

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204629Orig1s000

CHEMISTRY REVIEW(S)

NDA 204629

Jardiance[®] **(Empagliflozin) 10 and 25 mg tablets**

Boehringer Ingelheim **Pharmaceuticals, Inc.**

Chemistry, Manufacturing, and Controls **Division Director's Summary Basis of Action**

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road, Ridgefield, CT

Indication:

Empagliflozin is a selective inhibitor of sodium-dependent glucose co-transporter-2 (SGLT-2) and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes (T2DM). 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 formulated as an immediate-release tablet for once-daily oral administration at a recommended dose of 25 mg either as monotherapy or as an add-on with other oral antidiabetic treatments or insulin.

The drug substance, empagliflozin, is a New Molecular Entity but not first in a class.

Presentation:

Empagliflozin tablets are available in 30-, 90- (b) (4) bottles and blister configurations of 30 tablets/carton (3cards x 10 tablets). Physician samples of 7 tablets are available in a bottle or a blister card configuration.

EER Status: Recommendation: **All acceptable as of June 11, 2014.**

A "Withhold" recommendation was issued on February 26, 2014 by the Office of Compliance for the drug substance manufacturer, Boehringer Ingelheim, Rheinland-Pfalz, Germany. As a result, a Complete Response action was taken on March 4, 2014 until resolution of deficiencies. Inspection of the facility for general GMPs during February 27 through March 3, 2014 and review of the facility resolved the GMP issues.

Consults – CMC related reviews:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending.		
Pharm/Toxicology	Proposed limits for impurities in drug substance and drug product specifications are acceptable.	23-Aug-2013	Mukesh Summan
Biopharmaceutics	Recommended for Approval.	4-Nov-2013	Houda Mahayni
Methods Validation	Not required. No novel methods.		
EA	Conducted by CMC reviewer. Granting the categorical exclusion as per 21 CFR 25.31(b).	10-Sep-2013	Joseph Leginus
Microbiology	Not required. Solid oral dosage form.		

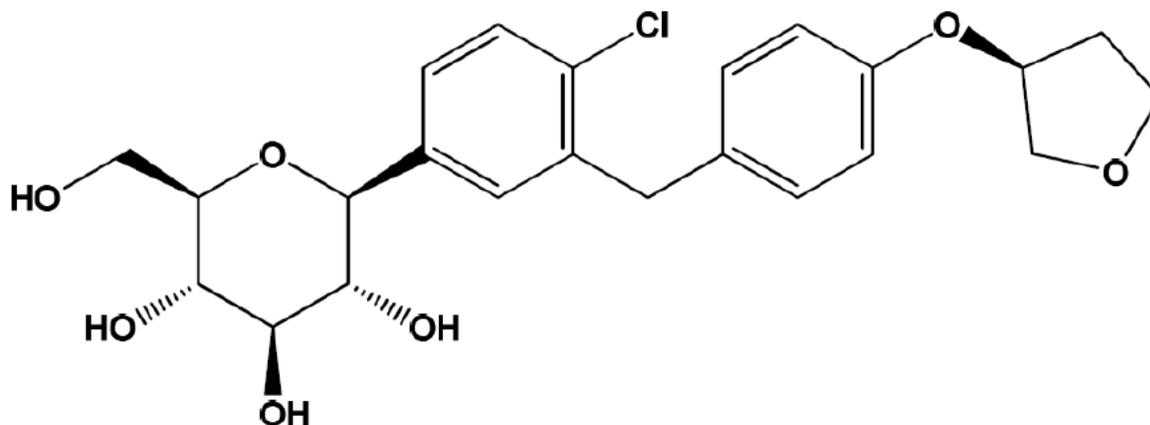
Background:

Empagliflozin, immediate release, coated tablets are manufactured in 2 strengths. The applicant is proposing to commercialize the 25 mg strength. The application includes CMC and clinical data for both strengths. The CMC review by Dr. Joe Leginus assessed both strengths. The 10 mg tablets are pale yellow, round, biconvex, bevel-edged, film-coated tablets. The 25 mg tablets are pale yellow, oval, biconvex, film-coated tablets. The two strength tablets are formulated with the same excipients (b) (4). The tablet (b) (4) includes common pharmaceutical excipients, USP grade: lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose, croscarmellose sodium, colloidal anhydrous silica, and magnesium stearate. The film coat (b) (4) consists of hypromellose (b) (4), titanium dioxide, talc (b) (4). All excipients are identified in FDA's Inactive Ingredients Guide as inactive ingredients found in other oral tablet products at levels higher than those in the current product. Empagliflozin tablets are manufactured (b) (4). Tablets are packaged in a) high density polyethylene plastic bottles (b) (4) containing 30, 90 (b) (4) tablets, and b) aluminum (b) (4) blisters containing 10 tablets. 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 29 clinical 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 tablets packaged in either HDPE bottles or blister packs remain stable through a) 24 months at the long-term storage condition of 25°C/60% RH, and b) 6 months at the accelerated condition of 40°C/75% RH. 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, ashelf-lifeof 36 months is granted for empagliflozin tablets.

Drug product: Satisfactory.

Empagliflozin drug substance has a Chemical Abstracts' name of D-glucitol, 1,5- anhydro-1-C-[4-chloro-3-[[4-[[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S). Its molecular formula is C₂₃H₂₇ClO₇ and the molecular weight is 450.91 g/mol. Empagliflozin has six chiral centers with four

found in the sugar moiety of the molecule (b) (4). Empagliflozin has an S-configuration at the chiral center where the sugar moiety connects to the phenyl ring and an S-configuration at the chiral center in the tetrahydrofuran moiety. The chemical structure has been determined by X-Ray crystallography and spectrophotometric techniques:



Empagliflozin is a non-hygroscopic white to yellowish powder. (b) (4)

The drug substance does not exist as a hydrate or as a solvate and no polymorphism has been observed.

The manufacture of empagliflozin is (b) (4)

The starting materials for the synthesis of empagliflozin were agreed upon with the applicant (IND 102145 amendment of April 11, 2011).

