CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215309Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

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

NDA 215309
Assessment # 1

Drug Product Name	OPZELURA™ (ruxolitinib)
Dosage Form	Cream
Strength	1.5%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Incyte Corporation
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original NDA submission	12/21/2020	All
Proprietary Name Request	12/22/2020	All
Response to Information Request - Quality	02/12/2021	ONDP - Biopharmaceutics
Response to Information Request - Quality	02/22/2021	ONDP and Microbiology
Response to Information Request - Quality	03/09/2021	ONDP
Clinical Safety Update	03/19/2021	Clinical
Proprietary Name Request	04/01/2021	All
Response to Information Request - Quality	04/02/2021	OPMA
Response to Information Request - Clinical	04/23/2021	Clinical
Response to Information Request – Clinical Amendment	05/03/2021	Clinical
Response to Information Request - Quality	05/05/2021	OPMA

Response to Information Request - Clinical	05/07/2021	Clinical
Response to Information Request - Clinical	05/17/2021	Clinical
Response to Information Request - Quality	06/02/2021	ONDP
Response to Information Request - Clinical	06/04/2021	Clinical
Container and Carton Labels	08/27/2021	All
PI Labeling	09/03/2021	All

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Jeffrey Medwid, Ph.D.	Donna Christner, Ph.D.
Drug Product	Caroline Strasinger, Ph.D.	Wendy Wilson-Lee, Ph.D.
Manufacturing	Raeann Wu, Ph.D.	Frank Wackes, Ph.D.
Microbiology	Dustin Thomas, Ph.D.	Jesse Wells, Ph.D.
Biopharmaceutics	Kalpana Paudel, Ph.D.	Tapash Ghosh, Ph.D.
Regulatory Business Process Manager	Melinda Bauerlien, M.S.	
Application Technical Lead	Hamid Shafiei, Ph.D.	
Laboratory (OTR)	N/A	N/A
Environmental	Caroline Strasinger, Ph.D.	Wendy Wilson-Lee, Ph.D.

EXECUTIVE SUMMARY

For more details about the items in this template, please see the Executive Summary chapter of the NDA IQA Guide

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

- The applicant of this 505(b)(1) new drug application has provided **sufficient CMC information** to assure the identity, purity, strength, and quality of the drug substance, ruxolitinib phosphate and the drug product, OPZERULA® (ruxolitinib) Cream, 1.5%.
- Labels/labeling issues have been **satisfactorily** addressed.
- The Office Pharmaceutical Manufacturing Assessment has made an overall "**Acceptable**" recommendation regarding the facilities involved in this NDA.
- The claim for categorical exclusion from the preparation of environmental assessment has been granted.

Therefore, from the OPQ perspective, this NDA is recommended for **APPROVAL** with expiration dating period of **24 months**.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Incyte Corporation has submitted this 505(b)(1) application for OPZELURA (ruxolitinib) Cream, 1.5%. OPZELURA cream is indicated for the topical treatment of atopic dermatitis in patients 12 years of age and older. OPZELURA is intended for topical administration as a thin layer to the affected skin areas for up to 20% of body surface area, twice daily.

OPZELURA contains the active ingredient ruxolitinib phosphate, the phosphate salt of the active moiety ruxolitinib. Ruxolitinib phosphate is a white to off-white to light pink powder and is a Janus kinase (JAK) inhibitor. It was first approved in November 16, 2011 as the active ingredient of JAKAFI (ruxolitinib) tablets under NDA 202192 for the treatment of intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis in adults, polycythemia vera in adults who have had an inadequate response to or are intolerant of hydroxyurea, and steroid-refractory acute graft-versus-host disease in adult and pediatric patients 12 years and older.

OPZELURA is a white to off-white oil-in-water, solubilized emulsion

cream. Each gram of OPZELURA contains 15mg of ruxolitinib equivalent to 19.8mg of ruxolitinib phosphate as the active ingredient and cetyl alcohol, dimethicone 350, edetate disodium, glyceryl stearate SE, light mineral oil, medium chain triglycerides, methylparaben, phenoxyethanol, polyethylene glycol 200, polysorbate 20, propylene glycol, propylparaben, stearyl alcohol, purified water, white petrolatum, and xanthan gum as inactive ingredients.

