CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212614Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 212614
Review 1

Drug Name/Dosage Form	Trijardy™ XR (empagliflozin, linagliptin, and metformin hydrochloride extended release) tablets
Strength	5 mg empagliflozin/2.5 mg linagliptin/ 1000 mg metformin HCl 10 mg empagliflozin/5 mg linagliptin/ 1000 mg metformin HCl 12.5 mg empagliflozin/2.5 mg linagliptin/ 1000 mg metformin HCl 25 mg empagliflozin/5 mg linagliptin/ 1000 mg metformin HCl
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Boehringer Ingelheim Pharmaceuticals Inc.
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original and amendments (NDA 212614)	Original submission (3/27/2019). Amendments: 5/07/19, 5/17/19, 6/07/19, 6/14/19, 6/26/19, 7/17/19, 8/05/19, 8/16/19, 8/29/19, 9/04/19, and 11/22/19	Quality modules 3, 1.14 and 1.11

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joseph Leginus	Branch II/New Drug API/ONDP
Drug Product	Elise Luong	Branch VI/Division of New Drug Products II/ Office of New Drug Products
Process/Microbiology/ Facility	Christina Capacci-Daniel	Branch II/ Inspectional Assessment/OPF
Regulatory Business Process Manager	Leeza Rahimi	Branch I/Regulatory Business Process Management I
Biopharmaceutics	Hansong Chen	Division of Biopharmaceutics/ ONDP
Application Technical Lead	Muthukumar Ramaswamy	Branch VI/Division of New Drug Products II/ONDP
Environmental Analysis (EA)	Elise Luong	Office of New Drug Products

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	Active	Adequate information in the NDA	LOA 1/12/2010
	III			Active		LOA 9/29/2014
	III			Active		LOA 3/30/2010
	III			Active		LOA 8/22/2014
	II			Adequate	6/27/19 (Dr. Leginus)	LOA 7/27/2015

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		
NDA	204,629, Jardiance® (empagliflozin) tablets 201,280 Tradjenta® (linagliptin) tablets 201,281 Jentadueto® (linagliptin/metformin hydrochloride) tablets	CMC information for empagliflozin drug substance CMC information for linagliptin drug substance CMC information for metformin HCl drug substance

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER

Executive Summary

I. Recommendations and Conclusion on Approvability

The recommendation from the Office of Pharmaceutical Quality (OPQ) for NDA 212614 is approval, which includes acceptable recommendation for the facilities listed in the application.

II. Summary of Quality Assessments

A. Product Overview

Trijardy™ XR (empagliflozin, linagliptin, and metformin hydrochloride extended - release) tablets are intended for use as an adjunct to diet and exercise to improve glycemic controls in adults with type 2 diabetes. Trijardy™ XR tablets will be available as oval shaped film-coated tablets for oral administration in 4 strengths containing:

- 5 mg empagliflozin/2.5 mg linagliptin/1000 mg metformin hydrochloride extended-release as grey oval-shaped tablets in 60ct and 180ct bottles.
- 10 mg empagliflozin/5 mg linagliptin/1000 mg metformin hydrochloride extended-release as tan oval shaped tablet in 30ct and 90ct bottles.
- 12.5 mg empagliflozin/2.5 mg linagliptin/1000 mg metformin hydrochloride extended-release as red, oval-shaped tablets in 60ct and 180ct bottles.
- 25 mg empagliflozin/5 mg linagliptin/1000 mg metformin hydrochloride extended-release as brown, oval-shaped tablets in 30ct and 90ct bottles.

Tablets are differentiated by tablet color and imprint. Trijardy™ XR tablets should to be stored in original packaging (HDPE bottles with desiccant and screw cap closure at USP controlled temperature at 25°C (77 °F) excursions permitted to 15 ℃ to 30 ℃ (59 ℉ to 86 ℉).

Proposed Indication(s) including Intended Patient Population	Intended for use as an adjunct to diet and exercise to improve glycemic controls in adults with type 2 diabetes
Duration of Treatment	*Chronic*
Maximum Daily Dose	25mg of empagliflozin, 5 mg of linagliptin and 2000mg of metformin HCl.
Alternative Methods of Administration	*Not applicable*

B. Quality Assessment Overview

Drug Substance

The applicant has referenced the following NDAs and DMF for CMC information related to drug substances used in the manufacturing of drug product: Metformin hydrochloride

(MF (b) (4) and NDA 201280), empagliflozin (204629) and linagliptin (NDA 201280). Dr. J. Leginus reviewed the drug substance information for metformin hydrochloride, empagliflozin, and linagliptin. His review concluded that the CMC information provided in the application is adequate to support the approval of this NDA.

Drug Product

The drug product is a fixed dose combination product containing a metformin HCl extended release core tablet that is coated (b) (4) .

Trijardy™ XR tablets will be available as film-coated oval shaped tablets in 4 different strengths containing:

- 5 mg empagliflozin/2.5 mg linagliptin/1000 mg metformin hydrochloride extended-release as grey oval-shaped tablets.
- 10 mg empagliflozin/5 mg linagliptin/1000 mg metformin hydrochloride extended-release as tan oval shaped tablets.
- 12.5 mg empagliflozin/2.5 mg linagliptin/1000 mg metformin hydrochloride extended-release as red, oval-shaped tablets.
- 25 mg empagliflozin/5 mg linagliptin/1000 mg metformin hydrochloride extended-release as brown, oval-shaped tablets.

Various strength tablets are differentiated by their color and imprinting on the tablet. Top line will have BI logo/number and the bottom line will have either "5/2.5" or "10/5" or "12.5/2.5" or "25/5". The tablets are packaged in either 30ct or 60ct or 90ct or 180ct HDPE bottles with desiccant and (b) (4) screw closure.

The tablet contains the following inactive ingredients: polyethylene oxide, hypromellose, and magnesium stearate, hydroxypropyl cellulose, talc, titanium dioxide, arginine, polyethylene glycol, carnauba wax, purified water, shellac glaze, n-butyl alcohol, propylene glycol, ammonium hydroxide, and isopropyl alcohol. In addition, the following (b) (4) are present in each strength tablet: ferrosoferric oxide and ferric oxide yellow (5 mg/2.5 mg/1000 mg and 25 mg/5 mg/1000 mg), ferric oxide yellow and ferric oxide red (10 mg/5 mg/1000 mg), and ferrosoferric oxide and ferric oxide red (12.5 mg/2.5 mg /1000 mg and 25 mg/5 mg/1000 mg).

With the exception of coating agents, all excipients used in the drug product are compendial grade. The components of coating agents meet compendial standards and are acceptable for intended use. With the exception of printing ink, the composition of the drug product used in clinical studies (pilot bioavailability study and pivotal bioequivalence studies) are the same. Acceptability of the final product formulation was established based on data available from BE studies and available dissolution data.

Drug product composition, excipient compatibility, batch analysis, container closure system, and stability information were reviewed by the drug product reviewer, Dr. Luong. Her review concluded that the drug product information provided in the NDA is

adequate to support the approval of the NDA. Please refer to drug product review dated 9/4/19 in panorama for details.

Trijardy™ XR tablet manufacturing process uses (b) (4) metformin extended release (ER) tablet core. The finished product is (b) (4) tablets are printed with their strength and packaged.

The applicant's control strategy for producing acceptable quality drug product is based on prior knowledge, process design, control of input materials (e.g., specifications for drug substance and excipients, and container closure components), in-process controls, and in-process tests, finished product specifications, and appropriate product packaging to ensure control of the quality of the finished product.

Dr. Christina Capacci-Daniel reviewed the manufacturing process/control information and facility compliance information. Her process review includes risk assessment for manufacturing process control and its relationship to drug product critical quality attributes. Dr. Capacci-Daniel's review concluded that the process and facilities information provided in the NDA is adequate. Please refer to process/facilities review in Panorama dated 9/26/2019. Dr. Ramaswamy also performed a risk assessment for the finished product critical quality attributes and his assessment concluded that the final quality risk is low for the proposed product (Refer to Appendix I).

The finished product specification was finalized by drug product and biopharmaceutics reviewers. The drug product is tested using validated methods for description, identity by RPHPLC/UV, assay, uniformity of dosage units (empagliflozin and linagliptin), weight variation of metformin HCl, impurities, microbial purity, arginine content water content, and dissolution. The quality attributes included in the drug product specification are in alignment with the attributes recommended for oral dosage forms. The applicant performed a risk assessment for elemental impurities per ICH Q3D and provided justification for not including routine elemental impurities testing in the product. Please refer to Dr. Luong's drug product review dated 9/4/19 for additional information.

A dissolution test is proposed for measuring the quality of Trijardy™ XR tablets (Apparatus I, paddles; 100 rpm with 900ml 50 mM phosphate buffer pH 6.8). A dissolution acceptance criterion of Q= (b) (4)% in 45 minutes and Q= (b) (4)% in 30 minutes was accepted by biopharm reviewer for empagliflozin and linagliptin release respectively. For metformin HCl (the extended release component), an acceptance criterion of NLT (b) (4)% release in 12 hours was accepted . Biopharmaceutics reviewer, Dr. Hansong Chen reviewed the dissolution method, supporting dissolution data, dissolution acceptance criteria, alcohol induced dose dumping data, and the biowaiver request.

The bioequivalence (BE) studies used the highest (25 mg/5 mg/1000 mg) and lowest (5 mg/2.5 mg/1000 mg) strength empagliflozin/linagliptin/ metformin HCl extended release

tablets. The applicant sought biowaiver for the two intermediate strengths 10 mg/5 mg/1000 mg and 12.5 mg/2.5 mg/1000 mg based on dissolution profiles.

Dr. Chen's review concluded that the dissolution profiles of the intermediate strengths were similar to the dissolution profiles of the highest and lowest strength tablets. His review concluded that a biowaiver for both intermediate strengths (10 mg/5 mg/1000 mg and 12.5 mg/2.5 mg/1000 mg) of empagliflozin/linagliptin/metformin HCl extended release XR tablets can be granted based on acceptable BE studies.

Dr. Chen also reviewed the dissolution studies conducted to address the concern of dose dumping when taken with alcohol and concluded that the risk of dose dumping is low. Dr. Hansong Chen's recommendation for this NDA is adequate. Please refer to biopharma review dated 11/17/19 in Panorama.

The applicant submitted exemption from environmental assessment for empagliflozin, linagliptin, and metformin hydrochloride extended-release tablets under 21 CFR 25.31 (a) and (b). Dr. Luong reviewed the environmental assessment and concluded that it is adequate to support the NDA. Please refer to drug product review dated 9/4/19 in panorama for details.

Expiration Date & Storage Conditions: The application contains 6 month accelerated stability (40°C/75% RH) and 18 months of long-term storage stability data (25°C/60% RH) for 3 commercial scale primary stability batches of each strength packaged in smallest and largest bottle size (as well as 1 batch of each strength in intermediate size bottles. The drug product reviewer reviewed stability information. Dr. Luong's review concluded that the product is stable when stored in the proposed commercial packaging (in 30ct or 60ct or 90ct or 180ct HDPE bottles with desiccant and screw closures) with respect to assay, appearance, impurities dissolution, water content and microbial quality. A shelf-life of 18 months is granted when stored at 68 -77°F ((20°-25°C) in original packaging. Excursions permitted to 59°-86°F (15°-30°C) [see USP Controlled Room Temperature]. Please refer to drug product review dated 9/4/19 in Panorama for additional information.