Specifications for empagliflozin drug substance include appearance, identification by 1) IR, and 2) HPLC, assay (HPLC), organic impurities (HPLC and chiral HPLC), residual solvents (GC), water content, sulphated ash, and particle size. Descriptions of analytical methods and validation of these methods are appropriately described and justified. Information on batch analyses, reference standards and container closure system is acceptable.

24 months of stability data are available on three primary stability batches of empagliflozin stored at the proposed long term storage condition of 25°C/60% RH (b) (4). Based on acceptable stability data, and following ICH Q1E Guidelines, a retest period of (4) months at 25°C/60% RH is granted for the drug substance.

Drug Substance: Satisfactory.

Labeling:

Container labels and package insert are acceptable.

Overall Conclusion:

From a CMC perspective, the application is recommended for approval.

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

/s/

DANAE D CHRISTODOULOU
07/31/2014
For Eric Duffy

MEMORANDUM

Date: 11-Jun-2014

From: Joseph Leginus, Review Chemist, Branch VII/ONDQA

To: NDA 204629 Empagliflozin Tablet

Subject: Status of Inspections of Manufacturing and Testing Sites – Acceptable.

Background:

A Withhold Recommendation was issued on 26-Feb-2014 by the Office of Compliance for the Drug Substance manufacturer, Boehringer Ingelheim, Rheinland-Pfalz, Germany. As a result, a Complete Response was taken on 4-Mar-2014 until satisfactory resolution of these deficiencies could be evidenced.

Current Status:

- On 11-Jun-2014, an Overall Compliance Recommendation of Acceptable was issued by the Office of Compliance for NDA 204629. See copy of Summary Report below.
- Biopharmaceutics has recommended approval.
- Microbiology review was not required for the solid oral dosage form.

Conclusion:

NDA 204629 is recommended for Approval from the standpoint of chemistry, manufacturing and controls.

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 204629/000	Sponsor:	BOEHRINGER PHARMS		
Org. Code:	510		900 RIDGEBURY RD		
Priority:	1		RIDGEBURY, CT 068770368		
Stamp Date:	05-MAR-2013	Brand Name:	EMPAGLIFLOZIN TABLETS		
PDUFA Date:	05-MAR-2014	Estab. Name:	EMPAGLIFLOZIN TABLETS		
Action Goal:		Generic Name:			
District Goal:	05-OCT-2013	Product Number; Dosage Form; Ingredient; Strengths	001; TABLET; EMPAGLIFLOZIN; 10MG 002; TABLET; EMPAGLIFLOZIN; 25MG		
FDA Contacts:	J. LEGINUS	Prod Qual Reviewer	(HFD-810)	3017964102	
	R. MCKNIGHT	Product Quality PM		3017961765	
	P. MADARA	Regulatory Project Mgr	(HFD-510)	3017961249	
	S. TRAN	Team Leader		3017961764	
Overall Recommendation:	ACCEPTABLE	on 11-JUN-2014	by S. IYER	(HFD-310)	3017963319
	PENDING	on 09-JUN-2014	by EES_PROD		
	WITHHOLD	on 26-FEB-2014	by S. HERTZ	(HFD-320)	3017963203

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

/s/

JOSEPH LEGINUS
06/11/2014

MEMORANDUM

Date: 26-Feb-2014
From: Joseph Leginus, Review Chemist, Branch VII/ONDQA
To: NDA 204629 Empagliflozin Tablet
Subject: Status of Inspections of Manufacturing and Testing Sites

Background:

On 6-Nov-2013, Chemistry Review #2 of NDA 204629 was completed. From a CMC perspective, the applicant provided adequate responses to each of the 4 deficiency comments outlined in the CMC IR letter dated 16-Sep-2013. However, The EER for the NDA was pending.

Current Status:

- A Withhold Recommendation was issued on 26-Feb-2014 by the Office of Compliance for the Drug Substance manufacturer, Boehringer Ingelheim, Rheinland-Pfalz, Germany. See copy of Summary Report below.
- Biopharmaceutics has recommended approval.
- Microbiology review not required for the solid oral dosage form.

Conclusion:

From a CMC perspective, the recommendation for NDA 204629 continues to be for Approval pending an acceptable cGMP recommendation from the Office of Compliance.

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment:	CFN: 9610492	FEI: 3002806556
	BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG BINGER STREET 173 INGELHEIM AM RHEIN, RHEINLAND-PFALZ, GERMANY	
DMF No:		AADA:
Responsibilities:	DRUG SUBSTANCE MANUFACTURER FINISHED DOSAGE MANUFACTURER	
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	OAI Status: POTENTIAL OAI
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	26-FEB-2014	
Decision:	WITHHOLD	
Reason:	DISTRICT RECOMMENDATION	
Profile:	TABLETS, PROMPT RELEASE	OAI Status: POTENTIAL OAI
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	26-FEB-2014	
Decision:	WITHHOLD	
Reason:	DISTRICT RECOMMENDATION	

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

/s/

JOSEPH LEGINUS
02/26/2014

DANAE D CHRISTODOULOU
03/03/2014

NDA 204629**Jardiance®
(empagliflozin) 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 #2**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s).....	7
B. Description of How the Drug Product is Intended to be Used.....	10
C. Basis for Approvability or Not-Approval Recommendation.....	10
III. Administrative.....	11
A. Reviewer's Signature: in DAARTS.....	11
B. Endorsement Block: in DAARTS.....	11
C. CC Block: in DAARTS.....	11
Chemistry Assessment	12

Chemistry Review Data Sheet

1. NDA 204629
2. REVIEW #: 2
3. REVIEW DATE: 6-Nov-2013
4. REVIEWER: Joseph Leginus, PhD
5. PREVIOUS DOCUMENTS:

Previous Documents

Original NDA

Document Date

5-Mar-2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

NDA Amendment

Document Date

1-Oct-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Boehringer Ingelheim Pharmaceuticals, Inc
Address:	900 Ridgebury Road, PO Box 368 Ridgefield, CT 06877
Representative:	Daniel Coleman, PhD, Sr. Associate Director, Regulatory Affairs
Telephone:	203-798-5081

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Jardiance®
- b) Non-Proprietary Name (INN): Empagliflozin
- c) Code Name/# (ONDC only): Laboratory Code: BI 10773; (CAS): 864070-44-0.
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: This NDA is submitted as a 505(b)(1) application.

