CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214373Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	214373		
Applicant Name	Theracos Sub LLC		
Drug Product Name	Brenzavvy (bexagliflozin) tablet		
Dosage Form.	Tablet		
Proposed Strength(s)	20mg		
Route of Administration	Oral		
Maximum Daily Dose	20mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Glycemic control in adults with type 2 diabetes		
Drug Product Description	Blue, caplet-shaped, biconvex, bevel-edged, film-coated tablets debossed with “2” and inverted “2” on one side and no markings on the other side. Tablets are packaged in 30ct or 90ct high density polyethylene (HDPE) bottles with (b) (4) closure (b) (4).		
Co-packaged product information	Not applicable		
Device information:	NA		
Storage Temperature/ Conditions	Store at 20 °C to 25 °C with excursions permitted between 15 °C to 30 °C.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Daniel Jansen	Zhengfu Wang
	Drug Product/ Labeling	Ali Mohamadi	Muthukumar Ramaswamy
	Manufacturing	Kejun Cheng	Aditi Thakur/N. Chidambaram/ Erin Kim

	Biopharmaceutics	Zhoujun Zhao	Haritha Mandula
	Microbiology	NA	NA
	Other (specify):ORA	Caryn McNab	
	RBPM	Nowrin Kakon	
	ATL	Muthukumar Ramaswamy	
Consults	Pharm./Toxicology: Karen Hao/Federica Basso regarding (b) (4).		

2. Final Overall Recommendation - Approval with QPA(s)

3. Action Letter Information

a. Expiration Dating: Based on stability data review, an expiration period of 60 months is granted for Brenzavvy when stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

b. Additional Comments for Action
You have committed to the following quality agreements:

Post Marketing Commitment 1:
Perform additional (b) (4) testing on the next 25 (at a minimum) commercial scale batches of Bexagliflozin tablets, 20 mg, and provide the data to FDA in the annual reports after the completion of each production campaign that is tentatively scheduled from 3Q 2022 through 2Q 2024.

Post Marketing Commitment 2:
Perform comprehensive stratified (b) (4) at appropriate interval for at least 25 commercial batches to demonstrate (b) (4) Provide the data to FDA in the annual reports,

after the completion of each production campaign that is tentatively scheduled from 3Q 2022 through 2Q 2024.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

(Include summary of deficiencies, pending issues, benefit-risk considerations, etc. according to recommendation. Not intended to be a summary of review.)

- The Office of Pharmaceutical Quality Review team has assessed the Chemistry, Manufacturing, and Controls (CMC) information for NDA 214373 and determined that the NDA meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, OPQ recommends approval of this NDA from a quality perspective.

The proposed product, Brenzavvy (bexagliflozin) tablet, 20mg is for once daily oral use. Bexagliflozin is a new chemical entity. The chemical name for bexagliflozin is (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.

Brenzavvy tablets are blue film-coated tablet debossed with "2" and inverted "2" on one side and no markings on the other side. Tablets contain 20mg of bexagliflozin along with colloidal silicon dioxide, glyceryl dibehenate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene oxide, and poloxamer 188. The film coat contains FD&C Blue #1/Brilliant Blue FCF aluminum lake, FD&C Blue #2/Indigo carmine aluminum lake, macrogol 3350, polyvinyl alcohol, talc, and titanium dioxide. Brenzavvy tablets are packaged in 30ct or 90ct HDPE bottle.

Tablets are manufactured by (b) (4) The original manufacturing process control strategy did not (b) (4) Per FDA recommendation, the applicant agreed to implement (b) (4) testing as well as comprehensive stratified (b) (4) at appropriate interval for at least 25 commercial batches to demonstrate drug product (b) (4)

Although the drug product contains excipients that facilitate the release of the drug over a period of 8 hour under in vitro dissolution conditions, the proposed dosage form will not be considered as an extended release tablet. The established name for this product will be bexagliflozin tablet. Please refer to Biopharm review.

CMC labeling comments will be finalized during the OND labeling team review.

As of 1/9/2023, all manufacturing facilities associated with this application are compliant. The overall manufacturing inspection recommendation is approve.

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: Please note the applicant's product quality agreement to collect and provide (b) (4) data and in-process (b) (4) data to FDA from next 25 commercial scale batches.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MUTHUKUMAR RAMASWAMY
01/09/2023 02:06:36 PM

NDA Executive Summary

1. Application/Product Information

NDA Number.	214373		
Applicant Name	Theracos Sub LLC		
Drug Product Name	Brenzavvy (bexagliflozin) tablet		
Dosage Form.	Tablet		
Proposed Strength(s)	20mg		
Route of Administration	Oral		
Maximum Daily Dose	20mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Glycemic control in adults with type 2 diabetes		
Drug Product Description	Blue, caplet-shaped, biconvex, bevel-edged, film-coated tablets debossed with “2” and inverted “2” on one side and no markings on the other side. Tablets are packaged in 30ct or 90ct high density polyethylene (HDPE) bottles with (b) (4) closure (b) (4).		
Co-packaged product information	Not applicable		
Device information:	NA		
Storage Temperature/ Conditions	Store at 20 °C to 25 °C with excursions permitted between 15 °C to 30 °C.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Daniel Jansen	Zhengfu Wang
	Drug Product/ Labeling	Ali Mohamadi	Muthukumar Ramaswamy
	Manufacturing	Kejun Cheng	Aditi Thakur/N. Chidambaram/ Erin Kim

	Biopharmaceutics	Zhoujun Zhao	Haritha Mandula
	Microbiology	NA	NA
	Other (specify):ORA	Caryn McNab	
	RBPM	Nowrin Kakon	
	ATL	Muthukumar Ramaswamy	
Consults	Pharm./Toxicology: Karen Hao/Federica Basso regarding (b) (4).		

2. Final Overall Recommendation - Approval with QPA(s)

3. Action Letter Information

a. Expiration Dating: Based on stability data review, an expiration period of (b) (4) months is granted for Brenzavvy, when should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

b. Additional Comments for Action
You have committed to the following quality agreements:

Post Marketing Commitment 1:
Perform additional (b) (4) testing on the next 25 (at a minimum) commercial scale batches of Bexagliflozin tablets, 20 mg, and provide the data to FDA in the annual reports after the completion of each production campaign that is tentatively scheduled from 3Q 2022 through 2Q 2024.