Container and Carton Label Review: Drug product reviewer completed review of container and carton label. Dosage form, strength, established name, NDC #, Lot #/expiry, and storage conditions are described in the carton and container label, which meets relevant regulatory requirements for labeling. Refer to drug product review for a copy of the label.

OVERALL ASSESSMENT AND SIGNATURES:

OPQ CMC review concludes that there are no outstanding deficiencies related to drug substance, drug product, process, facilities, biopharmaceutics, environmental analysis, container and carton label. *OPQ overall recommendation for NDA 212614 is approval.*

Muthukumar Ramaswamy, Ph.D. 12/9/2019

Application Technical Lead Name and Date:

Attachment I: Final Risk Assessments

From Initial Risk Identification			*Review Assessment*		
Attribute/ CQA	*Factors that can impact the CQA*	*Initial Risk Ranking*	*Risk Mitigation Approach*	*Final Risk Ranking*	*Lifecycle Considerations/ Comments*
Drug content (potency)	Formulation, process, container/ stability/Method	M	(b) (4)	Acceptable	None
Dose Uniformity	Formulation, process, container/ stability/ Method	M		Acceptable	
Particle Size Distribution of API (empagliflozin and linagliptin)	Formulation, process	M		Acceptable	none
Impurities	Formulation /process ((b) (4)), stability, Container closure	L		Acceptable	none
Appearance	Formulation, process, Container closure, stability	L		Acceptable	none
Microbial load	Container closure Process/water content	L		Acceptable	none
In vitro dissolution (immediate release and extended release)	Formulation, process, incoming materials	M		Acceptable	None.

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CHAPTER III: ENVIRONMENTAL

IQA NDA Assessment Guide Reference

R REGIONAL INFORMATION

Environmental Analysis (EA)

Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) is claiming an exemption from the requirement for an EA for Empagliflozin + Linagliptin + Metformin Hydrochloride Extended-Release Fixed Ratio Combination Tablets base on 21 CFR Part 25.31 (a) and (b) of the regulation which allows a categorical exclusion for an action which does not increase the use of the active moiety, of if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion.

BIPI claims that to the best of the company's knowledge, no extraordinary circumstances exist.

Assessment: ***Adequate from a CMC perspective.***

To the best knowledge of the applicant, no extraordinary circumstances exist associated with the proposed actions. The EA review team will document its review under the OND's Integrated Review Process (if applicable).

Primary Environmental Assessor Name and Date: Elise Luong, Ph.D.; 08/30/2019.

Secondary Assessor Name and Date (and Secondary Summary, as needed): Danae Christodoulou, Ph.D.; 08/30/2019 I concur with the reviewer's assessment.

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Trijardy®	Reviewed by DMEPA
Established name(s)	Empagliflozin, Linagliptin, and Metformin Hydrochloride Extended-Release tablets	Adequate
Route(s) of administration	Oral	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Extended-Release Film-coated Fixed Ratio Combination Tablets Empagliflozin/Linagliptin/Metformin HCl 5 mg / 2.5 mg / 1000 mg 10 mg / 5 mg / 1000 mg 12.5 mg / 2.5 mg / 1000 mg 25 mg / 5 mg / 1000 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A (The tablet is not scored)	N/A (The tablet is not scored)

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Ready to use tablet. Swallow tablets whole. Do not split, crush, dissolve, or chew before swallowing.	Adequate

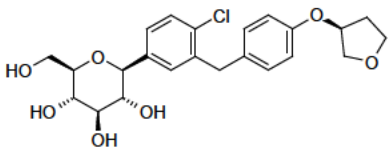
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

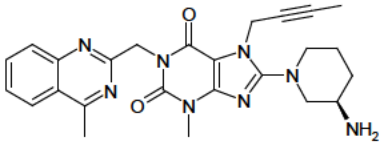
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Empagliflozin/Linagliptin/Metformin HCl Fixed Ratio Combination Tablets	Adequate
Strength(s) in metric system	Empagliflozin/Linagliptin/Metformin HCl 5 mg / 2.5 mg / 1000 mg 10 mg / 5 mg / 1000 mg 12.5 mg / 2.5 mg / 1000 mg 25 mg / 5 mg / 1000 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Section 3.2.P.1	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A (The tablet is not scored)	N/A
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

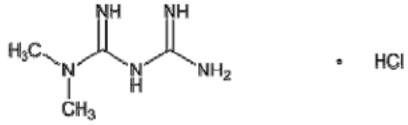
1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary Name Established name(s)	Trijardy® Empagliflozin, Linagliptin, and Metformin Hydrochloride Extended-Release tablets	Reviewed by DMEPA
Dosage form(s) and route(s) of administration	Extended-Release Fix-Ratio Combination Tablet / Oral	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	N/A

List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Tablet Core: Polyethylene oxide Hypromellose Magnesium stearate Film Coatings & Printing Ink: Hydroxypropyl cellulose Hypromellose Talc Titanium dioxide Arginine Polyethylene glycol Carnauba wax Purified water Shellac glaze n-butyl alcohol ammonium hydroxide (b) (4) isopropyl alcohol ferric oxide yellow (5 mg/2.5 mg/1000 mg and 10 mg/5 mg/1000 mg) ferric oxide red (12.5 mg/2.5 mg/1000 mg (b) (4))	Acceptable
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	N/A

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	(b) (4) n-butyl alcohol (b) (4)	The label does not have the quantitative amount of these 2 alcohols is acceptable.
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	Antihyperglycemic	Adequate
Empagliflozin Chemical name, structural formula, molecular weight	D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]-phenyl],(1S)  450.91 g/mol $C_{23}H_{27}ClO_7$	Adequate
If radioactive, statement of important nuclear characteristics	N/A	N/A

Other important chemical or physical properties (such as pKa or pH)	White to yellowish, non-hygroscopic powder, 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	Adequate
Linagliptin Chemical name, structural formula, molecular weight	1H-Purine-2,6-dione,8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[4-methyl-2-quinazolinyl)methyl]-  472.54 g/mol $C_{25}H_{28}N_8O_2$	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	White to yellowish, not or only slightly hygroscopic, very slightly soluble in water, soluble in methanol, sparingly soluble in ethanol, very slightly soluble in isopropanol, and very slightly soluble in acetone.	Adequate

Metformin HCl Chemical name, structural formula, molecular weight	N,N-dimethylimidodicarbonimidic diamide hydrochloride  165.63 g/mol $C_4H_{11}N_5 \bullet HCl$	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	White to off-white crystalline, freely soluble in water, insoluble in acetone, ether, and chloroform. pKa = 12.4 pH = 6.68 (1% aqueous solution)	Adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	There is no misleading statement on the labels	Adequate

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Solid	Adequate
Strength(s) in metric system	Empagliflozin/Linagliptin/Metformin HCl 5 mg / 2.5 mg / 1000 mg 10 mg / 5 mg / 1000 mg 12.5 mg / 2.5 mg / 1000 mg 25 mg / 5 mg / 1000 mg	Adequate
Available units (e.g., bottles of 100 tablets)	See inserted table below	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	See inserted table below	Adequate. The description has been provided in the NDA
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	The tablet is not scored N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

Tablet Strength	Film-Coated Tablet, Color/Shape	Tablet Markings	Package Size	NDC Number
5 mg/2.5 mg/1000 mg	grey oval-shaped	Printed on one side in white ink with the BI logo and “395” on the top line and “5/2.5” on the bottom line.	Bottles of 60 Bottles of 180	0597-0395-82 0597-0395-23
10 mg/5 mg/1000 mg	tan, oval-shaped	printed on one side in white ink with the BI logo and “380” on the top line and “10/5” on the bottom line.	Bottles of 30 Bottles of 90	0597-(b) (4) 0597-(b) (4)
12.5 mg/2.5 mg/1000 mg	red, oval-shaped	Printed on one side in white ink with the BI logo and “385” on the top line and “12.5/2.5” on the bottom line.	Bottles of 60 Bottles of 180	0597-(b) (4) 0597-(b) (4)
25 mg/5 mg/1000 mg	brown, oval-shaped	Printed on one side in white ink with the BI logo and “390” on the top line and “25/5” on the bottom line.	Bottles of 30 Bottles of 90	0597-(b) (4) 0597-(b) (4)

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Store at 25°C (77°F); excursions permitted to 15°C – 30°C (59-86°F) [See USP Controlled Room Temperature]. Protect from exposure to high humidity. (b) (4)	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	The desiccant sachets have different size, color, and shape from the dosage form. The desiccant sachets have a warning of 'Do not eat'	Adequate
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 25°C (77°F); excursions permitted to 15°C – 30°C (59-86°F) [See USP Controlled Room Temperature]. Protect from exposure to high humidity.	The storage condition is supported by data and is acceptable.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid	N/A	N/A

statements such as “latex-free.”		
Include information about child-resistant packaging	All HDPE bottles have (b) (4) closures	Adequate

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Distributed by: Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877 U.S.A. Marketed by: Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877 U.S.A. and Eli Lilly and Company Indianapolis, IN 46285 U.S.A. Licensed from: Boehringer Ingelheim International GmbH, Ingelheim, Germany	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

The product labels have all the relevant information in accordance with regulatory requirements from a CMC perspective. Labeling will be finalized through OND during labeling negotiations with the applicant.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

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

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Trijardy® Empagliflozin, Linagliptin, and Metformin Hydrochloride Extended-Release tablets	Adequate
Dosage strength	Empagliflozin/Linagliptin/Metformin HCl 5 mg / 2.5 mg / 1000 mg 10 mg / 5 mg / 1000 mg 12.5 mg / 2.5 mg / 1000 mg 25 mg / 5 mg / 1000 mg	Adequate
Route of administration	Oral	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A
Net contents (e.g. tablet count)	See Table 19 below	Adequate
"Rx only" displayed on the principal display	Yes	Yes
NDC number	Labels contain space for NDC number	Adequate
Lot number and expiration date	Labels contains space for Lot number and expiration date	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 25°C (77°F); excursions permitted to 15° – 30°C (59°-86°F) [See UPS Controlled Room Temperature]. Protect from exposure to high humidity.	Adequate

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	N/A
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	(b) (4) n-butyl alcohol (b) (4)	The label does not have the quantitative amount of these 2 alcohols is acceptable.
Bar code	Labels have space for bar code	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Boehringer Ingelheim Lilly	Adequate
Medication Guide (if applicable)	Labels have medication guide	Adequate
No text on Ferrule and Cap overseal	N/A	N/A
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	Drug product quality follows USP, ICH guidance. Acceptable.
And others, if space is available	N/A	N/A

Table 19 Packaging Configurations for Empagliflozin/Linagliptin/Metformin HCl ER Coated Tablets

Strength (mg empagliflozin/ mg linagliptin/ mg metformin HCl)	Bottle Size	Tablet Fill Count	Number of 2 g desiccants
5 mg/2.5 mg/1000 mg	90 cc	14	1
	215 cc	60	1
	22 oz	180	2
10 mg/5 mg/1000 mg	90 cc	7	1
	150 cc	30	1
	375 cc	90	2
12.5 mg/2.5 mg/1000 mg	90 cc	14	1
	215 cc	60	1
	22 oz	180	2
25 mg/5 mg/1000 mg	90 cc	7	1
	150 cc	30	1
	375 cc	90	2

Assessment of Carton and Container Labeling: *Adequate.*

The product labels have all the relevant information in accordance with regulatory requirements from a CMC perspective. Labeling will be finalized through OND during labeling negotiations with the applicant.

