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RESEARCH**

APPLICATION NUMBER:

216778Orig1s000

PRODUCT QUALITY REVIEW(S)



Title:	NDA IQA Template Title Page- EXEC SUMMARY		
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Total Pages:	5		



Template Revision: 03

Office of Pharmaceutical Quality

New Drug Application (NDA) Integrated Quality Assessment Template

NDA Executive Summary

1. Application/Product Information

NDA Number	216778
Applicant Name	Zydus Worldwide DMCC
Drug Product Name	Zituvimet XR (Sitagliptin and metformin hydrochloride extended release) tablets
Dosage Form	Tablet
Proposed Strength(s)	50 mg/500 mg, 50 mg/1000 mg, and 100/1000mg
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	50 mg/500 mg Tablets: Light orange to beige colored, oval shaped, film coated tablets debossed with “1804” on one side and plain on the other side. 50mg/1000 mg Tablets: yellow to beige colored, oval shaped, film coated tablets debossed with “1805” on one side and “plain on the other side. 100 mg/1000 mg Tablets: Reddish brown to brown colored, oval shaped, film coated tablets debossed with “1806” on one side and plain on the other side. Tablets are packaged in 30ct or 60ct 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
	<i>Drug Substance</i>	Ben Zhang	Zhengfu Wang
	<i>Drug Product/ Labeling</i>	Jennifer McChord	Muthukumar Ramaswamy
	<i>Manufacturing</i>	Peter Krommenhoek	Aditi Thakur
	<i>Biopharmaceutics</i>	Huang Moldthan	Haritha Mandula
	<i>Microbiology</i>	-	-
	<i>Other (specify)</i>	-	-
	<i>RBPM</i>	Oluwafunmike (Funke) Ajomale	
	<i>ATL</i>	Muthukumar Ramaswamy	
Consults			

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: A shelf-life of 18 months from the date of manufacture for Zituvimet XR (sitagliptin and metformin HCl extended release) tablets, 50mg/500mg, 50mg/1000mg and 100/1000mg tablets packaged in 30ct and 60ct bottles, when stored at long-term storage conditions 25°C/60% RH.

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 216778 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, 216778 is for a (b) (4) tablet containing sitagliptin free base (b) (4) and metformin hydrochloride (b) (4) provided as 50 mg/500mg, 50mg/1000mg and 100/1000mg in 30ct or 60ct high density polyethylene (HDPE) bottles with desiccant. The listed drug (LD) product, JANUMET® XR (sitagliptin and metformin hydrochloride extended

release) tablets (NDA 202270) contains sitagliptin phosphate monohydrate and metformin HCl.

The Applicant conducted bioequivalence studies to bridge the proposed drug product to JANUMET® XR tablets using 100/1000mg tablets. The in vivo BA/BE studies are evaluated by the Office of Clinical Pharmacology. The applicant requested biowaiver for the lower strengths (i.e., sitagliptin and metformin hydrochloride tablet, 50 mg/500 mg and 50mg/1000mg) on the basis that the proposed strength tablets are proportionally similar in composition of their active and inactive ingredients and provided in-vitro dissolution profile information. Biopharmaceutics reviewer reviewed the biowaiver request and concluded that adequate information was provided for the biowaiver request.

During review cycle, the applicant provided manufacturing and control information for nitrosamine impurities, (b) (4), (b) (4), and (b) (4) in the drug substance and drug product. OPQ review concluded that it is adequate to meet the FDA established lifetime acceptable intake (AI) limits.

Based on available stability data, a shelf-life of 18 month was granted for the 50mg/500mg, and 50mg/1000mg tablets packaged in (b) (4) 30ct or 60ct bottles, when stored at 25°C/60% RH.

The OPMA 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 6/12/2024).

Latest Overall Manufacturing Inspection Recommendation

Approve

Completion Date: 05/16/2024
NDA-216778-ORIG-1

Inspection Requested

0

Inspection Completed

1

pOAI/OAI Alerts

No

Pending Profile

No

Hint: Click Facility ID link to open Facility Program.
Click Facility Name to open Facility Status View; Detail.
To refresh the report, please click Refresh under Page Options.
Page Options can be found next to the "?" icon located at the top right.

Facility ID	FEE	Facility DUNS	Facility Name	Latest Facility Status / As of Date / Recommendation Reason	Profile Code	Facility Drug Supply Chain Role	Compliance Status / Alert Date	Compliance Status Change Reason
(b) (4)							Compliant	
							Compliant	
11000121	3002984011	91896198	ZYDUS LIFESCIENCE S LIMITED	Approve Facility 10/24/2023 Based on Profile	LCP LABORATORY, CHEMICAL/PHYSICAL TESTING	Product Supply Chain: RELEASE TESTER: SITAGLIPTIN AND METFORMIN HYDROCHLORIDE	Compliant as of 11/4/2022	OPQ review - VAI
110002136	3002806475	918917605	ZYDUS LIFESCIENCE S LIMITED	Approve Facility 10/25/2023 District Recommendation	CSH NON-STERILE API BY CHEMICAL SYNTHESIS	Product Supply Chain: RELEASE TESTER: SITAGLIPTIN AND METFORMIN HYDROCHLORIDE Substance Supply Chain: MANUFACTURER: SITAGLIPTIN RELEASE TESTER: SITAGLIPTIN STABILITY TESTER: SITAGLIPTIN SITAGLIPTIN PACKAGER: SITAGLIPTIN (b) (4)	Compliant	

110002136	3002806475	918917605	ZYDUS LIFESCIENCE S LIMITED	● Approve Facility 10 /25 /2023 District Recommendation	CSN NON-STERILE API BY CHEMICAL SYNTHESIS	Product Supply Chain: RELEASE TESTER: SITAGLIPTIN AND METFORMIN HYDROCHLORIDE Substance Supply Chain: MANUFACTURER: SITAGLIPTIN RELEASE TESTER: SITAGLIPTIN STABILITY TESTER: SITAGLIPTIN SITAGLIPTIN PACKAGER: SITAGLIPTIN	Compliant
(b) (4)							Compliant
110003412	3007938603	863362789	ZYDUS LIFESCIENCE S LIMITED	● Approve Facility 10 /25 /2023 District Recommendation	TTR TABLETS, EXTENDED RELEASE	Product Supply Chain: MANUFACTURER: SITAGLIPTIN AND METFORMIN HYDROCHLORIDE PACKAGER: SITAGLIPTIN AND METFORMIN HYDROCHLORIDE STORER: SITAGLIPTIN AND METFORMIN HYDROCHLORIDE RELEASE TESTER: SITAGLIPTIN AND METFORMIN HYDROCHLORIDE STABILITY TESTER: SITAGLIPTIN AND METFORMIN HYDROCHLORIDE LABELER: SITAGLIPTIN AND METFORMIN HYDROCHLORIDE	Compliant
110003757	3003696998	918596206	ZYDUS LIFESCIENCE S LIMITED	● Approve Facility 10 /24 /2023 Based on File Review	LCP LABORATORY, CHEMICAL/PHYSICAL TESTING	Substance Supply Chain: RELEASE TESTER: METFORMIN HYDROCHLORIDE SITAGLIPTIN	Compliant
				● Approve Facility 10 /24 /2023 Based on Profile	LCP LABORATORY, CHEMICAL/PHYSICAL TESTING	Substance Supply Chain: RELEASE TESTER: METFORMIN HYDROCHLORIDE SITAGLIPTIN	Compliant

