CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216403Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	216403		
Applicant Name	Travere Therapeutics, Inc.		
Drug Product Name	FILSPARI (sparsentan)		
Dosage Form.	Tablet		
Proposed Strength(s)	200 mg, 400 mg		
Route of Administration	Choose an item. APPEARS THIS WAY ON ORIGINAL		
Maximum Daily Dose	400 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Sparsentan is indicated for treatment of immunoglobulin A nephropathy (IgAN) in adults aged 18 years and older.		
Drug Product Description	Film-coated, modified oval, debossed immediate-release tablets packaged in HDPE bottles of 30 tablets each.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	Store at 20°C to 25°C in the original container.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Joseph Leginus ONDP/DNDAPI/NDB3	Sithamalli Chandramouli ONDP/DNDAPI/NDB3
	Drug Product/ Labeling	Dan Berger ONDP/DNDPIII/NDPB5	Theodore Carver ONDP/DNDPIII/NDPB5
	Manufacturing	Lixia Cai OPMA/DPMAIII/PMB7	Nancy Waites OPMA/DPMAIII/PMB7
	Biopharmaceutics	Debasis Ghosh ONDP/DB/BB3	Haritha Mandula ONDP/DB/BB3

	Microbiology	N/A	N/A
	Other (specify):	N/A	N/A
	RBPM	Grafton Adams OPQ/OPRO/DRBPMI/RBPMB2	
	ATL	Theodore Carver OPQ/ONDP/DNDPIII/NDPB5	
Consults	None.		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

The expiry dating period for FILSPARI (sparsentan) 200 mg and 400 mg tablets shall be 24 months from the date of manufacture when stored at 25 °C.

b. Additional Comments for Action
None.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1. Background:

Travere Therapeutics, Inc., the Applicant, has submitted an original 505(b)(1) NDA for sparsentan tablets for oral use. Sparsentan is a small molecule dual endothelin receptor antagonist that is indicated for treatment of immunoglobulin A nephropathy (IgAN) in adults aged 18 years and older. Sparsentan has been granted orphan drug designation.

2. Brief summary of the OPQ review and resolution of deficiencies identified during the review:

Drug Substance -The Sparsentan drug substance is a white to off-white powder that is not hygroscopic, not sensitive to light, and has been observed to have a single crystalline form in polymorph screening studies. In addition to tests for identity, assay, and purity, water content, microbiological quality, and particle size distribution are also controlled in the drug substance

specification. After the Applicant clarified the structure of an impurity and how water content testing was performed for development and commercial batches, the drug substance review concluded that the chemistry, manufacturing, and controls of the drug substance are adequate, and a retest period of (b) (4) months is appropriate for the drug substance.

Drug Product - Sparsentan tablets are film-coated, immediate-release tablets that are available as two strengths, 200 mg and 400 mg. The tablets are manufactured using compendial excipients at levels that were determined to be acceptable. In response to an FDA information request during the during the review, the Applicant (b) (4) . In addition to orthogonal identity tests and tests for appearance, assay, content uniformity, and impurities, the drug product specification includes tests for dissolution, (b) (4), and microbiological quality. The drug product review concluded that the CMC information was adequate with respect to controlling the quality of the drug product, and a 24-month shelf life for both strengths of tablets is deemed appropriate. The quality labeling was reviewed and found to be adequate after deficiencies were addressed by the Applicant.

Biopharmaceutics - With respect to biopharmaceutics aspects of the drug product, the Applicant classified the drug substance as BCS Class II (low solubility and high permeability). To ensure consistent performance of the drug product, particle size is controlled in the drug substance, and the Applicant tightened acceptance criteria for particle size in response to an information request. The biopharmaceutics review concluded that biopharmaceutics aspects of the scientific bridging of formulations and strengths used from clinical development to commercial product are adequate and that the dissolution method in the commercial specification is adequate.

Manufacturing and Facilities – The commercial manufacturing process consists of the following steps: (b) (4) were

inadequate. The Applicant addressed these deficiencies in amendments submitted during the manufacturing review, and the final review concluded that the manufacturing process and controls are adequate. The review of the drug substance (b) (4)) and drug product (Catalent CTS, LLC, FEI: 3002929455) manufacturing facilities recommended approval based on previous inspection history.

Therefore, no deficiencies are outstanding at the conclusion of the OPQ review of NDA 216403, and the OPQ recommendation is Approval.

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:
None.

Comparability Protocols (PACMP): No
Comments:
In response to an FDA comment, The Applicant agreed to (b) (4)

Additional Lifecycle Comments: None.

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

Section 11 has been edited to add the product description, alphabetize excipients and to add chemical properties of the API. With these edits, the prescribing information meet all regulatory requirements from a CMC perspective.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Listed as "Proprietary name"	Adequate
Established name(s)	Sparsentan	Adequate
Route(s) of administration	Oral	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	200 mg and 400 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	NA	NA

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Tablets	Adequate
Strength(s) in metric system	200 mg and 400 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	NA	NA
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	(b) (4) oval, film-coated white to off-white tablet debossed with "105" (200 mg strength) or "021" on one side (400 mg strength)	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Proprietary name, sparsentan	Adequate
Dosage form(s) and route(s) of administration	Added: Available as 200 mg and 400 mg strength tablets for oral admin.	Adequate, with edits.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	NA	NA
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Silicified microcrystalline cellulose, lactose anhydrous, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate. Coating: PVA-partially hydrolyzed, macrogol/PEG, talc, and titanium dioxide.	Edited to alphabetize the inactive ingredients.
For parenteral injectable dosage forms, include name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)	NA	NA
Pharmacological/ Therapeutic class	(b) (4) endothelin angiotensin receptor antagonist.	Adequate
Chemical name, structural formula, molecular weight	Chemical name*, 592.76 g/mol, $C_{32}H_{40}N_4O_5S$	Adequate
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	White to off-white powder, which is practically insoluble in water.	Adequate, with edits.

*2-[4-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methy]-2-(ethoxymethyl)phenyl]-N-(4,5-dimethyl-1,2-oxazol-yl)benzenesulfonamide.

