mg/1000 mg).	*TRADENAME* TRADENAME tablets for oral administration are available in (b) (4) dosage strengths containing 5 mg empagliflozin and 500 mg metformin hydrochloride, (b) (4) 5 mg empagliflozin and 1000 mg metformin hydrochloride, 12.5 mg empagliflozin and 500 mg metformin hydrochloride, (b) (4) or 12.5 mg empagliflozin and 1000 mg metformin hydrochloride. Each film-coated tablet of TRADENAME contains the following inactive ingredients: copovidone, corn starch, colloidal silicon dioxide, magnesium stearate. Film-coating: hypromellose, titanium dioxide, polyethylene glycol 400, and yellow ferric oxide (5 mg/500 mg, (b) (4) (b) (4) 5 mg/1000 mg) or red ferric oxide and black ferrosoferric oxide (12.5 mg/500 mg, (b) (4) 12.5 mg/1000 mg).

16 HOW SUPPLIED/STORAGE AND HANDLING

TRADENAME (empagliflozin and metformin hydrochloride) tablets are available in the following strengths and packages:

Tablet Strength	Film-Coated Tablet, Color/Shape	Tablet Markings	Package Size	NDC Code
5 mg/500 mg	orange yellow, oval, biconvex	Boehringer Ingelheim company symbol and "S5" debossed on one side; the other side is debossed with "500"	Bottles of 60 Bottles of 180 (b) (4)	0597-0159-60 0597-0159-18
(b) (4)				
5 mg/1000 mg	brownish yellow, oval, biconvex	Boehringer Ingelheim company symbol and "S5" debossed on one side; the other side is debossed with "1000"	Bottles of 60 Bottles of 180 (b) (4)	0597-0175-60 0597-0175-18
12.5 mg/500 mg	pale brownish purple, oval, biconvex	Boehringer Ingelheim company symbol and "S12" debossed on one side; the other side is debossed with "500"	Bottles of 60 Bottles of 180 (b) (4)	0597-0180-60 0597-0180-18

[redacted]				
12.5 mg/1000 mg	dark brownish purple, oval, biconvex	Boehringer Ingelheim company symbol and "S12" debossed on one side; the other side is debossed with "1000"	Bottles of 60 Bottles of 180	0597-0168-60 0597-0168-18
[redacted]				

[redacted]

Storage
Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Store in a safe place out of reach of children.

B. Environmental Assessment or Claim of Categorical Exclusion

Boehringer Ingelheim is requesting a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR §25.31 for empagliflozin/metformin HCl tablets. The claim of categorical exclusion is based upon paragraphs (a) and (b) of the regulation which allows a categorical exclusion for an action which does not increase the use of the active moiety (metformin hydrochloride), or if the action increases the use of the active moiety (empagliflozin), but the estimated concentration of the substance at the point of entry, referred to as the Expected Introduction Concentration (EIC), into the aquatic environment will be below 1 part per billion (ppb).

Empagliflozin
Using the Expected Introduction Concentration (EIC) calculation (based on the July 1998 Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications) described below, the estimated EIC of empagliflozin drug substance is [redacted] µg/L ([redacted] ppb).

The formula for calculation of EIC: EIC = A x B x C x D, where
A = kg drug substance/year (projected "peak" market usage of [redacted] kg in 2018)
B = $1/1.214 \times 10^{11}$ (liters/day entering publicly owned wastewater treatment plants)

C = 1/365 (days per year)
D = 10^9 µg/kg (conversion factor)

The EIC for empagliflozin = (b) (4) µg/L ((b) (4) ppb)

Metformin Hydrochloride
Metformin hydrochloride is not a new molecular entity and is currently marketed in the United States as a) metformin hydrochloride (mono therapy), b) in combination with other active pharmaceutical ingredients, and c) as a generic drug product. It is anticipated that this combination product will be used by patients currently being treated with metformin hydrochloride either alone or in combination with other active pharmaceutical ingredients. As a result, it may be expected that patients switching to empagliflozin/metformin hydrochloride combination tablets will discontinue treatment with other drug products containing metformin hydrochloride. Therefore, empagliflozin/metformin hydrochloride combination tablet is not expected to result in a significant increase in metformin hydrochloride use.

Evaluation: The request by the Applicant for a categorical exclusion from the requirements to prepare an Environmental Assessment for empagliflozin/metformin HCl tablets based on 21 CFR §25.31 is acceptable. It is estimated that approval of empagliflozin/metformin HCl tablets a) will not increase the concentration of empagliflozin drug substance at the point of entry into the aquatic environment to a level above the threshold value of 1 ppb, and b) should not significantly increase the use of the metformin hydrochloride.