Post Marketing Commitment 2:
Perform comprehensive stratified (b) (4) at appropriate interval for at least 25 commercial batches to demonstrate (b) (4) (b) (4) (b) (4) Provide the data to FDA in the annual reports,

after the completion of each production campaign that is tentatively scheduled from 3Q 2022 through 2Q 2024.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

(Include summary of deficiencies, pending issues, benefit-risk considerations, etc. according to recommendation. Not intended to be a summary of review.)

- The Office of Pharmaceutical Quality Review team has assessed the Chemistry, Manufacturing, and Controls (CMC) information for NDA 214373 and determined that the NDA meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, OPQ recommends approval of this NDA from a quality perspective.

  The proposed product, Brenzavvy (bexagliflozin) tablet, 20mg is for once daily oral use. Bexagliflozin is a new chemical entity. The chemical name for bexagliflozin is (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.

  Brenzavvy tablets are blue film-coated tablet debossed with "2" and inverted "2" on one side and no markings on the other side. Tablets contain 20mg of bexagliflozin along with colloidal silicon dioxide, glyceryl dibehenate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene oxide, and poloxamer 188. The film coat contains FD&C Blue #1/Brilliant Blue FCF aluminum lake, FD&C Blue #2/Indigo carmine aluminum lake, macrogol 3350, polyvinyl alcohol, talc, and titanium dioxide. Brenzavvy tablets are packaged in 30ct or 90ct HDPE bottle.

  Tablets are manufactured by [redacted] (b) (4). The original manufacturing process control strategy did not [redacted] (b) (4). Per FDA recommendation, the applicant agreed to implement [redacted] (b) (4) testing as well as comprehensive stratified [redacted] (b) (4) at appropriate interval for at least 25 commercial batches to demonstrate drug product [redacted] (b) (4).

  Although the drug product contains excipients that facilitate the release of the drug over a period of 8 hour under in vitro dissolution conditions, the proposed dosage form will not be considered as an extended release tablet. Tas he established name for this product will be bexagliflozin tablet. Please refer to Biopharm review.

  CMC labeling comments will be finalized during the OND labeling team review.

[redacted]

As of 6/22/2022, all manufacturing facilities associated with this application are compliant. The overall manufacturing inspection recommendation is approve. Panorama screen shot of Submission Facility Status view is shown below.

(b) (4)

[redacted]

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: Please note the applicant's product quality agreement to collect and provide [redacted] (b) (4) data and in-process [redacted] (b) (4) data to FDA from next 25 commercial scale batches.

[redacted]

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

The review team finalizes the labeling comments during OND labeling review. The labeling draft is adequate per revisions listed on page 9.

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items 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 Highlights		
Established name(s)[1]	Adequate	BRENZAVVY (bexagliflozin) tablets, for oral use
Route(s) of administration	Adequate	for oral use
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	Tablet and 20 mg
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	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	
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	N/A	

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

ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).		

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items 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, 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 crush or chew the tablet
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	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	N/A	

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 *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

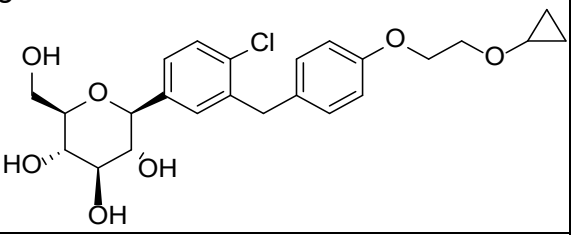
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items 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	Tablet
Strength(s) in metric system	Adequate	20 mg
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 (Tablets: 10 mg of drug-x hydrochloride).	N/A	
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	blue, caplet-shaped, biconvex, bevel-edged, (b) (4) debossed with "2" and inverted "2" on one side.
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 parental 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.	N/A	

Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

Item	Items 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)	Adequate	BRENZAVVY Bexagliflozin tablet
Dosage form(s) and route(s) of administration	Adequate	Tablet and 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 of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	Each film-coated tablet contains 20 mg of bexagliflozin and the inactive ingredients colloidal silicon dioxide, glyceryl dibehenate, lactose monohydrate magnesium stearate, microcrystalline cellulose, polyethylene oxide, and poloxamer 188. In addition, the film coating ingredient, opadry II Blue 85F99153, contains the inactive ingredients FD&C Blue #1/Brilliant Blue FCF and FD&C Blue #2/Indigo Carmine, macrogol 3350, polyvinyl alcohol, talc, and titanium dioxide.
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	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	inhibitor of sodium-glucose co-transporter 2 (SGLT2).

Chemical name, structural formula, molecular weight	Adequate	The chemical name of bexagliflozin is (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol. The molecular formula is $C_{24}H_{29}ClO_7$ and the molecular weight is 464.94 g/mol. The structural formula is: 
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	It is very slightly soluble in water, freely soluble in methanol, acetone, ethylene glycol, and propylene glycol. It is slightly soluble in heptane, cyclohexane, and toluene. Crystalline bexagliflozin is not hygroscopic.

Section 11 (DESCRIPTION) Continued

Item	**Items 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 oral prescription drug products, include gluten statement (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	N/A	

fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).		