Chemistry Review Data Sheet

10. PHARMACOL. CATEGORY:

Empagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 10 mg and 25 mg

13. ROUTE OF ADMINISTRATION: Oral

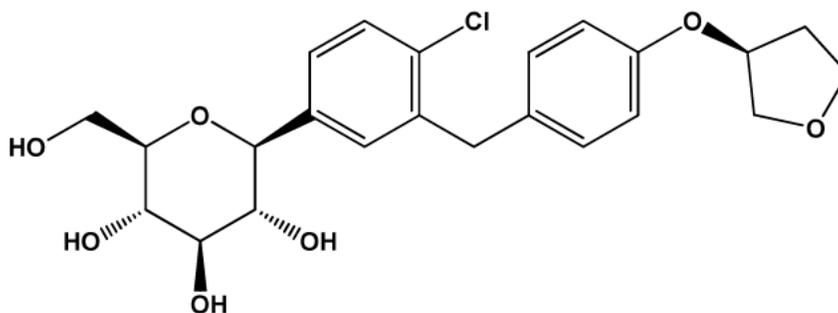
14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed
 Not a SPOTS product

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

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

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code ¹	Status ²	Date Review Completed
(b) (4)	III	(b) (4)	(b) (4)	3	Adequate	14-Dec-2012
	III			3	Adequate	26-Mar-2013
	III			3	Adequate	31-Aug-2011
	III			3	Adequate	17-May-2011
	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	5-Feb-2007

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	102145	Empagliflozin Tablet

Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending.		
Pharm/Tox	Proposed limits for impurities in drug substance and drug product specifications are acceptable.	23-Aug-2013	Mukesh Summan
Biopharmaceutics	Recommended for Approval.	4-Nov-2013	Houda Mahayni
Methods Validation	Not required. No novel methods.		
EA	Conducted by CMC reviewer. Granting the categorical exclusion as per 21 CFR 25.31(b).	10-Sep-2013	Joseph Leginus
Microbiology	Not required. Solid oral dosage form.		

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 204629

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 204629 is recommended for Approval from the standpoint of chemistry, manufacturing and controls pending acceptable cGMP recommendations.

At this time, the Office of Compliance has not issued an acceptable cGMP recommendation for 1) the drug substance manufacturer/finished dosage manufacturer (Boehringer Ingelheim Pharma GmbH & Co. KG), and 2) the drug product stability tester ([REDACTED] ^{(b) (4)}). An Overall Compliance recommendation is pending.

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

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

Not applicable.

II. Summary of Chemistry Assessments

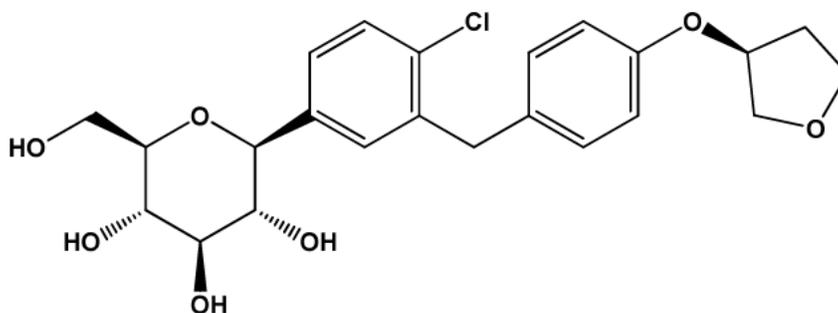
A. Description of the Drug Product(s) and Drug Substance(s)

DRUG SUBSTANCE

The drug substance, empagliflozin, is a new chemical entity (but not first in a class). Empagliflozin has a Chemical Abstracts name of D-glucitol, 1,5- anhydro-1-C-[4-chloro-3-[[4-[[[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S). Its molecular formula is C₂₃H₂₇ClO₇ and the molecular weight is 450.91 g/mol. Empagliflozin has six chiral centers with four found in the sugar moiety of the molecule [REDACTED] ^{(b) (4)} [REDACTED]. Empagliflozin has an S-configuration at the chiral center where the sugar moiety connects to the phenyl ring and an S-configuration at the chiral center in the tetrahydrofuran moiety.

Executive Summary Section

The molecular structure of empagliflozin is shown below.



Empagliflozin is a non-hygroscopic white to yellowish powder. (b) (4)

The drug substance does not exist as a hydrate or as a solvate and no polymorphism has been observed.

The structure of empagliflozin was elucidated by a variety of analytical and spectrophotometric techniques, including elemental analysis, infrared spectrophotometry, mass spectrometry, nuclear magnetic resonance spectroscopy (proton and carbon), and ultraviolet spectrophotometry.

The manufacture of empagliflozin is (b) (4)

The starting materials for the synthesis of empagliflozin were agreed upon by the Agency. See responses to the Applicant's Advice/Information Request (12/8/2009) and FDA's response (6/9/2011) to IND 102145 amendment of 4/11/2011.

Specifications for empagliflozin drug substance include appearance, identification by 1) IR, and 2) HPLC, assay (HPLC), organic impurities (HPLC and chiral HPLC), residual solvents (GC), water content, sulphated ash, and particle size. Descriptions of analytical methods and validation of these methods are appropriately described and justified. Information on batch analyses, reference standards and container closure system is acceptable.

24 months of stability data are available on three primary stability batches of empagliflozin stored at the proposed long term storage condition of 25°C/60% RH (b) (4). Based on acceptable stability data, and following ICH Q1E Guidelines, a retest period of (b) (4) months at 25°C/60% RH is granted for the drug substance when stored in the primary packaging (b) (4). This is in agreement with the applicant's proposed retest period for the drug substance.