List of Deficiencies To Be Communicated

None.

Joseph Leginus -S

Digitally signed by Joseph Leginus -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Joseph Leginus -S, 0.9.2342.19200300.100.1.1=1300437624
Date: 2015.04.14 11:44:27 -04'00'

Danae D. Christodoulou -S

Digitally signed by Danae D. Christodoulou -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300132624, cn=Danae D. Christodoulou -S
Date: 2015.04.14 11:49:46 -04'00'

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 <div align="center"><FONT SIZE =2><FONT COLOR="#000080"> No active OAI / POAI Alerts are present against the facilities on selected Projects</FONT></FONT></div>

Facility Status View for NDA 206111 Original 1

[illegible]

Overall Manufacturing Inspection Recommendations for NDA 206111 Original 1

Project Name	Sponsor Name	Overall Manufacturing Inspection Recommendation	Overall Manufacturing Inspection Re-Evaluation Date	Overall Manufacturing Inspection Task Status	Overall Manufacturing Inspection Recommendation Task Completion Date
NDA 206111-Orig1-New/NDA(1)	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	Approve	09/26/2015	Complete	1/7/2015
NDA 206111-Orig1-Resubmission/Class 1 (21)	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	N/A		New	

OPF Facility Recommendations for Facilities on NDA 206111 Original 1

Project Name	FEI	DUNS	Facility Name	Profile	OPF Facility Recommendation	OPF Facility Re-Evaluation Date	OPF Facility Recommendation Task Status	OPF Facility Recommendation Task Completion Date
NDA 206111-Orig1-New/NDA(1)	[redacted]	[redacted]	[redacted]	[redacted] (b) (4)	Approve Facility	[redacted] (b) (4)	Complete	[redacted] (b) (4)
NDA 206111-Orig1-New/NDA(1)	[redacted]	[redacted]	[redacted]	[redacted]	Approve Facility	[redacted]	Complete	[redacted]
NDA 206111-Orig1-New/NDA(1)	[redacted]	[redacted]	[redacted]	[redacted]	Approve Facility	[redacted]	Complete	[redacted]
NDA 206111-Orig1-New/NDA(1)	[redacted]	[redacted]	[redacted]	[redacted]	Approve Facility	[redacted]	Complete	[redacted]
NDA 206111-Orig1-New/NDA(1)	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	Cancelled	[redacted]
NDA 206111-Orig1-New/NDA(1)	[redacted]	[redacted]	[redacted]	[redacted]	Approve Facility	[redacted]	Complete	[redacted]
NDA 206111-Orig1-New/NDA(1)	[redacted]	[redacted]	[redacted]	[redacted]	Approve Facility	[redacted]	Complete	[redacted]
NDA 206111-Orig1-New/NDA(1)	3002804556	331147644	BOEHRINGER INGELHEIM PHARMA GMBH & CORPORATION KG	TCM TABLETS, PROMPT RELEASE	Approve Facility	03/03/2016	Complete	11/14/2014
NDA 206111-Orig1-New/NDA(1)	1310650	058839929	BOEHRINGER INGELHEIM ROXANE INC	TCM TABLETS, PROMPT RELEASE	Approve Facility	04/29/2016	Complete	11/14/2014
NDA 206111-Orig1-New/NDA(1)	[redacted]	[redacted]	[redacted]	[redacted] (b) (4)	Approve Facility	[redacted] (b) (4)	Complete	[redacted] (b) (4)