ITEMS FOR ADDITIONAL ASSESSMENT

None.

Overall Assessment and Recommendation:

The product labels are acceptable from a CMC perspective.

Primary Labeling Assessor Name and Date: Elise Luong, Ph.D., 08/30/2019

Secondary Assessor Name and Date (and Secondary Summary, as needed): Danae Christodoulou, Ph.D., 08/30/2019

Elise Luong

Digitally signed by Elise Luong
Date: 9/03/2019 08:31:05AM
GUID: 537253e70005b48ebb030e8b349f32e6

Danae Christodoulou

Digitally signed by Danae Christodoulou
Date: 9/04/2019 01:26:16PM
GUID: 5050dd27000012a4c69bfc70b47660b7

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BIOPHARMACEUTICS

Product Background:

NDA: NDA 212614

Drug Product Name / Strength: Trijardy® (Empagliflozin, Linagliptin, Metformin Hydrochloride) Extended-Release Tablets, 5mg/2.5mg/1000mg, 10mg/5mg/1000mg, 12.5mg/2.5mg/1000mg, and 25mg/5mg/1000mg

Route of Administration: Oral

Applicant Name: Boehringer Ingelheim

Review Recommendation: **Adequate**

Review Summary:

Boehringer Ingelheim developed Trijardy® (Empagliflozin, Linagliptin, Metformin Hydrochloride) Extended-Release Tablets, 5mg/2.5mg/1000mg, 10mg/5mg/1000mg, 12.5mg/2.5mg/1000mg, and 25mg/5mg/1000mg and submitted this application under NDA 212614 to seek approval through the 505(b)(1) regulatory pathway on 3/27/2019. The proposed drug product is indicated for an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4) .

The Biopharmaceutics review focuses on the dissolution method development, dissolution data, dissolution acceptance criteria, biowaiver for two intermediate strengths, and alcohol induced dose dumping study.

The proposed dissolution method was reviewed and found acceptable. The dissolution method has some discriminatory power based on the *in vitro* study conducted.
The following acceptance criteria were proposed by the Applicant and found acceptable by the Agency:

Empagliflozin
Q= (b) (4)% in 45 minutes
Linagliptin
Q= (b) (4)% in 30 minutes
Metformin
2 hours: (b) (4)%
4 hours: (b) (4)%
12 hours: NLT (b) (4)%
Overall, the following dissolution method and acceptance criteria have been approved:

Apparatus	USP Apparatus I (basket)
Speed	100 rpm
Dissolution medium	50 mM Phosphate Buffer, pH 6.8
Volume	900 mL
Sampling Time Points	Empagliflozin: 15, 20, 30, 45, and 60 minutes Linagliptin: 15, 20, 30, 45, and 60 minutes Metformin HCl: 2, 4, 6, 8, and 12 hours
Temperature	37 ± 0.5 °C
Approved dissolution acceptance criteria	Empagliflozin Q= (b) (4)% in 45 minutes Linagliptin Q= (b) (4)% in 30 minutes Metformin HCl 2 hours: (b) (4)% 4 hours: (b) (4)% 12 hours: NLT (b) (4)%

The Applicant provided sufficient data to support the biowaiver of two intermediate strengths (i.e. 10mg/5mg/1000mg, 12.5mg/2.5mg/1000mg). The biowaiver request for the two intermediate strengths (10mg/5mg/1000mg, 12.5mg/2.5mg/1000mg) is granted based on acceptable BE studies, which are still under review.

The in vitro alcohol induced dose dumpling study shows that alcohol does not cause dose dumping of the proposed drug products.

From the Biopharmaceutics perspective, this Reviewer concludes that NDA 212614 for Trijardy® (Empagliflozin, Linagliptin, Metformin Hydrochloride) Extended-Release Tablets, 5mg/2.5mg/1000mg, 10mg/5mg/1000mg, 12.5mg/2.5mg/1000mg, and 25mg/5mg/1000mg is **adequate** for approval.

List Submissions being reviewed (table):

3/27/2019	NDA 221614 / Original submission
8/5/2019	eCTD-0016/Response to Biopharmaceutics Information Requests
8/29/2019	eCTD-0018/Response to Biopharmaceutics Information Requests

Highlight Key Outstanding Issues from Last Cycle: None.

Concise Description Outstanding Issues Remaining: None.

BCS Designation

Reviewer's Assessment: The Applicant reported that Empagliflozin, Linagliptin, and Metformin Hydrochloride are BCS Class III drugs, which have high solubility and low permeability. The

solubility data provided by the Applicant confirmed that they are highly soluble drugs. This Reviewer also confirmed the BCS classification of Empagliflozin, Linagliptin, and Metformin Hydrochloride.

Table 1. Solubility of Empagliflozin at Different pH Values at 37 °C

Medium	pH after 2 hours	Solubility after 2 hours (mg/mL)	Solubility (mg/900 mL)
water	6.3	0.5	450
0.1 N HCl, pH 1	1.2	0.5	450
McIlvaine buffer, pH 3.0	3.0	0.5	450
acetate buffer 0.1 M, pH 4.5	4.5	0.5	450
phosphate buffer 0.1 M, pH 6.8	6.8	0.4	360
phosphate buffer 0.1 M, pH 7.5	7.5	0.4	360

Table 2. Solubility of Linagliptin at Different pH Values at 37 °C

Medium	pH of the Saturated Solution	Solubility (mg/mL)	Solubility (mg/900 mL)
0.1 N HCl, pH 1	1.1	> 10	> 9000
acetate buffer 50 mM, pH 4.5	5.1	9.5	8550
phosphate buffer 50 mM, pH 6.8	7.4	9.2	8280
phosphate buffer 50 mM, pH 8.0	8.1	1.4	1260

Table 3. Solubility of Metformin HCl at Different pH Values at 37°C

Medium	pH-Value	Solubility (mg/mL)	Solubility (mg/900 mL)
0.1 N HCl	1	> 10	> 9000
acetate buffer 50 mM	3.0 – 5.0	> 10	> 9000
phosphate buffer 50 mM	6.0 – 8.0	> 10	> 9000
water	7.2	> 200	> 180000

Dissolution Method and Acceptance Criteria

Reviewer's Assessment: ***Adequate***

1. Drug Product

Figure 1. Cross Section of an Empagliflozin/Linagliptin/Metformin HCl ER Coated Tablet

The proposed drug products consist of inside Metformin HCl ER core tablet and (b) (4) Empagliflozin and Linagliptin.

2. Dissolution method

The Applicant developed the following dissolution method for Trijardy® (Empagliflozin, Linagliptin, Metformin Hydrochloride) Extended-Release Tablets:

Table 4. The proposed dissolution method

Apparatus	USP Apparatus I (basket)
Speed	100 rpm
Dissolution medium	50 mM Phosphate Buffer, pH 6.8
Volume	900 mL
Sampling Time Points	Empagliflozin: 15, 20, 30, 45, and 60 minutes Linagliptin: 15, 20, 30, 45, and 60 minutes Metformin HCl: 2, 4, 6, 8, and 12 hours
Temperature	37 ± 0.5 °C
Proposed dissolution acceptance criteria	Empagliflozin Q= (b) (4)% in 45 minutes Linagliptin Q= (b) (4)% in 30 minutes Metformin HCl 2 hours: (b) (4)% 4 hours: (b) (4)% 12 hours: NLT (b) (4)%

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(b) (4)

4. Discriminatory power

a. Discriminatory power towards manufacturing variables related to the metformin HCl ER core tablet

1) Change in the amount of (b) (4)

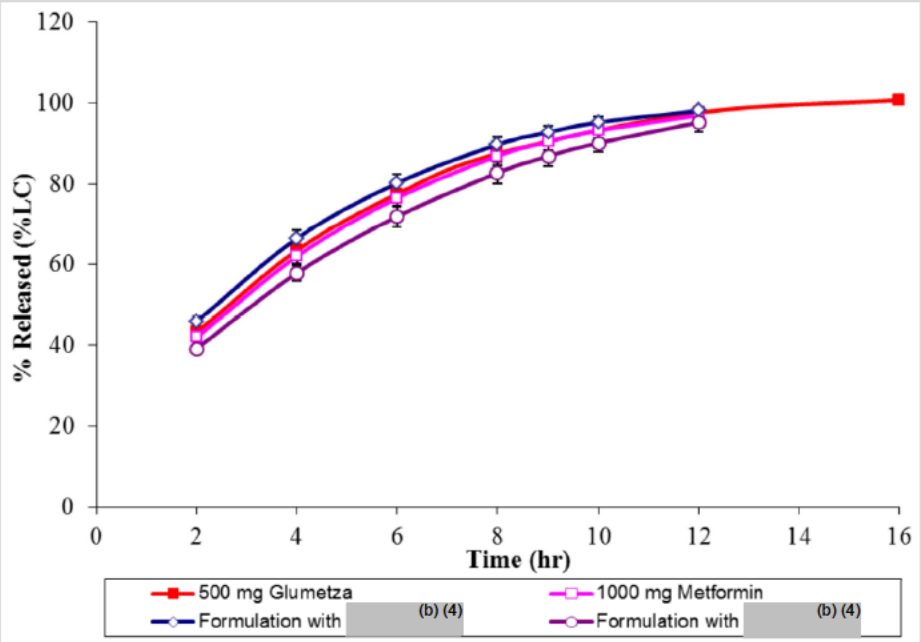
The proposed Trijardy® (Empagliflozin, Linagliptin, Metformin Hydrochloride) Extended-Release Tablets use (b) (4). The discriminatory power of the dissolution method towards changes in the metformin HCl ER core tablet was demonstrated (b) (4). Specifically, the Applicant intentionally manufactured the batches with different amount of (b) (4) .

The results shown in Figure 4 indicate that the changes in the amount of (b) (4) have an impact on the metformin dissolution of the finished product. However, the impact is not significant.

Reviewer's comments:

(b) (4) *is a* (b) (4). *Its amount in the formulation has direct impact on the dissolution of the finished product. Figure 4 shows that the batch with higher amount of* (b) (4) *has slower dissolution than that with lower amount of* (b) (4). *However, the differences in the dissolution profiles between the batches with different amount of* (b) (4) *are not significant. Therefore, the dissolution method has limited discriminatory power to discriminate the changes within the studied range of* (b) (4).