Executive Summary Section

DRUG PRODUCT

Empagliflozin tablets (immediate release) are manufactured in 2 strengths¹. The 10 mg tablets are pale yellow, round, biconvex, bevel-edged, film-coated tablets. One side is debossed with the code "S10", the other side is debossed with the Boehringer Ingelheim company symbol. The 25 mg tablets are pale yellow, oval, biconvex, film-coated tablets. One side is debossed with the code "S25", the other side is debossed with the Boehringer Ingelheim company symbol.

The two strength tablets are formulated with the same excipients (b) (4). Excipients including lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose, croscarmellose sodium, colloidal anhydrous silica, and magnesium stearate (b) (4). The film coat (b) (4) consists of hypromellose (b) (4), titanium dioxide, talc (b) (4). No novel excipients are used to manufacture empagliflozin 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 tablets.

Empagliflozin tablets are manufactured (b) (4). Tablets are packaged in a) high density polyethylene plastic bottles (b) (4) containing 30, 90 (b) (4), and b) aluminum (b) (4) blisters containing 10 tablets.

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 29 clinical 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 tablets packaged in either HDPE bottles or blister packs remain stable through a) 24 months 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 conditions for longer than the 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 36 months is granted for empagliflozin tablets 10 mg and 25 mg when maintained at 25°C/60% in the proposed container closure systems. This is in agreement with the Applicant's proposed expiry period for the drug product.

¹ The Applicant is proposing to commercialize only the 25 mg dose strength of empagliflozin tablet, as reflected in the proposed draft labeling. The NDA submission includes CMC, clinical and safety/effectiveness for empagliflozin tablets at two strengths - 25 mg and 10 mg tablets. Both strengths have been reviewed in Chemistry Review #1.

Executive Summary Section

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

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 formulated as an immediate-release tablet for once-daily oral administration at a recommended dose of 25 mg as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus either as monotherapy or as an add-on with other oral antidiabetic treatments or insulin.

C. Basis for Approvability or Not-Approval Recommendation

This is a 505(b)(1) application where the drug substance, empagliflozin, is a New Molecular Entity (NME). IND 102145 for empagliflozin tablet was received on 4/11/2008. An End-of-Phase 2 meeting was held on 5/4/2010, a pre-NDA meeting was held on 11/27/2012 and the original NDA was submitted on 3/5/2013.

All items in the List of Deficiencies from Chemistry Review #1 have been satisfactorily addressed in the 1-Oct-2013 amendment to the original NDA. See Chemistry Assessment section below for details.

Confirmation was received from Pharmacology/Toxicology that drug substance and drug product impurities have been adequately qualified at or above the proposed limits found in the drug substance and drug product specifications, respectively.

The drug substance (empagliflozin) will be manufactured for commercial use by Boehringer Ingelheim Pharma located in Ingelheim am Rhein, Germany. The drug product, empagliflozin tablets 10 mg and 25 mg, will be manufactured as immediate release tablets and is also manufactured at the Boehringer Ingelheim Pharma facility in Ingelheim am Rhein, Germany. 29 clinical 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 and blister packs to grant a shelf-life of 36 months when stored at room temperature.

At this time, inspections of all manufacturing and testing facilities have not been completed. As a result, an overall recommendation has not yet been received from the Office of Compliance.

Executive Summary Section

III. Administrative

- A. Reviewer's Signature:** in DAARTS.
- B. Endorsement Block:** in DAARTS.
- C. CC Block:** in DAARTS.

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JOSEPH LEGINUS
11/06/2013

DANAE D CHRISTODOULOU
11/06/2013

I concur with the reviewer's conclusion and recommendation

NDA 204629**Jardiance®
(empagliflozin) 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

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	10
C. Basis for Approvability or Not-Approval Recommendation.....	10
III. Administrative.....	11
A. Reviewer's Signature: in DAARTS	11
B. Endorsement Block: in DAARTS	11
C. CC Block: in DAARTS.....	11
Chemistry Assessment	12
I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data	12
S DRUG SUBSTANCE.....	12
P DRUG PRODUCT	50
A APPENDICES	82
R REGIONAL INFORMATION	82
II. Review of Common Technical Document-Quality (Ctd-Q) Module 1	83
A. Labeling & Package Insert.....	83
B. Environmental Assessment or Claim of Categorical Exclusion	88

Chemistry Review Data Sheet

1. NDA 204629
2. REVIEW #: 1
3. REVIEW DATE: 10-Sept-2013
4. REVIEWER: Joseph Leginus, PhD
5. PREVIOUS DOCUMENTS:

Previous Documents

N/A

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original NDA

Document Date

5-Mar-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Boehringer Ingelheim Pharmaceuticals, Inc
Address:	900 Ridgebury Road, PO Box 368 Ridgefield, CT 06877
Representative:	Daniel Coleman, PhD, Sr. Associate Director, Regulatory Affairs
Telephone:	203-798-5081

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
- b) Non-Proprietary Name (INN): Empagliflozin
- c) Code Name/# (ONDC only): Laboratory Code: BI 10773; (CAS): 864070-44-0.
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: This NDA is submitted as a 505(b)(1) application.

Chemistry Review Data Sheet

10. PHARMACOL. CATEGORY:

Empagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 10 mg and 25 mg

13. ROUTE OF ADMINISTRATION: Oral

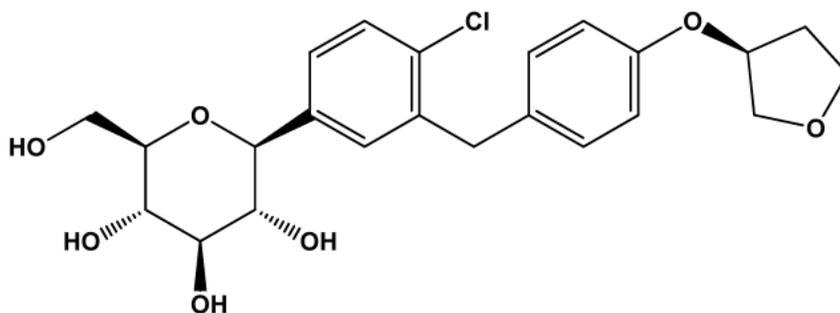
14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed
 Not a SPOTS product

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

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

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code ¹	Status ²	Date Review Completed
(b) (4)	III		(b) (4)	3	Adequate	14-Dec-2012
	III		3	Adequate	26-Mar-2013	
	III		3	Adequate	31-Aug-2011	
	III		3	Adequate	17-May-2011	
	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	5-Feb-2007	

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)

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	102145	Empagliflozin Tablet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending.		
Pharm/Tox	Proposed limits for impurities in drug substance and drug product specifications are acceptable.	23-Aug-2013	Mukesh Summan
Biopharm	Biopharmaceutics evaluation of dissolution data.	Pending	Houda Mahayni
Methods Validation	Not required. No novel methods.		
EA	Conducted by CMC reviewer. Granting the categorical exclusion as per 21 CFR 25.31(b).	10-Sep-2013	Joseph Leginus
Microbiology	Not required. Solid oral dosage form.		