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 6-12-2024

Application Technical Lead Name and Date:



Muthukumar
Ramaswamy

Digitally signed by Muthukumar Ramaswamy

Date: 6/12/2024 11:29:17AM

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Title:	NDA IQA Template CHAPTER IV-LABELING		
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CHAPTER IV: LABELING

For more details about the items in this template, please see [Chapter IV \(Labeling\) of the NDA IQA Guide \(OPQ-ALL-WI-0006\)](#)

NDA Number	216778
Assessment Cycle Number	1
Drug Product Name	Zituvimet XR

Assessment Recommendation: Adequate

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate following edits	
Patient Information	Adequate	0007 (Medication Guide)
Instruction for Use (IFU)	N/A	N/A
Container Labels	Adequate	0015
Carton Labeling	N/A	N/A

Brief Description of Outstanding Issues: NA

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
SD # 0007	09/22/2023	Prescribing Information, Medication guide
SD #0015	03/12/2024	Container labels, Package Insert

1.0 PRESCRIBING INFORMATION¹

Assessment of Product Quality Related Aspects of the Prescribing Information:

¹ [Labeling Review Tool \(LRT\) \(March 2022\)](#), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights² [21 CFR 201.57(a)(2)]		
Established name(s) ³	Adequate	(Sitagliptin and metformin hydrochloride) extended release tablets
Route(s) of administration	Adequate	For oral use
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	2007 (after edits from DMEPA)
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s) ⁴ and strength(s) in metric system ⁵	Adequate	Sitagliptin 100 mg and metformin HCl 1,000 mg; sitagliptin 50 mg and metformin HCl 500 mg; sitagliptin 50 mg and metformin HCl 1,000 mg
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). ⁶	Adequate	Metformin HCl nomenclature used to maintain consistency with other products
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored." ⁷	N/A	

² Draft guidance: [Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format](#) (January 2018)

³ Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).

⁴ Draft guidance: [Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format](#) (January 2018); USP <1151>; USP Nomenclature Guideline

⁵ Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>

⁶ Guidance: [Naming of Drug Products Containing Salt Drug Substances](#) (June 2015); MAPP 5021.1

⁷ Guidance: [Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation](#) (March 2013)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For injectable drug products for parenteral 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. ⁸	N/A	

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"**

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)⁹

- Take ZITUVIMET XR orally once daily with a meal. Patients taking two ZITUVIMET XR tablets should take the two tablets together once daily.
- Individualize the dosage of ZITUVIMET XR on the basis of the patient's current regimen, effectiveness, and tolerability.
- The maximum recommended daily dose is 100 mg of sitagliptin and 2,000 mg of metformin hydrochloride (HCl) extended-release.
- The recommended starting dose in patients not currently treated with metformin is 100 mg sitagliptin and 1,000 mg metformin HCl extended-release once daily, with gradual dose escalation recommended to reduce gastrointestinal side effects associated with metformin.
- The starting dose in patients already treated with metformin should provide 100 mg sitagliptin and the previously prescribed dose of metformin.

⁸ Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>

⁹ See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)

- For patients taking metformin HCl immediate-release 850 mg twice daily or 1,000 mg twice daily, the recommended starting dose of ZITUVIMET XR is two 50 mg sitagliptin and 1,000 mg metformin HCl extended-release tablets taken together once daily.
- Maintain the same total daily dose of sitagliptin and metformin when changing between (b) (4) (sitagliptin and metformin HCl immediate-release or sitagliptin and metformin extended-release) and ZITUVIMET XR.
- Do not split, crush or chew ZITUVIMET XR tablets [see Clinical Pharmacology (12.3)].

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food ¹⁰ , storage conditions needed to maintain the stability of the reconstituted or diluted product).	N/A	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	Adequate	Do not split, crush or chew ZITUVIMET XR tablets.
For parenteral products: include statement: <i>"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."</i> ¹¹	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. ¹² Note the labeling requirement may be applicable	N/A	

¹⁰ Draft Guidance: [Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments](#)

¹¹ §201.57(c)(3)(iv)

¹² USP General Notices 2.30 Legal Recognition

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
to another section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement " <i>DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.</i> " ^x with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"**

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)¹³

Tablets:

- sitagliptin 100 mg and metformin HCl 1,000 mg extended-release tablets are reddish brown to brown colored, oval shaped, film-coated tablets debossed with "1806" on one side and plain on the other side.
- sitagliptin 50 mg and metformin HCl 500 mg extended-release tablets are light orange to beige colored, oval shaped, film-coated tablets debossed with "1804" on one side and plain on the other side.
- sitagliptin 50 mg and metformin HCl 1,000 mg extended-release tablets are yellow to beige colored, oval shaped, film-coated tablets debossed with "1805" on one side and plain on the other side.

¹³ See § 201.57(c)(4); [Labeling Review Tool \(March 2022, page 29\)](#)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance . Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	Adequate	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable.	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"**

1.2.3 Section 11 (DESCRIPTION)¹⁴

(APIs described separately)

ZITUVIMET XR is available as film-coated tablets containing:

- 50 mg sitagliptin and 389.93 mg of metformin equivalent to 500 mg metformin HCl (ZITUVIMET XR 50/500).
- 50 mg sitagliptin and 779.86 mg of metformin equivalent to 1,000 mg metformin HCl (ZITUVIMET XR 50/1,000).
- 100 mg sitagliptin and 779.86 mg of metformin equivalent to 1,000 mg metformin HCl (ZITUVIMET XR 100/1,000).