OZELURA will be packaged and marketed as 60g cream in aluminum tubes.

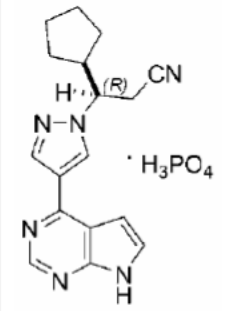
Proposed Indication(s) including Intended Patient Population	Topical treatment of atopic dermatitis in patients 12 years of age and older
Duration of Treatment	As prescribed by physician
Maximum Daily Dose	To be applied twice daily as a thin layer to the affected skin areas up to 20% of body surface area
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The active ingredient, ruxolitinib phosphate is a synthetic small molecule Janus kinase inhibitor with selectivity for JAK1 and JAK2 isoform. Ruxolitinib phosphate was first approved as the active ingredient of JAKAFI tablets under NDA 202192 on November 16, 2011. In this new drug application, ruxolitinib phosphate has been reformulated as a topical cream for the treatment of atopic dermatitis.

Ruxolitinib phosphate is a non-hygroscopic white to off-white to light pink powder with a melting point of 197.6ºC and pKa values of 4.3 and 11.8. The solubility of this API has been evaluated from pH of 1 to 8 and the results indicate that its solubility is increased at lower pH. Due to high solubility and high permeability, ruxolitinib phosphate has been classified as a BCS class 1 drug substance. Ruxolitinib phosphate has the chemical name, (R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate, a molecular formula of $C_{17}H_{21}N_6O_4P$ ($C_{17}H_{18}N_6$ as free base), a molecular mass of 404.36 g/mole (306.37 g/mole as free base), and the molecular structure below:



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(b) (4) manufacture of ruxolitinib phosphate have been developed and well characterized by Incyte. Ruxolitinib phosphate for this application is manufactured in accordance with the current good manufacturing practices (cGMP) by (b) (4)

(b) (4) It is tested and release against a specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its assigned retest date of (b) (4) months when stored at (b) (4)

The manufacturing details and supporting stability data for this API has been referenced to NDA 202192. The drug substance section and all it is update in NDA 202192 was reviewed as recently as November 2, 2020 by the drug substance reviewer, Dr. Wei-Hua Wu and found to be adequate.

Relaying on Dr. Wu's review and the review of the additional drug substance information provided in this application, the Drug Substance Reviewer, Dr. Jeffrey Medwid has recommended the approval of this application from the drug substance perspective. Dr. Medwid's review is provided in the Drug Substance Chapter of the Integrated Quality Assessment (IQA).

Drug Product: Adequate

The drug product, OPZELURA (ruxolitinib) Cream, 1.5% is a non-sterile white to off-white, oil-in-water, solubilized emulsion containing 19.8mg ruxolitinib phosphate equivalent 15mg of ruxolitinib per gram of cream. It will be packaged and marketed as 60g cream in aluminum tube. This drug product is indicated for the topical treatment of atopic dermatitis in patients 12 years of age and older. OPZELURA is intended for topical administration as a thin layer to the affected skin areas for up to 20% of body surface area, twice daily.

OPZELURA also contains cetyl alcohol, dimethicone 350, edetate disodium, glyceryl stearate SE, light mineral oil, medium chain

triglycerides, methylparaben, phenoxyethanol, polyethylene glycol 200, polysorbate 20, propylene glycol, propylparaben, stearyl alcohol, purified water, white petrolatum, and xanthan gum as inactive ingredients. All inactive ingredients used in the composition of OPZELURA are compendial materials with the exception of glyceryl stearate SE. All compendial material are tested, released, and accepted in accordance with the compendial procedures and requirement. The applicant has provided specification and justification for the use of the non-compendial glyceryl stearate SE which is also tested according to the compendial methods. The composition of the drug product has been reviewed and evaluated from the CMC and Pharm/Tox perspective and has been found to be adequate.