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 204629

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommendation from a CMC perspective is pending satisfactory responses to the deficiencies identified in Review #1.

At this time, the Office of Compliance has not issued an acceptable cGMP recommendation for 1) the drug substance manufacturer/finished dosage manufacturer (Boehringer Ingelheim Pharma GmbH & Co. KG), and 2) the drug product stability tester [REDACTED] (b) (4). An Overall Compliance recommendation is pending.

Note: The Applicant is proposing to commercialize only the 25 mg dose strength of empagliflozin tablet, as reflected in the proposed draft labeling. However, the NDA submission includes CMC, clinical and safety/effectiveness for empagliflozin tablets at two strengths - 25 mg and 10 mg tablets. As a result, assessment of the CMC information for both strengths of empagliflozin is included in this review.

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

Not applicable.

II. Summary of Chemistry Assessments

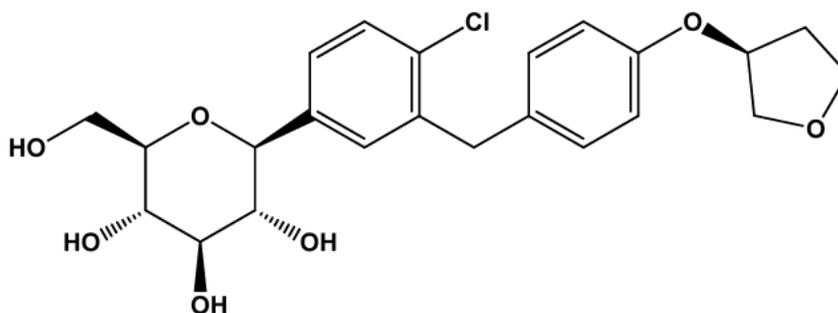
A. Description of the Drug Product(s) and Drug Substance(s)

DRUG SUBSTANCE

The drug substance, empagliflozin, is a new chemical entity (but not first in a class). Empagliflozin has a Chemical Abstracts name of 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. Empagliflozin has six chiral centers with four found in the sugar moiety of the molecule [REDACTED] (b) (4). Empagliflozin has an S-configuration at the chiral center where the sugar moiety connects to the phenyl ring and an S-configuration at the chiral center in the tetrahydrofuran moiety.

Executive Summary Section

The molecular structure of empagliflozin is shown below.



Empagliflozin is a non-hygroscopic white to yellowish powder. (b) (4)

The drug substance does not exist as a hydrate or as a solvate and no polymorphism has been observed.

The structure of empagliflozin was elucidated by a variety of analytical and spectrophotometric techniques, including elemental analysis, infrared spectrophotometry, mass spectrometry, nuclear magnetic resonance spectroscopy (proton and carbon), and ultraviolet spectrophotometry.

The manufacture of empagliflozin is (b) (4)

The starting materials for the synthesis of empagliflozin were agreed upon by the Agency. See responses to the Applicant's Advice/Information Request (12/8/2009) and FDA's response (6/9/2011) to IND 102145 amendment of 4/11/2011.

Specifications for empagliflozin drug substance include appearance, identification by 1) IR, and 2) HPLC, assay (HPLC), organic impurities (HPLC and chiral HPLC), residual solvents (GC), water content, sulphated ash, and particle size. Descriptions of analytical methods and validation of these methods are appropriately described and justified. Information on batch analyses, reference standards and container closure system is acceptable.

24 months of stability data are available on three primary stability batches of empagliflozin stored at the proposed long term storage condition of 25°C/60% RH (b) (4)

Based on acceptable stability data, and following ICH Q1E Guidelines, a retest period of (b) (4) months at 25°C/60% RH is granted for the drug substance when stored in the primary packaging (b) (4). This is in agreement with the applicant's proposed retest period for the drug substance.

Executive Summary Section

DRUG PRODUCT

Empagliflozin tablets (immediate release) are manufactured in 2 strengths¹. The 10 mg tablets are pale yellow, round, biconvex, bevel-edged, film-coated tablets. One side is debossed with the code "S10", the other side is debossed with the Boehringer Ingelheim company symbol. The 25 mg tablets are pale yellow, oval, biconvex, film-coated tablets. One side is debossed with the code "S25", the other side is debossed with the Boehringer Ingelheim company symbol.

The two strength tablets are formulated with the same excipients (b) (4). Excipients including lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose, croscarmellose sodium, colloidal anhydrous silica, and magnesium stearate (b) (4). The film coat (b) (4) consists of hypromellose (b) (4), titanium dioxide, talc (b) (4). No novel excipients are used to manufacture empagliflozin 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 tablets.

Empagliflozin tablets are manufactured (b) (4). Tablets are packaged in a) high density polyethylene plastic bottles (b) (4) containing 30, 90 (b) (4), and b) aluminum (b) (4) blisters containing 10 tablets.

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 29 clinical 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 tablets packaged in either HDPE bottles or blister packs remain stable through a) 24 months 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 conditions for longer than the 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 36 months is granted for empagliflozin tablets 10 mg and 25 mg when maintained at 25°C/60% in the proposed container closure systems. This is in agreement with the Applicant's proposed expiry period for the drug product.

¹ See previous note regarding the Applicant's proposal to commercialize only the 25 mg dose strength of empagliflozin tablet.