All doses of ZITUVIMET XR contain the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, dibasic calcium phosphate anhydrous, ferric oxide yellow, hypromellose, magnesium stearate, malic acid, microcrystalline cellulose, povidone, pregelatinized starch (maize) and sodium stearyl fumarate. In addition, the film-coating for all doses contains the following inactive ingredients: polyethylene glycol, polyvinyl alcohol-partially hydrolyzed, iron oxide yellow, talc and titanium dioxide. Additionally, ZITUVIMET XR 50 mg/500 mg and 100 mg/1,000 mg tablets film-coating contain the inactive ingredient red iron oxide and 50 mg/1,000 mg and 100 mg/1,000 mg tablets film-coating contain the FD&C yellow#6 Aluminum Lake.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s) ¹⁵ [§ 201.57(c)(12)(i)(A)].	Adequate after edit	ZITUVIMET XR, (sitagliptin and metformin hydrochloride) extended release tablet
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	Tablets for oral use
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP . For example: "TRADENAME contains 100 mg	Adequate	Metformin hydrochloride name used for consistency with products on the market approved prior to May 1, 2013

¹⁴ See § 201.57(c)(12); [Labeling Review Tool \(March 2022, page 56\)](#)

¹⁵ Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].		
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order. ¹⁶ Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Adequate	colloidal silicon dioxide, croscarmellose sodium, dibasic calcium phosphate anhydrous, ferric oxide yellow, hypromellose, magnesium stearate, malic acid, microcrystalline cellulose, povidone, pregelatinized starch (maize) and sodium stearyl fumarate
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. [§ 201.100(b)(5)(iii)].	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	
Pharmacological/Therapeutic class ¹⁷ [§ 201.57(c)(12)(i)(E)].	Adequate	inhibitor of the DPP-4 enzyme; antihyperglycemic
Chemical name ¹⁸ , structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	Sitagliptin: 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-

¹⁶ Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

¹⁷ Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in [FDA's Labeling Resources for Human Prescription Drugs](#) for the most recent EPC list.

¹⁸ Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
		triazolo[4,3-α]pyrazine; C₁₆H₁₅F₆N₅O; molecular weight of 407.31 Metformin: N,N-dimethylimidodicarbonimidic diamide HCl; C₄H₁₁N₅•HCl; molecular weight of 165.62
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate	White to off-white powder slightly soluble in water/ white crystalline powder freely soluble in water
For oral prescription drug products, include gluten statement ¹⁹ (if applicable).	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

Assessment: Adequate

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"**

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)²⁰

Tablets supplied as follows:

¹⁹ Draft guidance: [Gluten in Drug Products and Associated Labeling Recommendations \(December 2017\)](#)

²⁰ See § 201.57(c)(17); [Labeling Review Tool \(March 2022, page 70\)](#). Consider including proprietary name and established name.

Contents	Description	How Supplied	NDC
50 mg sitagliptin and 500 mg metformin HCl extended-release tablet	Light orange to beige colored, oval shaped, film-coated tablets debossed with "1804" on one side and plain on the other side.	Bottles of 60 tablets with child-resistant closure	NDC 70710-1804-6
50 mg sitagliptin and 1,000 mg metformin HCl extended-release tablet	Yellow to beige colored, oval shaped, film-coated tablets debossed with "1805" on one side and plain on the other side.	Bottles of 60 tablets with child-resistant closure	NDC 70710-1805-6
100 mg sitagliptin and 1,000 mg metformin HCl extended-release tablet	Reddish brown to brown colored, oval shaped, film-coated tablets debossed with "1806" on one side and plain on the other side.	Bottles of 30 tablets with child-resistant closure	NDC 70710-1806-3

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store in a dry place with cap tightly closed.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	Tablets
Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance . Clearly state whether the strength is based on the active moiety. No equivalency statement.	Adequate	Sitagliptin and metformin HCl
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	Bottles of 30, 60 tablets
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral 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 (see USP <659>).	N/A	
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.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures. ^x " with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate	
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: " <i>Not made with natural rubber latex.</i> "	N/A	

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
<i>Avoid statements such as "latex-free."²¹</i>		
Include information about child-resistant packaging ²² (if chosen by manufacturer).	Adequate	Adequate following edits marked above. Edits follow the language in the Zituvimet PI (NDA 216743).

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"**

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 review 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.

²¹ Guidance: [Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex](#) (December 2014)

²² Guidance: [Child-Resistant Packaging Statements in Drug Product Labeling](#) (August 2019)

1.2.6 Manufacturing Information After Section 17 (for drug products)²³

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.	Adequate	Manufactured by: Zydus Lifesciences Ltd. Ahmedabad, India Distributed by: Zydus Pharmaceuticals (USA) Inc. Pennington, NJ 08534 Added a comment to recommend they include the street addresses.

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"**

2.0 PATIENT LABELING

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ²⁴	Adequate	Sitagliptin and metformin hydrochloride extended-release
Special preparation instructions (if applicable).	N/A	
Storage and handling information (if applicable).	Adequate	Store Zituvimet XR at room temperature, between 68 °F to 77 °F (20 °C to 25 °C). Store in a dry place and keep the cap tightly closed.
If the product contains a desiccant, ensure the desiccant	Adequate	Per the desiccant DMF (b) (4) (b) (4)

²³ § 201.1(h)(5) and 201.1(i); [Labeling Review Tool \(March 2022, page 74\)](#)

²⁴ Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
has a warning (e.g., (b) (4) (b) (4)) and (b) (4) (b) (4)		(b) (4) DP tablets are ovals; (b) (4) (b) (4)
Active ingredient(s) (if applicable).	Adequate	Sitagliptin and metformin hydrochloride
Alphabetical listing of inactive ingredients (if applicable).	Adequate	Colloidal silicon dioxide, croscarmellose sodium, dibasic calcium phosphate anhydrous, ferric oxide yellow, hypromellose, magnesium stearate, malic acid, microcrystalline cellulose, povidone, pregelatinized starch (maize) and sodium stearyl fumarate.
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	Manufactured by: Zydus Lifesciences Ltd. Ahmedabad, India Distributed by: Zydus Pharmaceuticals (USA) Inc. Pennington, NJ 08534 Added a comment to recommend they include street addresses.

Assessment: Adequate

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"**

3.0 CONTAINER AND CARTON LABELING²⁵

²⁵ [Carton and Container Labeling Resources](#)

3.1 Container Labels²⁶

(b) (4)

3.2 Carton Labeling

NA

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name ²⁷ , (font size and prominence) [§ 201.10(g)(2)].	Adequate	N/A	Zituvimet XR, sitagliptin and metformin HCl

²⁶ Per § 201.10(h)(2)(i)(1), if the drug container is too small to bear all labeling information required by section 502(e)(1)(A)(ii) and (B) of the FD&C Act, the container label should bear: proprietary name, established name, lot number, the name of the manufacturer, packer, or distributor of the drug.

²⁷ Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)]. ²⁸	Adequate	N/A	Sitagliptin- 50 mg and metformin HCl- 500 mg
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	N/A	Not required for oral drug
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	N/A	N/A	Metformin HCl retained for consistency with drugs approved before May 1, 2013
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)]. ²⁹	Adequate	N/A	Bottles of 30,60 tablets
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	N/A	Present
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	N/A	Present
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	N/A	Placeholder present
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	N/A	20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms	N/A	N/A	

²⁸ Express as "XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See [Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors \(May 2022\)](#)

²⁹ § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement. (See USP <659>).			
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	N/A	N/A	Oral drug
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	N/A	
Linear Bar code [§ 201.25(c)(2)]. ³⁰	Adequate	N/A	Present
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	N/A	Present
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	N/A	Present
"Keep out of reach of children" statement, optional for Rx,	Adequate	N/A	Present

³⁰ See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
required for OTC [§ 201.66(c)(5)(x)].			
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	N/A	Pharmacist: Dispense the Medication Guide provided separately to each patient.
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	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. ³¹	N/A	N/A	
And others if space is available.	N/A	N/A	

Assessment of Carton Labels and Container Labeling: Adequate

Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"

³¹ USP General Notices 3.20 Indicating Conformance

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See [Carton/Container Labeling Specific Resources](#) for a presentation about inappropriate inconsistencies of product quality information between labeling. If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these issues in this section.