OPZELURA Cream is manufactured by (b) (4) in accordance with the cGMP requirements. It is tested and released against a specification that assures the identity, strength, purity, and quality of the drug product at release and throughout its proposed expiration dating period of 24 months. The proposed expiration dating period of 24 months is supported by the stability data submitted in the application and is granted.

In summary, the drug product module of this application has been reviewed by the Drug Product Reviewer, Dr. Caroline Strasinger. Dr. Strasinger has found the information provided in the application adequate and has recommended the approval of this application from drug product perspective. Dr. Strasinger's review is provided in the drug product chapter of the IQA.

The applicant's request for the categorical exclusion from the preparation of the environmental assessment has also been reviewed by Dr. Caroline Strasinger. Dr. Strasinger has found the applicant's request valid and has recommended granting the categorical exclusion to this application. The review of the categorical exclusion is also captured in the Drug Product Chapter of the IQA.

Labeling: Adequate

The CMC sections of the PI labeling as well as the container and carton labels for OPZELURA have been reviewed by the Drug Product Reviewer, Dr. Caroline Strasinger. Dr. Strasinger has found the proposed PI labeling as well as container and carton labels for OPZELURA adequate and has recommended the approval of this application from the labeling perspective. Dr, Strasinger's labeling review is provided in the Labeling Chapter of the IQA.

Manufacturing: Adequate

The manufacturing process for OPZELURA entails (b) (4) (b) (4)

Three clinical/registration batches, two batches (b) (4) kg scale and one batch at (b) (4) kg scale were manufactured with acceptable quality. The proposed commercial scale for this drug product is (b) (4) kg.

Both drug substance and drug product manufacturers have the appropriate experience as well as adequate inspectional history that support the proposed manufacturing operation. Therefore, based the manufacturers' inspectional profiles, the manufacturing sites involved in this application have been recommended as acceptable.

The manufacturing process and the facilities for this application have been reviewed by the Office of Pharmaceutical Manufacturing Assessment (OPMA) Reviewer, Dr. Raeann Wu. Dr. Wu has found both the process and the facilities described in this application adequate to support the approval of this application from the OPMA perspective. Dr. Wu's review is provided in the Manufacturing Chapter of the IQA.

Biopharmaceutics: Adequate

The applicant has developed and validated an in-vitro release testing (IVRT) method using a vertical diffusion cell apparatus which will mainly be used for the determination of comparability drug product if post-approval manufacturing changes are made. The proposed IVRT method is not intended for routine release and stability testing. However, the applicant has agreed to use the IVRT method for the release testing of at least the first five commercial batches of drug product to show consistent drug product quality. (b) (4) The applicant's plan is considered acceptable from the biopharmaceutics perspective.

Since the drug product formulation of the batches used in the pivotal clinical studies is the same the drug product formulation intended for the commercial use, no in-vivo or in-vitro formulation bridging studies are needed.

The biopharmaceutics information provided in this application has been reviewed by the Biopharmaceutics Reviewer, Dr. Kalpana Paudel. Dr.

Paudel has found the proposed IVRT method and acceptance criteria adequate and the (b) (4) testing of the first five commercial batches of drug product in an annual report acceptable. Dr. Paudel has recommended the approval of this application from biopharmaceutics perspective. Dr. Paudel's review is provided in Biopharmaceutics Chapter of the IQA.

Microbiology (if applicable): Adequate

OPZELURA is a non-sterile white to off white preserved cream packaged as 5g for physician samples and as 60g for commercial use in aluminum tubes and is a multi-dose product.

The applicant has performed antimicrobial effectiveness testing and the final drug product specification includes testing and acceptance criteria for the microbiological attributes that comply with USP <60>, USP <61>, and USP <62>.