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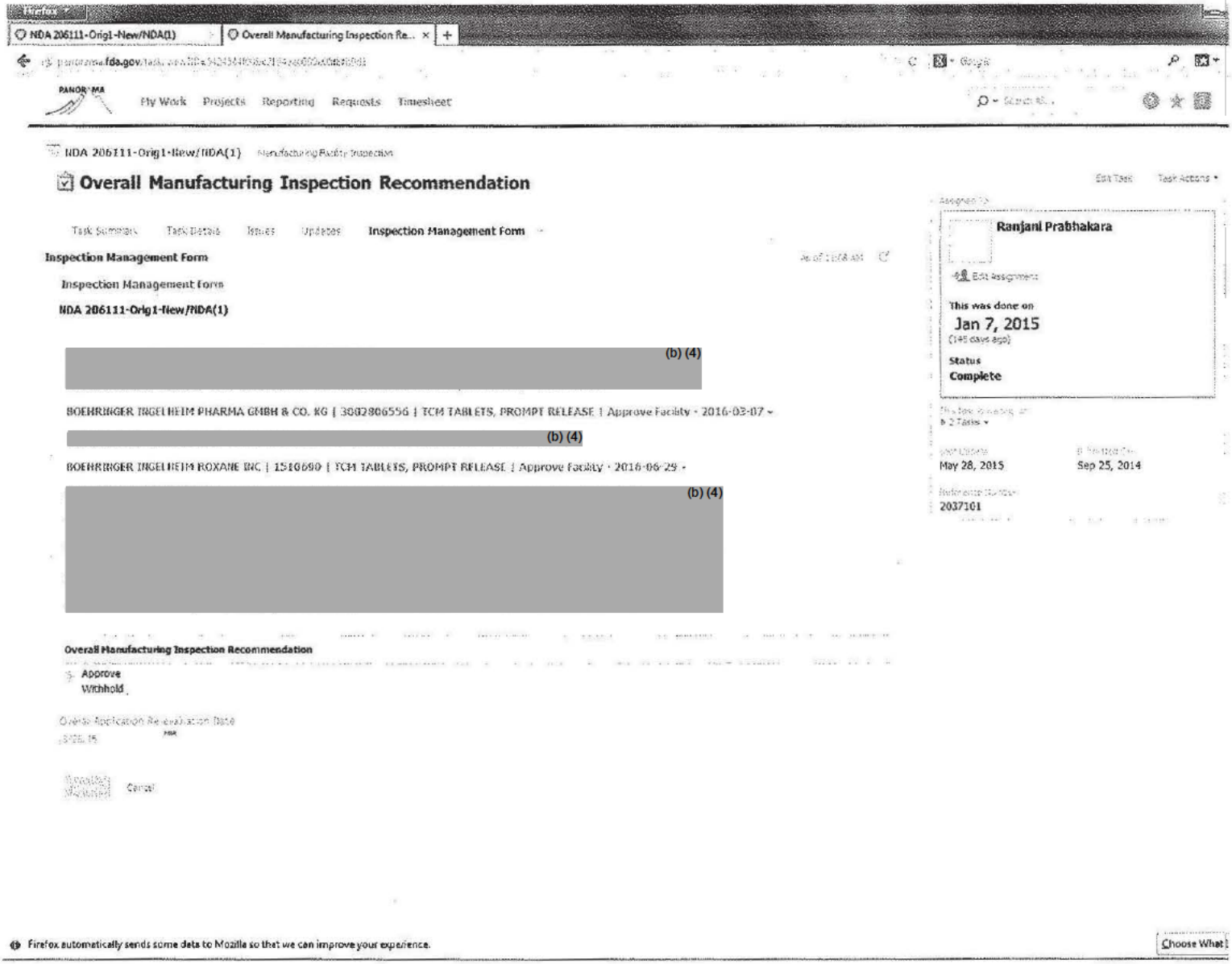

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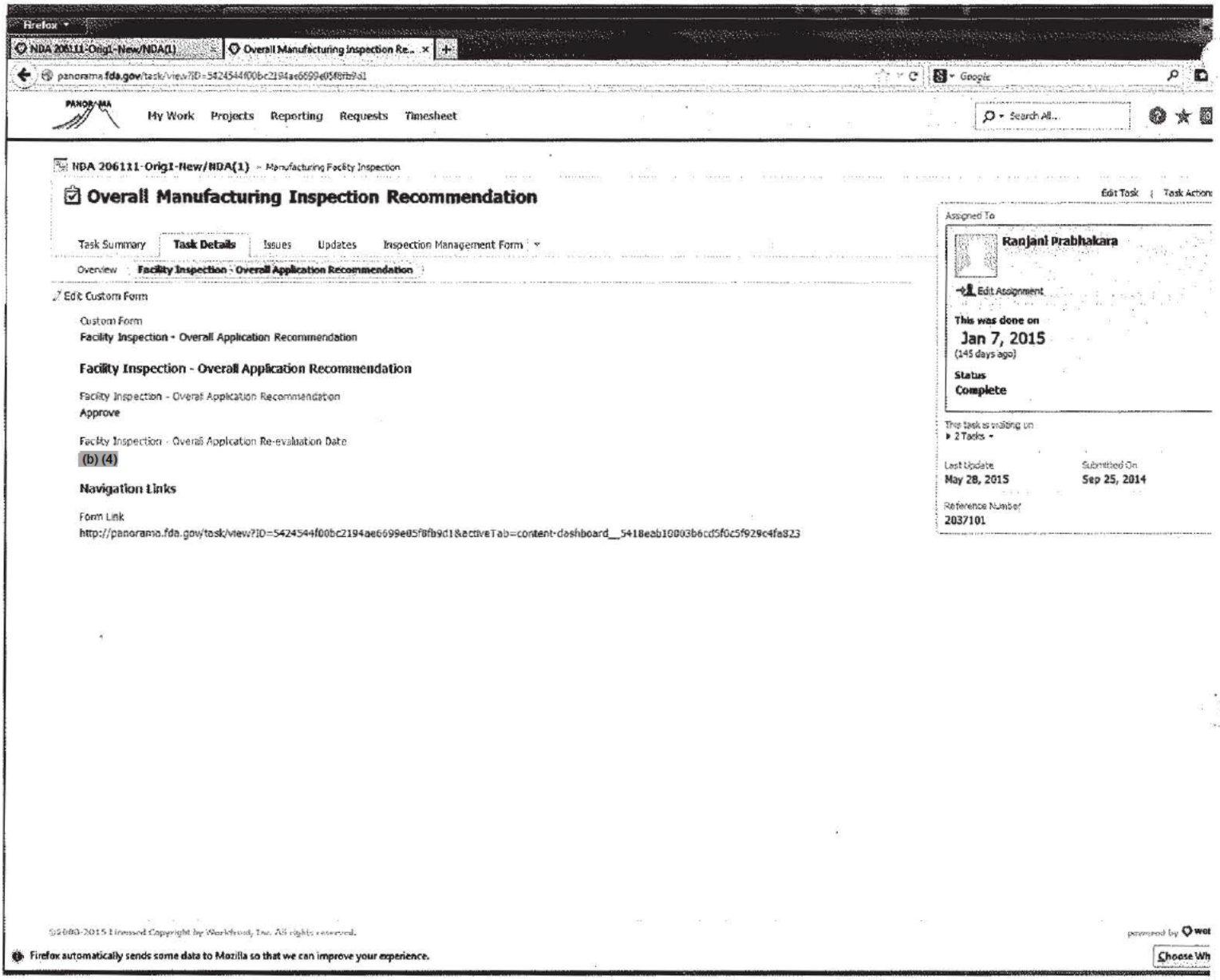