Figure 4. Comparative Dissolution for Results of Glumetza® 500 mg versus Metformin HCl ER tablets, 1000 mg, with (b) (4)%, (b) (4)% (selected formulation), and (b) (4) in SGF without enzymes



2) Influence of (b) (4) Used to Manufacture Metformin HCl ER Tablet on dissolution

The Applicant used different (b) (4) to manufacture Metformin HCl ER tablet cores with different (b) (4). The comparative dissolution test shows that different (b) (4) of Metformin HCl ER tablet cores has no impact on the metformin dissolution of the finished product.

b. Discriminatory power towards manufacturing variables related to empagliflozin /linagliptin/metformin HCl ER (b) (4)

(b) (4)/linagliptin/metformin HCl ER coated tablets have (b) (4)

(b) (4)

(b) (4)

Figure 5. Empagliflozin Dissolution as a Function of (b) (4) for Empagliflozin/Linagliptin/Metformin HCl ER Coated Tablets, 5 mg/2.5 mg/1000 mg

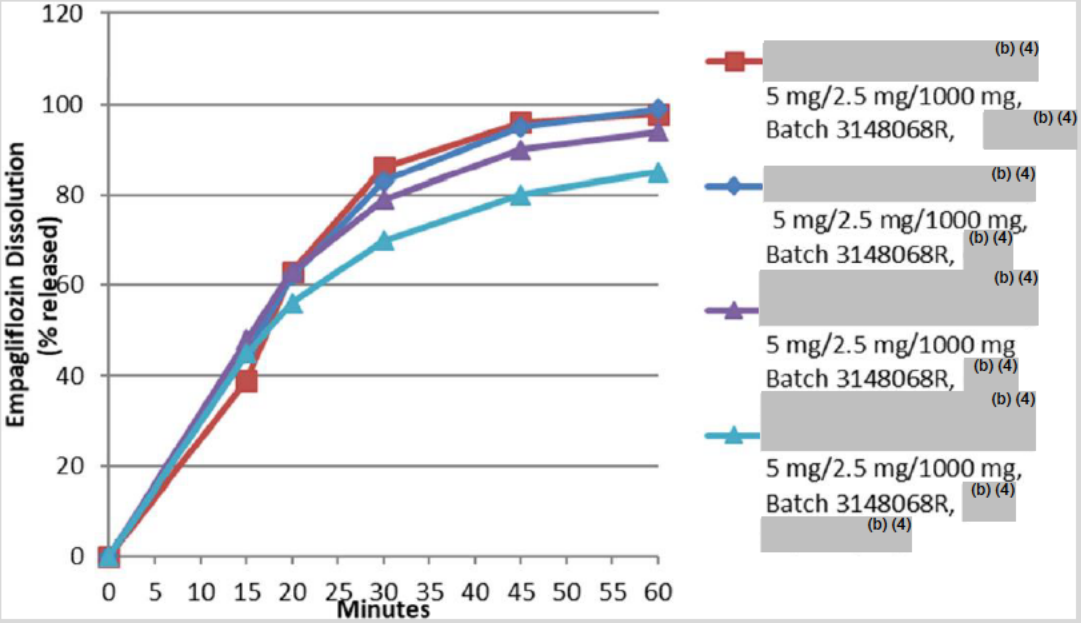
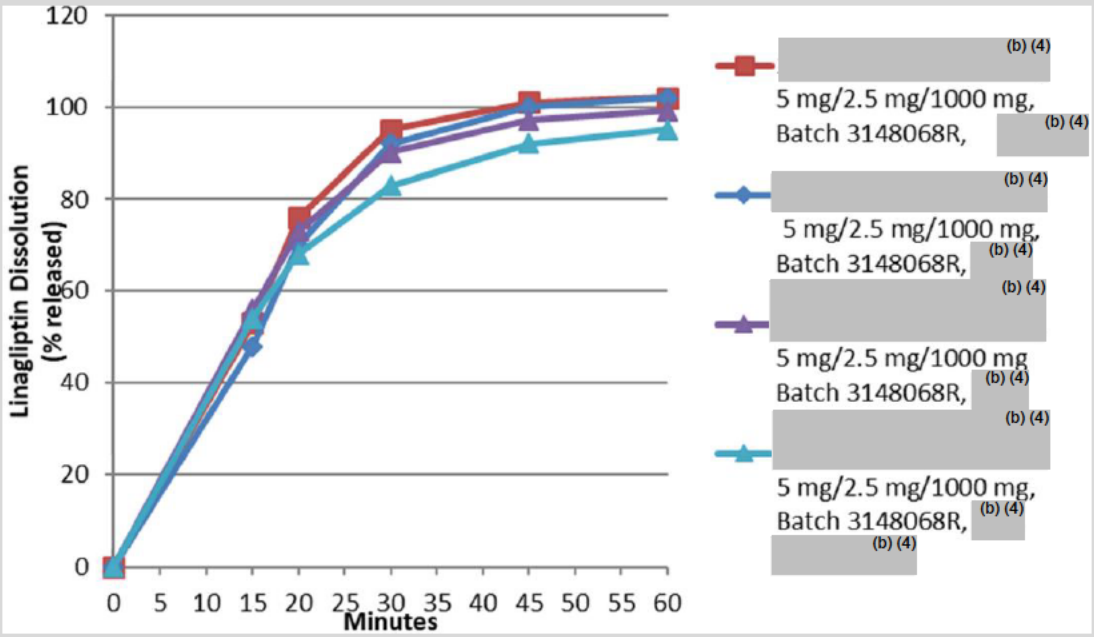


Figure 6. Linagliptin Dissolution as a Function of (b) (4) for Empagliflozin/ Linagliptin/Metformin HCl ER Coated Tablets, 5 mg/2.5 mg/1000 mg



c. Discriminatory power towards the changes in storage conditions on the dissolution behavior of empagliflozin/linagliptin/metformin HCl ER coated tablets

The Applicant also stored the proposed Trijardy® (Empagliflozin, Linagliptin, Metformin Hydrochloride) Extended-Release Tablets at 25° C/60% RH and 40° /75% RH for long time. The dissolution tests show that long term storage has no impact on the dissolution of the drug product.

5. Dissolution data and acceptance criteria

Table 7. Batch Information of clinical and primary stability batches

Batch number	Strength (mg/mg/mg)	Manufacture date	Use
3143705R	25/5 /1000	Jan 29, 2016	Clinical
3148076R	25/5 /1000	Jan 09, 2017	Primary stability
3148077R	25/5 /1000	Jan 11, 2017	Primary stability
3148078R	25/5 /1000	Jan 10, 2017	Clinical and primary stability
3148073R	12.5 /2.5 /1000	Jan 09, 2017	Primary stability
3148074R	12.5 /2.5 /1000	Jan 11, 2017	Primary stability
3148075R	12.5 /2.5 /1000	Jan 10, 2017	Primary stability
3141970R	10/5 /1000	Jan 29, 2016	Clinical
3148070R	10/5 /1000	Jan 09, 2017	Primary stability
3148071R	10/5 /1000	Jan 11, 2017	Primary stability
3148072R	10/5 /1000	Jan 10, 2017	Primary stability
3148067R	5 /2.5 /1000	Jan 09, 2017	Clinical and primary stability
3148068R	5 /2.5 /1000	Jan 11, 2017	Primary stability
3148069R	5 /2.5 /1000	Jan 10, 2017	Primary stability

Table 8. Mean empagliflozin dissolution data in Phosphate Buffer, pH 6.8

Lot number/Time (min)	15	20	30	45	60
25mg/5mg /1000mg 3148076R	26	49	78	93	96
25mg/5mg /1000mg 3148077R	28	51	78	91	94
25mg/5mg /1000mg 3148078R	32	57	83	94	96
12.5mg/5mg /1000mg 3148073R	36	60	83	93	96
12.5mg/5mg /1000mg 3148074R	32	55	81	95	98
12.5mg/5mg /1000mg 3148075R	35	58	81	93	96
10mg/5mg /1000mg 3148070R	34	57	83	93	96
10mg/5mg /1000mg 3148071R	36	61	87	97	99
10mg/5mg /1000mg 3148072R	28	52	81	95	98
5 mg /2.5 mg /1000mg 3148067R	37	60	83	95	98
5 mg /2.5 mg /1000mg 3148068R	39	63	86	96	98
5 mg /2.5 mg /1000mg 3148069R	35	59	85	97	100

Table 9. Mean linagliptin dissolution data in Phosphate Buffer, pH 6.8

Lot number/Time (min)	15	20	30	45	60
25mg/5mg/1000mg 3148076R	33	59	86	96	99
25mg/5mg/1000mg 3148077R	35	60	85	96	98
25mg/5mg/1000mg 3148078R	40	65	89	97	99
12.5mg/5mg/1000mg 3148073R	50	72	90	96	98
12.5mg/5mg/1000mg 3148074R	47	71	91	99	100
12.5mg/5mg/1000mg 3148075R	50	72	90	97	99
10mg/5mg/1000mg 3148070R	41	66	89	96	98
10mg/5mg/1000mg 3148071R	43	69	91	98	100
10mg/5mg/1000mg 3148072R	36	62	90	99	101
5 mg /2.5 mg/1000mg 3148067R	51	74	93	101	102
5 mg /2.5 mg/1000mg 3148068R	53	77	95	101	102
5 mg /2.5 mg/1000mg 3148069R	47	72	93	101	103

Table 10. Mean metformin dissolution data in Phosphate Buffer, pH 6.8

Lot number/Time (h)	3	4	6	8	12
25mg/5mg/1000mg 3148076R	35	57	72	84	98
25mg/5mg/1000mg 3148077R	35	57	73	84	99
25mg/5mg/1000mg 3148078R	35	56	71	81	97
12.5mg/5mg/1000mg 3148073R	36	58	72	84	99
12.5mg/5mg/1000mg 3148074R	36	58	73	84	99
12.5mg/5mg/1000mg 3148075R	35	57	72	83	96
10mg/5mg/1000mg 3148070R	36	57	72	84	98
10mg/5mg/1000mg 3148071R	36	57	72	83	97
10mg/5mg/1000mg 3148072R	36	57	73	84	99
5 mg /2.5 mg/1000mg 3148067R	36	57	73	84	99
5 mg /2.5 mg/1000mg 3148068R	36	58	73	84	99
5 mg /2.5 mg/1000mg 3148069R	36	57	72	83	98

The Applicant proposed the following dissolution acceptance criteria:

Empagliflozin

Q= (b)(4)% in 45 minutes

Linagliptin

Q= (b)(4)% in 30 minutes

Metformin

2 hours: (b)(4)%

4 hours: (b)(4)%

12 hours: NLT (b)(4)%

The individual dissolution data show that the proposed dissolution acceptance criteria are acceptable.

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim
Reviewer's Assessment: ***N/A***

The proposed Trijardy® (Empagliflozin, Linagliptin, Metformin Hydrochloride) Extended-Release Tablets has (b) (4) The extended release claim for metformin HCl has been addressed in the previously approved NDA 208,658 and NDA 208206.

Application of dissolution/IVIVC in QbD

Reviewer's Assessment:

Empagliflozin
The Applicant reported that empagliflozin is a BCS III drug, which has high solubility and low permeability.
Polymorphism
The Applicant reported that no polymorphism has been observed. They used XRD data to show that the polymorphic conversion of empagliflozin did not occur during the manufacturing process and after long term storage.
Particle size
Empagliflozin drug substance with a particle size specification (d90) of ≤ (b) (4) µm is used in empagliflozin IR (Jardiance®) tablets and has been selected for the proposed Trijardy® (Empagliflozin, Linagliptin, Metformin Hydrochloride) Extended-Release Tablets as well.

Linagliptin
The Applicant reported that linagliptin is a BCS III drug, which has high solubility and low permeability.
Polymorphism
The Applicant reported that linagliptin exists in two polymorphic forms – Form A and Form B. These two forms are enantiotropically related and reversibly interconvert at approximately room temperature. The Applicant stated that both forms are stable and highly soluble, and that both forms are equivalent with respect to equilibrium solubility and intrinsic dissolution rate, which indicates that the polymorphism of linagliptin drug substance does not affect dosage form manufacturability or bioavailability.
Particle size
Linagliptin drug substance with a particle size specification (d90) of ≤ (b) (4) µm is used in linagliptin IR (Tradjenta®) tablets and has been selected for the proposed Trijardy® (Empagliflozin, Linagliptin, Metformin Hydrochloride) Extended-Release Tablets as well.

Metformin HCl

The Applicant reported that metformin HCl is a BCS III drug, which has high solubility and low permeability.

Polymorphism

The Applicant did not report the polymorphism of metformin HCl.

Particle size

The Applicant stated that particle size of metformin is not expected to affect dissolution of metformin HCl because it exhibits high solubility (>10 mg/mL) across the entire physiological pH range. The Applicant did not propose a PSD specification for metformin HCl. The Applicant also used supporting data to demonstrate that the particle size of metformin HCl within the studied ranges has no influence on the dissolution of metformin HCl.

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping

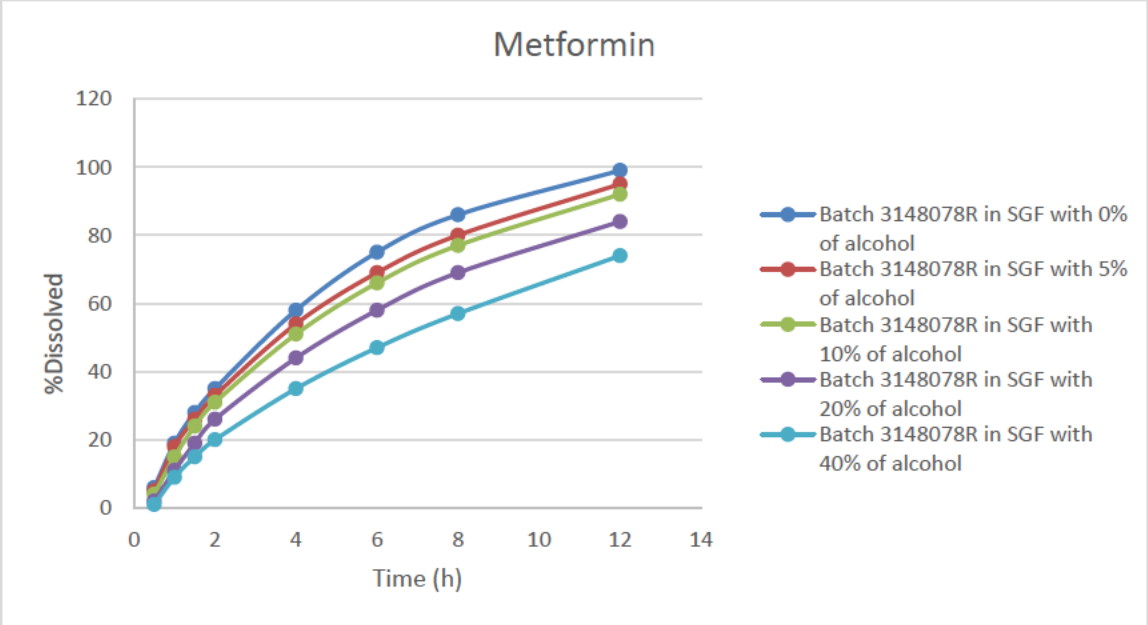
Reviewer's Assessment: ***{Adequate}***

Because the proposed products are extended release FDC tablets, the Applicant conducted an in vitro alcohol dose dumping study. (b) (4) , the 25 mg/5 mg/1000 mg strength of empagliflozin/linagliptin/metformin HCl ER coated tablets were selected for this study. Because the metformin dissolution of the FDC tablet is pH independent, the study was conducted in simulated gastric fluid (SGF) without enzymes (pH 1.2) only. The results are shown in Tables 11 and Figure 7.

Table 11. Mean metformin dissolution data of Batch 3148078R in SGF with different concentrations of alcohol

Batch Number/Time points (h)	0.5	1	1.5	2	4	6	8	12
Batch 3148078R in SGF with 0% of alcohol	6	19	28	35	58	75	86	99
Batch 3148078R in SGF with 5% of alcohol	5	18	26	33	54	69	80	95
Batch 3148078R in SGF with 10% of alcohol	4	15	24	31	51	66	77	92
Batch 3148078R in SGF with 20% of alcohol	2	11	19	26	44	58	69	84
Batch 3148078R in SGF with 40% of alcohol	1	9	15	20	35	47	57	74

Figure 7. Comparative Metformin Dissolution Profiles of Batch 3148078R in SGF Containing 0%, 5%, 10%, 20%, and 40% alcohol



Reviewer's comment

The data show that alcohol does not cause dose dumping. Instead, the metformin release is slower in the presence of alcohol, especially, in the presence of 20% and 40% alcohol. The reason for the slower release in the presence of alcohol could be that metformin is not soluble in alcohol.

Since SGF without enzymes is not the proposed QC method medium, per our current practice, the Applicant should conduct an in vitro alcohol induced dose dumping study in the QC medium (i.e. 50 mM Phosphate Buffer pH 6.8) as well. In the response to the IR, the Applicant stated that they had demonstrated that the metformin HCl ER dissolution profile is independent of pH and the dissolution in only 0.1N HCl was sufficient to indicate that alcohol dose dumping of metformin HCl ER does not occur in the proposed Trijardy® (Empagliflozin, Linagliptin, Metformin Hydrochloride) Extended-Release Tablets. This Reviewer finds that the Applicant's response is acceptable.

Bridging of Formulations

Reviewer's Assessment: ***Adequate.***

The commercial formulation is the same as the one used in pivotal clinical studies (Study 1361-0003 and Study 1361-0011.

Biowaiver Request

Reviewer's Assessment: ***{Adequate}***

The proposed drug products have four strengths: 5mg/2.5mg/1000mg, 10mg/5mg/1000mg, 12.5mg/2.5mg/1000mg, and 25mg/5mg/1000mg. The Applicant conducted bioequivalence studies on the highest (25 mg/5 mg/1000 mg) and lowest (5 mg/2.5 mg/1000 mg) strengths of empagliflozin/linagliptin/metformin HCl extended-release XR tablets to compare equivalence with the reference products Jardiance®, Tradjenta® and Glumetza®. The Applicant requested the biowaiver for two intermediate strengths: 10mg/5mg/1000mg and 12.5mg/2.5mg/1000mg.

a. BE studies between the reference products and test products

1) Bioequivalence of FDC versus free combination for strength 25 mg/5 mg/1000 mg under fed conditions

Study 1361-0011 title: Bioequivalence of a low strength fixed dose combination tablet of empagliflozin/linagliptin/metformin extended release compared to the free combination of empagliflozin, linagliptin, and metformin extended release tablets following oral administration in healthy male and female subjects (an open label, randomized, single-dose, two-period, two sequence crossover study)

The study results are listed in Table 12, which are pending on Clinical Pharm Review conclusion.

Table 12. Bioequivalence Analysis of 25 mg/5 mg/1000 mg empagliflozin/linagliptin/metformin HCl extended release XR versus free combination under Fed Conditions (Study 1361.3; N=29)

Analyte/ Parameter	Adjusted gMean		Adjusted gMean ratio T/R [%]	Two-sided 90% CI (lower limit, upper limit) [%]	Intra-individual gCV [%]
	FDC (T) N=29	Free combination (R) N=29			
Empagliflozin					
Primary endpoints					
AUC_{0-tz} [nmol·h/L]	5656.07	5488.31	103.06	(100.36, 105.83)	5.8
C_{max} [nmol/L]	540.01	540.26	99.95	(94.52, 105.70)	12.4
Secondary endpoint					
$AUC_{0-\infty}$ [nmol·h/L]	5727.20	5554.37	103.11	(100.38, 105.92)	5.9
Linagliptin					
Primary endpoints					
AUC_{0-72} [nmol·h/L]	238.84	238.11	100.31	(96.65, 104.10)	8.2
C_{max} [nmol/L]	5.69	5.86	97.17	(92.63, 101.93)	10.6
Secondary endpoint					
$AUC_{0-\infty}$ [nmol·h/L]	384.27	394.95	97.30	(91.65, 103.29)	13.2
Metformin					
Primary endpoints					
AUC_{0-tz} [ng·h/mL]	12455.82	12412.57	100.35	(96.11, 104.77)	9.5
C_{max} [ng/mL]	1237.16	1147.88	107.78	(102.52, 113.31)	11.0
Secondary endpoint					
$AUC_{0-\infty}$ [ng·h/mL]	12745.62	12724.27	100.17	(95.68, 104.86)	10.1

2) Bioequivalence of FDC versus free combination for the tablet strength 5 mg/2.5 mg/1000 mg under fed conditions

Study 1361-0003 title: Bioequivalence of a fixed dose combination tablet of empagliflozin /linagliptin/ metformin extended release compared to the free combination of empagliflozin, linagliptin, and metformin extended release tablets following oral administration in healthy male and female subjects (an open-label, randomized, single-dose, two-period, two-sequence crossover study)

The study results are listed in Table 13, which are also pending on Clinical Pharm Review conclusion.