The microbiology section of this application has been reviewed by the Microbiology Reviewer, Dr. Dustin Thomas. Dr. Thomas has concluded that the proposed testing and acceptance criteria for microbiological attributes of this drug product are adequate and support the approval of this application from microbiology perspective. Dr. Thomas's review is provided in the Microbiology Chapter of the IQA.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Uniformity in container	Uniformity of the bulk product	M	Controlled by the drug product specification	Acceptable	None

D. List of Deficiencies for Complete Response

None

Application Technical Lead:

Hamid Shafiei, Ph.D.
Branch IV/DNDP 2/ONDP/OPQ

APPEARS THIS WAY ON ORIGINAL

Hamid Shafiei

Digitally signed by Hamid Shafiei
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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)	----------	----------	Adequate information is provided in the NDA

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

Document	Application Number	Description
NDA	202192	Referenced for the API, Ruxolitinib Phosphate

2. CONSULTS

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

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

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	Ruxolitinib cream
Route(s) of administration	Adequate	For topical use
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	Cream: 1.5%
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	
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 strength is based on the active moiety, ruxolitinib. The salt equivalency statement appears in section 11.

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

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

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

For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Cream
Strength(s) in metric system	Adequate	15 mg of ruxolitinib per gram (1.5%)
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	Strength is stated correctly as active moiety: 15 mg of ruxolitinib per gram (1.5%) white to off-white cream.
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	

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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	TRADENAME (ruxolitinib) cream
Dosage form(s) and route(s) of administration	Adequate	Cream for topical use
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	Adequate	Revise to say Each gram of TRADENAME cream, 1.5% contains 15 mg of ruxolitinib (equivalent to 19.8 mg of ruxolitinib phosphate) in a cream containing cetyl alcohol, dimethicone 350, edetate disodium, glyceryl stearate SE, light mineral oil, medium chain triglycerides, methylparaben, phenoxyethanol, polyethylene glycol 200, polysorbate 20, propylene glycol, propylparaben, stearyl alcohol, purified water, white petrolatum, and xanthan gum. 03-SEP-2021 – This was agreed to by the applicant
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	Janus Kinase inhibitor
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	

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)

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	cream
Strength(s) in metric system	Adequate	1.5%
Available units (e.g., bottles of 100 tablets)	Adequate	60 g aluminum tube
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	White to off-white cream; NDC present
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."	Adequate	Room temperature

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.	Inadequate	Revise to read: Store TRADENAME cream, 1.5% at at 20ºC - 25ºC (68ºF - 77ºF); excursions permitted to 15ºC - 30ºC (59ºF - 86ºF) [See USP Controlled Room Temperature]
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	N/A	

1.2.6 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	Incyte Corporation 1801 Augustine Cut-off Wilmington, DE 19803

Assessment of Prescribing Information: ADEQUATE
The applicant agreed to include a salt equivalency statement in section 11 of the prescribing information on 03-SEP-2021.

3.0 CONTAINER AND CARTON LABELING

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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	Name revised to Opzelura on 27-AUG-2021(example revised labels provided above)
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	Adequate	Revise all container/carton labels to read **Each gram contains**: 15 mg of ruxolitinib (equivalent to 19.8 mg of ruxolitinib phosphate) in a cream containing…. On 27-AUG-2021 This was agreed to by the applicant (example revised labels provided above)
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	Location present on carton; Application states that lot number and expiration date will be applied on the tube crimp.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	N/A	

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

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

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	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	3
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: ADEQUATE

The applicant agreed to include a salt equivalency statement on the carton and container on 27-AUG-2021. The revised c/c is shown above.

Overall Assessment and Recommendation:

The Label and Labeling is Adequate from the OPQ/ONDP perspective.

QUALITY ASSESSMENT

Primary Labeling Assessor Name and Date:

Caroline Strasinger, PhD

OPQ/ONDP/DNDP2/B4

07-SEP-2021

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BIOPHARMACEUTICS

Product Background:

NDA: NDA 215309-ORIG-1

Drug Product Name / Strength: Ruxolitinib cream/1.5%

Indication: For the topical treatment of atopic dermatitis in patients 12 years of age and older.

Route of Administration: Topical

Applicant Name: Incyte Corporation

Review Recommendation: The submission is **ADEQUATE** from Biopharmaceutics perspective with key findings summarized below:

In Vitro Release Test (IVRT) and Acceptance Criteria

The Applicant has developed and validated an IVRT method using a vertical diffusion cell apparatus. The proposed IVRT method is acceptable. The Applicant proposed to use the method to assess the comparability of drug product following any change and not for a permanent routine quality control test. However, as recommended by the Agency, the Applicant has agreed to provide IVRT data at release (not stability) for at least the first five (5) commercial batches to show a consistent Quality Control of their product. The following IVRT method and acceptance criteria has been approved for (b) (4) 1.5% strength (b) (4) the Applicant is seeking regulatory approval for only ruxolitinib 1.5% cream strength in this submission.