Section 11 (DESCRIPTION) Continued

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

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Tablets	Adequate
Strength(s) in metric system	200 mg and 400 mg	Adequate
Available units (e.g., bottles of 100 tablets)	Bottles of 30 tablets	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Shape, color, debossing, NDC 68974-200-30 and 68974-400-30.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA

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

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.)	Store PROPRIETARY NAME in its original container.	Adequate. To maintain stability.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	NA	NA
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)	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: "Not made with natural rubber latex. Avoid statements such as "latex-free."	NA	NA
Include information about child-resistant packaging	Not present	NA

1.2.5 Other Sections of Labeling

No other sections of the labeling contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Distributed by Travere Therapeutics, Inc., San Diego, CA 92130	Adequate

2.0 PATIENT LABELING

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

The medication guide is acceptable, following edits made to alphabetize excipients.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

Bottle (200 mg strength):

3.2 Carton Labeling

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Item	Information Provided in the NDA	Assessor's Comments about Bottle and Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Filspari, sparsentan	Adequate
Dosage strength	200 mg and 400 mg	Adequate
Route of administration	Not required for oral drug	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	NA	NA
Net contents (e.g., tablet count)	Bottles of 30 tablets,	Adequate
"Rx only" displayed on the principal display	Present	Adequate
NDC number	NDC 68974-200-30 and 68974-400-30.	Adequate
Lot number and expiration date	Present	Adequate, following Applicant edits.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (59°F and 86°F)	Adequate, following Applicant edits.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	NA
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Bar code	Present	Adequate, following Applicant edits.

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured for: Travere Therapeutics, Inc., San Diego, CA 92130	Adequate
Medication Guide (if applicable)	Storage conditions and inactive ingredients.	Adequate, with edits to the inactive ingredients list.
No text on Ferrule and Cap overseal	NA	NA
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	NA	NA
And others, if space is available		

Assessment of Carton and Container Labeling: *Adequate*
Following edits made by the Applicant in response to Information Requests on July 12, 2022 (SD #28), the labels are acceptable and comply with all regulatory requirements from a CMC perspective.

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

All labeling deficiencies have been addressed. The Prescribing Information and labels comply with all regulatory requirements from a CMC perspective.

Primary Labeling Assessor Name and Date:

Dan Berger August 2, 2022

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

Theodore Carver August 2, 2022

Dan Berger

Digitally signed by Dan Berger
Date: 8/02/2022 09:23:54AM
GUID: 56e6e1b5001a2fedae663c62a5ce7513

Theodore Carver

Digitally signed by Theodore Carver
Date: 8/02/2022 01:53:04PM
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CHAPTER VI: BIOPHARMACEUTICS

Product Information	FILSPARI[1] (Sparsentan) Tablets, 200 mg and 400 mg, oral, immediate release
NDA Number	216403
Assessment Cycle Number	1
Drug Product Name/ Strength	Sparsentan Tablets, 200 mg, and 400 mg
Route of Administration	Oral
Applicant Name	Travere Therapeutics, Inc (previously known as Retrophin, Inc.)
Therapeutic Classification/ **OND Division**	Nephrology/ Division of Cardiology and Nephrology
RLD/RS Number	NA
Proposed Indication	For the treatment of IgA nephropathy (IgAN), a rare kidney disease (FDA Granted Orphan Drug Designation; 01/11/2021)

Assessment Recommendation: **Adequate**

Assessment Summary:

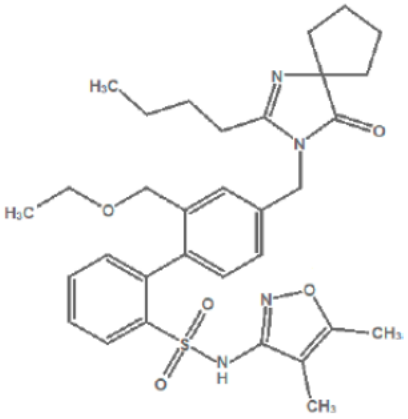
On March 14, 2022, the Applicant submitted an NDA under 505(b)(1), seeking approval for Sparsentan Tablets, 200 mg, and 400 mg (immediate release tablet for oral administration) as a treatment for Immunoglobulin A nephropathy (IgAN), a proteinuric glomerular disease also known as Berger's Disease, in adults aged 18 years and older. Sparsentan is a highly selective agonist of both endothelin A receptor and angiotensin II subtype I receptor. Based on clinical evidence, the Applicant stated that sparsentan could provide clinical benefits to patients with IgAN especially who are at high risk of disease progression. The product received Orphan Drug Designation from the Agency on Jan 11, 2021.

The drug substance is a white to off-white powder with low solubility in water and physiological pH. Based on Caco-2 cell study, the permeability of the molecule in GI tract is high. The Applicant designated drug substance as BCS Class II (low solubility and high

[1] Proprietary Name granted on 06/13/2022.

permeability). The Applicant stated that sparsentan exhibits non-linear pharmacokinetics (dose proportional between 50-200 mg and less than dose proportional between 200-1600 mg) possibly, due to solubility limited absorption and metabolism[2]. The polymorph screening studies revealed only one crystalline non-solvated form. The Applicant indicated that no form changes were observed on stability or release. The pKa values of sparsentan are 4.09, & 5.31. Since drug substance is poorly soluble, particle size is a critical quality attribute for dissolution. As a control strategy, the Applicant proposed three-tier particle size acceptance criteria for drug substance. Following Agency's recommendation, the Applicant tightened the particle size acceptance criterion for drug substance. The revised particle size specification is acceptable. However, in absence of BE study with aberrant batches, it is not clear whether the particle size specification can reject non-BE batches.

Fig 1. Structure of Sparsentan



Molecular Formula

$C_{32}H_{40}N_4O_5S$

Molecular Weight

592.76 g/mol

The drug product is a white to off-white, modified-oval, film-coated tablet, plain on one side with debossed number (for 200 mg: 105; for 400 mg: 021) on the other side. The tablets are not scored. The product, used in Phase 3 clinical studies and also proposed as commercial drug product, contains common inactive ingredients for tablet formulation including silicified microcrystalline cellulose ((b) (4)), lactose anhydrous, sodium starch glycollate, colloidal silicon dioxide, and magnesium stearate. The proposed commercial manufacturing process of drug product involves (b) (4) . Based on history of the product development, initial Phase 1 study was performed with sparsentan (b) (4) (powder-in-a-bottle), Phase 1 and Phase 2 studies were conducted with 100 mg capsule, over-encapsulated (OE) 200 mg tablet (for blinding purposes) and for Phase 3 clinical studies, film-coated 200 mg and 400 mg tablets were used. For OE 200 mg tablet, the capsules were (b) (4)

[2] Module 2.7.2 Summary of Clinical Pharmacology Studies.

(b) (4) While (b) (4) of OE tablets is not recommended, (b) (4) is not expected to have any adverse effect on bioavailability of the product.

The Applicant performed in vivo BE studies between 400 mg **tablet** and 4x100 mg **capsule** (BE Study#021HVOL16001) and between 400 mg **tablet** and 2x200 mg **tablet** (BE Study#RTRX-RE021-101) to demonstrate equivalency. Based on in vivo and in vitro studies, the Applicant concluded that "changes in formulation or process has no impact on the bioavailability of the product. BE Studies were assessed by Clinical Pharmacology Team. The reviewer verified with clinical pharmacology reviewer and the studies are acceptable from their end.