IQA and Filing Review

1. Application number: NDA 206111
2. DATES AND GOALS:

Letter Date: 04-AUG-2014 Submission Received Date : 04-AUG-2014	PDUFA Goal Date: 04-JUN-2015 (not NME application)

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Not yet finalized
Established Name (USAN):	Empagliflozin/metformin hydrochloride
Dosage Form:	Tablet, immediate release
Route of Administration	Oral
Strength/Potency	5/500, (b) (4) 5/1000, 12.5/500, (b) (4) 12.5/1000 mg/mg empagliflozin/metformin HCl
Rx/OTC Dispensed:	Rx

4. INDICATION: Treatment of type 2 diabetes
5. DRUG SUBSTANCE STRUCTURAL FORMULA:

Empagliflozin:

The drug substance empagliflozin is a hydroxymethyl-tetrahydropyrane derivative with the chemical abstracts name D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S).
The molecular formula is $C_{23}H_{27}ClO_7$ and the molecular weight is 450.91 g/mol.

(b) (4)

The molecular structure of empagliflozin is presented in Figure 1.

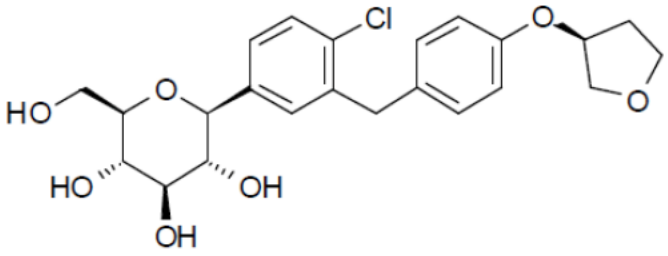

Figure 1 Molecular structure of empagliflozin

Metformin HCl:

Metformin hydrochloride (Metformin HCl; 1,1-Dimethylbiguanide hydrochloride) is a widely used antidiabetic drug. It has been monographed in all major pharmacopeias, *e.g.*, USP, Ph. Eur. and JP.

The structural formula is given in Figure 3:

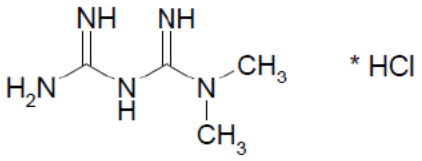

Figure 3 Molecular structure of metformin hydrochloride

The molecular weight of the hydrochloride is 165.62, and the formula is $C_4H_{11}N_5$ * HCl.