Apparatus	Stir rate RPM	Receptor medium/Temperature	Membrane type	Acceptance criteria
Vertical diffusion cell	600	30:70 ethanol:water v/v / 32°C	Nylon	(b) (4) 1.5% strength: (b) (4) $\mu g/cm^2/min^{1/2}$

The Applicant has proposed to (b) (4) The Applicant's proposal is acceptable.

Formulation development and bridging

The formulation used in the pivotal clinical studies is the same as the proposed commercial formulation. Therefore, no in vitro or in vivo formulation bridging study is needed.

Recommendation

From Biopharmaceutics perspective, NDA-215309 for Ruxolitinib 1.5% cream is adequate.

List of Submissions being reviewed:

Application 215309 - Sequence 0001

Application 215309 - Sequence 0003 and 0004

Application 215309 - Sequence 0005

Highlight Key Outstanding Issues from Last Cycle: The Applicant was requested to tighten the in vitro release acceptance criteria.

Concise Description Outstanding Issues Remaining: None.

BCS Designation

Reviewer's Assessment: Not relevant for cream formulation.

1. Composition of proposed drug product

The composition of ruxolitinib cream, along with the functions and quality standards of the components, are shown for 60 g and 5 g tubes in Table 1 and Table 2, respectively. (b) (4)

Table 1: Composition of Ruxolitinib Cream, 60 g Tubes

Component	Function	Quality Standard	(b) (4)	1.5% Cream	
				wt%	g per 60 g tube
Ruxolitinib Phosphate[a]	Active	Incyte specification			(b) (4)
Propylene Glycol	(b) (4)	USP/NF/Ph. Eur.			
Methylparaben		USP/NF/Ph. Eur.			
Propylparaben		USP/NF/Ph. Eur.			
Xanthan Gum		USP/NF/Ph. Eur.			
Light Mineral Oil		USP/NF/Ph. Eur.			
Glyceryl Stearate SE		Non-compendial			
Polysorbate 20		USP/NF/Ph. Eur.			
White Petrolatum		USP/NF/Ph. Eur.			
Cetyl Alcohol		USP/NF/Ph. Eur.			
Stearyl Alcohol		USP/NF/Ph. Eur.			
Dimethicone 350		USP/NF/Ph. Eur.			
Triglycerides, Medium Chain		USP/NF/Ph. Eur.			
Purified Water		USP/Ph. Eur.			
Edetate Disodium		USP/NF/Ph. Eur.			
Polyethylene Glycol 200		USP/NF			
Phenoxyethanol		USP/NF/Ph. Eur.			
Total				100%	60 g

(b) (4)

(b) (4)

Table 2: Composition of Ruxolitinib Cream, 5 g Tubes

Component	Function	Quality Standard	(b) (4)	1.5% Cream	
				wt%	g per 5 g tube
Ruxolitinib Phosphate[a]	Active	Incyte specification			(b) (4)
Propylene Glycol	(b) (4)	USP/NF/Ph. Eur.			
Methylparaben		USP/NF/Ph. Eur.			
Propylparaben		NF/Ph. Eur.			
Xanthan Gum		USP/NF/Ph. Eur.			
Light Mineral Oil		USP/NF/Ph. Eur.			
Glyceryl Stearate SE		Non-compendial			
Polysorbate 20		USP/NF/Ph. Eur.			
White Petrolatum		USP/NF/Ph. Eur.			
Cetyl Alcohol		USP/NF/Ph. Eur.			
Stearyl Alcohol		USP/NF/Ph. Eur.			
Dimethicone 350		USP/NF/Ph. Eur.			
Triglycerides, Medium Chain		USP/NF/Ph. Eur.			
Purified Water		USP/Ph. Eur.			
Edetate Disodium		USP/NF/Ph. Eur.			
Polyethylene Glycol 200		USP/NF			
Phenoxyethanol		USP/NF/Ph. Eur.			
Total				100%	5 g