Executive Summary Section

Boehringer Ingelheim requested a categorical exclusion from submitting an environmental assessment for the drug product empagliflozin 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

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 formulated as an immediate-release tablet for once-daily oral administration at a recommended dose of 25 mg as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus either as monotherapy or as an add-on with other oral antidiabetic treatments or insulin.

C. Basis for Approvability or Not-Approval Recommendation

This is a 505(b)(1) application where the drug substance, empagliflozin, is a New Molecular Entity (NME). The IND for empagliflozin tablet (102145) was received on 4/11/2008. An End-of-Phase 2 meeting was held on 5/4/2010, a pre-NDA meeting was held on 11/27/2012 and the original NDA was submitted on 3/5/2013.

Confirmation was received from Pharmacology/Toxicology that drug substance and drug product impurities have been adequately qualified at or above the proposed limits found in the drug substance and drug product specifications, respectively.

The drug substance (empagliflozin) will be manufactured for commercial use by Boehringer Ingelheim Pharma located in Ingelheim am Rhein, Germany. The drug product, empagliflozin tablets 10 mg and 25 mg, will be manufactured as immediate release tablets and is also manufactured at the Boehringer Ingelheim Pharma facility in Ingelheim am Rhein, Germany. 29 clinical 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 and blister packs to grant a shelf-life of 36 months when stored at room temperature.

The recommendation from a CMC perspective is pending a) satisfactory responses to the deficiencies identified in Review #1, and b) an Acceptable recommendation from the Office of Compliance for manufacturing facilities associated with this application.

Executive Summary Section

III. Administrative

A. Reviewer's Signature: in DAARTS.

B. Endorsement Block: in DAARTS.

C. CC Block: in DAARTS.

79 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JOSEPH LEGINUS
09/10/2013

DANAE D CHRISTODOULOU
09/13/2013

I concur with the reviewer's conclusions and recommendations

ONDQA
 IQA (Initial Quality/CMC Assessment)

Division of Metabolism and Endocrinology Products

NDA: 204629

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

Stamp Date: 05-MAR-2013

PDUFA Date: 05-MAR-2014

Proposed Proprietary Name: [None indicated]

Established Name: empagliflozin

Dosage form and strength: Tablet: immediate release
 10 mg and 25 mg

Route of Administration: oral

Indications: Treatment of type 2 diabetes

Submission type: 505(b)(1) NDA

CMC Lead: Su (Suong) Tran, ONDQA

Is the Product Quality Section of the application fileable from a CMC perspective?		
Yes	No	
<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Are there potential CMC review issues to be forward to the Applicant with the 74 day letter?		
Yes	No	
<input type="checkbox"/>	<input checked="" type="checkbox"/>	

QUALITY PARTNERS	COMMENT
Biopharmaceutics	The ONDQA Biopharmaceutics Reviewer (H. Mahayni) will review all dissolution-related information.
EA	<i>The categorical exclusion claim will be assessed as part of the primary review.</i>
EES	EER sent to Compliance by ONDQA PM on 08-MAR-2013.
Methods Validation	<i>Validation may be requested by FDA labs after test methods review is finalized.</i>
Microbiology	<i>Not applicable: solid oral dosage form.</i>
Pharmacology Toxicology	Review of qualification of impurities (including genotoxicity issues).

Reference is made to IND 102145 (same sponsor).
 Reference is made to the following DMFs:

ONDQA
IQA (Initial Quality/CMC Assessment)

Has all information requested during the IND phases and at the pre-NDA meetings been included? Yes.
See the discussion in the review.

From FDA's letter dated 08-DEC-2009:

QUESTION 1 Item 10.3 of this meeting package presents a detailed justification of the two proposed starting materials in the synthesis of BI 10773. Does the FDA concur with BI's designation of starting materials for the synthesis of the BI 10773 XX drug substance?

FDA Response: *No, we do not concur. (b)(4) is acceptable as a starting material, (b)(4) is not acceptable as a starting material. (b)(4)*

QUESTION 2 Does the Agency concur with the control strategy for the proposed starting materials of the BI 10773 XX drug substance presented in Item 10.3?

FDA Response: *Yes, the testing strategy for (b)(4) is acceptable. The acceptance criteria will be reviewed as part of the NDA review.*

Revised Question 3

BI developed the final formulation for BI 10773 tablets for use in all Phase 3 trials scheduled to start in 2010 and later. In addition, trial 1245.33, a 78-week trial of BI 10773 and placebo in patients being treated with basal insulin with or without concomitant metformin and/or sulfonylurea, started in late 2009, is being carried out with the Phase 2 formulation tablets (protocol submitted to IND 102,145 October 29, 2009/SN 0023). Data indicate that BI 10773 is a BCS Class III compound (see Item 10.1).

FDA input was sought concerning bridging that could be required for the Phase 2 and Phase 3 BI 10773 tablet formulations to allow inclusion of (b)(4) in labeling.

Is it required to bridge the two formulations in this case?
(b)(4)

PRE-MEETING COMMENTS:

FDA: (b)(4). The differences in the composition for the Phase II and Phase III formulations are classified as "Components and Composition – Level 3 changes". Therefore, in-vivo bioequivalence data would be needed to bridge these formulations. Please provide your in vivo bridging proposal to the Office of Clinical Pharmacology for review and comments.

SPONSOR'S RESPONSE: Per your request, BI plans to provide the final bioequivalence protocol for review in early 3Q 2010, with a goal of initiating the trial by approximately the end of 3Q 2010. Your timely feedback would be appreciated.

MEETING DISCUSSION:

FDA clarified that the objective of this in vivo bridging is to obtain the relative exposure of the Phase 2 formulation compared to that of the Phase 3 formulation. Therefore, even though the bioequivalence study is the best approach, relative bioavailability or an appropriate population PK comparison approach can also be considered.