To demonstrate bridging, the Applicant also provided comparative in vitro multimedia dissolution studies using proposed dissolution method with over-encapsulated 200 mg tablets and un-encapsulated 200 mg tablets. In a previous communication, the Agency recommended the use of multimedia comparative dissolution to demonstrate similarity between OE 200 mg tablets and 200 mg tablets. The dissolution in QC medium (0.1N HCl) was found to be similar for both formulations (f2=87 and 62 at 60 and 75 rpm, respectively). At pH 4.5 (acetate buffer 50 mM) and pH 6.8 (phosphate buffer, 50 mM) media, both samples exhibited low dissolution but mostly similar profiles.

In Module 3.2.P.2.2., the Applicant provided dissolution method development including choice of medium, volume, apparatus, and paddle speed. The discriminating ability of the method towards changes to critical biopharmaceutics attributes and method validation reports are provided. The Applicant proposed a dissolution specification of NLT (b) (4)%(Q) in 30 min. Based on individual dissolution data from pivotal clinical batches (both 200 mg and 400 mg strengths), the proposed specification is reasonable. All BE batches also met the proposed specification. However, in absence of additional in vivo data from aberrant batches, it is not clear whether the proposed specification can reject batches which are not bioequivalent or whether the proposed specification is clinically relevant. The recommended dissolution method and dissolution acceptance criteria are provided in Table 1.

Table 1. Proposed and Accepted Dissolution Method and Acceptance Criterion for Sparsentan Drug Product

Source	Strength	Apparatus	Speed (rpm)	Medium	Temp.	Volume (mL)	Acceptance criteria
In-house	all	USP II	60	0.1N HCl	37°C	1000	Q= (b) (4)% in 30 min

Risk Assessment for Dissolution:

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Particle Size of API	Medium	Since API is a low-soluble product, particle size is considered a CQA for dissolution. As a risk mitigation strategy, the Applicant proposed a three-tier particle size distribution (PSD) for API.	Low	While the clinical relevance of particle size specification is not yet established, the proposed revised drug substance particle size specification provides adequate control to ensure batch-to-batch consistency.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Original Application (SN 001)	03/14/2022
Response to Quality IR (SN 0024)	07/07/2022
Response to Quality IR (SN 0032)	07/15/2022

Highlight Key Issues from Last Cycle and Their Resolution: N/A

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

B.1 BCS DESIGNATION

Assessment: Based on solubility in physiological pH, drug substance, sparsentan, is a low solubility drug (BCS). As demonstrated by Caco-2 cell study, it is considered

a highly permeable or readily absorbed drug substance when administered orally. The Applicant designated sparsentan as BCS II.[3] However, the Applicant stated that sparsentan exhibits non-linear pharmacokinetics (dose proportional between 50-200 mg and less than dose proportional between 200-1600 mg). The Applicant indicated that this is possibly due to solubility limited absorption and/or dose dependent induction of metabolizing enzyme CYP3A. (b) (4), a two-compartment disposition model with first-order absorption and dose-dependent bioavailability adequately describe the sparsentan concentration-time profile. Following oral administration, the rate of absorption of sparsentan was moderate with a mean time to plasma concentration (Tmax) of approximately 3 hours (ranging from 2-(b) (4) hours).

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

B.2.1 Dissolution Method: The Applicant developed an in-house dissolution method to perform in vitro dissolution test for the proposed product. The Applicant stated that dissolution method employs the same principle that has been used throughout the clinical development.

B.2.1.1 Dissolution Method Development: (b) (4)

(b) (4)

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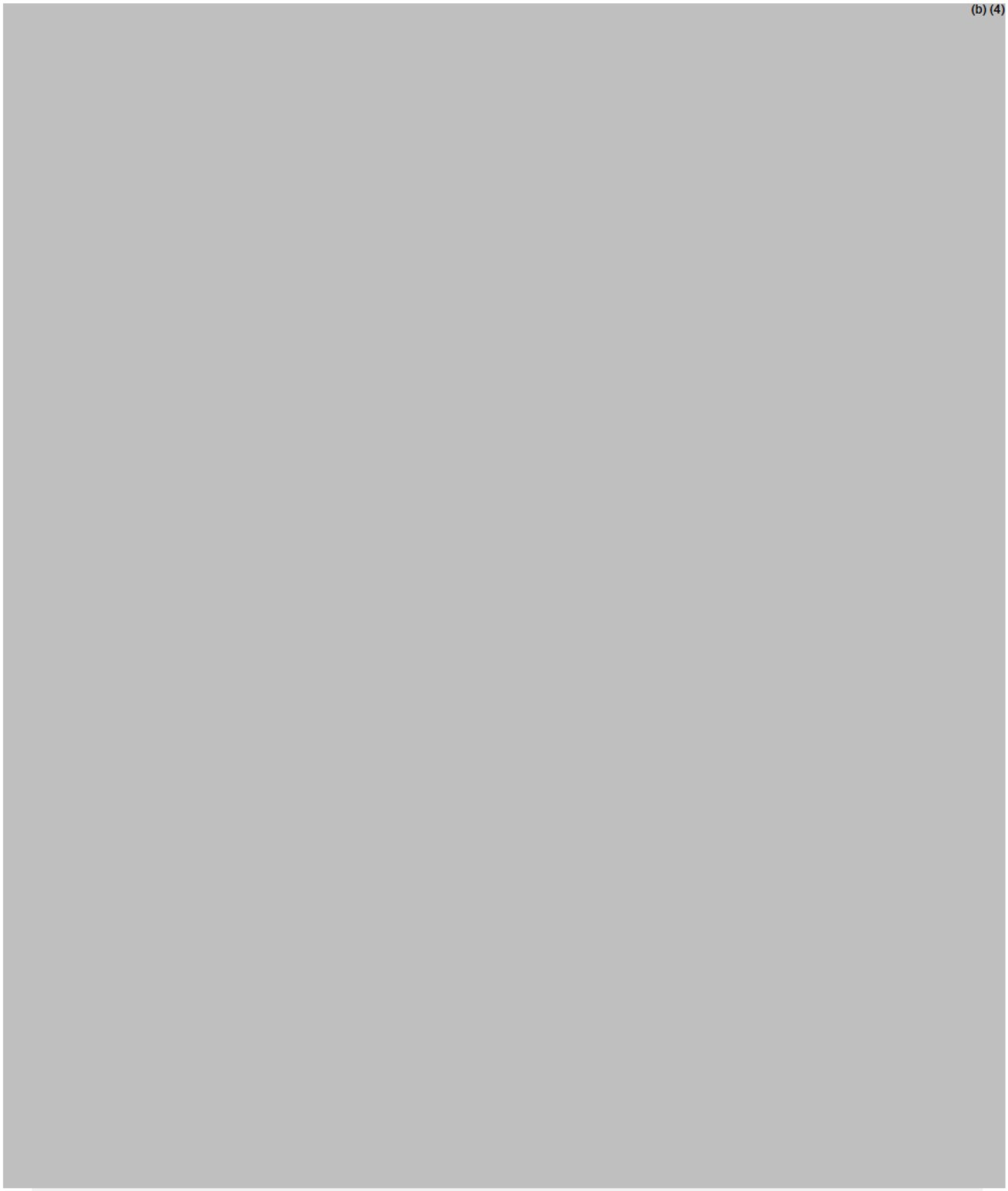


B.2.1.2 Discriminating Ability of the method: The Applicant provided data from product development report to establish discriminating ability of the method towards critical bioavailability attributes.