6. NAME OF APPLICANT (as indicated on Form 356h): Boehringer Ingelheim

7. SUBMISSION PROPERTIES:

Review Priority (select one)	Standard
Submission Classification (Chemical Classification Code)	4
Application Type	505(b)(2)
Breakthrough Therapy	No
Responsible Organization (Clinical Division)	Division of Metabolism and Endocrinology Products CMC Lead: Suong (Su) Tran

8. CONSULTS:

CONSULT	YES	NO	COMMENTS:
Biometrics		x	
Clinical Pharmacology		x	
Establishment Evaluation Request (EER)	x		To be sent by ONDQA-PM
Pharmacology/Toxicology		x	Degradant limits are below ICH qualification thresholds.
Methods Validation			To be determined by Primary Reviewer
Environmental Assessment		x	Categorical exclusion request to be reviewed by Primary Reviewer
CDRH		x	
Does the submission contain any of the following elements? No			
Nanotechnology	QbD Elements	PET	Other, please explain

Is a team review recommended?	Yes: reviewers for Drug Product, Biopharmaceutics, and Microbiology

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes
Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? No

Biopharmaceutics: See the Biopharmaceutics filing review attached at the end of this IQA.

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? Yes
Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? No

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective? Yes
Are there potential Microbiology review issues to be forwarded to the Applicant with the 74-Day letter? See Microbiology Filing Review in DARRTS for review issues.

Summary

This NDA is for a fixed dose combination product consisting of two approved drug substances: empagliflozin and metformin hydrochloride. The applicant of this NDA is the same applicant of the approved empagliflozin single-entity NDA 204629.

Previous quality-related meeting between ONDQA and the sponsor: None

Drug Substance

Reference is made to the approved NDA 204629 for all CMC information on the drug substance empagliflozin. The applicant is the same for both NDAs.

Reference is made to DMF (b) (4) for all CMC information on the drug substance metformin HCl. A letter of authorization from the DMF holder is included in the NDA for FDA to access the DMF. This DMF was previously reviewed in support of other applications and the reviewer will check for any new information since the last review.

Drug Product

The film-coated tablets consist of immediate release empagliflozin and immediate release metformin HCl with the strengths of 5/500, (b) (4) 5/1000, 12.5/500, (b) (4) 12.5/1000 mg/mg empagliflozin/metformin HCl.

Composition. (see the copied composition table at the end of this review) There is no novel excipient. (b) (4)

Comparability of the product used in the clinical studies, stability studies, and commercial product. All batches used in pivotal BE clinical studies 1276.6 (strengths 5/500 and 12.5/500), (b) (4) and 1276.8 (strengths 5/1000 and 12.5/1000) have the

commercial formulations and were manufactured at the commercial site/scale. The same batches (b) (4) are submitted as primary stability batches in the NDA.

Product manufacture. The manufacturing process (b) (4) for this type of dosage form (IR tablet for oral administration).

Empagliflozin / metformin hydrochloride film-coated tablets are manufactured using the following major unit operation steps:

(b) (4)

Drug product specification. (see the copied specification at the end of this review)
The drug product specification includes attributes standard for this type of dosage form and complies with ICH Q6A (e.g., hardness, enantiomeric purity). Limits on degradation products are within applicable identification and qualification ICH thresholds. Impurities and degradants were screened for mutagenicity and none was found to be positive (see the Pharmacology Toxicology review on this topic).
All dissolution-related information will be evaluated by the ONDQA Biopharmaceutics team.
The microbiology-related information (microbial limits, testing schedule, (b) (4)) will be evaluated by the OPS Microbiology team.

Container closure systems.

HDPE Bottles:			
Bottle type	**no. of film-coated tablets**	**Bottle size**	**Intended use**

(b) (4)

Safety of the product-contact packaging components is assured by compliance with USP <661> and indirect food additive regulations. Compatibility with the drug product is assured by long term and accelerated stability data.

Stability. Sufficient stability data are provided in the submission for filing. All stability were manufactured at full scale by the commercial process/site at the commercial site. Stability data at 25 °C/60% RH are provided for the 5 mg combinations with 18 months and for the 12.5 mg combinations with 24 months. Data at 40 °C/75% RH are provided for both strength combinations with 6 months. (b) (4) Additional data are provided for the open-storage studies (heat, humidity, and photostability).

Comparability protocol. None found in the application.