Drug substance (NME, not first in class)

The drug substance empagliflozin is a new chemical entity. Empagliflozin is a hydroxymethyl-tetrahydropyran 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 C₂₃H₂₇ClO₇ and the molecular weight is 450.91 g/mol. Empagliflozin has a total of six chiral centers. Four chiral centers in the sugar moiety are (b) (4) Empagliflozin has S-configuration at the chiral center in the sugar moiety in contact to the phenyl ring and S-configuration at the chiral center in the tetrahydrofuran moiety.

The molecular structure of empagliflozin is presented in [Figure 1](#).

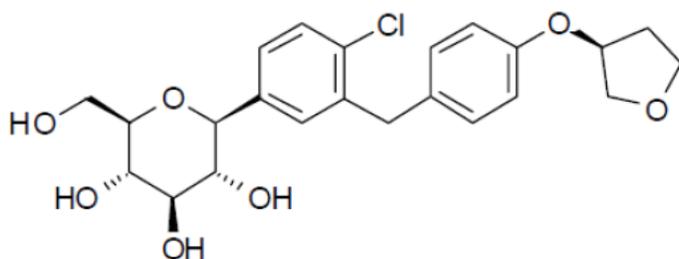


Figure 1 Molecular structure of empagliflozin

Empagliflozin is a white to yellowish powder with high solubility in aqueous media over the entire physiological pH range (> 0.4 mg/ml up to pH 7.5) according to BCS classification. (b) (4)

Empagliflozin is not hygroscopic. No polymorphism has been observed. The drug substance is neither a hydrate nor a solvate.

Physical appearance:	white to yellowish powder
Melting range:	150°C + 2°C
Dissociation constants:	not applicable (no ionisable centers)
Partition coefficient:	log P = log D (pH 7.4): 1.7
Hygroscopicity:	Not hygroscopic
Polymorphism:	Not observed
Solubility per Ph.Eur. descriptive term:	
pH 1.0	very slightly soluble
pH 4.0	very slightly soluble
pH 7.4	very slightly soluble
water	very slightly soluble
acetonitrile	slightly soluble
50 % methanol in water	slightly soluble
ethanol	slightly soluble
50% acetonitrile in water	soluble
methanol	sparingly soluble
toluene	practically insoluble

2.3.S.3.1 Elucidation of structure and other characteristics

Elucidation of structure

The structure of empagliflozin was elucidated by means of ^1H - and ^{13}C -NMR spectroscopy, mass spectrometry, UV- and IR spectroscopy as well as elemental analysis. All data are consistent with the assigned structure. The absolute structure of empagliflozin drug substance was derived by means of single X-ray crystallography. Empagliflozin has a total of six chiral centers (Figure 3). Four chiral centers in the sugar moiety are (b) (4). Empagliflozin has S-configuration at the fifth chiral center in the sugar moiety in contact to the phenyl ring and S-configuration at the chiral carbon atom in the tetrahydrofuran moiety.

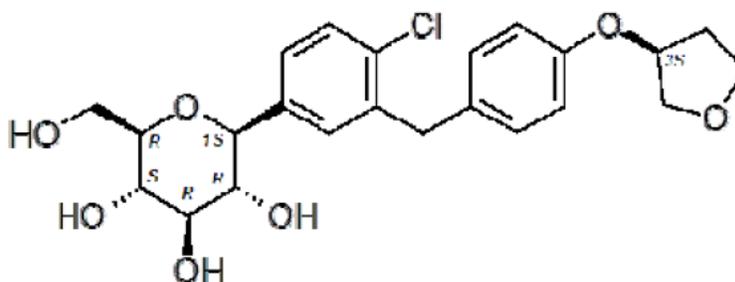


Figure 3 Configurations at chiral C-atoms of empagliflozin

Comments:

- **Starting materials.** At the end of Phase 2, FDA conveyed to the sponsor that compound (b) (4) is acceptable as a starting material but compound (b) (4) is not acceptable as a starting material. In the NDA, (b) (4) is still a starting material, and (b) (4) an intermediate, per FDA's earlier comment. Information is provided on the synthesis of (b) (4), which will be evaluated by the reviewer.
- **Manufacture of the drug substance.** The synthesis is copied on the next page. The NDA includes a summary of process changes during the IND development. Most importantly, (b) (4) was used to manufacture the drug substance and drug product primary stability batches and pivotal Phase 3 batches, and this process underwent two changes (b) (4) to yield the final commercial (b) (4). The applicant provides information to support that the two changes are deemed minor and that (b) (4) and commercial (b) (4) are comparable, which will be confirmed by the reviewer.

ONDQA
IQA (Initial Quality/CMC Assessment)

(b) (4)



Flow diagram of the synthetic process of empagliflozin

ONDQA
IQA (Initial Quality/CMC Assessment)

Drug substance specification. The drug substance specification is copied here.

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 (Attenuated total reflection or KBr)
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 ($\Delta RT \leq 0.2$ min)	Liquid chromatography
Organic impurities 1 (b) (4)	(b) (4) %	Liquid chromatography
Any unspecified impurity	%	
Total impurities	(b) (4) %	
Organic impurities 2 (b) (4)	(b) (4) %	Chiral liquid chromatography
Residual solvents (b) (4)	(b) (4) ppm (b) (4) ppm	Gas chromatography
Sulfated ash	(b) (4) %	Weighing
Water content	(b) (4) %	Biamperometric Karl Fischer titration
Assay	98.0 – 102.0 %	Liquid chromatography
Particle size (b) (4)	(b) (4) μ m	Laser diffraction

The attributes in the proposed drug substance specification are standard for this type of drug substance. No polymorph was found (only one crystalline form has been observed). Specific attributes are further discussed below. The proposed tests and acceptance criteria will be evaluated by the reviewer and finalized based on all available data (release, stability, and characterization).

- Particle size. The proposed limit is NMT (b) (4) μ m for the 90th percentile. The applicant explains that this control is adequate for a highly soluble drug substance and particle size has no effect on the manufacturability and performance of the drug product. Dissolution information in the drug product development section of the NDA shows that dissolution decreased when the 90th percentile was more than (b) (4) μ m (b) (4) μ m to be exact). The reviewer will evaluate the proposed particle size control and determine whether it is adequate as the applicant claims.
- Lack of testing for (b) (4). The drug substance specification does not include testing for residual levels of these compounds. The applicant explains that (b) (4) was below (b) (4) ppm and (b) (4) was below (b) (4) ppm in 11 consecutive

ONDQA
IQA (Initial Quality/CMC Assessment)

batches used in Phase 3 studies and in the commercial product. Both thresholds are safety limits with information provided in the Nonclinical section of the NDA. The reviewer will confirm these thresholds with the Pharmacology Toxicology team and determine whether the residual testing should be included in the drug substance specification.

