CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219839Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	219839
Applicant Name	Dizal (Jiangsu) Pharmaceutical Co., Ltd.
Drug Product Name	ZEGFROVY™ (sunvozertinib) tablets
Dosage Form.	Tablet
Proposed Strength(s)	150 mg and 200 mg
Route of Administration	Oral
Maximum Daily Dose	200 mg (Recommended dose)
Rx/OTC Dispensed	Rx
Proposed Indication	ZEGFROVY is a kinase inhibitor indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.
Drug Product Description	The drug product is an oral immediate release tablet containing 150 mg or 200 mg of sunvozertinib. The tablets are (b) (4) biconvex and yellow film-coated. The tablets are packaged in high-density polyethylene (HDPE) bottle with a child resistant (CR) (b) (4) cap. Each bottle contains 30 sunvozertinib tablets and a canned desiccant containing 1 g of silica gel. The bottle is induction sealed to provide additional tamper evidence.
Co-packaged product information	N/A
Device information:	N/A

Storage Temperature/ Conditions	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), USP controlled room temprature conditions.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Katherine Windsor	Katherine Windsor
	Drug Product/ Labeling	Rajiv Agarwal	Shalini Anand/David Claffey
	Manufacturing	Naresh Pavurala	Diane Goll
	Biopharmaceutics	Gerlie Gieser	Anitha Govada
	Other (specify):	N/A	N/A
	RBPM	Janell Artis	
	ATL	Shalini Anand	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: An expiration dating period of **36 months** is granted for the drug product 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: n/a

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends ***APPROVAL*** of NDA 219839 for the commercialization of ZEGFROVY™ (sunvozertinib) tablets. Based on our evaluation of the available information, the Applicant provided sufficient information to support an approval recommendation from the drug product quality perspective. The Applicant provided adequate information

on the proposed drug product to ensure the identity, strength, purity, and quality of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

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: N/A

Additional Lifecycle Comments: N/A

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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide

1.0 PRESCRIBING INFORMATION (ONLY primary and secondary labels are needed to complete this review. Cut and paste section 11 and 16 too)

Assessment of Product Quality Related Aspects of the Prescribing Information:

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	ZEGFROVY (sunvozertinib)
Route(s) of administration	Adequate	Oral
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	150 mg, 200 mg Tablet
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	Not applicable
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	Not applicable
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	Not applicable

[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	Not applicable
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	Not applicable
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	Not applicable
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	Not applicable

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	Not applicable
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	Not applicable

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	150 mg, 200 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	Not applicable
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	The tablets are (b) (4), biconvex and yellow film-coated. • *The 150 mg tablets* (b) (4) *debossed with "150" on one side and Dizal company logo on the other side.* • *The 200 mg tablets* (b) (4) *debossed with "200" on one side and Dizal company logo on the other side.*
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not applicable
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	Not applicable

Section 11 (DESCRIPTION): **Refer to the Amendment 0035 dated 4/24/2025.**

(b) (4)

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	ZEGFROVY (sunvozertinib)
Dosage form(s) and route(s) of administration	Adequate	Tablet/Oral
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	Not applicable
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	Yes
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	Not Applicable
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	Not Applicable
Sterility statement (if applicable)	N/A	Not Applicable
Pharmacological/Therapeutic class	Adequate	Yes (Tyrosine Kinase Inhibitor)
Chemical name, structural formula, molecular weight	Adequate	Yes (also list the structure of sunvozertinib)
If radioactive, statement of important nuclear characteristics.	N/A	Not applicable
Other important chemical or physical properties (such as pKa or pH)	N/A	Not Applicable

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	Not applicable
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	Not applicable
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	Not applicable

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING): Refer to the amendment SDN 0035 dated 4/24/2025)

(b) (4)

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	150 mg and 200 mg
Available units (e.g., bottles of 100 tablets)	Adequate	30 counts
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	Yes
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not applicable
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	Not applicable
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	Not applicable

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	Yes
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	Not applicable
Include information about child-resistant packaging	Adequate	added

1.2.5 Other Sections of Labeling

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

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

1.2.6 Manufacturing Information After Section 17 (for drug products)

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	**Manufactured for:** Dizal (Jiangsu) Pharmaceutical Co., Ltd. Shanghai, 201203, China

2.0 PATIENT LABELING:

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

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	sunvozertinib
Special preparation instructions (if applicable)	N/A	Not applicable
Storage and handling information (if applicable)	Adequate	Yes
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.	Adequate	Size and shape of the desiccant differs from the dosage form.
Active ingredient(s) (if applicable)	Adequate	sunvozertinib
Alphabetical listing of inactive ingredients (if applicable)	Adequate	Yes
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	**Manufactured for:** Dizal (Jiangsu) Pharmaceutical Co., Ltd. Shanghai, 201203, China

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

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

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	Yes
Strength(s) in metric system	Adequate	Yes
Route(s) of administration	Adequate	Yes
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	Not Applicable
Net contents (e.g., tablet count, volume of liquid)	Adequate	Yes
"Rx only" displayed on the principal display	Adequate	Yes
NDC	Adequate	Space is provided
Lot number and expiration date	Adequate	Yes
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Yes
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	Not Applicable
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	Not Applicable
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	Not applicable
Linear Bar code	Adequate	Yes

[3]

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	Yes
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	Yes
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	Not applicable
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Not applicable
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	Not applicable
And others, if space is available.	N/A	Not applicable

- **Assessment of Carton and Container Labeling: *{Adequate }***
- ***Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."***

- **Several tablet CMC related edits were made to the Tablet PI and this was communicated to the applicant via OND. A finalized version have been received on 4/24/2025 (SDN 0035) and it is adequate.**

- **DMEPA reviewer communicated the edits in storage temperature along with their edit on Labels.**

ITEMS FOR ADDITIONAL ASSESSMENT

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See Carton/Container Labeling Specific Resources for a presentation about inappropriate inconsistencies of product quality information between labeling.

If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these as deficiencies in this section.

Overall Assessment and Recommendation:

- Adequate

Primary Labeling Assessor Name and Date: Rajiv Agarwal 4/27/2025

Secondary Assessor Name and Date: David Claffey, Ph.D.

Rajiv Agarwal

Digitally signed by Rajiv Agarwal
Date: 4/28/2025 08:04:41AM
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David Claffey

Digitally signed by David Claffey
Date: 4/28/2025 08:06:06AM
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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	NDA-219839-ORIG-1
Assessment Cycle Number	1; Original NDA; 505(b)(1)
Drug Product Name/ Strength	Sunvozertinib (Immediate Release)Tablets/ 150 mg, 200 mg
Route of Administration	Oral
Applicant Name	Dizal (Jiangsu) Pharmaceutical Co. Ltd.
Therapeutic Classification/ OND Division	Anti-Cancer/ Division of Oncology 2
Proposed Indication/	Treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations (exon20ins), whose disease has progressed on or after platinum-based chemotherapy
Proposed Dosage	(b) (4) mg (b) (4) once daily taken with food With concomitant (b) (4) strong CYP3A inhibitors: Reduce dosage to (b) (4) mg (b) (4) once daily

*200 mg once daily taken with food will be recommended by FDA.

Assessment Recommendation: **Adequate**

Assessment Summary:

Sunvozertinib exhibits the characteristics of a low solubility (BCS-2 or BCS-4) drug substance/drug product.

The proposed dissolution method [USP Apparatus 2 (paddle) at 75 rpm, 900 mL of 50 mM citrate buffer (pH 5.1), 37 ± 0.5 °C] and acceptance criteria (Q = (b) (4)% at 20 min) are adequate for the quality control (QC) of sunvozertinib tablets at batch release and during shelf-life/stability testing.

The final proposed to-be-marketed drug product (i.e., Formulation B debossed film-coated tablets) has the same formulation, manufacturing process and manufacturing site as the tablets evaluated in the pivotal Phase 2 clinical trial and in primary/registration stability studies. (b) (4) Additionally, per the Clinical Pharmacology Reviewer, there are adequate *in vivo* PK data to support the bridge between the proposed commercial Formulation B tablets and the Formulation A (b) (4) tablets used in the pivotal Food-Effect and other Phase 1 clinical studies.