Initial Risk Assessment
Solid oral dosage form, immediate release

Product attribute/CQA	Factors that can impact the CQA	Probability (O)	Severity of effect (S)	Detectability (D)	FMECA RPN	Comment
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	4	2	Release (1) Stability (3)	8 24	
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	3	2	4	24	Both APIs: BCS III
Content uniformity	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	3	1	4	12	(b) (4)

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		

B. FACILITIES*				
*	**If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.**			
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**	x		
	Parameter	**Yes**	**No**	**Comment**

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		
	Parameter	**Yes**	**No**	**Comment**

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment or claim of categorical exclusion been provided?	x		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	x		Reference is made to the approved NDA 204629 (empagliflozin) and DMF (b) (4) (metformin HCl).
13.	Does the section contain identification and controls of critical steps and intermediates of the DS	x		
14.	Does the section contain information regarding the characterization of the DS?	x		
15.	Does the section contain controls for the DS?	x		
16.	Has stability data and analysis been provided for the drug substance?	x		

17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	

E.	DRUG PRODUCT (DP)			
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Has any biowaiver been requested?		x	
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	

F.	METHODS VALIDATION (MV)			
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	x		

G.	MICROBIOLOGY			
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product			Not applicable.

H.	MASTER FILES (DMF/MAF)			
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		

DMF#	TYPE	HOLDER	ITEM REFERENCED	LOA DATE
(b) (4)	II		(b) (4)	11-NOV-2013
	III			11-JAN-2013
	IV			22-MAY-2013
	III			29-JUL-2010
	IV			27-FEB-2013
	III			12-FEB-2013
	III			11-JAN-2013
	III			02-JAN-2013
	III			18-DEC-2012
	III			28-OCT-2011

I.	LABELING			
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		

See appended electronic signature page}

Table 4 Composition of empagliflozin / metformin hydrochloride film-coated tablets: 5 mg empagliflozin series

			Empagliflozin / metformin hydrochloride		
			5 mg / 500 mg	(b) (4)	5 mg / 1000 mg
Ingredient	**Reference to Standards**	**Function**	**[mg/tablet]**		**[mg/tablet]**
Empagliflozin	Company standard	Drug substance	5.000		5.000
Metformin hydrochloride	USP	Drug substance	500.000		1000.000
Corn starch	NF				(b) (4)
Copovidone	NF				
Colloidal silicon dioxide	NF				
Magnesium stearate	NF				
					(b) (4)
Total weight (film-coated tablet)					(b) (4)

(b) (4)

Table 5 Composition of the coating of empagliflozin / metformin hydrochloride film-coated tablets: 5 mg empagliflozin series

			Empagliflozin / metformin hydrochloride film-coated tablets		
			5 mg / 500 mg	(b) (4)	5 mg / 1000 mg
					(b) (4)
Ingredient	**Reference to standards**	**Function**	**Quantity [mg / tablet]**		
Hypromellose (b) (4)	USP				(b) (4)
Polyethylene glycol 400	NF				
Titanium dioxide	USP				
Ferric oxide, yellow	NF				
Talc	USP				
Total					

Table 6 Composition of empagliflozin / metformin hydrochloride film-coated tablets: 12.5 mg empagliflozin series

			Empagliflozin / metformin hydrochloride		
			12.5 mg/ 500 mg	(b) (4)	12.5 mg/ 1000 mg
Ingredient	**Reference to Standards**	**Function**	**[mg/tablet]**		**[mg/tablet]**
Empagliflozin	Company standard	Drug substance	12.500		12.500
Metformin hydrochloride	USP	Drug substance	500.000		1000.000
Corn starch	NF				(b) (4)
Copovidone	NF				
Colloidal silicon dioxide	NF				
Magnesium stearate	NF				
					(b) (4)
Total weight (film-coated tablet)					(b) (4)

(b) (4)

Table 7 Composition of the coating of empagliflozin / metformin hydrochloride film-coated tablets: 12.5 mg empagliflozin series

			Empagliflozin / metformin hydrochloride		
			12.5 mg/ 500 mg	(b) (4)	12.5 mg/ 1000 mg
					(b) (4)
Ingredient	**Reference to standards**	**Function**	**Quantity [mg / tablet]**		
Hypromellose (b) (4)	USP				(b) (4)
Polyethylene glycol 400	NF				
Titanium dioxide	USP				
Ferrosoferric oxide, black	NF				
Ferric oxide, red	NF				
Talc	USP				
Total					

Drug product specification:

Table 18 Proposed Specifications

Parameter	Specification	Method(s)
Description	5 mg / 500 mg: Orange yellow, oval, biconvex film-coated tablets; one side debossed with „S5“ and company symbol; the other side debossed with „500“ (b) (4)	Visual
	5 mg / 1000 mg: Brownish yellow, oval, biconvex film-coated tablets; one side debossed with „S5“ and company symbol; the other side debossed with „1000“ 12.5 mg / 500 mg: Pale brownish purple, oval, biconvex film-coated tablets; one side debossed with „S12“ and company symbol; the other side debossed with „500“ (b) (4)	
	12.5 mg / 1000 mg: Dark brownish purple, oval, biconvex film-coated tablets; one side debossed with „S12“ and company symbol; the other side debossed with „1000“	