(b) (4)

(b) (4)

2. IVRT method and acceptance criterion

IVRT method

The Applicant has developed an IVRT method for ruxolitinib cream 1.5% drug product using vertical diffusion cell in accordance with USP<1724>. Per the Applicant, IVRT will be used to assess the comparability of drug product following any change that could have a significant impact of drug product quality and performance, for example, changes in manufacturing site or significant process changes as defined in "Guidance for Industry, Nonsterile Semisolid Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation". The method will not be used for routine quality control test.

Per the Applicant, the IVRT method was (b) (4) . A summary of the changes in in vitro release method conditions are provided below.

Table 3: Description of Changes Made to IVRT Method conditions

Parameter	Original Method	Final Method
Membrane Type	Nylon, 25 mm diameter, 0.45 µm	
Receptor Medium	(b) (4)	30:70 ethanol : water v/v
Recirculating Batch Temperature (°C)		32
Stir Rate (RPM)		600
Waste Volume (mL)	1.5	
Sample Volume (mL)	1.0	
Sample Intervals (minutes)	(b) (4)	40, 60, 80, 100 and 120

Parameter	Final Method	
Column	Waters BEH C18, 1.7 µm, 2.1 × 50 mm	
Flow Rate (mL/min)	0.45	
Injection Volume (µL)	1	
Column Temperature (°C)	35	
Wavelength (nm)	326	
Run Time (min)	3	
Mobile Phase A (MPA)	Water with 0.1% phosphoric acid	
Mobile Phase B (MPB)	Methanol with 0.1% phosphoric acid	
Gradient	Time (Min)	%MPA
	0.0	80
	0.3	70
	1.6	55
	2.0	10
	2.25	80
	10.0	30
	--	--

The method is fully validated. The details of the analytical procedure and the method validation are provided in the links below:
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The Applicant was requested to add IVRT specification at release (and if possible, stability) for at least the first 5 batches (b) (4) (IR1.3 in Appendix 1). The Applicant agreed to implement IVRT as part of drug product specification to be tested at release only (not stability), minimally on the first five commercially distributed drug product batches (b) (4). The Applicant's response is acceptable.

The Applicant proposed the following acceptance criteria based on the IVRT data generated at release and stability (up to 12 months at the long-term stability condition of 25°C/60% RH) for the primary registration batches, and statistical analysis (+/- 3SD range) as shown in tables 8 and 9 below:

(b) (4)

1.5% strength: (b) (4) $\mu g/cm^2/min^{1/2}$

(b) (4)

Table 9: IVRT Statistical Analysis, 1.5% Registration Stability Batches

	Release Rate, $\mu g/cm^2/min^{1/2}$				
Batch	**Average**	**Min**	**Max**	**Ave – 3SD**	**Ave + 3SD**
PHN-1C	(b) (4)				
PHP-1C					
PHR-1C					
PHN-C					
PHP-C					
PHR-C					
OVERALL	**83.6**	(b) (4)		**65.8**	**101.5**

The Agency recommended to tighten the IVRT acceptance criteria as follows because statistically (b) (4)% of the data fall within mean +/- 3SD range and the ranges are still slightly wider than mean +/- 3SD range (see IR2.1 in Appendix 1):

(b) (4)

1.5% strength: (b) (4) $\mu g/cm^2/ min^{1/2}$

The Applicant accepted the Agency's recommendation and has updated the drug product specification.

Reviewer's Assessment:

- The Applicant has developed and validated an IVRT method using a vertical diffusion cell apparatus. The Applicant has provided method development report. The IVRT method is acceptable.
- The in vitro release acceptance criteria as recommendation by the Agency has been accepted by the Applicant.