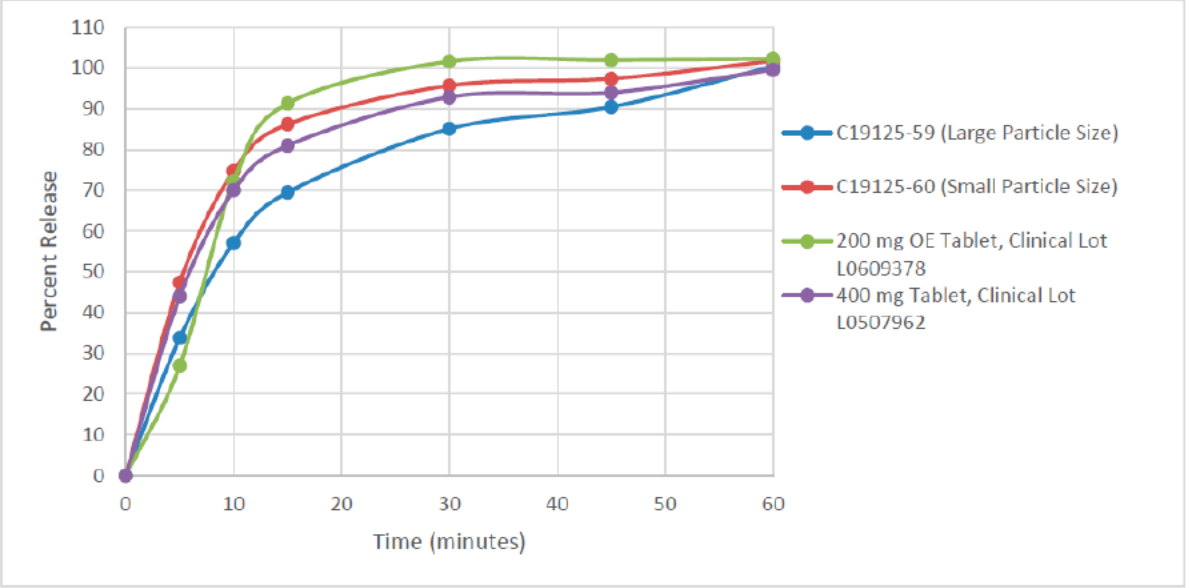
B.2.1.2.1 Critical Material Attributes (CMAs):

B.2.1.2.1.1 Drug Substance Particle Size: The study was performed with 400 mg tablets manufactured using various drug substance particle size. All other manufacturing processes remained same. Since 200 mg and 400 mg tablets (b) (4) .

Table 3. Average dissolution profile of 400 mg uncoated tablets (large and small particle), Over-encapsulated 200 mg Tablet, and 400 mg coated clinical tablet

Drug Product Batch Number	Percent Release (%) at Time (min)					
Time Points	5	10	15	30	45	60
C19125-59 Large Particle Size D_{10}: (b) (4) µm, D_{50}: (b) (4) µm, D_{90}: (b) (4) µm	34	57	70	85	90	100
C19125-60 Small Particle Size D_{10}: (b) (4) µm, D_{50}: (b) (4) µm, D_{90}: (b) (4) µm	47	75	86	96	97	102
Clinical Lot L0609378 (OE-200-mg tablet) D_{10}: (b) (4) µm, D_{50}: (b) (4) µm, D_{90}: (b) (4) µm	27	72	91	102	102	102
Clinical Lot L0507962 (400-mg tablet) D_{10}: (b) (4) µm, D_{50}: (b) (4) µm, D_{90}: (b) (4) µm	44	70	81	93	94	100

Fig 3. Dissolution profiles of 400 mg uncoated tablets (large and small particle), Over-encapsulated 200 mg Tablet, and 400 mg coated clinical tablet



Reviewer's Comment: Adequate

Based on the above data, the method is largely capable of discriminating large particle sizes only. Except, 400 mg uncoated large particle size tablet, dissolution profiles of other products including very small particle size are similar. Small particle size 400 mg

uncoated batch and OE-200 mg clinical batch exhibited rapid dissolution and demonstrated >85% dissolution in 15 min (Table 3). So, dissolution profiles of these two batches are considered similar (no f2 calculation is required). Since, API is a low solubility (BCS) material, drug substance particle size (DS PSD) is a critical quality attribute. As a control strategy, the Applicant proposed following three-tier DS PSD specification.

- D10 NMT (b) (4) µm
- D50 NMT µm
- D90 NMT (b) (4) µm

Based on dissolution data for batches manufactured with small particle size (C19125-60), Clinical Lot L0609378 and Clinical lot L0507962, the dissolution profiles are similar (>85% in 15 min). The range of particle size covered by these batches are: D10 (b) (4) µm; D50 (b) (4) µm; and D90 (b) (4) µm. Since these data include clinical lots, the PSD ranges are considered biorelevant. The Applicant proposed the limit of PSD based on (b) (4)

(b) (4)

(b) (4), the PSD specification for a low-soluble drug should be based on clinical data and not on (b) (4). Hence, we recommended a revised DS PSD specification to reflect the clinical experience.

	Proposed PSD Specification	Recommended PSD Specification
D10	NMT (b) (4) µm	NMT (b) (4) µm
D50	NMT µm	NMT µm
D90	NMT (b) (4) µm	NMT (b) (4) µm

The above values are based on the understanding that (b) (4) % increase of the particle size of the clinical lots will not adversely affect the dissolution and may remain bio-relevant. While we would like to have a range of particle size for a better control at each level, based on the size of very small particle size (Batch C9125-60), we believe a range would not be meaningful. Based on the PSD data from 15 DS commercial batches, maximum size for D10 is (b) (4) µm, for D50 is (b) (4) µm, and for D90 is (b) (4) µm (DS Batch RFI8601, DP OE-200 mg, used for Phase 2/3 studies). A comment was communicated to the Applicant on 06/25/2022. The Applicant provided a response on 07/07/2022 (SN 0024). In this response, Applicant acknowledged Agency's proposal to tighten the DS PSD specification.