Cont'd on next page

Parameter	Specification	Method(s)
Identification of empagliflozin	Retention time and UV spectrum obtained with the test solution must correspond to that of empagliflozin standard solution.	HPLC-UV (reversed phase column; (b) (4)
Identification of metformin hydrochloride	Retention time and UV spectrum obtained with the test solution must correspond to that of metformin hydrochloride standard solution.	HPLC-UV (b) (4). (b) (4)
Degradation of empagliflozin	(b) (4) ≤ (b) (4)% Any unspecified degradation product: ≤ % Total degradation products: ≤ %	HPLC-UV (same system as for identification of empagliflozin)
Degradation of metformin hydrochloride	Any unspecified degradation product: ≤ (b) (4)% Total degradation products: ≤ %	HPLC-UV (same system as for identification of metformin hydrochloride)
Assay of empagliflozin	(b) (4) % of stated content	HPLC-UV (same system as for identification of empagliflozin)
Assay of metformin hydrochloride	(b) (4) % of stated content	HPLC-UV (same system as for identification of metformin hydrochloride)
Dissolution: empagliflozin metformin hydrochloride	 Q = (b) (4)% at 20 min Q = (b) (4)% at 20 min	USP <711>, apparatus 2: Paddle method, 900 mL of phosphate buffer pH 6.8 at 37 °C and 50 rpm, quantification by HPLC with UV detection at 224 nm quantification by HPLC with UV detection at 218 nm
Uniformity of dosage units: Content uniformity of empagliflozin Mass variation of metformin hydrochloride	 Complies with USP Complies with USP	 HPLC-UV (reversed phase column; (b) (4). (b) (4)) Weighing
Microbiology	Total aerobic microbial count/g: ≤ (b) (4) cfu Total combined yeasts/molds count/g: ≤ cfu Escherichia coli/g: absent	Standard test USP *Tested on one batch per year at release*

Empagliflozin drug substance specification:

Table 3 Specification and analytical procedures for empagliflozin drug substance

Test Parameter	Acceptance Criterion	Analytical Procedure
Appearance	White to yellowish powder	Visual
Identification		
IR spectrum	The frequency and relative intensity of the absorption peaks in the sample spectrum correspond to those in the reference spectrum.	IR spectroscopy (b) (4)
HPLC retention time	The retention time of the principal component obtained with the test sample corresponds to the retention time obtained with the current reference substance (delta RT ≤ (b) (4) min).	Liquid chromatography
(b) (4)	(b) (4) %	Liquid chromatography
Any unspecified impurity	%	
Total impurities	%	
(b) (4)	(b) (4) %	(b) (4) liquid chromatography
Residual solvents (b) (4)	(b) (4) ppm (b) (4) ppm	Gas chromatography
(b) (4)	(b) (4) %	Weighing
Water content	%	Biamperometric Karl Fischer titration
Assay	(b) (4) %	Liquid chromatography
Particle size x_{90}	(b) (4) µm	Laser diffraction

Metformin HCl drug substance specification:

Boehringer Ingelheim's testing specification follows the USP monograph.

(b) (4)

The levels of the residual solvent (b) (4) and its impurities are quantified by a validated gas chromatography method.

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

NDA Number	206111
Submission Date	August 4, 2014
Product name, generic name of the active	Empagliflozin/Metformin Hydrochloride Fixed Dose Combination Tablets
Dosage form and strength	Tablets, 5+500 (b) (4) /1000 and 12.5+500 (b) (4) /1000mg
Route of Administration	Oral
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Clinical Division	Division of Metabolism and Endocrinology Products
Type of Submission	NDA 505(b)(2)
Biopharmaceutics Reviewer	Kelly M. Kitchens, Ph.D.
Biopharmaceutics Team Leader	Tapash Ghosh, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS
A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING

	Parameter	Yes	No	Comment
34.	Does the application contain dissolution data?	X		Module 2.3.P.2.2.3 Physicochemical Properties Module 3.2.P.2.3.2 Pharmaceutical Development
35.	Is the dissolution test part of the DP specifications?	X		Module 3.2.P.5.1 Specifications Empagliflozin: Q= (b) (4) % at 20 minutes Metformin HCl: Q= (b) (4) % at 20 minutes
36.	Does the application contain data to support the proposed dissolution acceptance criteria	X		Module 3.2.P.5.6 Justification of Dissolution Specifications
37.	Does the application contain the dissolution method development report?	X		Module 3.2.P.5.6 Justification of Dissolution Specifications
38.	Does the application contain data on the discriminating ability of the dissolution method	X		Module 3.2.P.5.6 Justification of Dissolution Specifications
39.	Is there a validation package for the analytical method and dissolution methodology?	X		Module 3.2.P.5.3 Validation of Analytical Procedures
40.	Does the application include a biowaiver request?		X	
41.	Does the application include an IVIVC model?		X	