Table 13. Bioequivalence Analysis of 5 mg/2.5 mg/1000 mg empagliflozin/linagliptin/metformin HCl extended release XR versus free combination under Fed Conditions (Study 1361.11; N=27)

Analyte/ Parameter	Adjusted gMean		Adjusted gMean ratio T/R [%]	Two-sided 90% CI (lower limit, upper limit) [%]	Intra-individual gCV [%]
	FDC (T) N=27	Free combination (R) N=27			
Empagliflozin					
Primary endpoints					
AUC_{0-tz} [nmol·h/L]	2134.53	2125.57	100.42	(98.17, 102.72)	4.8
C_{max} [nmol/L]	209.67	226.50	92.57	(85.21, 100.57)	17.9
Secondary endpoint					
$AUC_{0-\infty}$ [nmol·h/L]	2182.26	2166.54	100.73	(98.33, 103.18)	5.1
Linagliptin					
Primary endpoints					
AUC_{0-72} [nmol·h/L]	270.19	269.77	100.16	(96.17, 104.31)	8.6
C_{max} [nmol/L]	7.02	7.21	97.33	(89.99, 105.26)	16.9
Secondary endpoint					
$AUC_{0-\infty}$ [nmol·h/L]	471.40	455.13	103.57	(96.90, 110.71)	14.3
Metformin					
Primary endpoints					
AUC_{0-tz} [ng·h/mL]	21687.12	22748.21	95.34	(91.58, 99.24)	8.5
C_{max} [ng/mL]	1853.03	1767.69	104.83	(98.56, 111.50)	13.2
Secondary endpoint					
$AUC_{0-\infty}$ [ng·h/mL]	22288.72	23280.48	95.74	(92.29, 99.32)	7.8

b. Formulation of the test products

Table 14. Qualitative and Quantitative Composition of the Drug Products

Tablet Strength (mg empagliflozin/mg linagliptin/ mg metformin HCl)	5/2.5/1000	10/5/1000	12.5/2.5/1000	25/5/1000
Metformin HCl Tablet core				

Metformin HCl	1000.00	1000.00	1000.00	1000.00
Polyethylene Oxide (b) (4)				(b) (4)
Hypromellose (b) (4)				
Magnesium Stearate				
				(b) (4)
Empagliflozin	5.0	10.0	12.5	25.0
Linagliptin	2.5	5.0	2.5	5.0
				(b) (4)
Arginine				(b) (4)
Polyethylene Glycol (b) (4)				
Talc				
				(b) (4)
Carnauba Wax				(b) (4)
				(b) (4)
Total mass	1633.2	1650.7	1640.7	1665.7

Reviewer's comment

Table 14 shows that the proposed four strengths are (b) (4). *In Type C response letters dated Feb 13, 2018 and May 30, 2018, FDA recommended the use of a bracketing approach to justify a biowaiver for the two intermediate strength tablets. Specifically, the Applicant should meet the following requirements for the biowaiver:*

- *In-vivo bioequivalence (BE) has been established for the highest and lowest strength tablets and the free combination of the reference products.*
- *In-vitro dissolution similarity was established between the two intermediate strength tablets and the highest and lowest strength tablets where BE was established.*

c. Comparative dissolution assessment in multimedia

1) Empagliflozin

Table 15. Empagliflozin dissolution profile comparation between the clinical batches and two intermediate strengths in multimedia

Lot number/Time (min)	10	15	20	30	45	60
25mg/5mg/1000mg 3148078R in Phosphate Buffer, pH 6.8		32	57	83	94	96
12.5mg/5mg/1000mg 3148073R in Phosphate Buffer, pH 6.8		36	60	83	93	96

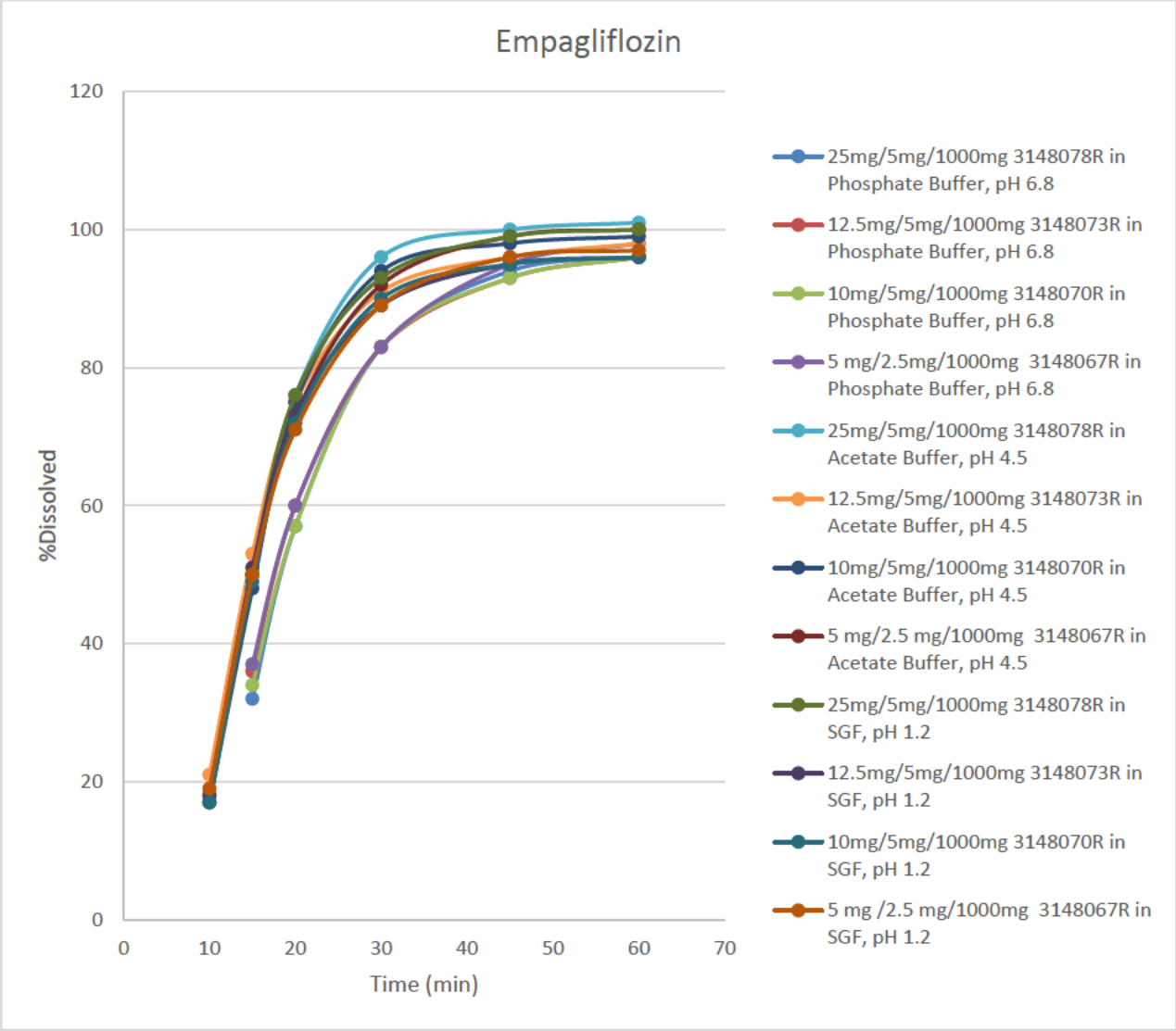
10mg/5mg/1000mg 3148070R in Phosphate Buffer, pH 6.8		34	57	83	93	96
5 mg/2.5mg/1000mg 3148067R in Phosphate Buffer, pH 6.8		37	60	83	95	98
25mg/5mg/1000mg 3148078R in Acetate Buffer, pH 4.5	17	50	76	96	100	101
12.5mg/5mg/1000mg 3148073R in Acetate Buffer, pH 4.5	21	53	75	91	96	98
10mg/5mg/1000mg 3148070R in Acetate Buffer, pH 4.5	17	48	75	94	98	99
5 mg/2.5 mg/1000mg 3148067R in Acetate Buffer, pH 4.5	18	50	73	92	99	100
25mg/5mg/1000mg 3148078R in SGF, pH 1.2	17	50	76	93	99	100
12.5mg/5mg/1000mg 3148073R in SGF, pH 1.2	18	51	73	89	95	96
10mg/5mg/1000mg 3148070R in SGF, pH 1.2	17	49	72	90	95	96
5 mg /2.5 mg/1000mg 3148067R in SGF, pH 1.2	19	50	71	89	96	97

*The batches highlighted in red has abnormal dissolution variability.

Table 16. Dissolution Similarity Factors f2 between clinical batches and two intermediate strengths in multimedia

Comparison	F2
3148078R vs 3148073R in Phosphate Buffer, pH 6.8	82.42
3148078R vs 3148070R in Phosphate Buffer, pH 6.8	93.49
3148067R vs 3148073R in Phosphate Buffer, pH 6.8	94.29
3148067R vs 3148070R in Phosphate Buffer, pH 6.8	82.70
3148078R vs 3148073R in Acetate Buffer, pH 4.5	71.95
3148078R vs 3148070R in Acetate Buffer, pH 4.5	87.78
3148067R vs 3148073R in Acetate Buffer, pH 4.5	79.69
3148067R vs 3148070R in Acetate Buffer, pH 4.5	72.47
3148078R vs 3148073R in SGF, pH 1.2	78.45
3148078R vs 3148070R in SGF, pH 1.2	79.21
3148067R vs 3148073R in SGF, pH 1.2	91.05
3148067R vs 3148070R in SGF, pH 1.2	89.54

Figure 8. Mean Comparative Empagliflozin Dissolution Profiles of the clinical batches and two intermediate strengths in multimedia



The dissolution variability of the following batches is out of the normal ranges (i.e. first time point RSD% >20%, and other time points RSD>10%), the mean dissolution data could not be used to compare dissolution profile similarity. So, this Reviewer used bootstrapping to compare the dissolution similarity between these batches and other relevant batches.

- 12.5mg/5mg/1000mg 3148073R in Phosphate Buffer, pH 6.8
- 25mg/5mg/1000mg 3148078R in Acetate Buffer, pH 4.5
- 10mg/5mg/1000mg 3148070R in Acetate Buffer, pH 4.5
- 25mg/5mg/1000mg 3148078R in SGF, pH 1.2

Table 17. Bootstrapping result table for the empagliflozin dissolution profile comparison between the clinical batches and two intermediate strengths (replicate number =2000)

Comparison	Lower 90% CI (BCA)	Upper 90% CI (BCA)	Mean from bootstrapping	Original f2	Similarity between the test and reference product

3148078R vs 3148073R in Phosphate Buffer, pH 6.8	67.02	92.93	79.57	80.55	Similar (Lower 90% CI (BCA) > 50)
3148067R vs 3148073R in Phosphate Buffer, pH 6.8	90.87	99.47	88.48	94.28	Similar (Lower 90% CI (BCA) > 50)
3148078R vs 3148073R in Acetate Buffer, pH 4.5	65.91	79.31	71.50	71.95	Similar (Lower 90% CI (BCA) > 50)
3148078R vs 3148070R in Acetate Buffer, pH 4.5	80.51	98.30	81.36	87.78	Similar (Lower 90% CI (BCA) > 50)
3148078R vs 3148073R in SGF, pH 1.2	71.88	86.40	77.10	78.45	Similar (Lower 90% CI (BCA) > 50)
3148078R vs 3148070R in SGF, pH 1.2	71.98	87.54	78.67	79.21	Similar (Lower 90% CI (BCA) > 50)

The results in Tables 16 and 17 show that clinical batches and two intermediate strengths are similar on Empagliflozin dissolution profiles in multimedia based on calculated f2 or bootstrapping results.