Both 150 mg and 200 mg strengths of the proposed commercial drug products were evaluated in the pivotal clinical and primary registration/stability studies.

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Dissolution	Medium	Low Solubility drug	Low	Dissolution specifications are adequate.

List of Submissions Assessed:

Document(s) Assessed	Date Received
Original NDA	11/7/2024
SN-7 (Response to Drug Product Information Request/IR – appearance, stability)	1/14/2025
SN-9 (Response to Early Biopharm IR) SN-25 (Response to Process IR – includes dissolution data)	1/21/2025 3/27/2025

Concise Description of Outstanding Issues:
None

B.1 BCS DESIGNATION

Assessment: *BCS-2 or BCS-4*

The Applicant considers sunvozertinib as a BCS-2 (low solubility, high permeability) drug substance. Thus, there is no BCS (1 or 3) designation request for sunvozertinib tablets.

Solubility: *Low*

Sunvozertinib solubility decreases with increasing pH, as shown in Table 3.2.P.2.2-60 and Figure 1 of the Dissolution Method Development Report (DMDR). Greater than 250 mL of pH (b) (4) medium is required to dissolve both 200 mg (the highest strength) and 300 mg ((b) (4)) of sunvozertinib.

The desired polymorphic form of the ingoing active pharmaceutical ingredient (API) is ' (b) (4) ' because it is (b) (4)

[redacted] which is '[redacted]'. The aqueous solubility of API [redacted] (the desired API polymorphic form) in various pH buffer media and in biorelevant media at 37 °C is generally slightly lower than those measured for API [redacted] but remains pH dependent (refer to Figure 3.2.P.2.1-7; Table 3.2.S.3.1-21 and Table 3.2.S.3.1-22).

Permeability: *Moderate to High*

The Absolute Bioavailability of Sunvozertinib Tablets was not investigated.

The proposed labeling states: "[redacted]." Thus, assuming the unchanged drug in the feces represents unabsorbed drug, and all of the urinary metabolites (comprising ~4.7% of the dose) are products of hepatic and/or gut metabolism (rather than by gut microbial hydrolysis), it is estimated that <85% (i.e., approximately 81.6%) of the administered dose is systemically absorbed. However, it is acknowledged that in the rat Mass Balance Study DZP/02, some conjugated metabolites in excreta and bile samples of bile duct cannulated rats following (oral and) intravenous dosing were identified, however the percentage contributions of these metabolites to the recovered dose were not reported. Thus, it was not possible for this Reviewer to determine with certainty the fraction of the parent drug in human fecal samples representing absorbed drug following enterohepatic circulation. Per the Applicant, there is no significant difference in bioavailability between the oral suspension and the oral tablet formulations (based on the clinical PK data from WU-KONG12C, WU-KONG1 and WU-KONG2).

According to the Clinical Pharmacology Reviewer, based on the results of the human radiolabeled mass balance study (and in the absence of data from a dedicated bioavailability study), it is not possible to determine the exact fraction of the administered dose of the sunvozertinib oral tablet that is systemically absorbed. However, it was noted that (***i***) sunvozertinib tablets is recommended to be administered with food (which results in ~10% to 20% higher sunvozertinib AUC as compared to under fasted conditions), and (***ii***) the solubility of sunvozertinib is significantly higher in fed simulated intestinal fluid (FeSSIF) than in fasted simulated intestinal fluid (FaSSIF), as shown in Table 3.2.S.3.1-22. Thus, based on the results of the human mass balance study and other information, the Clinical Pharmacology Reviewer considers that it is reasonable to say that sunvozertinib tablets when given *with food* has good absorption.

In vitro, using the Caco-2 monolayer system, at sunvozertinib dosing concentrations of 10, 30, and 85 µM (corresponding to 0.5%, 1.5%, and 4% of

the 300 mg/250 mL dose), the apparent permeability (P_{app}) of DZD9008 were 7.62, 13.4, and 23.3 × 10^{-6} cm/s, respectively, and the efflux ratios of 2.74, 1.25, and 1.74, respectively (Study DZD9008). At the middle and highest drug dosing concentrations (but not at the lowest dosing concentration) tested, the Caco-2 P_{app} values were higher than that measured for the high permeability marker (minoxidil; P_{app} = 9.08 × 10^{-6} cm/s) and the efflux ratios were <2.0. Since the efflux ratio is >2.0 at 10 µM, it can be concluded that at low drug concentrations, sunvozertinib is a substrate of a drug efflux transporter like P-glycoprotein (P-gp). Note that the proposed labeling states (and the Clinical Pharmacology Reviewer confirms) that sunvozertinib is a substrate of P-gp. Nevertheless, passive diffusion appears to be the predominant drug transport mechanism *in vivo* because in Study WU-KONG2, an approximately dose-proportional increase in DZD9008 exposure (i.e., Cmax and $AUC_{0\text{-}inf}$) was observed across the 50 mg to 400 mg dose range (as confirmed by the Clinical Pharmacology Reviewer). Furthermore, the Clinical Pharmacology Reviewer indicated that the effect of P-gp inhibition is not anticipated to be significant because the bioavailability of sunvozertinib is relatively high (i.e., >80%). [Note: In the Caco-2 study, higher than 85 µM dosing concentrations were not studied due to cytotoxicity. Thus, given the drug substance's very low solubility in pH 7.4 medium, and its potential to reduce cell monolayer integrity at more clinically relevant dosing concentrations, it appears that the *in vitro* Caco-2 monolayer system may not be suitable for assessing sunvozertinib permeability.]

Dissolution: *Not Rapid Across the Entire Physiologic pH Range*

Using USP Apparatus 2 (Paddle) at 75 rpm, and 900 mL volumes of dissolution media, sunvozertinib tablet exhibits rapid to very rapid dissolution (> (b) (4) % dissolved in (b) (4) minutes) in pH (b) (4) buffer media. However, in pH (b) (4) medium, sunvozertinib tablets exhibit incomplete dissolution (not more than (b) (4) % at (b) (4) min). Dissolution is not significantly dependent on sunvozertinib tablet strength.

Per the proposed labeling, the median Tmax of sunvozertinib is approximately (b) (4) hours.

Reviewer Note (Effect of Acid-Reducing Agents on Dissolution):
To support the proposal not to conduct drug interaction studies with concomitant acid-reducing agents (ARAs), the Applicant performed dissolution testing in pH 4.5 buffer (to approximate the stomach pH condition after a high-fat and high-calorie meal), in a pH 2.5 buffer (to approximate the pH condition after a light meal), and in fed state simulated intestinal fluid Version 2 (FeSSIF V2) at pH 5.8 (to mimic the increased bile salt concentrations in the fed intestine). Based on the results of these dissolution studies (as summarized in Section 3.4 of 2.7.1), the Applicant concluded that dissolution at gastric conditions is not the rate-limiting factor for absorption of sunvozertinib during the fed state. This Reviewer notes that the cumulative dissolution of the

proposed drug product (Formulation B debossed tablets) in pH (b) (4) medium is substantially lower as compared to in pH (b) (4) medium (i.e., (b) (4) % versus (b) (4) % at (b) (4) minutes), as reported in Table 3.2.P.2.2-31 and Table 3.2.P.2.2-25. Thus, since there is significant reduction in dissolution extent in pH (b) (4) medium, and considering that concomitant administration of ARAs like proton-pump inhibitors could potentially increase gastric pH to as high as pH 8.0, the available *in vitro* dissolution profile data generated is not considered adequate to establish the lack of an impact of concomitant ARAs on sunvozertinib bioavailability. However, it is acknowledged that in the July 2022 Type B Clinical Pharmacology meeting, the concomitant administration of ARAs was allowed when sunvozertinib was administered with food. Additionally, per the Clinical Pharmacology Reviewer, based on Population PK Analysis, concomitant proton pump inhibitor (PPI) use did not impact sunvozertinib PK.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: Adequate

DISSOLUTION METHOD

The parameters of the final proposed commercial QC dissolution method, i.e., Method 2, PDS-AMFP2695-05, are tabulated below.

Apparatus	USP Apparatus 2 (Paddle)
Rotation	75 rpm
Medium	50 mM citrate buffer/ pH 5.1
Volume	900 mL
Temperature	37 ± 0.5 °C
Sampling time point(s)	Dissolution testing: 20 minutes (Q point) Dissolution profile: 5, 10, 15, 20, 30, 45, 60 minutes

Source: Table 3.2.P.2.2-89. Refer also to 3.2.P.5.2 Analytical Procedures

Justification for Chosen Method Parameters

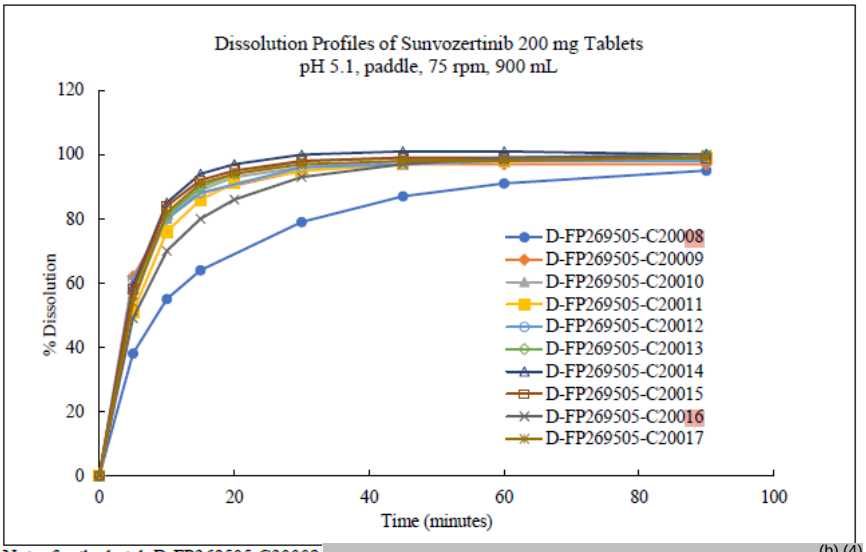
(b) (4)

Discriminating Capability

The proposed QC dissolution method is discriminating for differences in (b) (4) particle size distribution (PSD), which appears to be influenced by the cumulative effects of the (b) (4) process parameters

(b) (4) as shown in Figure 3.2.P.2.2-23. Refer also to Table 3.2.P.2.3-22 (for the (b) (4) process parameters and (b) (4) particle size distribution) and Table 3.2.P.2.3-23 and the excerpted figure below (for the disintegration and dissolution profile data of the various tablet lots evaluated in the Design of Experiment (DOE) studies.

Figure 3.2.P.2.3-21 DOE Experiments Results: Dissolution Profiles of Sunvozertinib 200 mg Tablets in pH 5.1 Medium



Note: for the batch D-FP269505-C20008, (b) (4) (b) (4) resulted in a significant decrease in dissolution rate.

Reviewer Note: D-FP269505-C20008 has the largest (b) (4) particle size compared to the other DOE tablet lots evaluated in the study.

(b) (4)

Additionally, the proposed QC dissolution method is able to show separation of the dissolution profile of a variant tablet lot manufactured with higher-than-target API particle size from other tablet lots manufactured using API with particle size within the acceptable range. Refer to Figure 3.2.P.2.2-22.

[API Particle Size Distribution: *The Biopharmaceutics Reviewer defers to the Drug Substance Reviewer regarding the acceptability of the proposed API particle size distribution acceptance criteria.* From the Biopharmaceutics perspective, the proposed drug substance particle size distribution acceptance criteria (D_{50} (b) (4) µm; D_{90} (b) (4) µm, by (b) (4)) is reasonable when considering the API PSD data of the 29 clinical batches [D_{10} (b) (4) µm; D_{50} (b) (4) µm; D_{90} (b) (4) µm] as listed in Table 3.2.S.4.5-21. Based on *in vitro* dissolution profile data, the proposed upper tolerance

limits of (b) (4) µM for D_{90} and (b) (4) µM for D_{50} are supported by the observation that there is no significant difference in the dissolution profiles of tablet lots manufactured with API D_{90} within the (b) (4) µM range and API D_{50} within the (b) (4) µM range (Figure 3.2.P.2.2-22). Furthermore, the proposed lower tolerance limit of (b) (4) µM for D_{50} is supported by the dissolution profile data of a development lot manufactured using API with D_{50} of (b) (4) µM (Figure 3.2.S.4.5-2).]

Per FDA recommendation during the Pre-NDA stage, additional studies were conducted by the Applicant to explore (b) (4)

(b) (4)

[API Polymorphic Form and (b) (4) *The Biopharmaceutics Reviewer defers to the Drug Product Reviewer regarding the acceptability of Applicant's proposal to exclude API polymorphic form testing and* (b) (4) *testing in the finished product QC specifications.* Per the Applicant, API polymorphic form change was monitored; (b) (4) was demonstrated to be stable at both the drug substance and drug product levels (during manufacture and storage). Refer to 3.2.P.5.6.2.4 for the supporting (b) (4) data provided to justify exclusion of API polymorphic testing in the finished product QC specifications of sunvozertinib tablets. Furthermore, API polymorphic form ((b) (4) by (b) (4)) is part of the proposed drug substance QC specifications.

Additionally, the (b) (4) content did not increase during drug product manufacturing process and stability testing (and thus, is considered as a drug substance process impurity, and therefore controlled at NMT (b) (4) % as part of the drug substance QC specifications).]

(b) (4) Process Parameters*: The Biopharmaceutics Reviewer defers to the Process Reviewer regarding the acceptability of the proven acceptable range (PAR) for* (b) (4) *.* From the Biopharmaceutics perspective, the proposed PAR is reasonable, considering that as shown in Table 3.2.P.3.3-23, the (b) (4) to the five pivotal clinical trial lots, and the 3 primary stability batches had an overall range of (b) (4) %. In Figure 3.2.P.2.2-23, the (b) (4) variant tablet lot with (b) (4) (and with the largest (b) (4) PSD) did not conform to the proposed dissolution acceptance criterion of "Q =(b) (4) % at 20 min". As indicated above, the Process Reviewer recommended (b) (4) control for both the (b) (4) and the (b) (4)

This Reviewer notes that the proposed dissolution method did not produce significant separation in the dissolution profiles of tablets manufactured with intentional variations within the studied ranges, i.e., (b) (4) Refer to Figure 3.2.P.2.2-24, Figure 3.2.P.2.2-25, and Figure 3.2.P.2.2-26, respectively. Per the Process Reviewer, the proposed acceptance ranges for (b) (4) are acceptable. Additionally, in 3.2.P.3.2, the Applicant stated that to ensure the composition is exactly the same as the batch formula, (b) (4)

Analytical Method Validation

HPLC with UV detection at 277 nm is used to quantify sunvozertinib in the dissolution samples. Specificity, linearity and range, accuracy, precision, robustness of the analytical method, as well as filter compatibility and solution stability were evaluated. Refer to Table 3.2.P.5.3-17 for the summary of the analytical method validation results. The dissolution method was shown to be robust in terms of dissolution temperature (37 ± (b) (4) C), (b) (4) citrate concentration (50 mmol/L (b) (4)), dissolution medium pH (5.1 (b) (4)), paddle speed (75 rpm (b) (4)), sampling technique (automatic and manual sampling), and presence/absence of medium degassing. The sample and standard solutions were stable for up to 4 days when stored at room temperature. Per the Drug Product Reviewer, the analytical method validation for dissolution is adequate.

Sink Conditions

As shown in Table 3.2.P.2.2-60, the solubility of sunvozertinib in pH 5.1 citrate buffer is 5.98 mg/mL at 37 °C. Thus, greater than sink conditions are anticipated to be achieved during dissolution testing of the 150 mg and (b) (4) mg sunvozertinib tablets in 900 mL medium.

DISSOLUTION ACCEPTANCE CRITERIA

Consistent with the FDA recommendation at the time of the Type B Breakthrough Designation Meeting for CMC on June 2, 2022, the Applicant tightened the dissolution acceptance criterion to Q =(b) (4)% at 20 min (refer to Table 3.2.P.5.1-1). Per the Applicant, "Q =(b) (4)% at 20 min" is adequate, i.e., based on (***i***) the dissolution profile data of tablet lots evaluated in Design of Experiment (DOE), Phase 1 clinical, pivotal clinical, and primary stability studies, and (***ii***) capability to reject the (b) (4) DOE tablet lot (refer to Figures 3.2.P.5.6-2 and Figure 3.2.P.5.6-3).

Based mainly on the dissolution profile data of the pivotal clinical trial lots (in Table 3.2.P.2.2-90 and Table 3.2.P.2.2-91), this Reviewer considers the proposed dissolution acceptance criterion (Q =(b) (4)% at 20 min) for sunvozertinib tablets to be reasonable. The recommended dissolution acceptance criterion is suitable for both proposed commercial strengths because the 150 mg and 200 mg strengths of the Formulation B (debossed) tablets exhibited superimposable to almost superimposable profiles using the proposed QC dissolution method and in various pH media (refer to Figure 3.2.P.2.2-13, and Table 3.2.P.2.2-46 to Table 3.2.P.2.2-49).

Per the proposed labeling (and as confirmed by the CDER QT-IRT), at the (b) (4) dosage (300 mg once daily), sunvozertinib is unlikely to cause QT prolongation. Additionally, considering that 9 of the 10 pivotal clinical trial lots exhibited very rapid dissolution, i.e., > (b) (4)% dissolves within (b) (4) minutes, in the proposed QC dissolution medium (pH 5.1 citrate buffer), and all the primary registration/stability and process validation batches of sunvozertinib tablets similarly exhibited at least(b) (4)% dissolution within(b) (4) minutes, it is reasonable not to have a second/earlier dissolution specification time point for routine QC testing of the 150 mg and 200 mg tablets.

Dissolution on Stability

Based on the individual unit dissolution profile data provided in Table 3.2.P.5.6-10 and Figure 3.2.P.5.6-2, the process validation and primary stability batches of the 150 mg and 200 mg tablets conformed to the proposed dissolution acceptance criterion (Q =(b) (4)% at 20 min) by USP Stage 1 testing. Dissolution testing was conducted over 24 months of long-term (30°C ± 2°C/65%RH ± 5%RH) testing and 6 months of accelerated (40°C ± 2°C/75%RH ± 5%RH) stability testing, as well as under stress testing under high heat and humidity and light exposure conditions, and in-use stability testing.

Similar findings were reported for the two supporting stability/pivotal clinical trial lots per tablet strength during 9 to 24 months or during 12 to 36 months of long-term storage, when using the final proposed commercial QC dissolution method (with pH 5.1 medium).

The proposed expiration dating period for sunvozertinib tablets is 36 months when stored under USP Controlled Room Temperature conditions.

B.12 BRIDGING OF FORMULATIONS

Assessment: Adequate

Various sunvozertinib powder and tablet formulations were used in Phase 1 and Phase 2 clinical studies; information on the strengths and the drug product manufacturers of these various formulations are provided in Table 3.2.P.2.2-1.

Per the Applicant, the proposed commercial drug product (i.e., the Formulation B *debossed* tablets) has the same formulation and manufacturing process and was manufactured at the same drug product manufacturing site ((b) (4) using equipment with the same design and operating principles as those tablet lots evaluated in the pivotal clinical trial and in primary registration/stability studies. The dissolution profiles in various pH media of one of the five pivotal clinical trial lots versus the three registration/stability lots per tablet strength are comparable (refer to Figure 3.2.P.2.2-14 and Figure 3.2.P.2.2-15). For a summary of the pharmaceutical changes during sunvozertinib tablet development, refer to Table 2.3.P.2-8.

Additionally, the proposed commercial product is the same as the pivotal clinical trial/primary registration/stability product in terms of (***i***) container-closure system (HDPE bottle with 1 gram silica gel, with child resistant cap), (***ii***) appearance (yellow, (b) (4), biconvex, and film-coated tablets, with debossing of either “150 mg” or “200 mg” on one side and the company logo on the other side, and (***iii***) (b) (4) and manufacturer ((b) (4)

The drug product batch sizes are similar between the pivotal clinical trial lots ((b) (4)) versus the primary registration/stability and the process performance qualification/proposed commercial tablet lots ((b) (4)).

REVIEWER NOTES:
As shown in Table 2.3.P.2-6 or Table 3.2.P.2.2.1.5, the formulation composition and manufacturing process of sunvozertinib tablets changed during clinical development. Formulation A (b) (4) tablets (25 mg, 50 mg, 100 mg) and Formulation B (b) (4) tablets (100 mg, 150 mg, 200 mg) were used in Phase 1 clinical studies (including the pivotal Food-effect study/WU-KONG1A); Formulation B (b) (4) tablets (100 mg) was also used in the pivotal Phase 2 clinical trial. Formulation B *debossed* tablets (the proposed commercial drug product, 150 mg and 200 mg) was used in the pivotal Phase 2 clinical trial, WU-KONG1B (and in the primary registration/stability studies), as well as in the ongoing confirmatory Phase 3 clinical study (WU-KONG28), and in two Phase 1 clinical studies [i.e., WU-KONG19 (drug-drug interaction study with enzyme/transporter substrates) and WU-KONG27 (PK in hepatic impairment)], and one additional Phase 2 clinical study (WU-KONG6).

(b) (4)

***In Vivo* PK Bridging of Formulation A Tablets and Formulation B Tablets**

Per the Applicant (and as confirmed by the Clinical Pharmacology Reviewer), there was no significant difference in *in vivo* drug exposures between Formulation A and Formulation B tablets. Specifically, the dose-normalized C_{max}, $C_{ss,max}$, AUC_{0-24} and AUC_{ss} were similar between the two formulations (based on the data from WU-KONG1 Part A and WU-KONG2). Additionally, based on Population PK analysis, formulation was not found to be a significant covariate of sunvozertinib PK.

Note that because of the formulation excipient and manufacturing process differences between the Formulation A tablets and the Formulation B tablets, *in vitro* (dissolution) comparison would not be deemed adequate/appropriate for bridging purposes.

B. 13 BIOWAIVER REQUEST

Assessment: Not Applicable

As indicated in Section B.12 above, both the 150 mg and 200 mg strengths of the Formulation B (debossed) tablet (i.e., the final to-be-marketed drug product) were evaluated in the pivotal clinical efficacy/safety/PK study (WUKONG-1 Part B), in two Phase 1 clinical studies (WU-KONG19 and WU-KONG27), in another Phase 2 clinical study (WU-KONG6) and in the ongoing confirmatory Phase 3 clinical trials. Per the Applicant, the exposures to the parent drug and the major metabolite were generally dose proportional at the 200 mg and 300 mg doses, administered as one 200 mg tablet and two 150 mg tablets, respectively. Thus, a biowaiver request for non-bio-strengths is not required.

Note that the two proposed commercial strengths of the Formulation B (debossed) tablets are compositionally proportional in terms of active and inactive ingredients (refer to Table 2.3.P.1-1).

Note also that the 100 mg strength of the Formulation B (b) (4) tablet was used in the pivotal clinical trial (WUKONG-1 Part B), but is currently not proposed for marketing.

R. REGIONAL INFORMATION

Comparability Protocols

None

Post-Approval Commitments

None

Lifecycle Management Considerations

None

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name and Date: Gerlie Gieser, Ph.D. (5/15/2025)

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