42.	Is information such as BCS classification mentioned, and supportive data provided?		X	
43.	Is information on mixing the product with foods or liquids included?		X	
44.	Is there any in *vivo* BA or BE information in the submission?	X		Module 5.3.1.2 Comparative BA and BE Study Reports There are 4 BA/BE studies in this submission: 1276.5 – reviewed by OCP 1276.6 – reviewed by Biopharm (b) (4) 1276.8 – reviewed by Biopharm
45.	Does the application include in *vitro* alcohol interaction studies?		X	

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
46.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		
47.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			N/A
48.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			N/A
49.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		X	

BIOPHARMACEUTICS GENERAL SUMMARY:

Empagliflozin is the subject of NDA 204629, resubmitted on June 2, 2014 and approved in August 2014. Metformin was approved for patients with type 2 diabetes in March 1995, subject of NDA 020357. The Applicant for the current NDA developed empagliflozin (BI 10773) and metformin hydrochloride fixed dose combination (FDC) tablets to improve glycemic control in adults with type 2 diabetes mellitus (b) (4) Boehringer Ingelheim developed empagliflozin (BI 10773) and metformin hydrochloride fixed dose combination (FDC) tablets to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)

The bioavailability and bioequivalence of empagliflozin (5 mg and 12.5 mg) and metformin (500 mg, (b) (4) and 1000 mg) FDC tablets compared with individual tablets was evaluated in the following pivotal bioequivalence studies:

- **1276.5** – Relative bioavailability of a 12.5 mg BI 10773/1000 mg metformin fixed dose combination tablet compared with its mono-components and administered with and without food (an open-label, randomized, single-dose, three-way crossover, Phase I trial in healthy volunteers).
- **1276.6** – Bioequivalence of empagliflozin/metformin (500 mg) fixed dose combination tablets compared to single tablets administered together in healthy male and female volunteers under fed conditions (an open-label, randomized, single-dose, four-way crossover study).
- (b) (4)
- **1276.8** – Bioequivalence of empagliflozin/metformin fixed dose combination tablets compared to single tablets administered together in healthy male and female volunteers under fed and fasted conditions (an open-label, randomized, single-dose, crossover study).

  Reviewer's note: the metformin component is the 1000 mg strength

On September 19 2014, an Office of Scientific Investigations (OSI) consult was submitted for the clinical and analytical sites of BE studies 1276.6, (b) (4) and 1276.8.

Dissolution testing was conducted to support the empagliflozin/metformin FDC development program. Empagliflozin / metformin hydrochloride film-coated tablets are immediate release tablets (b) (4) The following dissolution methods were developed for the empagliflozin and metformin components of the drug product:

Table 1 Dissolution conditions for metformin hydrochloride tablets

Parameter	**Conditions**
Instrument	Paddle (Apparatus 2, Ph. Eur., USP, JP)
Medium	Phosphate buffer pH 6.8
Rotation speed	50 rpm (500 mg) or 75 rpm (850 mg, 1000 mg)
Volume	1000 mL
Temperature	37 ± 0.5°C
Sampling time points	10, 15, 20, 30, and 45 minutes
Determination	UV spectrophotometry at 233 nm

Table 2 Dissolution conditions for empagliflozin film-coated tablets

Parameter	**Conditions**
Instrument	Paddle (Apparatus 2, Ph. Eur., USP, JP)
Medium	Phosphate buffer pH 6.8
Rotation speed	75 rpm
Volume	900 mL
Temperature	37 ± 0.5°C
Sampling time points	10, 15, 20, 30, and 45 minutes
Determination	HPLC/UV at 224 nm

The Applicant proposed a specification of Q = (b) (4)% after 20 minutes for both drug substances.

Potential review issues to be forwarded to the Applicant for the 74-day letter:
There are no potential review issues to be forwarded to the Applicant at this time.

RECOMMENDATION:
From the ONDQA-Biopharmaceutics perspective, NDA 206111 is fileable. The ONDQA Biopharmaceutics team will further assess this NDA to determine the acceptability of the pivotal bioequivalence studies (1276.6, (b) (4) and 1276.8), and the proposed dissolution method and acceptance criteria.

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

/s/

SUONG T TRAN
09/22/2014

KELLY M KITCHENS
09/22/2014

TAPASH K GHOSH
09/22/2014

DANAE D CHRISTODOULOU
09/22/2014