CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216743Orig1s000

PRODUCT QUALITY REVIEW(S)

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Office of Pharmaceutical Quality

New Drug Application (NDA)
Integrated Quality Assessment Template

NDA Executive Summary

1. Application/Product Information

NDA Number	216743		
Applicant Name	Zydus Pharmaceuticals (USA) Inc.		
Drug Product Name	Zituvimet (Sitagliptin and metformin hydrochloride) tablets		
Dosage Form	Tablet		
Proposed Strength(s)	50 mg/500 mg, and 50 mg/1000 mg		
NDA Classification	Type 2 – New Active Ingredient		
Route of Administration	Oral		
Maximum Daily Dose	100 mg sitagliptin/2000mg metformin HCl		
Rx/OTC Dispensed	Rx		
Proposed Indication	Glycemic control in adults with Type 2 diabetes		
Drug Product Description	White to off white, oval, biconvex, film coated tablets debossed with: 50 mg/500 mg Tablets: White to off white, oval, biconvex, film coated tablets debossed with “1786” on one side and plain on the other side. 50mg/1000 mg Tablets: reddish brown, oval, biconvex, film coated tablets debossed with “1787”” on one side and “plain on the other side. Tablets are packaged in 60ct and 180ct high density polyethylene (HDPE) bottles with desiccant and (b) (4) child resistant closure.		
Co-packaged product information	NA		
Device information	N/A		
Storage Temperature/ Conditions	20°C to 25˚C excursions permitted between 15° and 30°C		
Review Team	**Discipline**	**Primary**	**Secondary**

	Drug Substance	Daniel Jansen	Zhengfu Wang
	Drug Product/ Labeling	Dan Berger	Muthukumar Ramaswamy
	Manufacturing	Naresh Pavurala	Erin Kim
	Biopharmaceutics	Rebecca Moody-	Haritha Mandula
	Microbiology	-	-
	Other (specify)	-	-
	RBPM	Oluwafunmike (Funke) Ajomale	
	ATL	Muthukumar Ramaswamy	
Consults			

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: A shelf-life of 12 months from the date of manufacture for Zituvimet (sitagliptin and metformin HCl) tablets, 50mg/500mg, and 50mg/1000mg tablets packaged in 60ct and 180ct bottles, when stored at long-term storage conditions 25°C/60% RH or 3 months after first use.

b. Additional Comments for Action- none

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The Office of Pharmaceutical Quality Review team has assessed the Chemistry, Manufacturing, and Controls (CMC) information for NDA 216743 resubmission and determined that the NDA meets all applicable standards to support the quality and purity of the drug product. As such, OPQ recommends approval of this NDA from a quality perspective.

This 505(b)(2) NDA, 216743 is for a fixed combination product containing sitagliptin and metformin hydrochloride provided as 50 mg/500mg and 50mg/1000mg in 60ct and 180ct high density polyethylene (HDPE) bottles. The listed drug (LD) product, JANUMET® (Sitagliptin and Metformin Hydrochloride) tablets (NDA 022044) contains Sitagliptin Phosphate Monohydrate, whereas the proposed drug product contains Sitagliptin as a free base.

The Applicant conducted single-dose bioequivalence studies in the fasting and fed state to bridge the proposed drug product (Sitagliptin and Metformin Hydrochloride Tablets, 50 mg/1000 mg) to JANUMET® (50 mg/1000 mg) in support of their NDA submission. The applicant provided information in support of a biowaiver request for the lower strength (i.e., sitagliptin and metformin hydrochloride tablet, 50 mg/500 mg) in accordance with 21 CRF 320.22 (d)(2) and FDA guidance. Biopharmaceutics reviewer reviewed the biowaiver request and concluded that adequate information was provided for the biowaiver request.

(b) (4)

Based on available stability data, a shelf-life of 12 month was granted for the 50mg/500mg, and 50mg/1000mg tablets packaged in sealed 60ct and 180ct bottles, when stored at 25°C/60% RH. Per FDA recommendation, the applicant

(b) (4)

The process and facility review concluded that the process and facilities information provided in the NDA is adequate. The Panorama screen shot of facility assessment is shown below (recorded on 9/27/2023).

(b) (4)

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**N/A**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:
None

Muthukumar Ramaswamy 9-29-2023

Application Technical Lead Name and Date:

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

Preliminary CMC comments related to the prescribing information and container labels were communicated to the applicant. As of 9/28/2023, the applicant accepted the labeling changes (storage instructions) for container label. The established name, strength, in-use period, and storage temperature are harmonized between the container label and prescribing information. Labeling review for prescribing information will be completed along with the OND labeling review team. This review supersedes original labeling review in Panorama dated 9/20/2023.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Zituvimet	Adequate
Established name(s)	Sitagliptin and metformin hydrochloride	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.	Sitagliptin 50 mg and metformin HCl 500 mg, Sitagliptin 50 mg and metformin HCl 1000 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
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	NA	NA

pharmacy bulk package and imaging bulk package.		

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)	NA	NA

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)	Tablets	Adequate
Strength(s) in metric system	Sitagliptin 50 mg/ metformin HCl 500 mg, Sitagliptin 50 mg/ metformin HCl 1000 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Metformin HCl is retained for consistency with drug approved before May 1, 2013	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	White/reddish brown oval, biconvex, film coated tablet debossed with "1786" on one side/ 1787" on one side respectively for 50/500 and 50/1000 mg strengths	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
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.	NA	NA

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Zituvimet, sitagliptin and metformin HCl	Adequate
Dosage form(s) and route(s) of administration	Tablets, added "for oral use"	Adequate, with edits.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Metformin HCl is retained for consistency with drug approved before May 1, 2013	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Colloidal silicon dioxide, croscarmellose sodium, low substituted hydroxypropylcellulose, magnesium stearate, malic acid, microcrystalline cellulose, povidone, sodium stearyl fumarate. Coating: polyethylene glycol, poly vinyl alcohol, talc, titanium dioxide; The 50 mg/1000 mg tablet contains iron oxide red & yellow, Yellow #6 aluminum lake.	Adequate, following alphabetization
For parenteral injectable dosage forms, include name and quantities of all inactive ingredients.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)	NA	NA
Pharmacological/ Therapeutic class	DPP-4 enzyme inhibitor/ antihyperglycemic	Adequate
Chemical name, structural formula, molecular weight	Chemical names*, 407.31/165.62 g/mol, $C_{16}H_{15}F_6N_5O/C_4H_{11}N_5$•HCl	Adequate
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	White to off-white powder slightly soluble in water/white crystalline powder soluble in water.	Adequate

*7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine/ N,N-dimethylimidodicarbonimidic diamide hydrochloride

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	NA
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	NA	NA

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)	Tablets	Adequate
Strength(s) in metric system	50 mg sitagliptin & 500 mg metformin HCl 50 mg sitagliptin & 1000 mg metformin HCl	Adequate
Available units (e.g., bottles of 100 tablets)	Bottles of 60, 180 tablets	Adequate. Per FDA advice, (b) (4)
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Shape, color, debossing, NDC 70710-1786-6/8, NDC 70710-1787-6/8	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
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.	NA	NA

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.)	We recommend adding a statement to use within 3 months after opening (b) (4) (b) (4)	Adequate. The applicant accepted in-use period statement for container labels on 9/28/2023
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.”	(b) (4)	Adequate
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F)	Adequate, as of 9/28/2023, Zydus accepted the following edits for the container label: “Dispense in original container to protect from moisture. Once the bottle has been opened, the product must be used within 3 months.
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 statements such as “latex-free.”	NA	NA
Include information about child-resistant packaging	Included.	Adequate

1.2.5 Other Sections of Labeling

No other sections of the labeling 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 Zydus Pharmaceuticals (USA) Inc. Pennington, NJ 08534	Adequate, following recommended edit to include street address.