- Genotoxicity. Information on the evaluation of impurities and degradants (including potential compounds) for potential genotoxicity is provided in the Nonclinical section of the NDA. The applicant concludes that there is no compound with this potential, which will be confirmed by the Pharmacology Toxicology team.
- Process impurities. There are two specified impurities, (b) (4), with limits of (b) (4)% and (b) (4)% respectively (claimed to be qualified, which will be confirmed by the Pharmacology Toxicology team) (b) (4) results from (b) (4)

Neither is a degradant.

- (b) (4)

(b) (4)

- Lack of microbial control. The applicant states (b) (4)

ONDQA
 IQA (Initial Quality/CMC Assessment)

below the USP limit of 0.60 (threshold for supporting microbial growth). Therefore, the drug substance specification does not include a microbial limits test.

Packaging and stability. Information is provided in the NDA, with reference to DMFs, for the container closure system of the drug substance. The product-contact components comply with food additive regulations, and stability batches were packaged in the proposed commercial packaging. Primary stability data include three drug substance batches manufactured at the commercial site, commercial scale, using (b) (4) (comparability with the commercial (b) (4) was already discussed, to be a review issue), 24 months at 25 °C/60% RH (b) (4). Stress and photostability studies were also conducted. The reviewer will evaluate the proposed retest period of (b) (4) months at 25 °C/60% RH.

Drug product

Table 18 Qualitative and quantitative composition of empagliflozin film-coated tablets, 10 mg and 25 mg

Ingredient	[mg / tablet] 10 mg	[mg / tablet] 25 mg	Function	Reference to Standards
(b) (4)				
Empagliflozin	10.000	25.000	Drug substance	Company standard
Lactose monohydrate	(b) (4)			NF
Microcrystalline cellulose				NF
Hydroxypropylcellulose				NF
Croscarmellose sodium				NF
Colloidal silicon dioxide				NF
Magnesium stearate				NF
(b) (4)				USP
Film-coat	(b) (4)			Company standard
				USP
Total mass of film-coated tablet	257.0	206.0		

*) Removed during processing; does not appear in the final drug product

ONDQA
 IQA (Initial Quality/CMC Assessment)

PRODUCT QUALITY
FILING REVIEW FOR NDA (ONDQA)

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*				
	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.			Small synthetic API
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> • 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 identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • 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		

ONDQA
 IQA (Initial Quality/CMC Assessment)

9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • 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) 			
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

* 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.

C. ENVIRONMENTAL ASSESSMENT				
D. drug substance/active pharmaceutical ingredient (DS/api)				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	x		
12.	Does the section contain a description of the DS manufacturing process?	X		
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	

ONDQA
 IQA (Initial Quality/CMC Assessment)

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.	Have any biowaivers 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?		x	Drug product is not sterile.
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		
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		
J. filing conclusion				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		x	

{See appended electronic signature page}

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
04/17/2013

DANAE D CHRISTODOULOU
04/17/2013

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

NDA Number	204-629
Submission Date	March 5, 2013
Product name, generic name of the active	(b) (4) (Empagliflozin)
Dosage form and strength	Film-Coated Immediate-Release Tablet, 10 mg and 25 mg
Indication	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Clinical Division	DMEP
Type of Submission	505(b)(1) NDA
Biopharmaceutics Reviewer	Houda Mahayni, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.

The following parameters from the ONDQA Quality (CMC and Biopharmaceutics) joint filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS				
<u>A. INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?	x		Empagliflozin tablets are film-coated with immediate release characteristics.
2.	Is the dissolution test part of the DP specifications?	x		The proposed dissolution acceptance criterion is Q= (b) (4) % in (b) (4) minutes
3.	Does the application contain the dissolution method development report?	x		
4.	Is there a validation package for the analytical method and dissolution methodology?	x		
5.	Does the application include a biowaiver request?		x	Trial formulation II and Final Formulation (TBM) were assessed in a relative bioavailability study (1245.51, U11-1756).
6.	Is there enough information to assess the extended release designation claim?		x	Not applicable. This is an IR formulation.
7.	Does the application include an IVIVC model?		x	Not applicable
8.	Does the application include information/data on in vitro alcohol dose-dumping potential?		x	Not applicable, as the dosage form is immediate-release.
9.	Is information such as BCS classification mentioned, and supportive data provided?	x		The Applicant claims that Empagliflozin is BCS Class III compound.

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

10.	Is information on mixing the product with foods or liquids included?		x	The dosage form to be swallowed whole.
11.	Is there any <i>in vivo</i> BA or BE information in the submission?	x		Several BA studies are included. These studies will be reviewed by OCP.
12.	Is there any design space proposed using <i>in vitro</i> release as a response variable?		X	Not applicable. This NDA does contain QbD elements, but no design space is proposed using <i>in vitro</i> release as a response variable.
13.	Is the control strategy related to <i>in vitro</i> drug release?		X	Not applicable. The Applicant does not propose a design space, nor is seeking alternative control strategies.

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
14.	IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	x		<ul style="list-style-type: none"> • The NDA is fileable from Biopharmaceutics Perspective. • The acceptability of the proposed dissolution test and proposed acceptance criterion will be a review issue.
15.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not Applicable.
16.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not Applicable.
17.	Are there any potential review issues identified?		x	
18.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	

{See appended electronic signature page}

Houda Mahayni, Ph.D.

Biopharmaceutics Reviewer

Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Angelica Dorantes, Ph.D.

Biopharmaceutics Team Leader

Office of New Drug Quality Assessment

Date

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

/s/

HOUDA MAHAYNI
04/12/2013

ANGELICA DORANTES
04/12/2013