APPEARS THIS WAY ON ORIGINAL

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Items 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)	Adequate	Tablet
Strength(s) in metric system	Adequate	20 mg
Available units (e.g., bottles of 100 tablets)	Adequate	Bottles of 30 tablets Bottles of 90 tablets
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	pale blue, caplet-shaped, biconvex, bevel-edged, film-coated tablets debossed with "2" and inverted "2" (b) (4) one side
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 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	
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."	N/A	

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

Item	Items 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)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Store from 20 to 25 °C (68 to 77 °F); excursions permitted between 15 to 30 °C (59 to 86 °F) [see USP Controlled Room Temperature].
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."*	N/A	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

1.2.6 Manufacturing Information After Section 17

Item	Items 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)
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	Distributed by: (b) (4) LLC 225 Cedar Hill Street, Suite 200 Marlborough, MA 01752 USA

2.0 PATIENT LABELING

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	BRENZAVVY® (bren ZA vee) (bexagliflozin) Tablets
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	Adequate	Store BRENZAVVY at room temperature between 68 °F to 77 °F (20 °C to 25 °C); excursions permitted between 59 °F to 86 °F (5 to 30 °C)
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	Adequate	Each film-coated tablet contains 20 mg of bexagliflozin and the inactive ingredients colloidal silicon dioxide, glyceryl dibehenate, lactose monohydrate magnesium stearate, microcrystalline cellulose, polyethylene oxide, and poloxamer 188. In addition, the film coating ingredient, opadry II Blue 85F99153, contains the inactive ingredients FD&C Blue #1/Brilliant Blue FCF and FD&C Blue #2/Indigo Carmine, macrogol 3350, polyvinyl alcohol, talc, and titanium dioxide.
Alphabetical listing of inactive ingredients (if applicable)	N/A	See above
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	Distributed by: (b) (4) LLC (b) (4) Marlborough, MA 01752 USA

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

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

N/A

3.2 Carton Labeling

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	Brenzavvy® (bexagliflozin)
Strength(s) in metric system	Adequate	20 mg
Route(s) of administration	N/A	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	30 and 90
"Rx only" displayed on the principal display	Adequate	(b) (4)
NDC, Lot number, and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	
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, and these products require a "Not for direct infusion" statement.	N/A	

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

For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	**Adequate per revision:** Provide the linear bar code in the carton label

APPEARS THIS WAY ON ORIGINAL

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	Distributed by: (b) (4) LLC (b) (4) Marlborough, MA 01752 USA
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	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	
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	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: ***Adequate per revisions below:***

(a) Express the temperature first in °C and then °F: Store (b) (4) 20 °C to 25 °C (68 °F to 77 °F).

(b) **Add the linear bar code**

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date:

Ali Mohamadi, Ph.D 5/25/2022

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

Ali Mohamadi

Digitally signed by Ali Mohamadi
Date: 6/03/2022 03:19:55PM
GUID: 508da6ea0002750ec7c6cb7cfc37f10e

Muthukumar Ramaswamy

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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	214373
Assessment Cycle Number	001
Drug Product Name/ Strength	Bexagliflozin Tablets/ 20 mg
Route of Administration	Oral
Applicant Name	Theracos Sub, LLC
Therapeutic Classification/ OND Division	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Proposed Indication	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Assessment Recommendation: **Adequate**

Assessment Summary:
Theracos Sub, LLC submitted a 505(b) (1) application for the proposed Bexagliflozin Tablets, 20 mg.

The proposed Bexagliflozin tablets are blue film-coated immediate release tablet with prolonged in vitro drug release profiles in the proposed dissolution method.

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

Dissolution method and Acceptance Criterion:
Based on the provided information, the proposed dissolution method and dissolution acceptance criteria are found acceptable:

Dissolution Method		**Acceptance Criteria**	
Medium	0.1 N HCl	**Sampling Time (hr)**	**% Drug Release**
Apparatus	USP I (Basket)	1	NMT (b) (4)%
Volume	900 mL	3	(b) (4)%
Rotation Speed	50 RPM	5	(b) (4)%
Temperature	37ºC	8	NLT (b) (4)%

List Submissions Being Assessed:

Document Assessed	**Date Received**
Original Submission (0001)	**10/22/2021**

Highlight Key Issues from Last Cycle and Their Resolution: None
Concise Description of Outstanding Issues: None

B.1 BCS DESIGNATION

Solubility:

The Applicant determined the saturation concentrations of Drug Substance, Bexagliflozin, in KCl/HCl buffer (pH 1.0), NaOAc/HOAc buffer (pH 4.5), and $NaOH/KH_2PO_4$ buffer (pH 7.6). No significant variation of solubility with pH was observed. The mean values were 0.44, 0.46 and 0.46 mg/mL after 16 h of incubation at 37 °C and 0.45, 0.51 and 0.43 mg/mL after 24 h of incubation at 37 °C for pH 1.0, 4.5 and 7.6, respectively.

The intended commercial dosage strength is 20 mg, which will easily dissolve in 250 mL in any of the above media and hence the Applicant considers Bexagliflozin is a highly soluble compound by BCS criteria.

Permeability:

The Applicant did not directly determine the absolute bioavailability but stated that in humans the bioavailability lies in the range of 40 to 60%. In vitro permeability studies have shown that the compound is highly permeable but subject to P-gp export that diminishes the net permeation.

Assessment: *{Adequate}*

The Applicant did not request an official BCS designation. Based on the provided information, the Applicant reported the drug substance, Bexagliflozin, to be a highly soluble, low to moderately permeable, rapidly dissolving substance according to regulatory criteria.

B.2 FORMULATION

The proposed Bexagliflozin tablets, 20 mg, are blue film-coated, caplet-shaped, prolonged release tablets debossed with a "2 Ƶ" on one face, and no marking on the other face of the tablet.

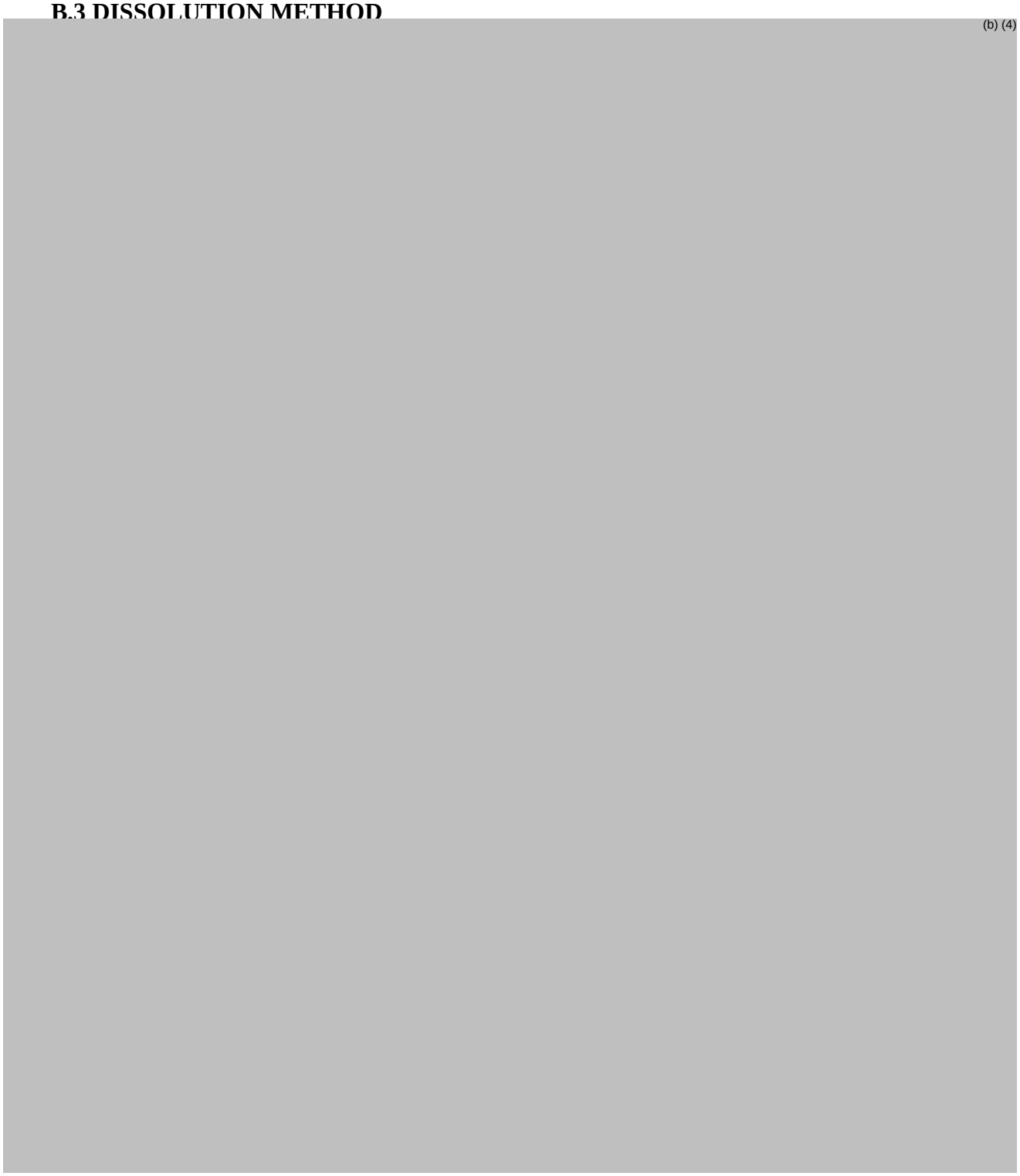
Table 1: Composition of the Proposed Bexagliflozin Tablets

Component	Amount per Tablet (mg)	Function	Quality Standard
Tablet core:			
Bexagliflozin	20.00	Active Ingredient	Internal
Polyethylene oxide	(b) (4)		USP/NF
Glyceryl dibehenate			USP/NF; EP
Lactose monohydrate			USP/NF; EP; JP
Poloxamer 188, (b) (4)			USP/NF; EP; JP
Microcrystalline cellulose			USP/NF; EP; JP
Colloidal silicon dioxide			USP/NF; EP; JP
Magnesium stearate			USP/NF; EP; JP
Total (tablet core)			
Film coat:			
Opadry II Blue 85F99153	(b) (4)	Coating	Internal
Total (film-coated tablet)	385.22		

Review Note: The Applicant utilized the release controlling excipient in the proposed formulation to target prolonged in vitro drug release. Based on the OCP reviewer Dr. Li Li's assessment on Study THR-1442-C-418, the proposed commercial Bexagliflozin tablets did not show dosing frequency reduction compared to the immediate release capsules, which supports the proposed designation as immediate release tablet.

B.3 DISSOLUTION METHOD

(b) (4)



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(b) (4)

Discriminating Power Assessment

The Applicant evaluated the rate of dissolution of Bexagliflozin tablets, 20 mg of varying excipient proportions and grades using the proposed dissolution method.

Increased Tablet Weight

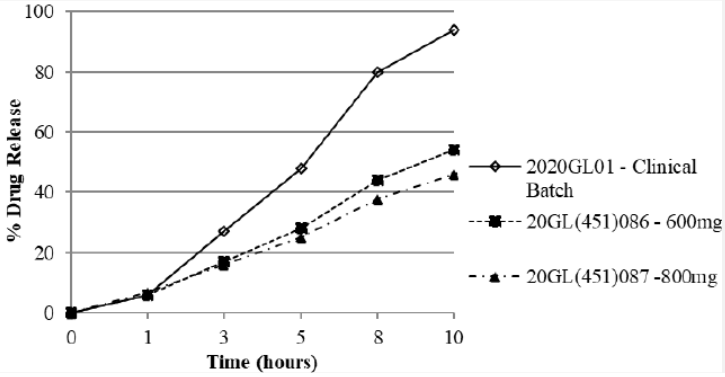
The Applicant performed a series of experiments to determine the effect of increasing the total tablet weight on the dissolution profile. The total tablet weight changes involved adding excipients that did influence the release profile of the tablets. Specifically, the (b) (4) were varied as shown in (Table 3).

Table 3: Formula for Bexagliflozin Tablets, 20 mg with Increased Tablet Weight

Batch No	2020GL01	20GL(451)086	20GL(451)087	20GL(504)006
Description (Tablet Weight)	374 mg ("Clinical Batch" / Reference)	600 mg	800 mg	700 mg
Batch Size	(b) (4) Tablets	(b) (4) Tablets	(b) (4) Tablets	(b) (4) Tablets
Quantity	Qty/Tablet (mg)	Qty/Tablet (mg)	Qty/Tablet (mg)	Qty/Tablet (mg)
Bexagliflozin	20.00	20.00	20.00	20.00
Polyethylene oxide	(b) (4)			
Glyceryl dibehenate				
Lactose Monohydrate				
Poloxamer 188 (b) (4)				
Microcrystalline cellulose (b) (4)				
(b) (4)				
Colloidal silicon dioxide				
Magnesium Stearate				
Total core tablet weight				
Opadry II 85F99153 Blue (b) (4)				
Total coated tablet weight	385.2	618.0	824.0	721.0

The Applicant observed that an increase in the total tablet weight using (b) (4) (b) (4) produced tablets that had slower release profiles (Figure 3).

Figure 3: Dissolution Profiles of Bexagliflozin Tablets of Increasing Weight



Excipients Change at SUPAC level

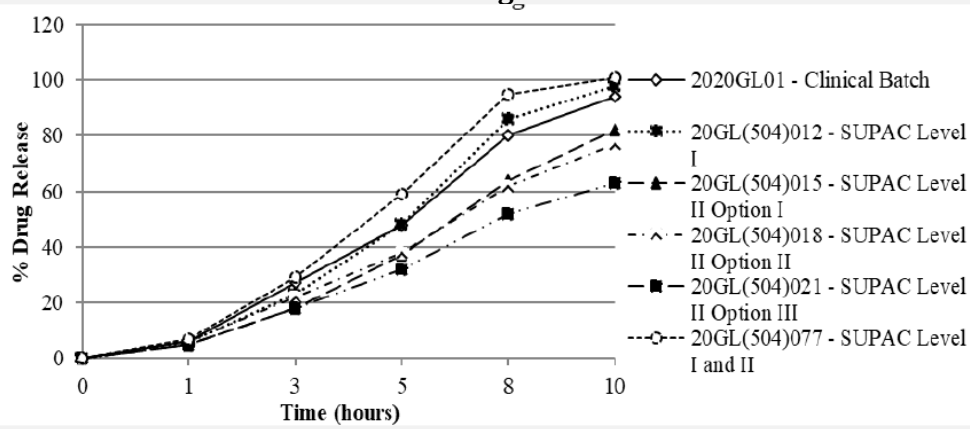
The Applicant conducted a series of studies to determine the effect of SUPAC Level I and II changes to the formulation (Table 4).

Table 4: Formula for Bexagliflozin Tablets, 20 mg with SUPAC Level Changes

Batch No	**2020GL01**	**20GL(504) 012**	**20GL(504) 015**	**20GL(504) 018**	**20GL(504) 021**	**20GL(504) 077**
Description	**Clinical Batch / Reference**	**SUPAC Level I**	**SUPAC Level II – Option I**	**SUPAC Level II – Option II**	**SUPAC Level II – Option III**	**SUPAC Level I and II**
Batch Size	(b) (4)					
	Tablets	**Tablets**	**Tablets**	**Tablets**	**Tablets**	**Tablets**
Quantity	**Qty/Tablet (mg)**	**Qty/Tablet (mg)**	**Qty/Tablet (mg)**	**Qty/Tablet (mg)**	**Qty/Tablet (mg)**	**Qty/Tablet (mg)**
Bexagliflozin	20.00	20.00	20.00	20.00	20.00	20.00
Polyethylene oxide	(b) (4)					
Glyceryl dibehenate						
Lactose Monohydrate						
Poloxamer 188 (b) (4)						
Microcrystalline cellulose (b) (4)						
(b) (4)						
Colloidal silicon dioxide						
Magnesium Stearate						
Total core tablet weight						
Opadry II 85F99153 Blue (b) (4) w/w)						
Total coated tablet weight	385.2	385.2	385.2	422.3	422.3	422.3

The Applicant observed that a change in quantities of (b) (4) (b) (4) would affect the dissolution profile of Bexagliflozin tablets using the proposed dissolution method (Figure 4).

Figure 4: Dissolution Profiles of Bexagliflozin Tablets at Various SUPAC Level Changes

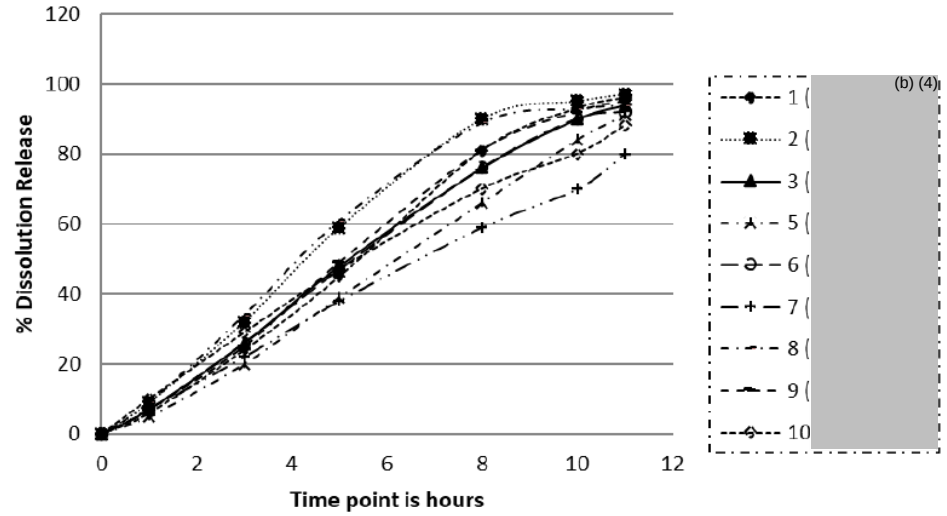


The Applicant conducted additional confirmatory studies on variation of excipient quantities from the proposed commercial formulation. The formulation center points (runs 3, 4 and 11 in Table 5) represent the commercial formulation. The other runs (1, 2, 5, 6, 7, 8, 9 and 10) used the variable excipient quantities shown in the first row of Table 5.

Table 5: Dependence of Dissolution Profiles on Excipient Proportions[2]

Run Order	1	2	3	4	5	6	7	8	9	10	11	Ave Center Points (3, 4, 11)
(b) (4)	(b) (4)											
Time (h)												
1	6	9	7	7	5	7	7	9	7	10	7	7
3	24	32	26	28	20	26	22	34	25	29	25	26.3
5	45	59	48	49	39	47	38	61	49	47	46	47.7
8	81	90	76	80	66	76	59	89	81	70	74	76.7
10	93	95	90	91	84	90	70	93	92	80	90	90.3
f_2 Value	**76**	**53**	**NA**	**NA**	**56**	**98**	**44**	**52**	**81**	**62**	**NA**	**NA**

Figure 5: Formulation Change DOE Study



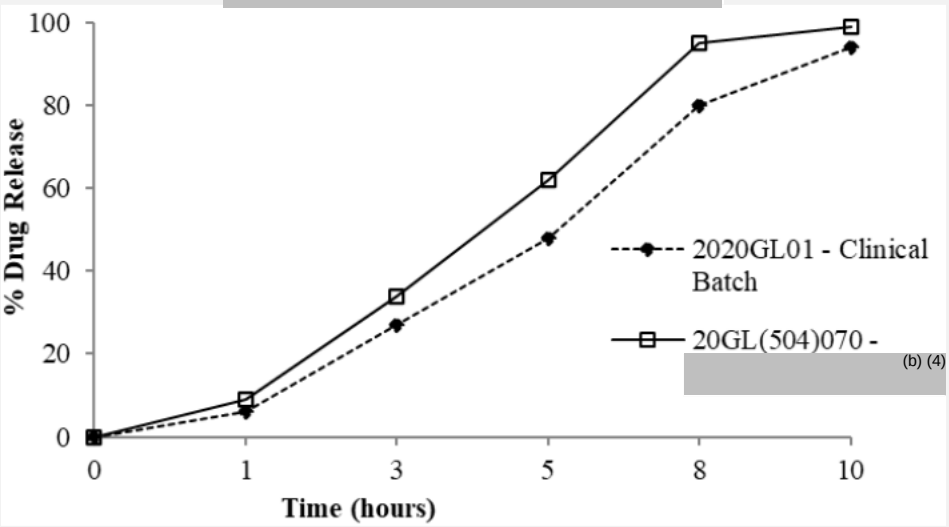
As shown in Table 5 and Figure 5, the Applicant observed that a change in quantity of (b) (4) did not drastically affect the dissolution profile compared to the center points. Similarly, the concerted increase or decrease in the quantities of (b) (4) (b) (4) (runs 6 and 9) relative to the center points did not greatly affect the dissolution profile. However, (b) (4) affected the dissolution rates to a greater extent (runs 2, 5, 7 and 8). The effects of changes in the relative quantities of (b) (4) used in the formulation could be discriminated using the proposed dissolution method.

[2] The values listed in parentheses represent the quantities (in mg) of (b) (4) (b) (4) (abbreviated (b) (4), respectively).

Excipients Particle Size Change

The Applicant conducted a trial using large particle sized [redacted]

Figure 6: Dissolution Profile of Bexagliflozin Tablets, 20 mg Using [redacted]



This was a direct 1:1 substitution of [redacted]. This study found that the large particle size version of [redacted] (d(0.9) ~ [redacted] µm for [redacted] versus ~[redacted] µm for [redacted]) provided a faster releasing tablet compared to [redacted] version of the tablet (Figure 6).

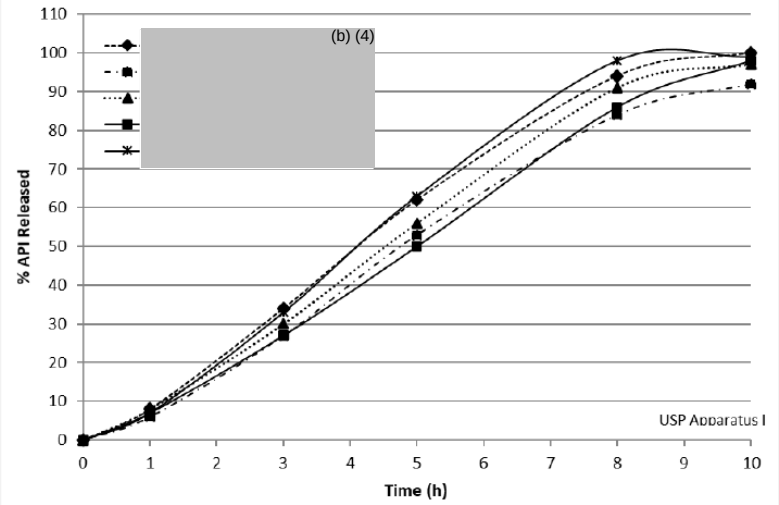
Excipients Particle Size Change

The Applicant examined the effects on formulation properties of different grades of non-critical excipients and [redacted] and could not detect an effect of the grade of [redacted] on dissolution profile of the proposed Bexagliflozin Tablets.

API Particle Size Change

The Applicant prepared Bexagliflozin Tablets from drug substance lots have different PSD and found only little systematic variation in dissolution rate.

Figure 7: Dissolution Profile of Bexagliflozin Tablets, 20 mg, as a Function of Drug Substance Particle Size d(0.9)



Assessment: ***{Adequate}***

The Applicant adequately demonstrated and justified the suitability of the proposed dissolution method for batch release and stability testing of the proposed Bexagliflozin Tablets. The proposed dissolution method shows discriminating ability towards variations in excipients ((b) (4)) amount and particle size of excipient (b) (4) .

Based on the provided information, the proposed dissolution method (900 mL 0.1 N HCl, USP Apparatus I at 50 rpm) is found acceptable for the QC of the proposed Bexagliflozin Tablets.

B.4 DISSOLUTION METHOD ACCEPTANCE CRITERIA

The Applicant states that only the clinical batches have been used to determine the appropriate acceptance criteria for dissolution and the validation batch information is provided for information purpose only (Appendix II).