Primary Labeling Assessor Name and Date: Jennifer McCord 05/28/2024

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



Jennifer
McCord

Digitally signed by Jennifer McCord

Date: 5/30/2024 05:52:58PM

GUID: 63221b9c007a3580cbffb5160db88fe7



Muthukumar
Ramaswamy

Digitally signed by Muthukumar Ramaswamy

Date: 5/31/2024 08:39:12AM

GUID: 508da7210002a0c0870017f6c83398f4

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CHAPTER VI: BIOPHARMACEUTICS

For more details about the items in this template, please see [Chapter VI \(Biopharmaceutics\) of the NDA IQA Guide](#)

Product Information	
NDA Number	NDA 216778
Assessment Cycle Number	0001
Drug Product Name/ Strength	Zituvimet XR (Sitagliptin and Metformin Hydrochloride Extended-Release Tablets) / 50mg/500mg, 50mg/1000mg, 100mg/1000mg
Route of Administration	Oral
Applicant Name	Zydus Worldwide DMCC
Therapeutic Classification/ OND Division	Antidiabetic Agents, Non-Insulin /CDER/OND/OCHEN/DDLO
RLD/RS Number	Janumet® XR (sitagliptin and metformin hydrochloride) Extended-Release Tablets (NDA # 202270)
Proposed Indication	It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Assessment Recommendation: Adequate

Assessment Summary: The Sponsor, Zydus Worldwide DMCC, seeks for an approval of Zituvimet XR (Sitagliptin and Metformin Hydrochloride Extended-Release Tablets, 50 mg/500 mg, 50 mg/1000 mg and 100 mg/1000 mg. Both drug substances, Sitagliptin and Metformin HCl are highly soluble compounds per the Biopharmaceutics Classification System. The submission is under section 505(b)(2) pathway using Janumet®XR as a listed drug (LD). Biopharmaceutics review is focused on the bridging between the proposed drug product and the LD, including discriminating ability of the proposed dissolution method, comparative dissolution data between the proposed drug and LD, proposed acceptance criteria, biowaiver of lower strength and other attributes related to quality of the proposed drug product. The Sponsor submitted sufficient data to demonstrate the discriminating ability of the dissolution method. The proposed acceptance criteria for both drug substances of all strengths are acceptable. The waiver request for submission of evidence of in vivo bioequivalence for lower strengths (50 mg/500 mg and 50 mg/1000 mg) is acceptable. Alcohol dose dumping studies illustrate no evidence of dose dumping at all concentrations tested for the proposed drug. From Biopharmaceutics perspective, the NDA 216778 is recommended for approval.

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Discriminating of Dissolution method for Metformin HCl Acceptance criteria for Sitagliptin and Metformin HCl	High	The IRs sent to request the Sponsor to demonstrate the discriminating ability of the proposed dissolution method. The Sponsor also was asked to revise acceptance criteria	Medium	The Sponsor provide sufficient data to prove the discriminating ability of the proposed dissolution method. The revised acceptance criteria are supported by submitted dissolution data

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
Sequence 0007 (SDN 7) Sequence 0014 (SDN 14) Sequence 0016 (SDN 16) Sequence 0020 (SDN 20)	09/22/2023 02/06/2024 03/21/2024 05/07/2024

Highlight Key Issues from Last Cycle and Their Resolution: None

Concise Description of Outstanding Issues (list bullet points with key information and update as needed): None

B.1 BCS DESIGNATION

Assessment: Based on submitted solubility data, both drug substances are high soluble compounds according to the Biopharmaceutics Classification System (BCS).

Solubility:

Metformin Hydrochloride, USP:

Table 1. Solubility data of Metformin Hydrochloride, USP across the physiological pH range (Batch No. MFH200330AFP)¹

Media	Solubility	
	mg/mL	mg/250 mL
0.1 N HCl	310.90	77.7
pH 4.5, Acetate buffer	324.39	81.1
pH 6.8, Phosphate buffer	310.03	77.5
pH 7.5 Phosphate Buffer	334.90	83.7
Purified Water	312.42	78.1

Calculated dose solubility volume:

Based on solubility observation, Metformin hydrochloride highest strength (1000 mg)/Lowest solubility (310.03 mg/mL) = 3.23 ml which is less than 250 ml quantity of aqueous media.

Therefore, Metformin hydrochloride is considered a high soluble BCS class III drug according to the Biopharmaceutics Classification System (BCS).

Sitagliptin:

Table 2. Saturated solubility data of the Sitagliptin Free Base across physiological pH range (Batch no.: SFA1MWH03D)²

Media	Solubility	
	mg/mL	gm/250 mL
0.1 N HCl	51.3950	12.8
pH 4.5, Acetate buffer	22.1557	5.5
pH 6.8, Phosphate buffer	17.1853	4.3
pH 7.5 Phosphate Buffer	11.0650	2.8
Purified Water	8.3372	2.1

Calculated dose solubility volume:

Based on solubility observation, sitagliptin free base highest strength (100 mg) / Lowest solubility (8.3372 mg/mL) = 11.99 ml which is less than 250 ml quantity of aqueous media.

Therefore, sitagliptin free base is considered a high solubility drug according to the Biopharmaceutics Classification System (BCS).

Permeability:

¹ <\\CDSESUB1\EVSPROD\nda216778\0007\m3\32-body-data\32s-drug-sub\metforminhcl-exemed\32s1-gen-info\general-properties-met.pdf>

² <\\CDSESUB1\EVSPROD\nda216778\0007\m3\32-body-data\32s-drug-sub\sita-base-zll-dabhasa\32s1-gen-info\general-properties-sita.pdf>

(b) (4)

. No permeability data available for sitagliptin in the current submission.

Dissolution:

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

(b) (4)

³ <\\CDSESUB1\EVSPROD\nda216778\0007\m3\32-body-data\32p-drug-prod\sitametertab-tab-all-st-zll-sez\32p2-pharm-dev\pharmaceutical-development.pdf>

⁴ <\\CDSESUB1\EVSPROD\nda216778\0007\m3\32-body-data\32p-drug-prod\sitametertab-tab-all-st-zll-sez\32p2-pharm-dev\pharmaceutical-development-dissol-deve-repo-sita.pdf>

1.3. Finalized Proposed Dissolution Method

Based on above mentioned studies and observations, the following dissolution conditions were finalized for dissolution testing of Sitagliptin in Sitagliptin and Metformin hydrochloride extended-release tablets 50mg/500mg, 50mg/1000mg and 100mg/1000mg (Table 10)

Table 10. Finalized dissolution method for Sitagliptin in Sitagliptin and Metformin hydrochloride extended-release tablets

Details	In-house dissolution condition
Drug name	Sitagliptin
Dosage form	Tablets (Extended-release)
USP apparatus	For 50mg/500mg strength - I (Basket with tablet holder) For 50mg/1000mg & 100mg/1000mg strength - I (Modified Basket with tablet holder)*
Speed (RPM)	100 RPM
Medium	Phosphate Buffer, pH 6.8
Volume (mL)	900
Specification	NLT (b) (4) % (Q) of Sitagliptin is dissolved in (b) (4) minutes

(b) (4)

1.4. Discriminatory nature of dissolution method (for Sitagliptin)

The Sponsor identified CBAs based on the manufacturing process, various materials, formulation, and process variables that may impact the drug release. Aberrant batches were manufactured with the intentionally changes in formulation composition and the hardness of the tablet.

- Change in formulation composition by decreasing (b) (4) quantity (Critical Formulation Variable, CFV). The Sponsor prepared aberrant batch with decreasing concentration of (b) (4) and increasing concentration of (b) (4) at different level was compared with the batch prepared with optimum level of (b) (4) and (b) (4). Based on the above dissolution data, discriminatory batch (0794-F079) are not meeting the specifications criteria of (b) (4) % (Q) in (b) (4) minutes time point and f2 value was observed below 50. Based on the observations, it could be inferred that selected drug dissolution method, i.e., 900 mL, pH 6.8 phosphate buffer, modified Basket with tablet holder ((b) (4)), 100 RPM is discriminatory in nature (Figure 8).

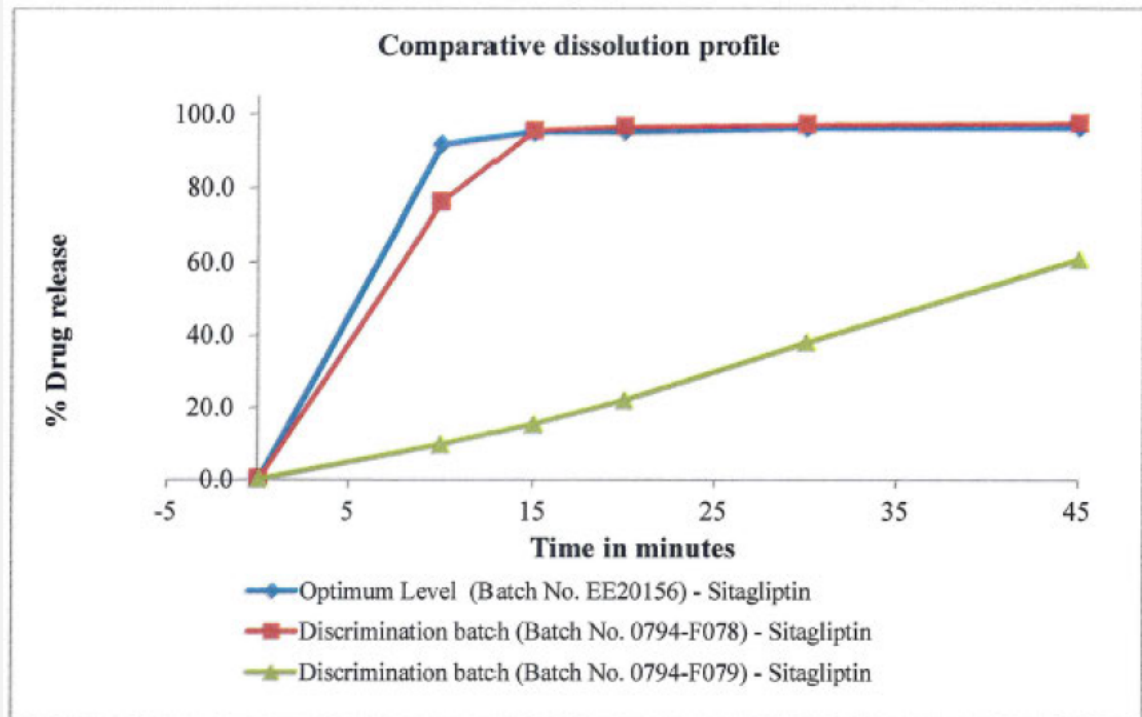


Figure 8. Comparative dissolution profile of batches prepared with different level of (b) (4)

- Change in process by changing the hardness of the drug product (Critical Process Parameter, CPP). Dissolution profile of the batch prepared with optimum hardness (b) (4) to (b) (4); Batch no. 0794-F053) was compared with the batch prepared with High hardness (b) (4) to (b) (4) Batch No. 0794-FI20A) and low hardness (b) (4) to (b) (4) Batch no. 0794-F053). The dissolution results showed no significant impact of hardness on dissolution. However, low hardness tablets showed fast dissolution at initial time point (10 minutes). The dissolution profile of optimum and high hardness samples was found comparable (b) (4). Hence, tablet hardness has no significant impact on the drug dissolution profile (Figure 9).

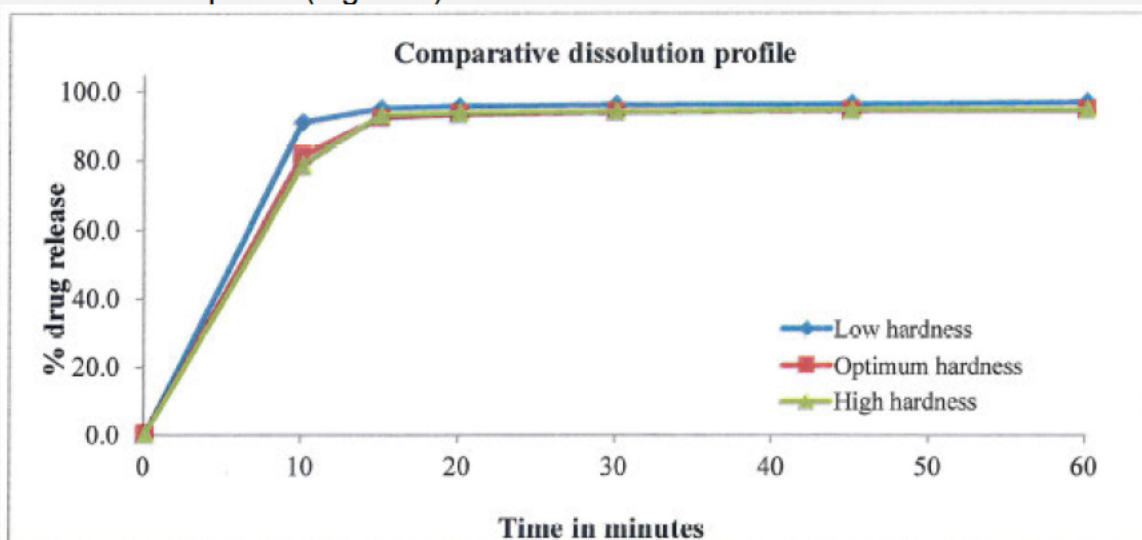


Figure 9. Comparative dissolution profile of batches prepared with different hardness

- Selection of dissolution specification time point: Based on the study results, QC release time point of (b) (4) minutes was selected for drug release of Sitagliptin in Sitagliptin and Metformin hydrochloride extended-release tablets 50mg/1000mg, 50mg/500mg and 100mg/1000mg. The discriminating ability of the proposed dissolution method is also evaluated at finalized dissolution time point for critical formulation variables and critical process parameters.

1.5. Dissolution Profile of the Proposed Drug Product vs LD (for Sitagliptin) using the proposed dissolution method for QC method:

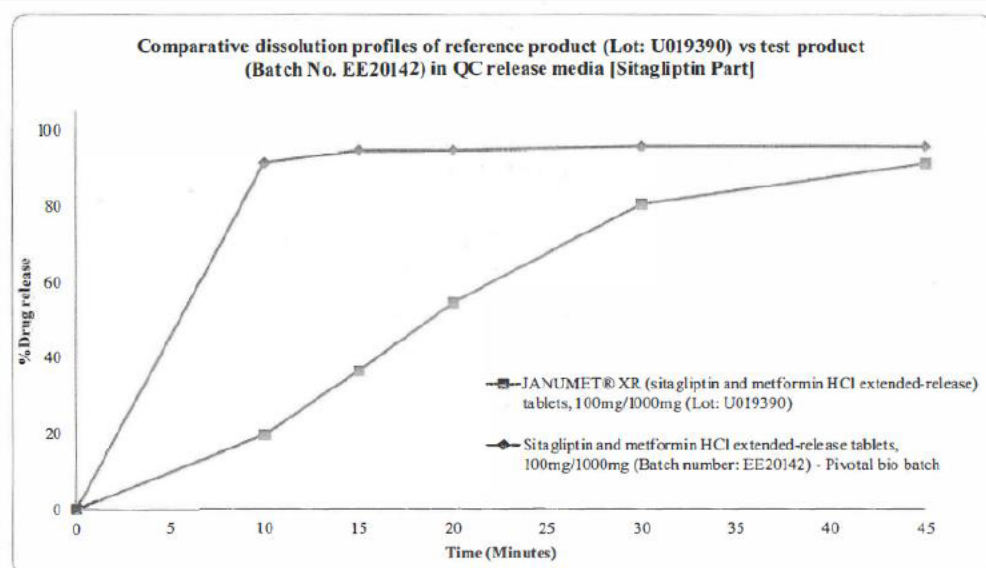


Figure 10. Comparative dissolution profile of Janumet® XR tablets, 100 mg/1000 mg (Lot: U019390) vs Sitagliptin and Metformin hydrochloride extended-release tablets, 100mg/1000mg (batch # EE201142) in QC media [Sitagliptin part].

Based on total submitted information/data, the proposed dissolution method for QC of Sitagliptin is acceptable. However, the proposed acceptance criterion is permissive. An IR was issued on 04/29/2024 to request to tighten the acceptance criterion. The IR response dated 05/07/2024 is acceptable (the detail review assessment is under section "BIOPHARMACEUTICS LIST OF DEFICIENCIES, RESPONSE & REVIEWER ASSESSMENT". The final dissolution specifications are presented in Table 11.

Table 11. Final Dissolution Conditions and Acceptance Criterion

Dissolution Conditions	Dissolution Parameters
Method	In-house dissolution method
Drug name	Sitagliptin part
Dosage form	Tablets (Extended-release)

Apparatus	For 50mg/500mg strength – USP type I (Basket with tablet holder) For 50mg/1000mg & 100mg/1000mg strength- USP type I (Modified Basket with tablet holder)
Dissolution medium	Phosphate buffer, pH 6.8
Volume	900 mL
Rotation speed	100 rpm
Temperature	37.0°C±0.5°C
Acceptance Criterion	Not less than (b) (4) % (Q) of the labeled amount of Sitagliptin is dissolved in 30 minutes.

2. Dissolution Method Development for Metformin HCL of the Proposed Product

(b) (4)

- 2.4. Discriminatory nature of dissolution method (for Metformin hydrochloride)
- Change in Critical Process Parameter, CPP (e.g., changing the hardness of the drug product) (Table 15, Figure 13).

The results showed that the hardness of the drug product has no impact on dissolution profile of Metformin hydrochloride in Sitagliptin and Metformin hydrochloride extended-release tablets.

Table 15. Comparative dissolution profile of batches prepared with different hardness

Product Name	Sitagliptin and Metformin hydrochloride extended-release tablets, 100mg/1000mg		
Aberrant Change	Tablets (Extended-release)		
Apparatus	Paddle with sinker (USP type II apparatus)		
Media volume	75 RPM		
Temperature	37.0°C ±0.5°C		
Agitation speed	Phosphate Buffer, pH 6.8		
Media	900		
Aberrant change (Hardness)	Low Hardness (B. No. 0794-F053)	Optimum Hardness (B. No. 0794-F053)	High Hardness (B. No. 0794-F120A)
Time (Hours)	Cumulative % drug release		
Drug substance	Metformin hydrochloride		
1	(b) (4)		
2			
3			
4			
6			
8			
10			
12			

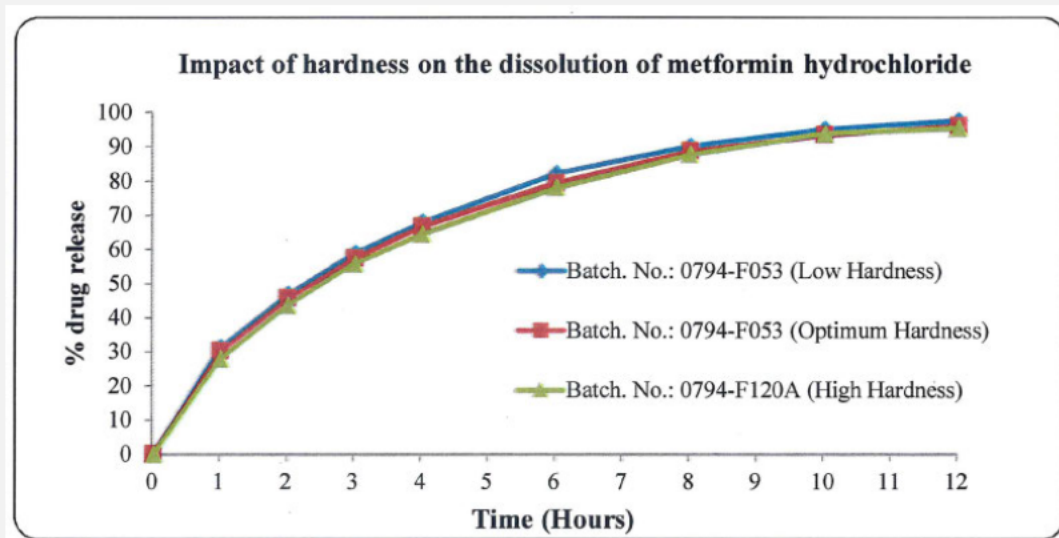


Figure 13. Dissolution profiles of batches prepared with different hardness

- Change in Critical Formulation Variable, CFV [e.g., changing in formulation composition: (b) (4), (b) (4)]

Two batches were prepared by increasing the (b) (4) concentration by (b) (4) % and (b) (4) % and one batch was prepared by decreasing the (b) (4) concentration by (b) (4) %. Dissolution profiles of batches prepared with higher and lower level of (b) (4) were compared with the batch prepared with optimum level of (b) (4). Dissolution profiles of batches prepared with different (b) (4) quantity are in Figure 14.

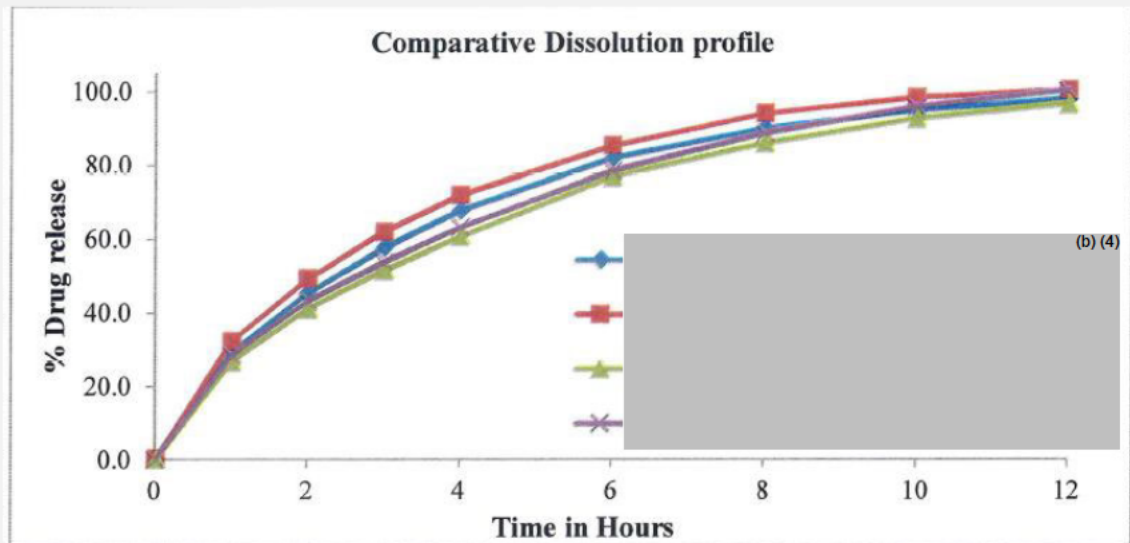


Figure 14. Dissolution profiles of batches prepared with different (b) (4) quantity

The results showed that there is no significant difference in drug release when changing (b) (4). Therefore, the dissolution method has limited discriminating ability.

Several IRs were sent to the Applicant to optimize the dissolution method and revised acceptance criteria. The IR responses, and reviewer assessment are presented under section, titled **“BIOPHARMACEUTICS LIST OF DEFICIENCIES, RESPONSE & REVIEWER ASSESSMENT”**. The first IR was sent to request the Sponsor to demonstrate dissolution method discriminating ability for Metformin HCl; the second IR was sent to request the Sponsor to optimize the proposed dissolution method for Metformin HCl; and the third IR was sent to request the Sponsor to tighten/revise acceptance criteria for both Sitagliptin and Metformin HCl. The Sponsor submitted sufficient data to illustrate the dissolution method discriminating ability. The revised and newly acceptance criteria for both APIs, Sitagliptin and Metformin HCl for all strengths are acceptable.

2.5. Dissolution Profile of the Proposed Drug Product vs LD (for Metformin HCl) using the proposed dissolution method for QC method:

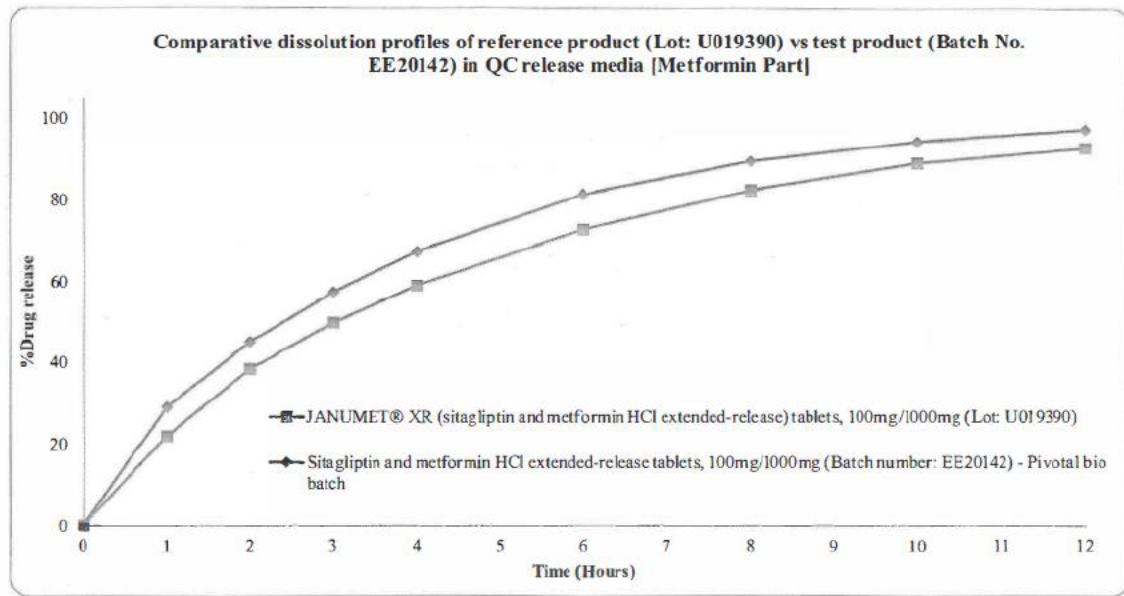


Figure 15. Comparative dissolution profile of Janumet® XR tablet 100 mg/1000 mg vs the proposed drug product Sitagliptin and Metformin HCl ER 100 mg/1000 mg (BE Batch # EE201142)

The final dissolution condition and acceptance criteria are presented in Table 16.

Table 16. Dissolution Conditions & Acceptance Criteria for Metformin HCL in Sitagliptin and Metformin hydrochloride extended-release tablets

Details	In-house dissolution condition
Drug name	Sitagliptin and Metformin HCl Extended-Release Tablets
Dosage form	Tablet (Extended-release)
USP apparatus	USP Apparatus II (Paddle with sinker)
Speed	75 rpm
Medium	pH 6.8 Phosphate buffer
Volume	900 mL
Temperature	37.0°C ±0.5°C
Acceptance criteria	Sitagliptin and Metformin HCl Extended-Release Tablets 50 mg/500 mg strength (metformin HCl part) 1 hour: (b) (4) % - (b) (4) % 2 hours: (b) (4) % - (b) (4) % 4 hours: (b) (4) % - (b) (4) % 8 hours: NLT (b) (4) % (Q)

	Sitagliptin and Metformin HCl Extended-Release Tablets 50 mg/1000 mg and 100 mg/1000 mg strengths (metformin HCl part)
	1 hour: (b) (4) % - (b) (4) %
	2 hours: (b) (4) % - (b) (4) %
	4 hours: (b) (4) % - (b) (4) %
	8 hours: NLT (b) (4) % (Q)

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

Assessment: {Adequate/Inadequate} Adequate (Refer to B2 section)

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD

Assessment: {Adequate/Inadequate} NA

B.5 MODIFIED RELEASE ORAL DRUG PRODUCTS – In-Vitro Alcohol Dose Dumping

Assessment: {Adequate/Inadequate} Adequate

In vitro alcohol dose dumping studies were performed using various concentrations of alcohol on lowest (50 mg/500 mg) and highest (100 mg/1000 mg) strengths. Drug release for Metformin hydrochloride in the proposed product of Sitagliptin and Metformin Hydrochloride Extended-Release Tablets, 50 mg/500 mg and 100 mg/ 1000 mg was found to be lower in 0.1 N hydrochloric acid and 0.05 M pH 6.8 phosphate buffer with 5% (v/v), 20% (v/v) and 40% (v/v) alcohol as compared to drug release in 0.1 N hydrochloric acid and 0.05 M pH 6.8 phosphate buffer respectively. This study demonstrates that proposed product does not hold additional risk of alcohol induced dose dumping and not alter bioavailability of the proposed drug product⁵.

B.6 IN-VITRO SOFT-FOOD INTERACTION STUDY

Assessment: {Adequate/Inadequate} NA

B.7 IN-VITRO RELEASE TESTING (IVRT) FOR SEMI-SOLID PRODUCTS

Assessment: {Adequate/Inadequate}

The proposed drug product is solid form, hence the IVRT for semi-solid product is not applicable

B.8 IN-VITRO PERMEATION TESTING (IVPT) FOR TRANSDERMAL/TOPICAL PRODUCTS

Assessment: {Adequate/Inadequate} NA

⁵ <\\CDSESUB1\EVSPROD\nda216778\0007\m2\27-clin-sum\summary-biopharm-alcohol-dose-dumping.pdf>

The proposed drug product is oral dosage form; hence the in vitro permeation testing is not applicable.

B.9 IN-VITRO DISSOLUTION TESTING FOR ABUSE-DETERRENT PRODUCTS

Assessment: {Adequate/Inadequate}
Not applicable

B.10 IN-VITRO BE EVALUATION FOR PULMONARY PRODUCTS

Assessment: {Adequate/Inadequate}
Not applicable

B.11 EXTENDED-RELEASE DOSAGE FORMS –Extended-Release Claim

Assessment: {Adequate/Inadequate} Adequate

The Applicant references an existing extended-release drug product JANUMET® XR (Sitagliptin and Metformin hydrochloride) Extended-Release Tablets. BE studies have been conducted on the 100 mg/1000 mg strength of the proposed product and the LD. Therefore, additional demonstration of and ER claim is not required. The extended-release claim is adequate.

B.12 BRIDGING OF FORMULATIONS

Assessment: {Adequate/Inadequate} NA

The formulation used in the clinical studies is the same as the to-be-marketed formulation. Therefore, bridging of formulation is not needed.

B. 13 BIOWAIVER REQUEST

Assessment: {Adequate/Inadequate} Adequate

The Sponsor conducted BE studies under fasting and fed condition on the highest (100 mg/1000 mg) strength of the drug product. The in vivo BA/BE studies are being evaluated by the Office of Clinical Pharmacology.

Excipient proportional calculation of the 50 mg/500 mg and 50 mg/1000 mg to the highest strength 100 mg/1000 mg is presented below:

	Total non-release control excipient	Total release control excipient	Justification
50 mg/500 mg to 100 mg/1000 mg	(b) (4) %	(b) (4) %	Within limit of (b) (4)
50 mg/1000 mg to 100 mg/1000 mg	(b) (4) %	(b) (4) %	Within limit of (b) (4) %

Based on the submitted information, the dissolution profiles of the lower strength (50 mg/500 mg; 50 mg/1000 mg) and the highest strength are comparable. Based on submitted data⁶, the

⁶ \\CDSESUB1\EVSPROD\nda216778\0007\m2\27-clin-sum\summary-biopharm-unit-disso-study-rep.pdf

reviewer used Biopharmaceutics Automation Tool to evaluate comparative dissolution profiles of all strengths to (Listed Drug) LD in multimedia (e.g., pH 1.2 0.1 N HCL, pH 4.5 acetate buffer, pH 6.8 phosphate buffer) and all similarity f2-factor values are greater than 50, indicating that dissolution profiles of all strengths are comparable to corresponding strengths of the LD. Additionally, f2 calculations are also performed in dissolution comparisons of the lowest vs highest strength in above multiple media. The detailed calculations are presented in Figures (from Figure 16 to Figure 27).

The proportional similarity in active and inactive ingredients across all strengths are within the acceptable limit of (b) (4) (the differences in non-release control of 50 mg/500 mg and 50 mg/1000 mg to the highest strength 100 mg/1000 mg are (b) (4)% and (b) (4)%; respectively; and that of release control excipients are (b) (4)% and (b) (4) , respectively) for granting biowaiver request. Additionally, the BE study is found acceptable on the higher strength and linearity has been established. Therefore, from Biopharmaceutics perspective, biowaiver request for lower strengths is granted in accordance with CFR 320.22 (d)(2).



Figure 16. Comparative Dissolution Profile of Proposed Product 100 mg/1000 mg strength to List Drug in 0.1 N HCl

(b) (4)

Figure27 . Comparative Dissolution Profile of Proposed Product 50 mg/500 mg strength to 100 mg/1000 mg strength in pH 6.8 Phosphate Buffer (QC medium)

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: {Adequate/Inadequate} NA

Post-Approval Commitments

Assessment: {Adequate/Inadequate} NA

Lifecycle Management Considerations: NA

BIOPHARMACEUTICS LIST OF DEFICIENCIES, RESPONSE & REVIEWER ASSESSMENT

(b) (4)



Huong
Moldthan

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