2.0 PATIENT LABELING

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

The medication guide contains storage conditions and excipients and is acceptable following alphabetization of excipients.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

Bottle (50 mg/500 mg strength representative example):

3.2 Carton Labeling

NA

Item	Information Provided in the NDA	Assessor's Comments about Bottle Labeling
Proprietary name, established name, and dosage form (font size and prominence	Zituvimet, sitagliptin and metformin HCl	Adequate
Dosage strength	50 mg sitagliptin & 500 mg metformin HCl 50 mg sitagliptin & 1000 mg metformin HCl	Adequate
Route of administration	Not required for oral drug	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Metformin HCl is retained for consistency with drug approved before May 1, 2013	Adequate
Net contents (e.g., tablet count)	Bottles of 60, 180 tablets.	Adequate. Per CMC (b) (4)
"Rx only" displayed on the principal display	Present	Adequate
NDC number	NDC 70710-1786-6/8, NDC 70710-1787-6/8	Adequate
Lot number and expiration date	Present	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F)	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	NA
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Bar code	Present	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured by: Zydus Lifesciences Ltd., Ahmedabad, India.	Adequate
Medication Guide (if applicable)	Storage conditions and inactive ingredients.	Adequate, with edits made.
No text on Ferrule and Cap overseal	NA	NA
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.	NA	NA
And others, if space is available	Use within 3 months after first use. Date of opening: Expiry date: 3 months after first use.	Adequate

Assessment of Carton and Container Labeling: *Adequate*
Labels are acceptable and comply with all regulatory requirements from a CMC perspective.

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation: Adequate

The established name, strength, in-use period, and storage temperature are adequate and consistent between the container label and prescribing information.

Primary Labeling Assessor Name and Date:

Dan Berger September 20, 2023 (Original labeling review)

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Muthukumar Ramaswamy September 29, 2023

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	505(b)(2); Type 5: New Formulation or New Manufacturer- Sitagliptin and Metformin Hydrochloride Tablet
NDA Number	216743
Assessment Cycle Number	1
Drug Product Name/ Strength	Zituvimet (sitagliptin and metformin hydrochloride) Tablet; 50 mg/500 mg and 50 mg/1000 mg
Route of Administration	Oral
Applicant Name	Zydus Worldwide DMCC
Therapeutic Classification/ OND Division	Antidiabetic Agents, Non-Insulin/Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
RLD/RS Number	NDA 022044 (JANUMET® (sitagliptin and metformin hydrochloride) Tablets
Proposed Indication	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Assessment Recommendation: **Adequate**

Assessment Summary:

Zydus, the Applicant, submitted a 505(b)(2) application for the proposed Sitagliptin and Metformin Hydrochloride Tablets, 50 mg/500 mg and 50 mg/1000 mg, on January 3, 2023. The listed drug (LD) product, JANUMET® (Sitagliptin and Metformin Hydrochloride) tablets (NDA 022044) contains Sitagliptin Phosphate Monohydrate, whereas the proposed drug product contains Sitagliptin as a free base. The Applicant conducted single-dose bioequivalence studies in the fasting and fed state to bridge the proposed drug product (Sitagliptin and Metformin Hydrochloride Tablets, 50 mg/1000 mg) to JANUMET® (50 mg/1000 mg) in support of their NDA submission.

The Biopharmaceutics review is focused on the evaluation and acceptability of the proposed quality control dissolution method and acceptance criterion and the evaluation of the biowaiver request.

Dissolution method and Acceptance Criterion:

The FDA approved quality control dissolution method and acceptance criterion (finished drug product batch release and stability testing) for Zituvimet (sitagliptin and metformin hydrochloride) Tablet; 50 mg/500 mg and 50 mg/1000 mg are as follows:

Medium	0.1N HCl
Volume/Temp	500 mL; 37°C
USP Apparatus	1 (Basket)

Rotational Speed	100 rpm
Acceptance Criterion	NLT (b) (4)% (Q) of the labeled amount of sitagliptin and metformin hydrochloride are dissolved in 30 minutes

Biowaiver:

The Applicant provided adequate information to support the biowaiver request for the lower strength (i.e., sitagliptin and metformin hydrochloride tablet, 50 mg/500 mg) in accordance with 21 CRF 320.22 (d)(2) and FDA guidance.