Release testing of clinical batches was performed to either of two acceptance criteria: a 5-point (1, 3, 5, 8 and 10 h) or a 3-point (1, 5 and 8 h) dissolution profile. Specifically, clinical batches B17217 and B17218 were released according to the 3-point (1, 5 and 8 h) criteria, whereas the B09706, B10904, B11421, B13445 and B13446 were released according to the 5-point criteria. The validation batches B22329, B22331 and B23014 were released to 4-point criteria (1, 3, 5 and 8 h).

The Applicant presented composite data of all units tested as shown in Table 6, while a summary of the data from only the clinical batches are shown in Table 7 and that from the process validation batches in Table 8. There is no significant difference between the obtained values.

Table 6: Composite Dissolution Data from Manufacturing Release Testing of the Clinical and Validation Batches

Hour	Overall Mean % Dissolution	%RSD	Min	Max
1	6.71	8.18	5.50	8.48
3	28.81	9.14	23.22	36.43
5	54.32	8.91	45.46	69.06
8	91.84	4.78	78.18	98.33

Table 7: Composite Dissolution Data from Manufacturing Release Testing of Clinical Batches (B09706, B10904, B11421, B13455, B13456, B17217 and B17218)

Hour	Overall Mean % Dissolution	%RSD	Min	Max
1	6.76	9.01	5.57	8.48
3	30.44	9.40	25.57	36.43
5	55.21	10.79	45.46	69.06
8	91.09	6.15	78.18	98.33

Table 8: Composite Dissolution Data from the Validation Batches (B22329, B22331 and B23014)

Hour	Overall Mean % Dissolution	%RSD	Min	Max
1	6.67	7.48	5.50	7.64
3	27.90	7.19	23.22	31.40
5	53.63	6.82	47.12	61.32
8	92.42	3.35	84.22	97.75

Samples from 4 of the clinical batches of Bexagliflozin tablets, 20 mg, in 60 mL HDPE bottles with an induction seal and (b) (4) closure at 90 tablets per bottle (specifically B09706, B10904, B11421, B13446) were placed in controlled environmental chambers for stability studies at ICH compliant 25 °C/60% RH, 30 °C/75% RH and 40 °C/75% RH conditions. The Applicant did not observe trend of the dissolution profile change over time.

The Applicant used Table 9 to set the acceptance criteria (Table 10) for dissolution testing.

Table 9: Summary of Mean % Dissolution Values for all Clinical, 25 °C/60%RH and 30 °C/75%RH Stability Study Batches

Batches	Hours			
	1	3	5	8
B09706 Release	6.73	27.49	49.86	86.25
B10904 Release	6.81	29.54	52.11	87.83
B11421 Release	6.57	32.63	62.65	97.61
B13445 Release	7.10	Not Tested	52.24	85.76
B13446 Release	7.74	Not Tested	63.79	96.68
B17217 Release	6.32	Not Tested	54.36	92.95
B17218 Release	6.07	Not Tested	51.50	90.61
B09706 @ 25 °C/60% RH	7.65	33.16	60.39	92.96
B09706 @ 30 °C/75% RH	8.57	36.53	64.36	92.87
B10904 @ 25 °C/60% RH	7.04	30.89	58.60	92.59
B10904 @ 30 °C/75% RH	7.64	32.48	61.01	93.62
B11421 @ 25 °C/60% RH	7.78	34.20	65.12	96.28
B11421 @ 30 °C/75% RH	8.04	34.63	66.36	95.98
B13446 @ 25 °C/60% RH	7.72	34.28*	63.74	96.61
B13446 @ 30 °C/75% RH	7.87	34.56*	66.34	96.92
MEAN	7.31	32.39	59.49	93.03

*: the 3 hour time point was tested at 36 and 48 months after updating the stability protocol.

Table 10: Proposed Acceptance Criteria for in vitro Dissolution of Bexagliflozin Tablets

Testing Point	Hours	MEAN from Table 3.2.P.5.6-14	Proposed Dissolution Acceptance Criteria (%)
1	1	7.31	NMT (b) (4)
2	3	32.39	(b) (4)
3	5	59.49	
4	8	93.03	NLT (b) (4)

The percentages of the labeled amount of bexagliflozin dissolved at the times specified conform to USP Dissolution <711>, Acceptance Table 2.

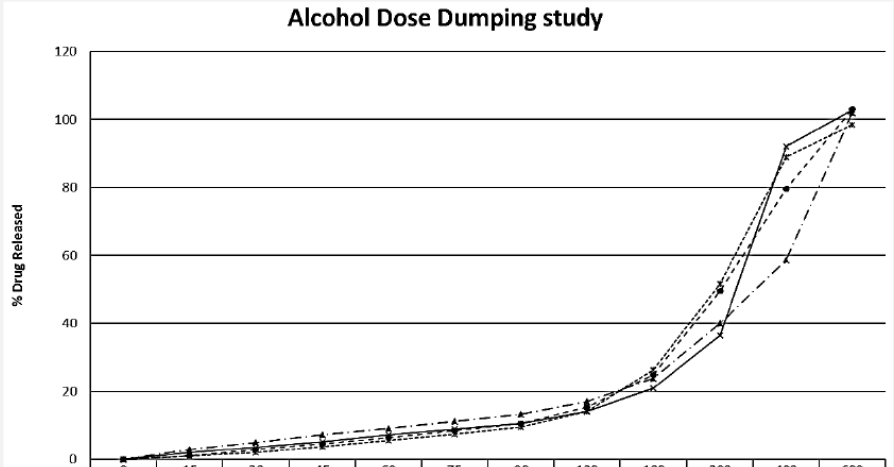
Assessment: ***{Adequate}***

Although the proposed Bexagliflozin tablets are immediate release tablets, the Applicant proposed multi time points acceptance criteria for the prolonged *in vitro drug release. Based on the dissolution data of the clinical batches, the proposed dissolution acceptance criteria are found acceptable.*

B.5 ALCOHOL DOSE DUMPING

The Applicant conducted alcohol dose dumping study on the proposed Bexagliflozin tablets, 20 mg using 0.1 N HCl (with 0%, 5%, 20% and 40 % alcohol) at 50 RPM in USP Apparatus I (Figure 8).

Figure 8: Comparison of the Dissolution Profiles from 20GL(451)001 versus Concentration of Ethanol in Dissolution Media Conclusion



min	0	15	30	45	60	75	90	120	180	300	480	600
40%	0	3	5	7	9	11	13	17	24	40	59	102
20%	0	2	4	5	7	9	11	14	21	37	92	103
0%	0	1	2	4	6	8	10	14	26	52	89	98
5%	0	1	3	5	7	9	11	15	25	50	80	103

Assessment: ***{Adequate}***

The Applicant concludes that there is no significant impact on quickening the release of Bexagliflozin tablets, 20 mg, due to alcohol dose dumping. As the proposed dosage form is immediate release tablets, the Applicant's alcohol dose dumping study is for information only.

B.6 BRIDGING OF FORMULATIONS

Assessment: ***{N/A}***

Seven phase 3 clinical trials and 6 clinical pharmacology studies have been conducted using the proposed Bexagliflozin tablets, 20 mg (Table 11). Note that the clinical formulation of Bexagliflozin tablets, 20 mg, is the same as the proposed commercial product, and the manufacturing process of the clinical tablets is essentially the same as that of the commercial product. Only minor process changes to the manufacturing process, such as (b) (4) *, have been implemented for the intended commercial process. Both are considered minor changes that do not affect the quality of the product. Therefore, no bridging is needed.*

Table 11: Clinical Trials Using Bexagliflozin Tablets, 20 mg

Protocol/Phase	Status	Design	Duration (w)	No. of Subjects
THR-1442-C-449/2	complete	dose range-finding study with HbA_{1c} endpoint	12	290
THR-1442-C-450/3	complete	bexagliflozin monotherapy vs placebo in subjects with diabetes	24	210
THR-1442-C-448/3	complete	bexagliflozin vs placebo in subjects with diabetes and renal impairment who are taking other approved therapies for glycemic control	24	312
THR-1442-C-423/3	complete	bexagliflozin vs sitagliptin in subjects with diabetes who are taking metformin alone	24	383
THR-1442-C-419/3	complete	bexagliflozin vs placebo in subjects with diabetes who are taking metformin alone	24	352
THR-1442-C-480/3	complete	bexagliflozin vs glimepiride in subjects with diabetes who are taking metformin alone	96	427
THR-1442-C-476/3	complete	bexagliflozin vs placebo in subjects with diabetes and increased cardiovascular risks who are taking other approved therapies for glycemic control	various; 2 to 3 years	1701
THR-1442-C-603/3	complete	bexagliflozin vs placebo in subjects with hypertension who are taking other approved therapies	36	678
THR-1442-C-481/1	complete	definitive food effect PK study	*	24
THR-1442-C-453/1	complete	drug-drug interaction PK study with approved oral hypoglycemic drugs	*	54
THR-1442-C-458/1	complete	drug-drug interaction PK study with exenatide	*	20
THR-1442-C-443/1	complete	drug-drug interaction PK study with digoxin	*	20
THR-1442-C-454/1	complete	drug-drug interaction PK study with drugs affecting xenobiotic metabolism	*	48
THR-1442-C-455/1	complete	PK/PD study in subjects with hepatic impairment	*	16

* = Single dose or less than 5 doses based on the cross-over study design. Duration was less than 1 week.

B. 7 BIOWAIVER REQUEST

Assessment: N/A

A biowaiver is not submitted nor required for this NDA.

Primary Biopharmaceutics Assessor's Name and Date: Zhuojun Zhao, Ph.D., 6/5/2022

Secondary Assessor Name and Date: Haritha Mandula, Ph.D., 06/07/2022

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Appendix II: Mean Dissolution Profile at the Time of Manufacturing Release

Batch	Tablet	1 hour	3 hours	5 hours	8 hours
B09706	1	(b) (4)			
	2				
	3				
	4				
	5				
	6				
	Mean (RSD)	6.73 (5.3)	27.49 (5.3)	49.86 (5.5)	86.25 (5.1)
B10904	1	(b) (4)			
	2				
	3				
	4				
	5				
	6				
	Mean (RSD)	6.81 (6.0)	29.54 (6.7)	52.11 (6.0)	87.83 (4.9)
B11421	1	(b) (4)			
	2				
	3				
	4				
	5				
	6				
	Mean (RSD)	6.52 (6.8)	32.31 (5.2)	62.13 (4.8)	97.46 (0.6)
B13445	1	(b) (4)			
	2				
	3				
	4				
	5				
	6				

Batch	Tablet	1 hour	3 hours	5 hours	8 hours
	Mean (RSD)	7.09 (3.3)	28.68 (6.1)	51.44 (6.9)	83.86 (7.2)
B13446	1	(b) (4)			
	2				
	3				
	4				
	5				
	6				
	Mean (RSD)	7.70 (6.3)	33.39 (6.9)	63.46 (5.8)	96.55 (0.7)
B17217	1	(b) (4)			
	2				
	3				
	4				
	5				
	6				
	Mean (RSD)	6.33 (3.5)	Not applicable	53.92 (3.5)	92.93 (1.2)
B17218	1	(b) (4)			
	2				
	3				
	4				
	5				
	6				
	Mean (RSD)	6.04 (4.9)	Not applicable	51.19 (4.4)	91.44 (3.7)
B22329 (validation batch)	1	(b) (4)			
	2				
	3				
	4				
	5				
	6				
	Mean (RSD)	6.23 (3.7)	26.12 (5.2)	50.98 (4.7)	91.78 (1.5)
B22331 (validation batch)	1	(b) (4)			
	2				
	3				
	4				
	5				
	6				
	Mean (RSD)	7.02 (5.2)	29.40 (6.5)	56.57 (6.7)	93.98 (2.0)

Batch	Tablet	1 hour	3 hours	5 hours	8 hours
B23014 (validation batch)	1	(b) (4)			
	2				
	3				
	4				
	5				
	6				
	Mean (RSD)	6.65 (6.2)	29.97 (3.9)	57.22 (2.1)	95.19 (1.5)

Zhuojun Zhao

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Haritha Mandula

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Date: 6/08/2022 06:27:43AM
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