Based on in vitro dissolution data, both drug products manufactured with DS PSD D90 (b) (4) µm and D90 (b) (4) µm showed > (b) (4) % dissolution in 30 min. However, (b) (4) µm showed slower dissolution at earlier time points. With no clinical data with large particle size, the impact of bioavailability of a low-soluble product is unknown. Hence, we reiterate the implementation of the recommended specification for DS PSD. Based on risk assessment, we could allow the proposed D10 (same as clinical lot) and D50 ((b) (4) µm, (b) (4) % above

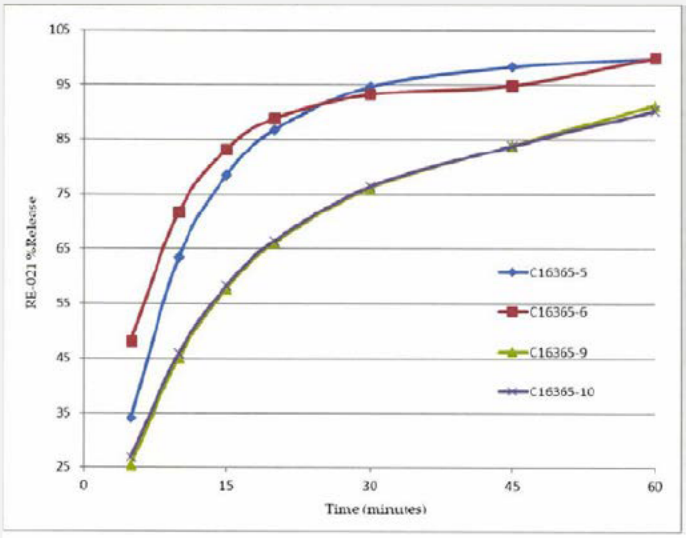
clinical lot data) specification. However, proposed D90 (b) (4) µm is (b) (4)% above the clinical lot data ((b) (4) µm clinical vs proposed (b) (4) µm). The Applicant proposed following revised DS PSD specification and updated the DS PSD specification in the NDA, accordingly. The proposed revised specification is acceptable.

	Proposed PSD Specification	Revised & Accepted PSD Specification
D10	NMT (b) (4) µm	NMT (b) (4) µm
D50	NMT µm	NMT µm
D90	**NMT (b) (4) µm**	**NMT (b) (4) µm**

B.2.1.2.1.2 Drug Substance Polymorphic form: Based on polymorph screening studies, only one crystalline non-solvated form is available. The Applicant observed no change of polymorphic form of drug substance during stability. So, no dissolution study was performed with DS polymorphic forms.

B.2.1.2.2 Critical Process Parameters (CPPs): During the product development stage, the Applicant performed feasibility study using (b) (4) method. The dissolution testing was performed using the proposed dissolution method. Based on dissolution data, (b) (4) batches showed >85% dissolution in 20 minutes compared to an average of 66% for (b) (4) batches. So, the method can detect changes to critical process parameters like process change.

Fig 4. Dissolution profiles of 400 mg tablets manufactured by (b) (4) (C16365-5 using (b) (4) and C16365-6 using (b) (4)) and (b) (4) (C16365-9 and C16365-10 with (b) (4))



NOTE: Dissolution profiles of C16365-5 and C16365-6 are similar (based on our assessment, calculated f2=54 using 5. 10. 15. 20 min timepoints).

A design-of-experiment (DOE) study was conducted to evaluate the effects of process parameters in unit operations on manufacturability and DP quality attributes. The factors include (b) (4) . Based on the dissolution data from all process variants (e.g. (b) (4) etc.), a cumulative dissolution of 90% was accomplished in 30 min. However, the largest variability of dissolution was demonstrated at the 5 min testing period. The Applicant stated that the (b) (4) caused a decrease in dissolution at earlier time point. The Applicant concluded that there is discriminating ability at the early timepoints (5, 10, 15 min). However, discriminating ability is limited after 30-minute timepoint.

(b) (4)

Reviewer's Comment: Based on process development work, the proposed method is capable of detecting changes to CPPs like (b) (4) and (b) (4). The method can also detect the (b) (4) process where (b) (4) or (b) (4) can be used.

B.2.1.2.3 Critical Formulation Variables (CFVs): During formulation development study, the Applicant identified ratio of (b) (4) had the most significant impact on the finished product dissolution profile and thereby were considered critical formulation variables. Seven different aberrant batches (400 mg coated) were manufactured along with target batch. The same manufacturing process was used for this study (Table 4).

Table 4. Design of batches used in dissolution studies to detect formulation changes

Batch	(b) (4)
1, Control, C22812-34	
2, C22812-35	
3, C22812-36	
4, C22812-37	
5, C22812-38	
6, C22812-39	
7, Negative Control, C22812-40	

Fig 7. Dissolution profiles of batches used to detect formulation changes

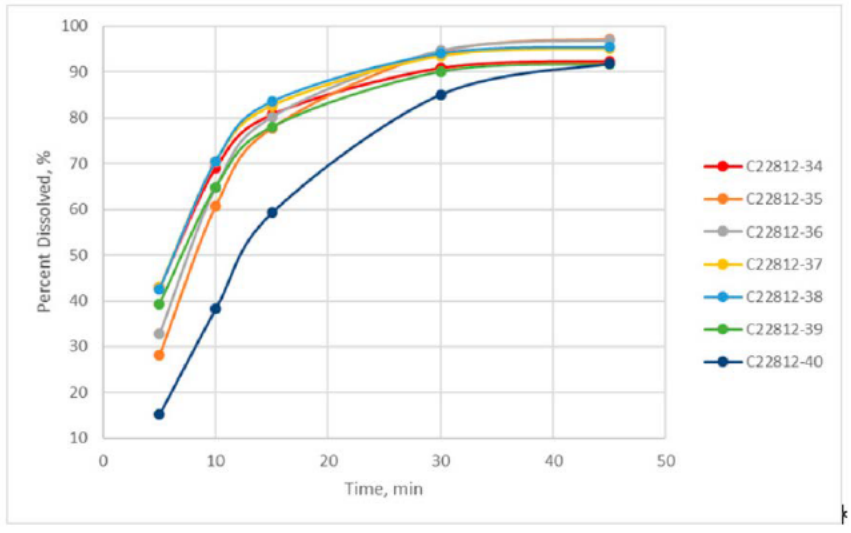


Table 5. F2 dissolution calculation (as submitted in the NDA)

Batch No.	Average Percent Dissolved (n = 12)					F2 Calculation[a]
	Time, min					
	5	10	15	30	45	
1, Control, C22812-34	(b) (4)					NA[b]
2, C22812-35						54
3, C22812-36						62
4, C22812-37						83
5, C22812-38						79
6, C22812-39						76
7, C22812-40						34

So, most of the aberrant batches when compared with control showed similar dissolution profile as evidenced form f2 values (>50). However, aberrant batch #7 with large (b) (4)%) variation of excipients exhibited significant changes to the dissolution.

Reviewer's Comment: Based on above data. the proposed dissolution method can detect large variation of CFVs.