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
0006 (6) Original Submission	**January 3, 2023**

Highlight Key Issues from Last Cycle and Their Resolution: None

Concise Description of Outstanding Issues: None

B.1 BCS DESIGNATION

Assessment: Not applicable. The Applicant did not request an official BCS claim. Therefore, no assessment is necessary. It is noted that Metformin HCl USP is classified as a BCS Class III (high solubility, low permeability) drug substance according to the chemistry Review of Janumet® (sitagliptin and metformin hydrochloride) Tablets (NDA 022044).[1]

Solubility: The Applicant conducted solubility testing across the pH range of 1.2-7.2 and found that sitagliptin free base and metformin hydrochloride exhibit high solubility across the entire physiological pH range. Solubility of sitagliptin free base and metformin are provided below in Tables 1 and 2:

Table 1. Solubility of Sitagliptin Free Base

Sitagliptin Free Base			
Vendor Batch No.	(b) (4)		
(b) (4) **No.**			
Medium	**BCS Solubility (mg/mL)**	**BCS Solubility (mg/250 mL)**	**Solubility**
0.1 N Hydrochloric Acid	0.41	102.5	Soluble
pH 4.5 Acetate Buffer	0.40	100.0	Soluble
pH 6.8 Phosphate Buffer	0.41	102.5	Soluble
pH 7.2 Phosphate buffer	0.40	100.0	Soluble
Purified water	0.40	100.0	Soluble

[1] NDA 022044 Chemistry Review

Table 2. Solubility of Metformin Hydrochloride

Metformin Hydrochloride USP			
Vendor Batch No.	(b) (4)		
(b) (4) No.			
Medium	**BCS Solubility (mg/mL)**	**BCS Solubility (mg/250 mL)**	**Solubility**
0.1 N Hydrochloric Acid	8.04	2010.0	Soluble
pH 4.5 Acetate Buffer	8.11	2027.5	Soluble
pH 6.8 Phosphate Buffer	8.07	2017.5	Soluble
pH 7.2 Phosphate buffer	8.16	2040.0	Soluble
Purified water	8.13	2032.5	Soluble

Permeability: The absolute bioavailability of sitagliptin is approximately 87%, while the absolute bioavailability of a metformin hydrochloride 500 mg tablet given under fasting conditions is approximately 50-60%.

Dissolution: See Assessment below.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: Adequate

The proposed dissolution test method and acceptance criterion for Sitagliptin and Metformin Hydrochloride tablets, 50 mg/500 mg and 50 mg/1000 mg are as follows:

Medium	0.1N HCl
Volume/Temp	500 mL; 37°C
USP Apparatus	1 (basket)
Rotational Speed	100 rpm
Acceptance Criterion	NLT (b) (4)% (Q) of the labeled amount of sitagliptin and metformin hydrochloride are dissolved in 30 minutes

Figure 1. Comparative Dissolution Data of RLD (50 mg/1000 mg) vs Test Product (50 mg/1000 mg)-Sitagliptin

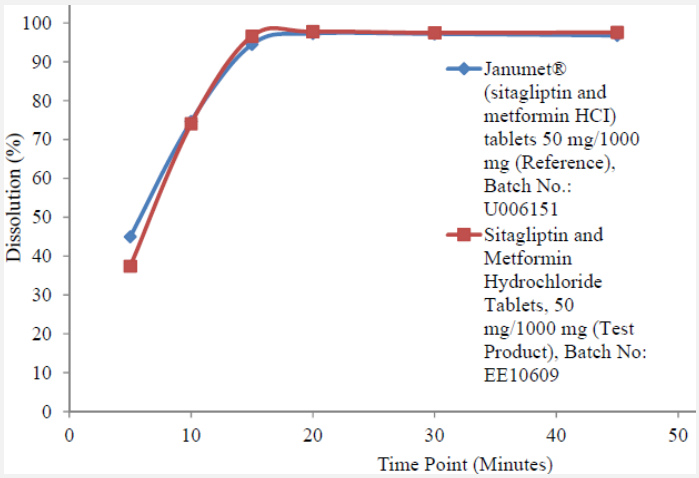
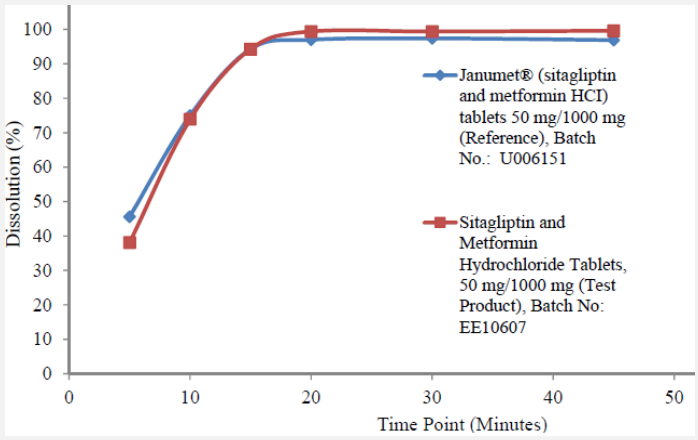


Figure 2. Comparative Dissolution Data of RLD (50 mg/1000 mg) vs Test Product (50 mg/1000 mg)-Metformin HCl



No discriminating ability was demonstrated for the dissolution method; however, as sitagliptin and metformin are considered highly soluble drug substances, the standardized dissolution method and acceptance criterion as outlined in the FDA Guidance (August 2018) "Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances" is acceptable.

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA *(e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)*

Assessment: Adequate

The product is designed as an immediate release tablet containing high solubility drug substances; therefore, there is relatively low risk with respect to the impact of dissolution on in vivo performance especially with the proposed drug product meeting the recommendations set forth in the FDA Guidance (August 2018) "Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances" is acceptable.

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD

Assessment: Adequate

The Applicant used dissolution testing throughout drug product development and to evaluate robustness of final formulation.

B.12 BRIDGING OF FORMULATIONS

Assessment: N/A

No bridging is necessary. The formulation of the drug product used in the pivotal clinical studies (see Table 3 for formulation) is representative of the to-be-marketed product. The Applicant notes there is no difference between the manufacturing process and type of equipment in the manufacturing of the biobatch and proposed production batches.

Intended Batch Size is the same as the Exhibit Batch. Comparative details of the Exhibit and Intended Commercial Batch Sizes are listed below:

Product	Total Tablets Weight (mg)	Exhibit Batch Size		Intended Commercial Batch Size	
		kg	Tablets	kg	Tablets
Sitagliptin and Metformin Hydrochloride Tablets, 50 mg/500 mg	(b) (4)				
Sitagliptin and Metformin Hydrochloride Tablets, 50 mg/1000 mg					

B. 13 BIOWAIVER REQUEST

Assessment: Adequate

The proposed Sitagliptin and Metformin HCl tablets consist of two strengths: 50 mg/500 mg and 50 mg/1000 mg. The 50 mg/1000 mg strength was used for the pivotal BE studies and the Applicant requested a biowaiver for the lower strength, i.e., 50 mg/500 mg tablet, in accordance with 21 CFR 302.22(d)(2). The following information was provided in support of the biowaiver request:

1. Established bioequivalence for the higher strength 50 mg/1000 mg compared to the RLD, JANUMET, in healthy adults under fasting and fed conditions.
2. Sitagliptin and Metformin Hydrochloride Tablets, 50 mg/500 mg, is proportionally similar in composition of its active and inactive ingredients to the biobatch (50 mg/1000 mg).

Table 3. Composition of Sitagliptin and Metformin HCl Tablets 50 mg/500 mg and 50 mg/100 mg

Ingredient(s)	50 mg/500 mg		50 mg/1000 mg	
	mg/tablet	% w/w	mg/tablet	% w/w
(b) (4)				
Metformin Hydrochloride USP	500.00	(b) (4)	1000.00	(b) (4)
Microcrystalline Cellulose (b) (4) (b) (4)				(b) (4)
Croscarmellose Sodium (b) (4) (b) (4)				
Povidone (b) (4) (b) (4)				
(b) (4)				
Sitagliptin free base (b) (4)	50.00	(b) (4)	50.00	(b) (4)
Low Substituted Hydroxypropylcellulose (b) (4) (b) (4)				(b) (4)
Malic Acid (b) (4)				
Colloidal Silicon Dioxide (b) (4) (b) (4)				
Sodium Stearyl Fumarate (b) (4)				
Magnesium Stearate (b) (4)				
Film Coating				
(b) (4)				
Total weight of film coated tablet (mg)				

3. Comparable dissolution profiles of Sitagliptin and Metformin Hydrochloride Tablets 50 mg/500 mg and 50 mg/1000 mg in 0.1N HCl, USP I (Basket), 100 RPM, 37°C.