3. Formulation bridging

The formulation development history of ruxolitinib cream is provided in the link below:
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Ruxolitinib cream (oil-in-water) has been formulated at 5 strengths (0.15%, 0.5%, 0.75%, 1.0%, and 1.5% w/w free base equivalent) during the course of development. Ruxolitinib 0.75% and 1.5% cream strengths were evaluated in the pivotal Phase 3 studies for the treatment of atopic dermatitis (INCB 18424-303 and INCB 18424-304). The Applicant is seeking approval of ruxolitinib 1.5% cream strength in this submission. The formulation used in the pivotal clinical studies is the same as the proposed commercial formulation. No in vitro or in vivo formulation bridging study is needed.

Appendix 1

List of Deficiencies communicated to the Applicant during review cycle

Information Request 1 (IR1)

The following deficiencies were conveyed to the Applicant in the 74-day letter.

(b) (4)

(b) (4)

(b) (4)

3. As you have successfully developed an IVRT method, we request that you add IVRT specification at release (and if possible, stability) for at least the first 5 batches (b) (4) .

Reviewer's comments:
The Applicant responded to the above IRs and the response is provided in the link below. It has been discussed in the relevant sections above.
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Information Request 2 (IR2)

1. You have proposed an IVRT acceptance criteria (b) (4) and (b) (4) $\mu g/cm^2/hr^{1/2}$ for 1.5% strength of your drug product. Statistically (b) (4) of the data fall within mean +/- 3SD. Considering that, based on your provided results, we recommend the following acceptance criteria (b) (4) still slightly wider than mean +/- 3SD range:

(b) (4)

1.5% strength: (b) (4) $\mu g/cm^2/hr^{1/2}$

Implement the recommended acceptance criteria for your drug product and update the specifications of your drug product with the revised acceptance criteria.

Reviewer's comments:
The Applicant responded to the above IRs and the response is provided in the link below. It has been discussed in the relevant sections above.
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Primary Biopharmaceutics Reviewer Name: Kalpana Paudel, Ph.D.

***Secondary Reviewer Name*:** Tapash Ghosh, Ph.D.

Kalpana Paudel

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Tapash Ghosh

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	215309
Assessment Cycle Number	R01
Drug Product Name/ Strength	(b) (4) (ruxolitinib cream) (b) (4) 1.5%
Route of Administration	Topical (b) (4)
Applicant Name	Incyte Corporation
Therapeutic Classification/ OND Division	
Manufacturing Site	(b) (4)
Method of Sterilization	N/A – Drug product is non-sterile

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
NDA 211882 0001(2)	**12/21/2020**
0003 (4)	**02/12/2021**
0004 (5)	**02/22/2021**

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

Remarks: The submission is in the eCTD format. Some tables and figures are copied from the submission. The amendment dated 02/12/2021 is in response to an IR sent 02/03/2021. The amendment dated 02/22/2021 updates module 3 of the eCTD document to reflect the changes of the previous submission.

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

Supporting Documents: N/A

S DRUG SUBSTANCE – N/A Drug substance is non-sterile

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- Description of drug product – non-sterile, smooth white to off-white cream with no visible signs of phase separation. The drug product is a multi-dose, preserved cream, pH (b) (4) (1.5% configuration) (b) (4) for topical, cutaneous use. Packaged as 60g (commercial packaging) or 5g (physician sample) in an aluminum tube.

- Drug Product Composition

For 60 g tube:

Component	Function	Quality Standard	(b) (4)	1.5% Cream	
				wt%	g per 60 g tube
Ruxolitinib Phosphate*	Active	Incyte specification		(b) (4)	(b) (4)
Propylene Glycol	(b) (4)	USP/NF/Ph. Eur.			
Methylparaben		USP/NF/Ph. Eur.			
Propylparaben		USP/NF/Ph. Eur.			
Xanthan Gum		USP/NF/Ph. Eur.			
Light Mineral Oil		USP/NF/Ph. Eur.			
Glyceryl Stearate SE		Non-compendial			
Polysorbate 20		USP/NF/Ph. Eur.			
White Petrolatum		USP/NF/Ph. Eur.			
Ceryl Alcohol		USP/NF/Ph. Eur.			
Stearyl Alcohol		USP/NF/Ph. Eur.			
Dimethicone 350		USP/NF/Ph. Eur.			
Triglycerides, Medium Chain		USP/NF/Ph. Eur.			
Purified Water		USP/Ph. