CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215830Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 215830
Assessment 1

Drug Product Name	Litfulo (ritlecitinib)
Dosage Form	Capsules
Strength	50 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Pfizer Inc.
US agent, if applicable	NA

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original Submission, eCTD SN 0001	06/24/2022	DS, DP, OPMA, labeling, and Biopharm
Amendment, SN 0002	07/21/2022	DP, labeling
Amendment, SN 0003	07/27/2022	DP, OPMA
Amendment, SN 0004	09/15/2022	DP, OPMA, Biopharm
Amendment, SN 0005	09/19/2022	DP, labeling
Amendment, SN 0011	11/28/2022	DS, DP
Amendment, SN 0012	12/09/2022	OPMA
Amendment, SN 0016	01/13/2023	Biopharm, OPMA
Amendment, SN 0017	02/01/2023	DS
Amendment, SN 0021	04/18/2023	DP, labeling

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the NDA IQA Guide

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	N/A	N/A	Adequate info provided in the NDA
	III			N/A	N/A	Adequate info provided in the NDA
	III			N/A	N/A	Adequate info provided in the NDA
	III			N/A	N/A	Adequate info provided in the NDA
	III			N/A	N/A	Adequate info provided in the NDA
	III			N/A	N/A	Adequate info provided in the NDA
	III			N/A	N/A	Adequate info provided in the NDA

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	131503 (b) (4)	Conducted clinical studies

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

NDA Executive Summary

1. Application/Product Information

NDA Number.	215830		
Applicant Name	Pfizer Inc.		
Drug Product Name	Litfulo (ritlecitinib)		
Dosage Form.	Capsule		
Proposed Strength(s)	50 mg		
Route of Administration	Oral		
Maximum Daily Dose	50 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	For the treatment of alopecia areata (AA) (b) (4)		
Drug Product Description	50 mg of ritlecitinib: Size 3, opaque capsules with yellow body and blue cap. The body is printed with “RCB 50” and the cap is printed with “Pfizer” in black.		
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 between 15°C to 30°C (59°F to 86°F). [see USP Controlled Room Temperature]. Keep in original package.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Sukhamaya Bain	Lawrence Perez
	Drug Product/ Labeling	Hitesh Shroff	Nina Ni

	Manufacturing	Amit Kokate	Jean Tang
	Biopharmaceutics	Kamrun Nahar	Tapash Ghosh
	Microbiology	Amit Kokate	Jean Tang
	Other (specify):	N/A	N/A
	RBPM	Grafton Adams	
	ATL	Nina Ni	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: 30 months

b. Additional Comments for Action N/A

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends APPROVAL of NDA 215830 for commercialization of LITFULO (ritlecitinib) capsules, 50 mg. Based on our evaluation of the available information, the applicant provided sufficient information to support an approval recommendation from the product quality perspective. The applicant provided adequate chemistry, manufacturing, and controls (CMC) information 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	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): Yes

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: N/A

Comparability Protocols (PACMP): No
Comments: N/A

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: Submitted on April 18, 2022 Sequence: 0022 SDN: 21

(b) (4)

[redacted]

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	
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	

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

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple- dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	Adequate The following equivalency statement is in Sec. 11 DESCRIPTION Each capsule contains 50 mg ritlecitinib (equivalent to 80.13 mg ritlecitin b tosylate)	

1.1 FULL PRESCRIBING INFORMATION

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

(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)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	Adequate The following equivalency statement is in Sec. 11 DESCRIPTION Each capsule contains 50 mg ritlecitinib (equivalent to 80.13 mg ritlecitinib tosylate)	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	

Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for 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	

1.2.2 Section 3 (Section 11 DESCRIPTION)

(b) (4)

QUALITY ASSESSMENT

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	
Dosage form(s) and route(s) of administration	Adequate	
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)"	Adequate	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	
Chemical name, structural formula, molecular weight	Adequate	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	Ritlecitinib tosylate is a white to off white to pale pink solid which is freely soluble in water.

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

Store LITFULO at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Keep in original package.

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	
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	

Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple- dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[X]" with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Add the following statement: [See USP Controlled Room Temperature]
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	Adequate	

1.2.6 Manufacturing Information After Section 17 (for drug products)

(b) (4)

[redacted]

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	

2.0 PATIENT LABELING

CONTAINER AND CARTON LABELING: Submitted on April 18, 2023 Sequence 0022 SDN 21

3.0 Container Labels

(b) (4)

[redacted]

QUALITY ASSESSMENT

Sample Labeling

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2], (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	N/A	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	Adequate	
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Add the following statement: [See USP Controlled Room Temperature]
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	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	

Linear Bar code	Adequate	Location present
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of 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[1]	Adequate	
Special preparation instructions (if applicable)	Adequate	
Storage and handling information (if applicable)	Adequate	
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	
Active ingredient(s) (if applicable)	Adequate	
Alphabetical listing of inactive ingredients (if applicable)	Adequate	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	

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

Assessment of PI: *ADEQUATE*

Assessment of Carton and Container Labeling: *ADEQUATE*

Assessment of Medication Guide: *ADEQUATE*

ITEMS FOR ADDITIONAL ASSESSMENT: None

List of Deficiencies: None

Overall Assessment and Recommendation:

All PI and container/carton labels revisions, shown in green, have been conveyed to the review team and will be conveyed to the applicant.

This NDA is recommended for "**Approval**" from the labeling perspective.

Primary Labeling Assessor Name and Date:
Hitesh Shroff
OPQ, ONDP, DNDP II, Branch 4
04-22-2023

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

Nina Ni, Ph.D.
Branch Chief
OPQ, ONDP, DNDP II, Branch 4

Nina Ni

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Hitesh Shroff

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QUALITY REVIEW

BIOPHARMACEUTICS
NDA: NDA 215830
Drug Product Name / Strength: Ritlecitinib capsule, 50 mg
Route of Administration: Oral
Applicant Name: Pfizer Inc
Indication: For the treatment of alopecia areata.
Submission date: 06/24/2022
Primary Reviewer: Kamrun Nahar, Ph.D.
Secondary Reviewer: Tapash Ghosh, Ph.D.
Recommendation: Adequate

BACKGROUND:

The Applicant is seeking approval under 505(b)(1) regulatory pathways for ritlecitinib capsule, 50 mg, for oral administration, indicated for the treatment of alopecia areata.

REVIEW SUMMARY:

The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting: 1) the proposed dissolution method and acceptance criteria, and 2) formulation bridging throughout product development, 3) biowaiver. Summary of the key findings are presented below, based on the review of the provided information/data:

1) **Dissolution Method and Acceptance Criteria:**
The Applicant used FDA dissolution guidance (August 2018) based dissolution method for the ritlecitinib capsule, 50 mg which is as follows- USP apparatus II (paddle) with stainless steel sinker, 50 rpm, 500 mL of 0.1N HCl, pH 1.2 at 37°C. The Applicant's proposed a dissolution acceptance criterion of "Q= (b)(4)% in 30 minutes" as quality control for batch release and stability testing of the proposed drug product.

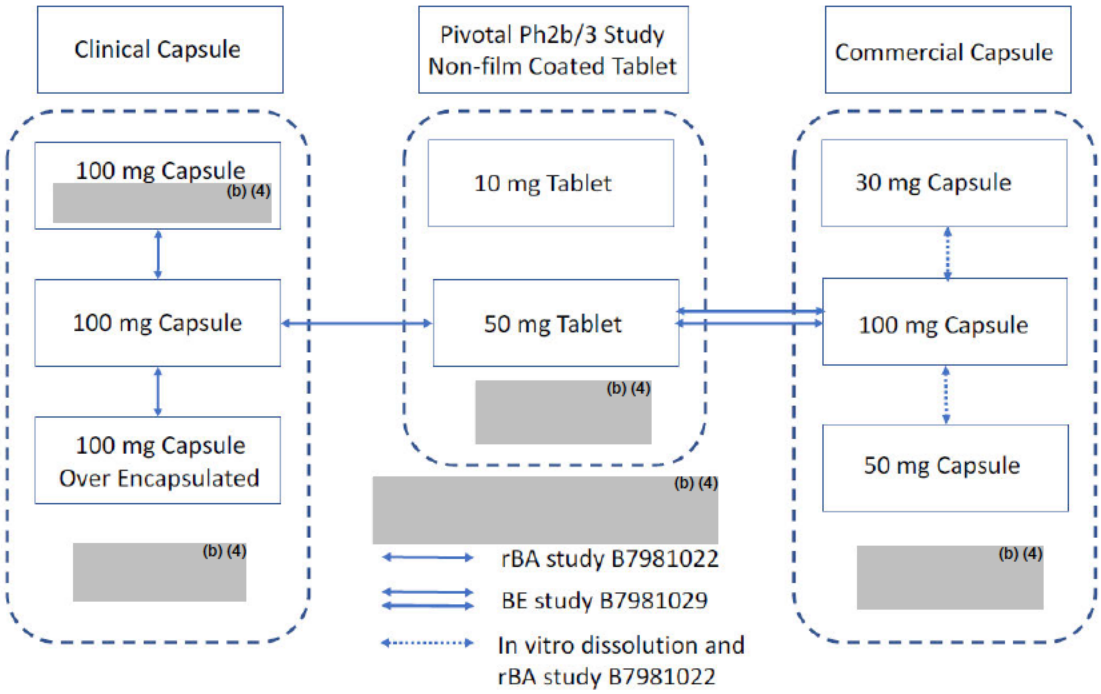
The approved dissolution method and acceptance criterion for quality control and stability testing of the proposed ritlecitinib capsule, 50 mg:

Dissolution apparatus	Dissolution apparatus rotation speed (rpm)	Dissolution media, temperature	Dissolution media volume (mL)	Dissolution acceptance criterion
USP Apparatus II (paddle) with Stainless steel sinker comprising a few turns of stainless steel	50	pH 1.2, 0.1 N Hydrochloric acid; 37°C±0.5°C	500 mL	Q= (b)(4)% in 30 minutes

2) **Bridging of Formulations:**

Various formulations were used in the clinical studies to determine the safety and/or efficacy of ritlecitinib. Extemporaneously prepared ritlecitinib oral solutions were used in the single ascending dose study# B7981001 and for the absolute bioavailability study# B7981011. An intravenous (IV) solution was developed for use in the absolute bioavailability study# B7981011. Ritlecitinib tablets, 10 mg and 50 mg were developed to support clinical pharmacology, safety and efficacy studies including the pivotal Phase 2b/3 study# B7981015. These tablets (b) (4) the multiple units (up to 4 tablets) were required to administer to support the proposed doses. Therefore, these are not suitable for commercialization. The Applicant manufactured ritlecitinib capsules, 100 mg. Ritlecitinib 100 mg light gray/gray capsule formulations were used in the relative bioavailability (rBA) study# B7981022 to enable estimation of the rBA of the proposed commercial capsule formulation to the tablet formulation used in the safety and efficacy studies as well as the impact of drug substance particle size distribution on bioperformance. The Applicant used ritlecitinib capsule, 100 mg for clinical studies. (b) (4) Capsules from the first 100 mg registration stability batch were used in the bioequivalence study B7981029. The clinical ritlecitinib capsule, 100 mg (b) (4) . Although, the Applicant manufactured three different strengths of ritlecitinib capsules, i.e., 30 mg, 50 mg, and 100 mg, in the current NDA, they only proposed to commercialize ritlecitinib capsules, 50 mg. The Applicant bridged the ritlecitinib capsules, 100 mg and 50 mg through in vitro dissolution test using QC dissolution method.

Figure 1: Summary of biopharmaceutics relationships of ritlecitinib formulations



3) Biowaiver request:

The Applicant submitted a biowaiver request for ritlecitinib capsule, 50 mg. In support of their request, they submitted the following information-

a. Ritlecitinib capsules, 50 mg and 100 mg [redacted] (b) (4)
b. Dissolution data showed similar drug release profiles in QC dissolution method.
c. The Applicant claimed that across the dose range from 10 mg to 200 mg, dose proportional pharmacokinetics parameters were observed.

Based on the information provided in the NDA, i.e., ritlecitinib capsules, 50 mg and 100 mg [redacted] (b) (4) dissolution data showed rapid drug release (i.e., [redacted] (b) (4) % drug is released from the capsule in 30 minutes), showed dose proportional PK parameters, the Applicant's request for biowaiver of the 50 mg strength is adequate.

BIOPHARMACEUTICS ASSESSMENT:

List Submissions being reviewed:

1. 0001 06/24/2022 Original submission
2. 0004 09/15/2021 Response to FDA Quality Information Request
3. 0016 01/13/2023 Response to FDA Quality Information Request

Highlight Key Outstanding Issues from Last Cycle: None

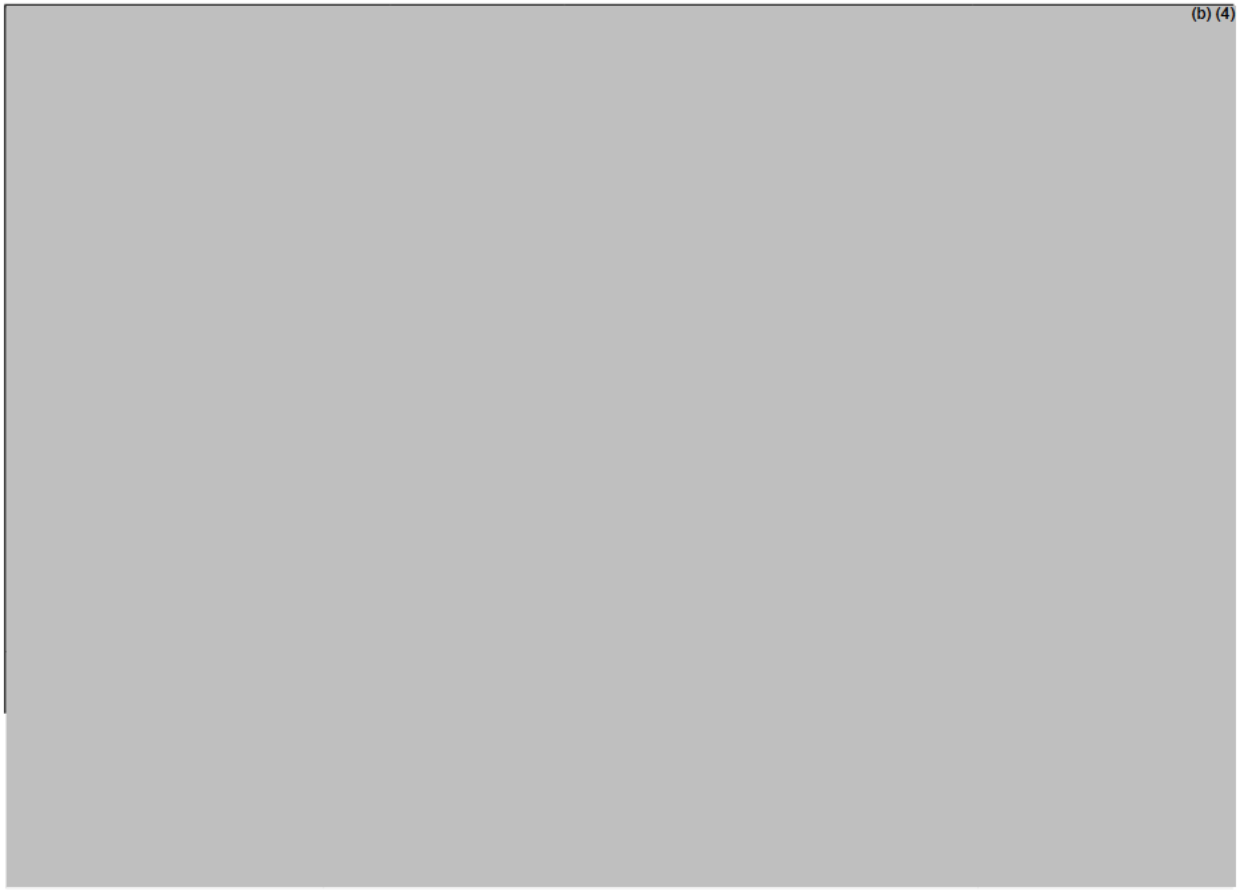
Composition of ritlecitinib capsule, 50 mg:

Ritlecitinib capsule is an immediate release Hypromellose (HPMC) opaque capsule formulation for oral administration. The Applicant manufactured ritlecitinib capsule, 30 mg, 50 mg, and 100 mg [redacted] (b) (4) Ritlecitinib capsule, 30 mg has size #4, yellow body and cap, and the body is printed with "RCB 30" and the cap is printed with "Pfizer" in black; 50 mg has size #3, yellow body/ blue cap, the body is printed with "RCB 50" and the cap is printed with "Pfizer" in black; and 100 mg has size #1, blue body and cap, the body is printed with "RCB 100" and the cap is printed with "Pfizer" in black. Ritlecitinib capsule, 100 mg is used in the clinical studies. However, only ritlecitinib capsule, 50 mg is proposed for approval in the current NDA.

Table 1: Formulation composition of ritlecitinib capsules, 50 mg

Name of Ingredients	Function	Reference to Standard	Unit formula	
			mg/unit	%
				(b) (4)
Ritlecitinib Tosylate	Active	Pfizer	80.128[1]	(b) (4)
Microcrystalline Cellulose	(b) (4)	Ph. Eur., USP/NF, JP		(b) (4)
Lactose Monohydrate		Ph. Eur., USP/NF, JP		
Crospovidone		Ph. Eur., USP/NF, JP		
Glyceryl Dibehenate		Ph. Eur., USP/NF, JFSA		
(b) (4)				
HPMC Capsule Shell				
Capsule Shells (size #3, Yellow/ Blue HPMC Capsules)[3]		Pfizer		
(b) (4)				
Hypromellose (b) (4)		Ph. Eur., USP/NF, JP		
Titanium Dioxide (b) (4)		Ph. Eur., USP/NF, JP		
Yellow Iron Oxide (b) (4)		USP/NF, JPE		
(b) (4)				
		Ph. Eur., USP/NF, JP		
		Ph. Eur., USP/NF, JP		
Brilliant blue FCF – FD&C Blue (b) (4)		JFSA, MHLW 126		
Approximate Weight of Capsule Shell				
				(b) (4)

Table 2: Formulation composition of ritlecitinib capsules, 100 mg



a. Dissolution method:

Solubility:

The Applicant claimed that ritlecitinib is a BCS Class 3 drug. Solubility data showed that ritlecitinib has high solubility across the physiological pH range.

Table 3: Solubility data of ritlecitinib

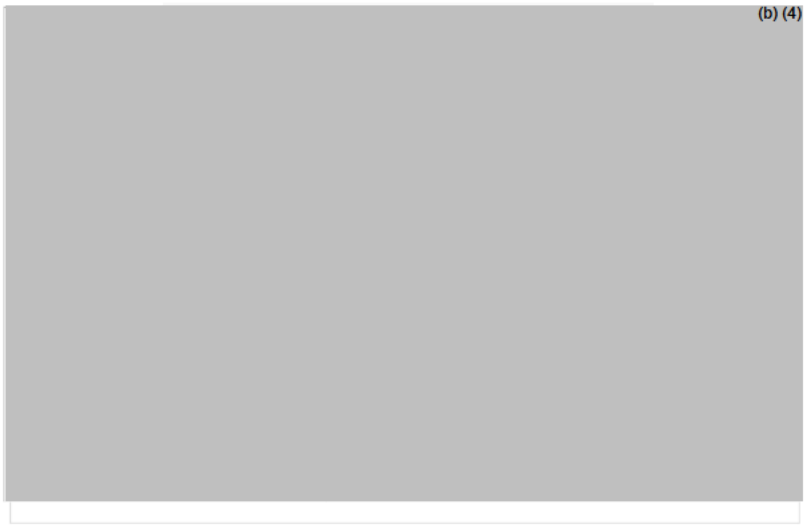
Aqueous media	Solubility (mg/mL) 37°C	Dose Number* (mg/mL)
pH 0.8	28.1	0.028
pH 1.8	25.0	0.032
pH 3.0	31.0	0.026
pH 3.5	34.1	0.023
pH 4.0	35.6	0.022
pH 4.1	32.2	0.025
pH 4.2	30.1	0.027
pH 4.3	26.8	0.030
pH 4.4	25.0	0.032
pH 4.5	22.0	0.036
pH 4.6	18.9	0.042
pH 5.0	13.1	0.061
pH 5.5	8.3	0.096
pH 6.0	7.6	0.105
pH 6.8	6.8	0.118

*Dose Number = Highest dose in mg (200 mg)/ (250 mL*Solubility) in mg/mL; a Dose Number less than 1 indicates that the entire dose is soluble thus meeting the BCS high solubility criteria.

Dissolution method parameters:

The Applicant used FDA dissolution guidance, August 2018 recommended dissolution method, i.e., USP apparatus II (paddle) with stainless steel sinker, 50 rpm, 500 mL of 0.1N HCl, pH 1.2 at 37°C. The Applicant compared the dissolution profiles generated by the dissolution guidance (August 2018), paddle and basket methods. Both methods showed similar profile with (b) (4)% release at 30 minutes and similar high variance through the capsule disintegration phase. The Applicant finally choose dissolution guidance (August 2018) recommended paddle method.

Figure 1: Dissolution profile for ritlecitinib 100 mg capsules using dissolution guidance (August 2018) recommended standard basket and paddle methods



Discriminating ability:
The Applicant used FDA dissolution guidance (August 2018) recommended dissolution method since the drug substance (DS) is highly soluble. They did not provide discriminating ability of the dissolution method. However, high solubility of ritlecitinib along with the use of FDA dissolution guidance (August 2018) based dissolution method, demonstration of discriminating ability of the dissolution method is not considered significant.

Dissolution data:
The Applicant compared the dissolution profile of the ritlecitinib capsule, 50 mg with ritlecitinib capsule, 100 mg. Dissolution comparisons between 50 mg capsules (lot DC5781) and 100 mg capsules (lot DC5777) were conducted in QC dissolution method. Ritlecitinib capsules, 50 mg and 100 mg strengths has different rupture time, i.e., ritlecitinib capsules, 50 mg size 3 capsules ruptures earlier with a rupture time (b) (4) minutes than the larger 100 mg size 1 capsules with a rupture time (b) (4) minutes. This effect is observed across all three media, pH 1.2, 4.5 and 6.8 and did not improve significantly when multiple capsules (2 x 50 mg) were compared against the 100 mg capsule. The Applicant claimed that the differences in rupture time is unlikely to affect the rate or extent of absorption from the higher strength capsules. To support this claim, they conducted a rBA study# study# B7981022 using an overencapsulated (100 mg capsule was placed inside a size #0 capsule shell) vs encapsulated capsule, 100 mg. The difference between the overencapsulated vs encapsulated capsule, 100 mg is the overencapsulated capsule had a longer disintegration time of approximately 15 min as shown compared to the encapsulated capsule. The over-encapsulated capsule with longer rupture time was bioequivalent to the prototype commercial capsule in Study B7981022.

Figure 2: Dissolution comparison study of ritlecitinib capsules, 50 mg (batch# DC5781) vs 100 mg (batch#DC5777)

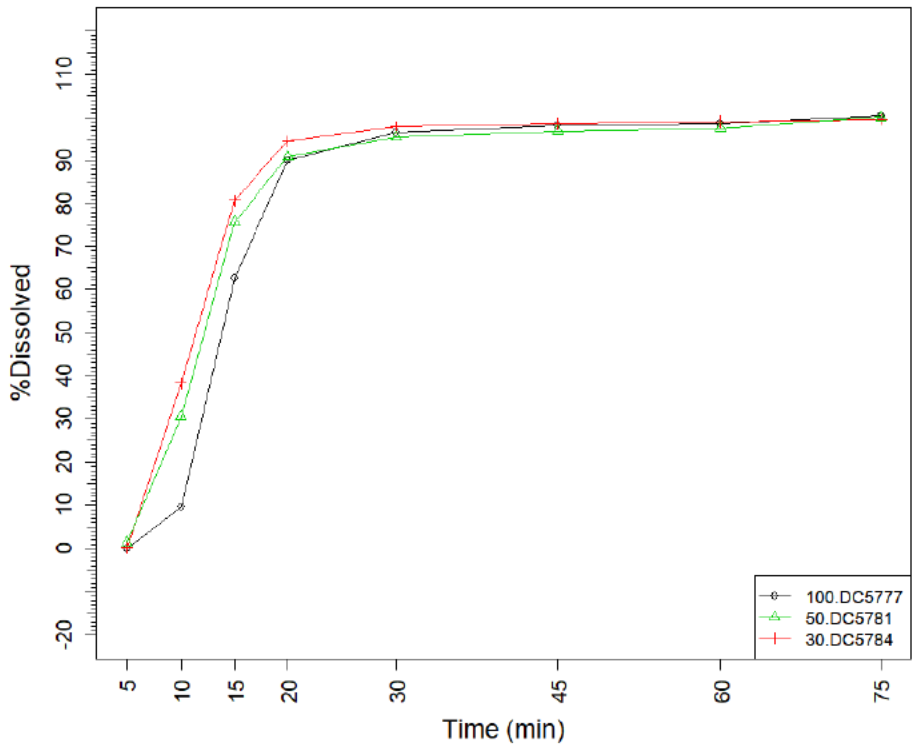
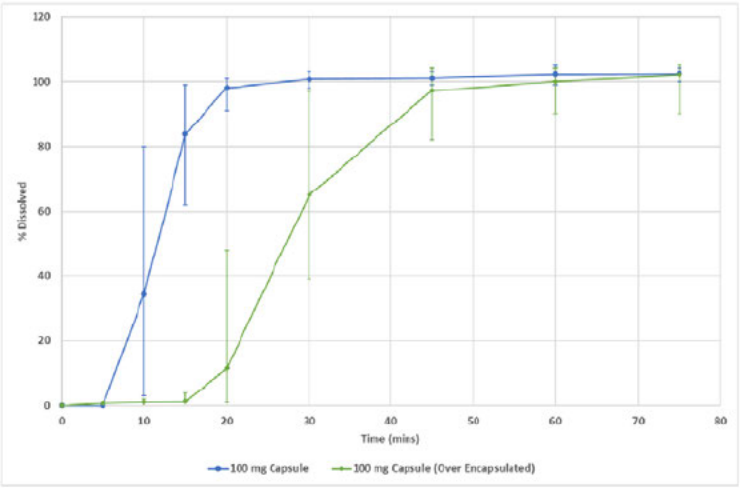


Figure 3: Dissolution comparison study of ritlecitinib capsules, 100 mg vs 100 mg (overencapsulated)



The profiles show that dissolution is rapid for 50 mg and 100 mg strengths, i.e., (b) (4) % drug is released in 30 minutes in the QC dissolution media. The 100 mg capsule has slower drug release at early time points up to 20 minutes compared to the 50 mg strength. The Applicant stated that the reason for slower drug release from 100 mg capsule is due to the increased rupture time of the capsule shell compared to the 50 mg capsules shell. Both 100 mg and 50

mg showed rapid drug release and meeting the FDA dissolution guidance (August 2018) recommended dissolution acceptance criterion.

Dissolution acceptance criterion:
Dissolution data showed (b) (4)% drug is release from the capsules at 30 minutes. Dissolution data showed high variability at early time points up to 10 to 15 minutes; and for some formulations up to 20 minutes. The Applicant justified the reasons for high variability is due to the differences in rupture time of the shell. For capsules formulation this type of variability at early time points is not uncommon. The Applicant proposed dissolution acceptance criterion as "Q= (b) (4)% in 30 minutes" which is acceptable and is in line with the FDA guidance recommended dissolution acceptance criterion.

Approved dissolution method and acceptance criterion:

Dissolution apparatus	Dissolution apparatus rotation speed (rpm)	Dissolution media, temperature	Dissolution media volume (mL)	Dissolution acceptance criterion
USP Apparatus II (paddles) with Stainless steel sinker comprising a few turns of stainless steel	50	pH 1.2, 0.1 N Hydrochloric acid; 37°C±0.5°C	500 mL	Q= (b) (4)% in 30 minutes

4) Biowaiver:
The Applicant submitted a biowaiver request for ritlecitinib capsule, 50 mg. In support of their request, they submitted the following information-

i. Ritlecitinib capsules, 50 mg and 100 mg (b) (4)
ii. Dissolution data showed similar drug release profiles in QC dissolution method.
iii. The Applicant claimed that across the dose range from 10 mg to 200 mg, dose proportional pharmacokinetics (PK) parameters were observed.

Based on the information provided in the NDA, i.e., ritlecitinib capsules, 50 mg and 100 mg (b) (4) dissolution data showed rapid drug release (i.e., (b) (4)% drug is released from the capsule in 30 minutes), showed dose proportional PK parameters, the Applicant's request for biowaiver of the 50 mg strength is adequate.

CONCLUSION AND RECOMMENDATION:

Form a Biopharmaceutics perspective, NDA 215830 ritlecitinib capsule, 50 mg is **adequate** for approval.

Appendix 1. Dissolution Data

Dissolution data: \\CDSESUB1\EVSPROD\nda215830\0016\m3\32-body-data\32r-reg-info\batch-dissolution-data-updated-dec-22.xlsx
Dissolution method: \\CDSESUB1\EVSPROD\nda215830\0001\m3\32-body-data\32p-drug-prod\ritlecitinib-capsule\32p5-contr-drug-prod\32p52-analyt-proc\analytical-procedures.pdf

Appendix 2. Information Request and Responses

(b) (4)

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Tapash Ghosh

Digitally signed by Tapash Ghosh
Date: 3/06/2023 11:38:58AM
GUID: 508da7230002a2433ddcef616ca190df

Kamrun Nahar

Digitally signed by Kamrun Nahar
Date: 3/06/2023 11:08:43AM
GUID: 57b38236009c032e2a84627cd295a5cd

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

/s/

NINA NI
04/23/2023 04:00:58 PM