B.2.1.5. Dissolution Method Validation: The dissolution method was validated for both 400 mg and 200 mg tablets. Method validation parameters include specificity, linearity, accuracy, precision, repeatability, solution stability, intermediate precision, and robustness. Quantification of HPLC method was assessed by drug substance review and found to be adequate[6].

Robustness of Dissolution Method: The robustness of the proposed dissolution method was ascertained by changing dissolution parameters from the target level. The acceptance criterion was set at ± (b) (4)% of the mean at 30 min.

Table 6. Data to demonstrate the robustness of the dissolution method

400 mg tablet		200 mg tablet
Parameter	Reported Result	Reported Result
(b) (4) dissolution medium	3%	2%
Medium temperature NMT (b) (4) °C	1%	3%
Medium temperature NLT °C	3%	2%
Paddle speed (b) (4) rpm	2%	6%
Paddle speed rpm	2%	1%
Paddle height mm	1%	3%
Paddle height mm	0%	3%
(b) (4) mL HCl/L	1%	3%
mL HCl/L	2%	3%

[6] NDA 216403 DS#1 07/05/2022; https://panorama fda.gov/task/view?ID=624df9590071cc0b93191d149deedb5d

Based on the results, none of the dissolution parameters analyzed were determined to be critical to the performance of the method.

Reviewer's Overall Comments on Dissolution Method: Adequate

For the proposed dissolution method, the Applicant provided method development report including discriminating ability of the method to detect changes to critical bioavailability attributes including CMAs, CFVs, and CPPs. While the method exhibited some limitations in regard to discriminating ability towards changes to critical bioavailability attributes, it can detect large variations in CMAs and CPPs. The Applicant provided validation report of the method for the intended use.

B.2.2. Proposed Dissolution Acceptance Criteria:

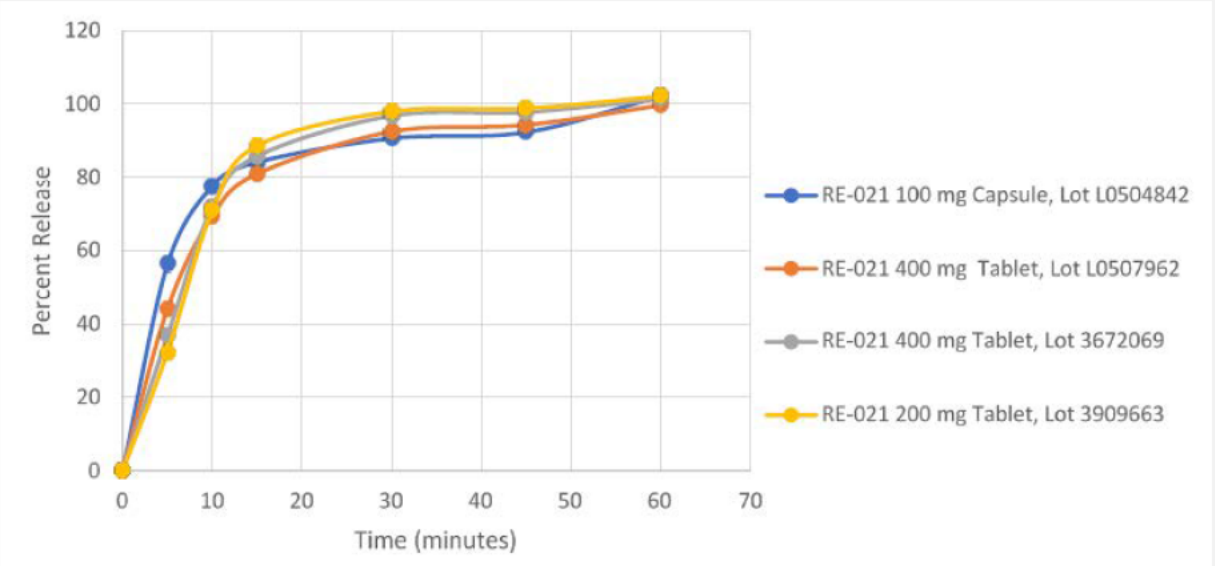
The Applicant proposed a dissolution specification of NLT (b) (4)%(Q) in 30 min. The Applicant provided a summary of dissolution data at 30 min time point from 19 clinical batches (10 batches 200 mg strength, 9 batches 400 mg strength).

Table 7. 30-minute dissolution data for clinical batches

Batch No.	Dissolution; Q = (b) (4)% at 30 minutes												
Vessel	1		2		3		4		5		6		Avg
200-mg Tablets													
L0602847	(b) (4)												90
L0702475													95
3909663													98
3933845													97
4141771													98
4141777													97
4141782													97
Vessel	1	2	3	4	5	6	7	8	9	10	11	12	Avg
4213271	(b) (4)												98
4206405													97
4206136													97
Vessel	1		2		3		4		5		6		Avg
400-mg Tablets													
L0507962	(b) (4)												93
L0600331[a]													90
L0600522[a]													88
L0600523[a]													88
L0701490													96
3672069													97
4045199													95
Vessel	1	2	3	4	5	6	7	8	9	10	11	12	Avg
4206408	(b) (4)												97
4206139													97

A comparative dissolution profile of 400 mg and 200 mg clinical batches and other dosage forms used in BE study showed following dissolution profile:

Fig 8. Comparative Dissolution of Dosage Forms used in BE studies



Reviewer's Comment: Adequate

Based on dissolution data and dissolution profiles from clinical batches, the proposed dissolution acceptance criterion is reasonable. However, we could not locate individual dissolution data for pivotal clinical and registration batches to have a better understanding of the dissolution profiles. A comment was communicated to the Applicant on 06/27/2022. A response was received on 07/07/2022 (SN 0024). The Applicant provided individual dissolution data from pivotal batches and registration batches for 200 mg tablet, 400 mg tablet and over-encapsulated 200 mg tablet. Here is the summary of the submission (Cumulative percent mean (n=6-12) dissolution: range):

Dosage Form	10 min	15 min	30 min	45 min
200 mg tablet Lots (10 lots) (clinical)	(b) (4)			
400 mg tablet lots (9 lots) (clinical)	(b) (4)			

%RSD <5%

Based on above dissolution data, the proposed dissolution acceptance criterion (NLT (b) (4) %(Q) in 30 min) is reasonable. However, we do not have adequate in vivo data for aberrant batches to confirm the bio-relevance of the proposed dissolution acceptance criterion. For example, based on dissolution data from the drug product batch C19125-59 manufactured with large out-of-specification (OOS) particle size (D10 (b) (4) µm, D50 (b) (4) µm, D90 (b) (4) µm), demonstrated 85% dissolution after 30 min. In absence of in vivo data, it is unclear whether this aberrant batch which met dissolution acceptance criterion is

biorelevant or not. So, the clinical relevance of dissolution acceptance criterion can't be established at this time. However, the proposed dissolution acceptance criterion is acceptable as the QC acceptance criterion for dissolution to assess batch-to-batch consistency.

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

Assessment: NA

The Applicant did not provide any in vivo study to support the clinical relevance of dissolution method and acceptance criterion. Also see above discussion in B2.2.

B.12 BRIDGING OF FORMULATIONS

Assessment: Adequate

Based on historical data, the innovator (BMS) initially developed a capsule which has never been used for clinical study. Later, the new owner ((b) (4)) developed a **powder-in-a-bottle** (PIB) formulation (oral) for initial clinical studies. (b) (4) . It is intended to be mixed prior to dosing. Later, (b) (4) developed a **100 mg capsule formulation** (b) (4) The formulation was based on BMS's formulation experience. (b) (4) used this study for a pilot clinical BA/BE study (PIB vs 100 mg capsule, #PCO-C-004), a pilot food effect clinical study, Phase 1 safety studies and a Phase 2 hypertension study.

Later, the Applicant developed **100 mg capsule formulation using** (b) (4) while keeping the same Q1/Q2 formulation that was used for (b) (4) . (b) (4) . These 100 mg capsules were used for Phase 2 blinded and open label extension program of the clinical study (also known as DUET study). Because, up to 800 mg was required for clinical study, the Applicant explored 200 mg and 400 mg tablet formulation. Initially (b) (4) was used for the manufacture of tablets but those were not used for clinical study. In addition, (b) (4) which were not used in any previous clinical trial batches. Finally, (b) (4) was found to be suitable and was used for the tablet manufacturing. The 400 mg tablet formulation used silicified MCC (SMCC) (b) (4) were used in 100 mg capsule formulation. It is finally selected as the commercial process. Both **200 mg and 400 mg tablets were manufactured** (b) (4) . The **200 mg tablets were also over-encapsulated (OE)** in size 00 (b) (4) capsules (b) (4) and were used

for blinded Phase 2 and 3 clinical trials. (b) (4) (b) (4)), there is no change of chemical composition (b) (4). The Applicant reasoned that (b) (4) is not expected to change bioavailability of the product.

Table 8. History of Formulation Development and use

Capsule (developed by BMS)	Never used for Clinical study
Powder-in-a-bottle + Vehicle ((b) (4))	Initial Clinical Study
Capsule 100 mg ((b) (4)) ((b) (4))	Used for Pilot clinical and BA/BE study, Phase 1, and Phase 2 safety study
Tablet IR 100 mg ((b) (4))	Never used for Clinical study
Capsule 100 mg ((b) (4)) (Catalent)	Phase 2
Tablet 200 mg, 400 mg ((b) (4)) Over encapsulated 200 mg Tablet 400 mg ((b) (4)	For Phase 2 and Phase 3 clinical trial For blinded clinical trial For 1 BA and 2 additional clinical trials

Table 9. Historical and Commercial Quantitative Composition of Sparsentan

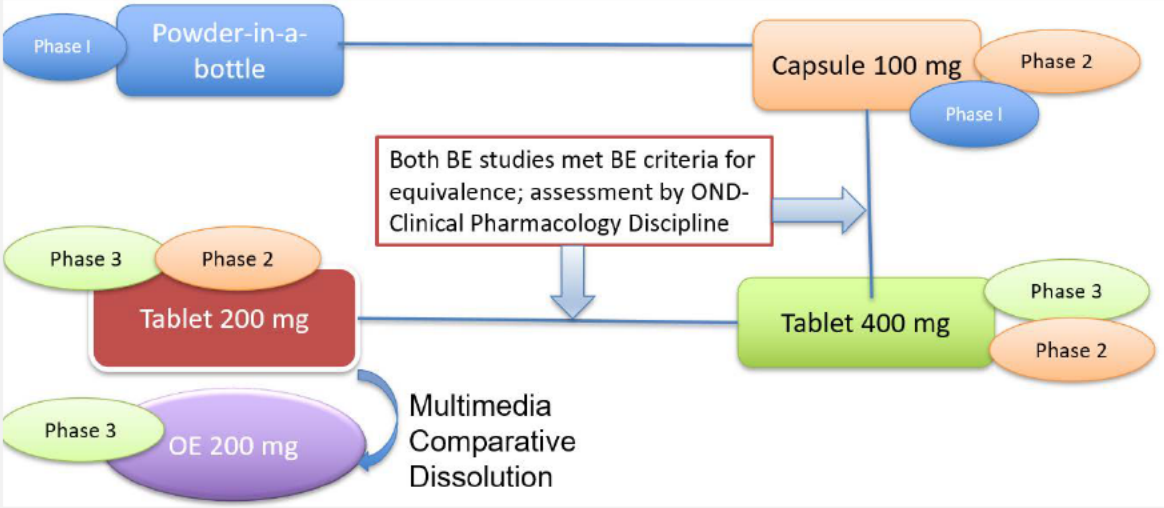
Component	Quantity (mg/capsule or tablet [%])				
	Powder-in-a-Bottle	100-mg Capsule	200-mg Tablet (OE)	200-mg Coated Tablet	400-mg Coated Tablet
Use	Initial Phase 1	Phase 1 and 2	Phase 3	Phase 3 and commercial	Phase 3 and commercial
Manufacturer	(b) (4)		Catalent	Catalent	Catalent
Sparsentan Drug Substance	(b) (4)				(b) (4)
(b) (4)					
Silicified Microcrystalline Cellulose NF					
Lactose Anhydrous NF, Ph. Eur., JP (b) (4)					
Sodium Starch Glycolate NF, Ph. Eur., JP					
Colloidal Silicon Dioxide NF, Ph. Eur., JP					
Magnesium Stearate NF, Ph. Eur., JP (b) (4)					
Coating, (b) (4)					
Total Tablet Weight/capsule Content					
OE for clinical studies; over encapsulation will not be used for the commercial product					
(b) (4)					
a (b) (4)					

Bridging studies:

(1) Bridging study to demonstrate BE of **100 mg capsule vs 400 mg tablet**: BE Study#021HVOL16001: A prospective, randomized, open-label non-replicated cross-over study to compare the bioavailability of a tablet formulation of sparsentan to a capsule formulation of sparsentan in healthy volunteer subjects (n=32). The study met BE criteria (90%CI: 80%-125%).

(2) Bridging study to demonstrate BE of **400 mg tablet vs 200 mg tablet**: Study #RTRX-RE021-101: Open label, randomized, two-way cross-over study to evaluate the single-dose bioequivalence of Sparsentan 400 mg tablets compared to Sparsentan 200 mg tablets in healthy adult subjects (n=32). The study met BE criteria.

Fig 9. Formulation Bridging: BE studies



Reviewer's Comment: The BE studies were reviewed by Clinical Pharmacology team. The reviewer verified with clinical pharmacology reviewer and the studies are acceptable from their end.

A comparative in vitro dissolution profiles of products used in BE studies (#021HVL16001: 400 mg tablet vs 100 mg Capsule, and RTRX-RE-021: 400 mg tablet vs 200 mg tablet) are also provided (see Fig 8). Based on the dissolution profile comparison of drug products used in BE studies, the in vitro drug release profiles are similar.

(3) Bridging study to demonstrate equivalency of **OE 200 mg tablets and un-encapsulated 200 mg tablets**, comparative dissolution profiles in multimedia are provided.

Reviewer's Comment: Noted, in a response to the question regarding the use of in vitro study for bridging of over-encapsulated 200 mg tablets and unencapsulated 200 mg tablets, the FDA opined the approach is reasonable. According to Guidance

for Industry – BA and BE Studies Submitted in NDAs or INDs -General Considerations (March 2014)[7], for over-encapsulated capsule if used only for blinding purpose and no other excipients are added to the capsule, in vitro dissolution data in three media (pH 1.2, pH 4.5, and pH 6.8) would be required to establish equivalency of to-be-marketed drug product and clinical trial formulation. The Applicant provided dissolution data in 0.1N HCl (500 mL/60 rpm or 75 rpm), pH 4.5 (900 mL, 75 rpm), pH 6.8 (900 mL, 75 rpm) media. While the proposed dissolution method requires 1000 mL volume, 500 mL volume also provides adequate sink condition in this case. Higher volumes were used for pH 4.5 (solubility 0.004 mg/mL) and pH 6.8 (solubility 0.055 mg/mL). The dissolution in acidic medium was similar for both formulations (f2=87 at 60 rpm and 62 at 75 rpm). Both pH 4.5 (acetate buffer 50 mM) and pH 6.8 (phosphate buffer, 50 mM) exhibited low dissolution but similar dissolution profile.

While the OE 200 mg tablet and unencapsulated 200 mg tablet exhibited similar dissolution profiles, it did not meet the FDA recommendation that no other excipients should be added to the OE product. However, we believe, (b) (4) is expected to have no implication on the bioavailability of the product, it is deemed acceptable in this case.

B. 13 BIOWAIVER REQUEST

Assessment: N/A

The Applicant did not provide a biowaiver request. In vivo study was performed with over-encapsulated (OE) 200 mg tablet, 200 mg tablet and 400 mg tablet. Based on information provided, bridging to OE 200 mg strength, 200 mg tablet and 400 mg tablet were established by a combination of BE study and dissolution profile comparisons (Fig 9).

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: *N/A*

Post-Approval Commitments

Assessment: *None*

Lifecycle Management Considerations

[7] https://www.fda.gov/media/88254/download

None

BIOPHARMACEUTICS LIST OF DEFICIENCIES (Outstanding)

Following comments were communicated to the Applicant on 06/25/2022:

(1) We acknowledge your justification for drug substance particle size distribution based on (b) (4). However, based on dissolution data for (b) (4) tablets (Large and small particle size), OE-200 mg clinical lot and Coated 400 mg clinical lot, the proposed particle size distribution (PSD) should be tightened. We recommend following revised PSD specification based on clinical lots data. Note, PSD data for all 15 commercial drug substance batches provided in the submission (3.2.S.4.5), also meet the recommended specification.

	Proposed PSD Specification	Recommended PSD Specification
D10	NMT (b) (4) µm	NMT (b) (4) µm
D50	NMT µm	NMT µm
D90	NMT (b) (4) µm	NMT (b) (4) µm

Implement drug substance particle size specification in your NDA or provide further justification for the proposed or revised drug substance PSD specification.

(2) In the NDA, we could not locate individual dissolution data from pivotal Phase III clinical batches and registration batches. Provide complete dissolution data (n=12, mean, range, %RSD at each time point) for the above drug product batches. Report the dissolution data as the cumulative percentage of drug dissolved with time (the percentage based on product's label claim). The individual dissolution data of these batches should be presented in tabular (including MS Excel ".xls or .xlsx format) and graphical formats. Include batch/lot number, batch size, manufacturing date, manufacturing site, testing date, and dissolution testing protocol effective date.

Response:

A response was received on 07/07/2022 (SN 0024). Based on the response, following comment was communicated to the Applicant.

We acknowledge your justification for the proposed acceptance criteria for drug substance particle size (DS PSD). You reiterated that DS PSD acceptance criteria are based on (b) (4). Note that DS PSD acceptance criteria for a low soluble drug like sparsentan should be based on clinical experience. In our recommendation, we used drug product clinical lots manufactured with DS PSD: D10 NMT (b) (4) µm; D50 NMT (b) (4) µm; and D90 NMT (b) (4) µm plus an increase of about (b) (4)% to account for batch-to-batch variability. Based on risk assessment, a modest (b) (4)% increase of the acceptance criteria for DS PSD of the clinical lots may not adversely affect the bioavailability of the product. While we agree with proposed acceptance criteria for D10 and D50, we recommended a revision of D90 DS PSD acceptance criterion.

	Proposed PSD Specification	Recommended PSD Specification
D10	NMT (b) (4) µm	NMT (b) (4) µm
D50	NMT µm	NMT µm
D90	NMT (b) (4) µm	NMT (b) (4) µm

Implement the recommended DS PSD acceptance criteria in your NDA. As you continue to evaluate the effect of DS PSD on bioavailability of the product, you may provide additional information to justify the wider DS PSD acceptance criteria.

Response:

A response was received on 07/15/2022 (SN 0032). The Applicant revised the DS PSD specification as:

- *D10 NMT (b) (4) um*
- *D50 NMT um*
- *D90 NMT (b) (4) um*

The Applicant updated the submission, accordingly.

Reviewer's Comment:

The proposed revised specification for DS-PSD is acceptable.

We have no unresolved issues.

Primary Biopharmaceutics Assessor's Name and Date:

Debasis Ghosh Aug 3, 2022

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

Haritha Mandula, Aug 3, 2022

APPENDIX 1

Measured Particle Size Distribution at the Time of Release

#	Lot Number	Final Isolation Site/Scale	Particle Size Distribution (µm)		
-			D_{10}	D_{50}	D_{90}
1	RF16002	[redacted]	[redacted]	[redacted]	[redacted]
2	RF16601				
3	RF17601				
4	RF17602				
5	RF17603				
6	RF17604				
7	RF18601				
8	RF18602				
9	[redacted]-RF19001				
10	[redacted]-RF19002				
11	[redacted]-RF19003				
12	[redacted]-RF19004				
13	[redacted]RF19001				
14	[redacted]RF19002				
15	[redacted]RF19003				
Mean			[redacted]		
Standard Deviation (SD)					
Mean - 3SD					
Mean + 3SD					

Debasis Ghosh

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Haritha Mandula

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Theodore Carver

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/s/

THEODORE E CARVER
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