Figure 3. Comparative Dissolution Data of Biobatch (50 mg/1000 mg) vs Lower Strength Test Product (50 mg/500 mg)-Sitagliptin

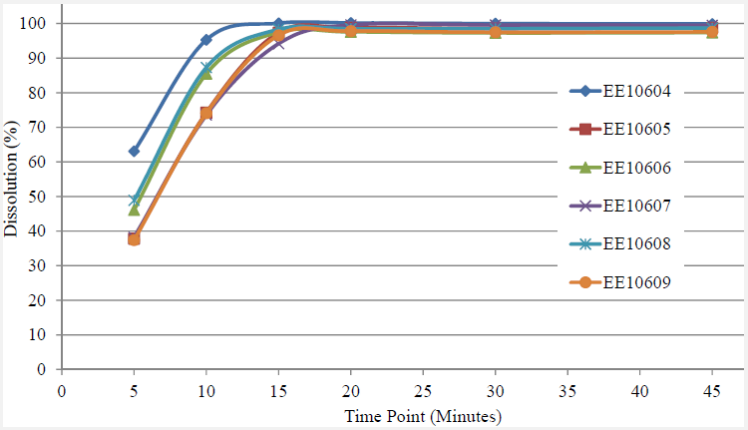
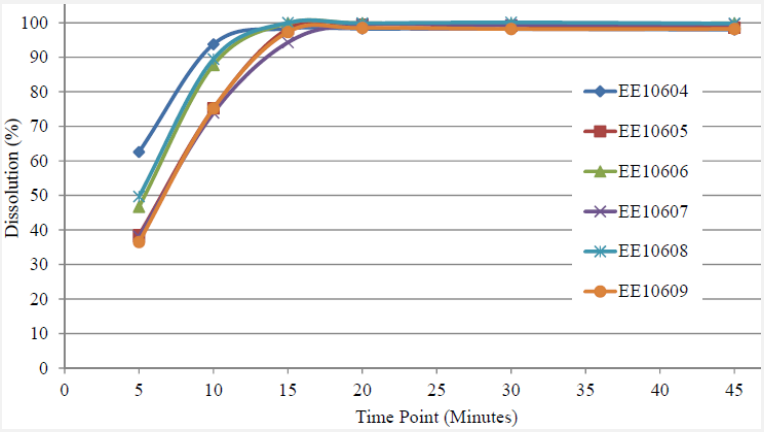


Figure 4. Comparative Dissolution Data of Biobatch (50 mg/1000 mg) vs Lower Strength Test Product (50 mg/500 mg)-Metformin HCl



Reviewer Comment: The results of the fasting and fed bioequivalent studies for the highest strength of the proposed drug product, Sitagliptin and Metformin HCl Tablets 50 mg/1000 mg, were adequate to demonstrate bioequivalence between the test product and the RLD as assessed by the Clinical Pharmacology Review (refer to clinical pharmacology review for additional details).

While the active and inactive ingredients are (b) (4)

(b) (4)

(b) (4)

Lastly, the Applicant provided comparative dissolution data for 3 exhibit batches of both strengths (including the biobatch, batch EE10609) using the proposed QC dissolution method. All batches exhibit similar release (note that *f2* similarity factor was not calculated as all batches exhibited greater than (b) (4) % release in (b) (4) minutes).

Therefore, the Applicant's request for a biowaiver for the lower strength is acceptable.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None.

Primary Biopharmaceutics Assessor's Name and Date: Rebecca R. Moody, Ph.D. 9/6/2023

Secondary Assessor Name and Date (and Secondary Summary, as needed): Haritha Mandula, Ph.D. 9/14/2023

Haritha Mandula

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Rebecca Moody

Digitally signed by Rebecca Moody
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