2) Linagliptin

Table 18. Linagliptin dissolution profile comparation between the clinical batches and two intermediate strengths in multimedia

Lot number/Time (min)	10	15	20	30	45	60
25mg/5mg/1000mg 3148078R in Phosphate Buffer, pH 6.8		40	65	89	97	99
12.5mg/5mg/1000mg 3148073R in Phosphate Buffer, pH 6.8		50	72	90	96	98
10mg/5mg/1000mg 3148070R in Phosphate Buffer, pH 6.8		41	66	89	96	98
5 mg/2.5mg/1000mg 3148067R in Phosphate Buffer, pH 6.8		51	74	93	101	102
25mg/5mg/1000mg 3148078R in Acetate Buffer, pH 4.5	24	60	84	98	101	102
12.5mg/5mg/1000mg 3148073R in Acetate Buffer, pH 4.5	36	69	85	95	98	99
10mg/5mg/1000mg 3148070R in Acetate Buffer, pH 4.5	23	60	84	98	101	102
5 mg/2.5 mg/1000mg 3148067R in Acetate Buffer, pH 4.5	30	68	87	100	104	105
25mg/5mg/1000mg 3148078R in SGF, pH 1.2	35	69	88	98	100	101
12.5mg/5mg/1000mg 3148073R in SGF, pH 1.2	42	75	89	96	97	98
10mg/5mg/1000mg 3148070R in SGF, pH 1.2	33	68	86	95	97	97
5 mg /2.5 mg/1000mg 3148067R in SGF, pH 1.2	42	76	91	100	102	102

*The batches highlighted in red has abnormal dissolution variability.

Figure 9. Mean Comparative Linagliptin Dissolution Profiles of the clinical batches and two intermediate strengths in multimedia

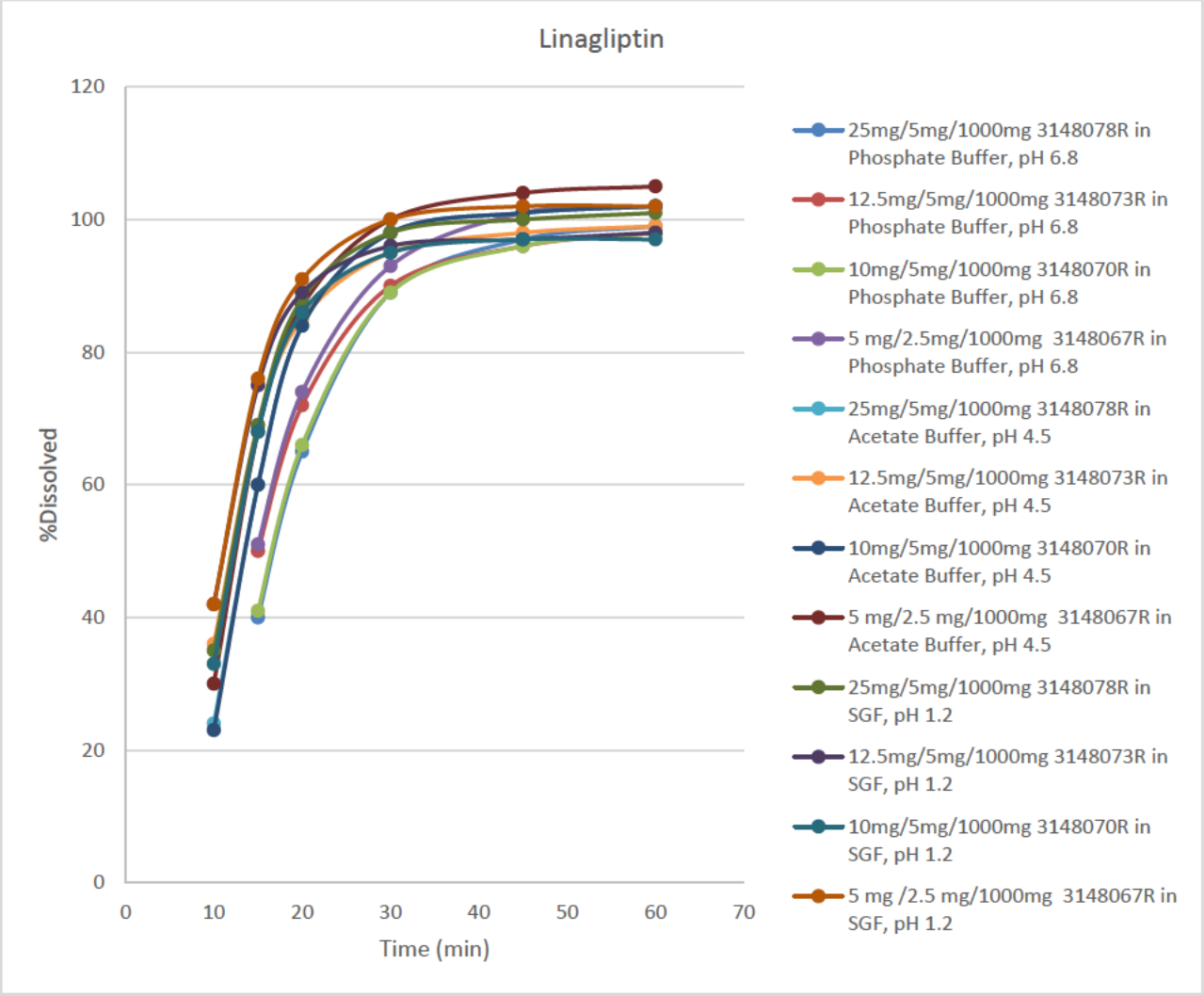


Table 19. Dissolution Similarity Factors f2 between clinical batches and two intermediate strengths in multimedia

Comparison	F2
3148078R vs 3148073R in Phosphate Buffer, pH 6.8	61.93
3148078R vs 3148070R in Phosphate Buffer, pH 6.8	93.49
3148067R vs 3148073R in Phosphate Buffer, pH 6.8	78.91
3148067R vs 3148070R in Phosphate Buffer, pH 6.8	55.75
3148078R vs 3148073R in Acetate Buffer, pH 4.5	55.39
3148078R vs 3148070R in Acetate Buffer, pH 4.5	97.55
3148067R vs 3148073R in Acetate Buffer, pH 4.5	70.26
3148067R vs 3148070R in Acetate Buffer, pH 4.5	60.58
3148078R vs 3148073R in SGF, pH 1.2	62.03
3148078R vs 3148070R in SGF, pH 1.2	85.25
3148067R vs 3148073R in SGF, pH 1.2	88.30
3148067R vs 3148070R in SGF, pH 1.2	55.84

The dissolution variability of the following batches is out of the normal ranges (i.e. first time RSD%>20%, and other time points RSD%>10%), the mean dissolution data could not be used to compare dissolution profile similarity. So, this Reviewer used bootstrapping to compare the dissolution similarity between these batches and other relevant batches.

- 25mg/5mg/1000mg 3148078R in Acetate Buffer, pH 4.5
- 10mg/5mg/1000mg 3148070R in Acetate Buffer, pH 4.5

Table 20. Bootstrapping result table for the linagliptin dissolution profile comparison between the clinical batches and two intermediate strengths (replicate number =2000)

	Lower 90% CI (BCA)	Upper 90% CI (BCA)	Mean from bootstrapping	Original f2	Similarity between the test and reference product
3148078R vs 3148073R in Acetate Buffer, pH 4.5	50.62	60.83	55.60	55.39	Similar (Lower 90% CI (BCA) > 50)
3148078R vs 3148070R in Acetate Buffer, pH 4.5	98.21	99.76	84.16	97.55	Similar (Lower 90% CI (BCA) > 50)
3148067R vs 3148070R in Acetate Buffer, pH 4.5	49.79	84.62	62.47	60.58	Dissimilar (Lower 90% CI (BCA) < 50)

Table 21. MSD result for linagliptin dissolution profile comparison of 3148067R vs 3148070R in Acetate Buffer, pH 4.5

	Similarity limit	Dm-Max	Dm-Lower	Dm-Upper	Similarity between the test product and RLD
3148067R vs 3148070R in Acetate Buffer, pH 4.5	10	3.50	NP	2.26	Similar (Dm-upper < Dm-Max)

The results in the above tables show that clinical batches and two intermediate strengths are similar on linagliptin dissolution profiles in multimedia except 3148067R vs 3148070R in Acetate Buffer, pH 4.5 based on calculated f2 or bootstrapping results.
This Reviewer used MSD method to compare the dissolution profile similarity between 3148067R vs 3148070R in Acetate Buffer and the result is listed in Table 21.

In summary, Batch 3148070R is still considered to be similar to Batch 3148067R due to the following reasons:

a) The conventional f2 is 60.58.
b) MSD analysis result shows that they are similar on dissolution profiles.
c) Lower 90% CI (BCA) of bootstrapping f2 is borderline lower than 50.

3) Metformin

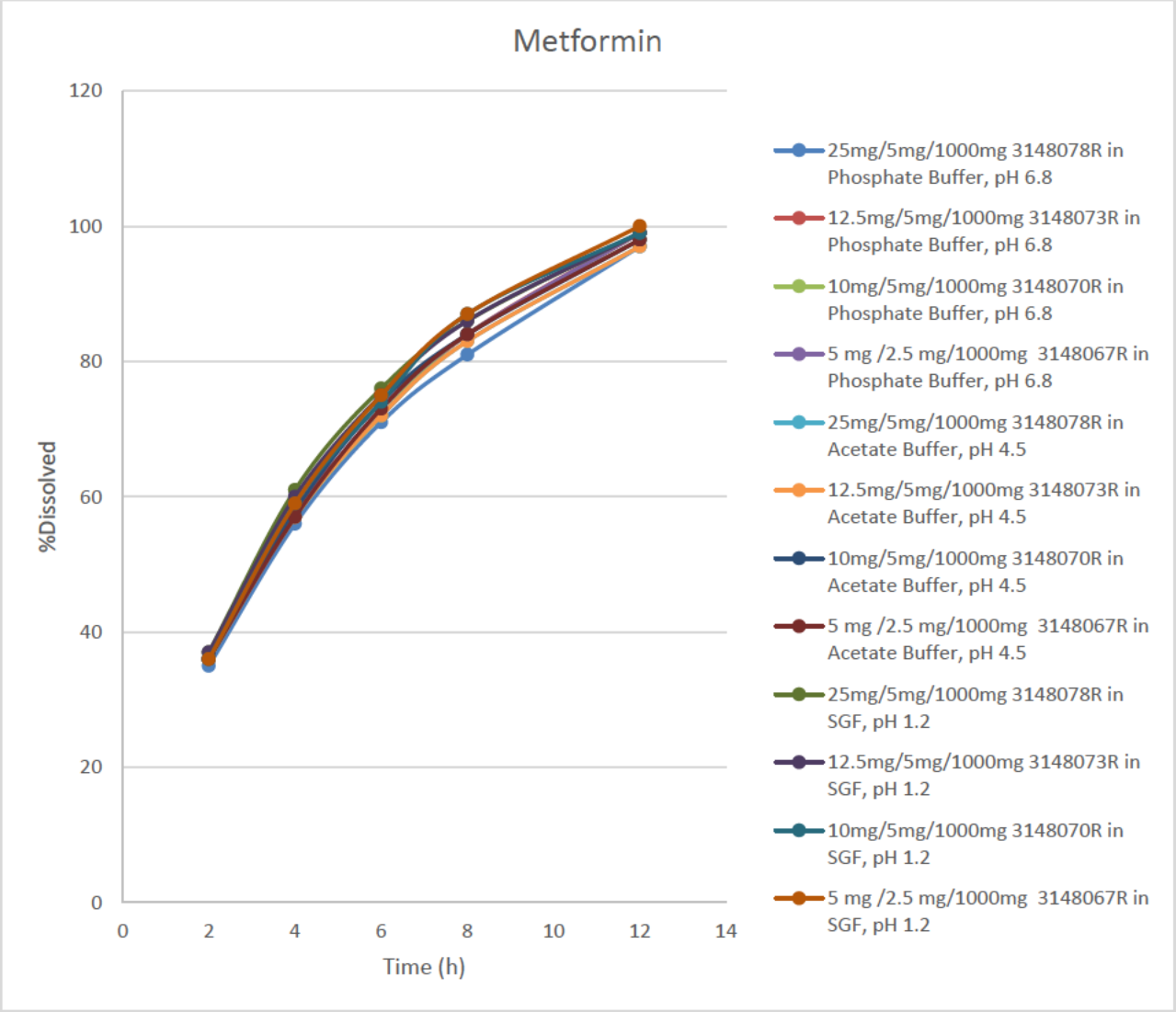
Table 22. Metformin dissolution profile comparation between the clinical batches and two intermediate strengths in multimedia

Lot number/Time (h)	2	4	6	8	12
25mg/5mg/1000mg 3148078R in Phosphate Buffer, pH 6.8	35	56	71	81	97
12.5mg/5mg/1000mg 3148073R in Phosphate Buffer, pH 6.8	36	58	72	84	99
10mg/5mg/1000mg 3148070R in Phosphate Buffer, pH 6.8	36	57	72	84	98
5 mg /2.5 mg/1000mg 3148067R in Phosphate Buffer, pH 6.8	36	57	73	84	99
25mg/5mg/1000mg 3148078R in Acetate Buffer, pH 4.5	36	57	72	83	97
12.5mg/5mg/1000mg 3148073R in Acetate Buffer, pH 4.5	36	57	72	83	97
10mg/5mg/1000mg 3148070R in Acetate Buffer, pH 4.5	36	58	74	84	98
5 mg /2.5 mg/1000mg 3148067R in Acetate Buffer, pH 4.5	36	57	73	84	98
25mg/5mg/1000mg 3148078R in SGF, pH 1.2	37	61	76	86	99
12.5mg/5mg/1000mg 3148073R in SGF, pH 1.2	37	60	75	86	99
10mg/5mg/1000mg 3148070R in SGF, pH 1.2	36	59	74	87	99
5 mg /2.5 mg/1000mg 3148067R in SGF, pH 1.2	36	59	75	87	100

Table 23. Dissolution Similarity Factors f2 between clinical batches and two intermediate strengths in multimedia

Comparison	F2
3148078R vs 3148073R in Phosphate Buffer, pH 6.8	83.31
3148078R vs 3148070R in Phosphate Buffer, pH 6.8	85.32
3148067R vs 3148073R in Phosphate Buffer, pH 6.8	98.95
3148067R vs 3148070R in Phosphate Buffer, pH 6.8	98.57
3148078R vs 3148073R in Acetate Buffer, pH 4.5	98.47
3148078R vs 3148070R in Acetate Buffer, pH 4.5	90.74
3148067R vs 3148073R in Acetate Buffer, pH 4.5	92.38
3148067R vs 3148070R in Acetate Buffer, pH 4.5	98.05
3148078R vs 3148073R in SGF, pH 1.2	96.09
3148078R vs 3148070R in SGF, pH 1.2	90.02
3148067R vs 3148073R in SGF, pH 1.2	93.48
3148067R vs 3148070R in SGF, pH 1.2	98.20

Figure 8. Mean Comparative Metformin Dissolution Profiles of the clinical batches and two intermediate strengths in multimedia



The calculated similarity factors shown in Table 23 indicate that clinical batches and two intermediate strengths are similar on metformin dissolution profiles in multimedia.

d. Biowaiver

Provided bioequivalence is demonstrated between the highest (25 mg/5 mg/1000 mg) and lowest (5 mg/2.5 mg/1000 mg) strengths of empagliflozin/linagliptin/metformin HCl extended-release XR tablets and the free combination of the reference products Jardiance®, Tradjenta® and Glumetza®, the biowaiver is granted for the two intermediate strengths due to the following reasons:

1) The two intermediate strengths are in the same dosage form, but in different strengths.
2) The two intermediate strengths are similar to the highest strength and the lowest strength on dissolution profiles in multimedia.

Appendix I. Dissolution Data

Dissolution data of clinical batches
5 mg/2.5 mg/1000 mg, Batch 3148067R
Empagliflozin

Replicate	% Empagliflozin Released				
	15 minutes	20 minutes	30 minutes	45 minutes	60 minutes
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean (n=12)	37	60	83	95	98
RSD (%) (n=12)	11.1	5.3	3.1	2.7	2.7

Linagliptin

Replicate	% Linagliptin Released				
	15 minutes	20 minutes	30 minutes	45 minutes	60 minutes
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean (n=12)	50	74	93	101	102
RSD (%) (n=12)	8.8	4.6	2.2	2.2	2.2

Metformin HCl

Replicate	% Metformin HCl Released				
	2 hours	4 hours	6 hours	8 hours	12 hours
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean (n=12)	35	57	73	84	99
RSD (%) (n=12)	1.4	1.0	0.9	1.3	0.8

25 mg/5 mg/1000 mg, Batch 3148078R
Empagliflozin

Replicate	% Empagliflozin Released				
	15 minutes	20 minutes	30 minutes	45 minutes	60 minutes
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean (n=12)	32	57	83	94	96
RSD (%) (n=12)	17.1	10.4	4.4	2.8	2.3

Linagliptin

Replicate	% Linagliptin Released				
	15 minutes	20 minutes	30 minutes	45 minutes	60 minutes
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean (n=12)	40	65	89	97	99
RSD (%) (n=12)	15.5	8.7	3.2	2.4	2.1

Metformin HCl

Replicate	% Metformin HCl Released				
	2 hours	4 hours	6 hours	8 hours	12 hours
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean (n=12)	35	56	71	81	97
RSD (%) (n=12)	1.7	1.0	0.6	0.8	0.8

The other batches' dissolution data:

The other complete dissolution data can be located by the following link:
\\cdsesub1\evsprod\nda212614\0000\m3\32-body-data\32p-drug-prod\empa-lina-met-er-fdc-tablet\32p2-pharm-dev\19-015-01.pdf

Appendix II. Information Requests (IR)

Biopharmaceutics Information Request 1

After the filling review, the first Biopharmaceutics IR was sent to the Applicant on 7/26/2019. On 8/5/2019, the Applicant responded to the IR. The following are the Biopharmaceutics IR, the Applicant's response, and this Reviewer's assessment of the Applicant's response.

IR 1 Item 1

1. Submit a full dissolution development report to the agency for review. Include the following information in your report:
   - Detailed description of the dissolution test being proposed for the evaluation of the proposed drug product, along with the developmental parameters supporting the selection of the proposed dissolution method as the optimal test for the drug product (i.e., selection of the apparatus, in vitro dissolution medium, rotation speed, pH, sink conditions, etc.).
   - Data supporting the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) drug product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical material attributes, critical formulation variables, and critical process parameters (e.g., ± 10-20% change to the specified values or ranges for these variables). Submit the dissolution profile data and similarity testing results obtained with appropriate statistical test (e.g., f2 values) comparing the test and reference drug products. In addition, if available, submit data showing that the selected dissolution method is able to reject product that is not bioequivalent to the reference-target drug product.

The Applicant's response to IR 1 Item 1

Boehringer Ingelheim Pharmaceuticals Inc. (BIPI) provides the content found in a dissolution development report in the Pharmaceutical Development (3.2.P.2) and Justification of Dissolution Specification (3.2.P.5.6) reports. The information associated with dissolution development can be found in these documents in the BIPI NDA application submitted for the empagliflozin/linagliptin/metformin HCl ER drug product (NDA 212,614). (b) (4)

Reviewer's comment

The response is adequate. The Applicant's response was thoroughly reviewed in Section-Dissolution Method and Acceptance Criteria.

IR 1 Item 2

2. In Module 3.2.P.2 Pharmaceutical Development (q00263655-01), you stated that an in-vitro alcohol dose dumping study has been conducted and the results are reported in section 3.2.P.2 "Alcohol-induced Dose Dumping Assessment by In-vitro Dissolution". However, this report could not be located in this submission. Submit the report to the Agency for review.

The Applicant's response to IR 1 Item 2

The Alcohol-Induced Dose Dumping assessment was inadvertently omitted from the original application. The document, Alcohol Induced Dose Dumping (q00262935-01) is provided in this amendment.

Reviewer's comment
The response is adequate. The study results were thoroughly reviewed in Section-MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping.

Biopharmaceutics Information Request 2
The second Biopharmaceutics IR was sent to the Applicant on 8/19/2019. On 8/29/2019, the Applicant responded to the second IR. The following are Biopharmaceutics IR 2, the Applicant's response, and this Reviewer's assessment of the Applicant's response.

IR 2
The in vitro alcohol induced dose dumping study report (Document number: q00262935-01) shows that the comparative dissolution tests were conducted in SGF without enzymes with different concentrations of alcohol. Since SGF without enzymes is not your proposed QC method medium, per our current practice, you should conduct and submit in vitro alcohol induced dose dumping study in the QC medium (i.e. 50 mM Phosphate Buffer pH 6.8) as well.

The Applicant's response to IR 2

Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) stated that the empagliflozin + linagliptin + metformin HCl ER tablet that is the subject of NDA 212614 is comprised of the immediate release active components empagliflozin and linagliptin and the extended release active component metformin HCl. As per the above cited FDA Guidance, the in-vitro alcohol dose dumping requirement applies only to the metformin HCl ER component of this product.

The information provided in Section 3.2.P.5.6 ("Justification of Dissolution Specification, Section 3.2.1.6) shows that the dissolution profile of metformin HCl ER from the empagliflozin +linagliptin + metformin HCl ER coated tablet is independent of pH.

BIPI had demonstrated that the metformin HCl ER dissolution profile is independent of pH and, consistent with the FDA February 2019 Draft Guidance: "Bioavailability Studies Submitted in NDAs or INDs — General Considerations", concluded that the dissolution in only 0.1N HCl was sufficient to indicate that alcohol dose dumping of metformin HCl ER does not occur in the empagliflozin + linagliptin + metformin HCl ER coated tablets and that no additional studies would be needed

Reviewer's comment
The response is adequate.

Primary Biopharmaceutics Reviewer Name:
Hansong Chen, PharmD, Ph.D.
Biopharmaceutics Reviewer
OPQ/ONDP/DB

Secondary Reviewer Name:
Haritha Mandula, Ph.D.
Biopharmaceutics Quality Assessment Lead
OPQ/ONDP/DB

Hansong Chen

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Haritha Mandula

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Muthukumar Ramaswamy

Digitally signed by Muthukumar Ramaswamy
Date: 12/09/2019 07:00:40PM
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/s/

MUTHUKUMAR RAMASWAMY
12/09/2019 07:14:48 PM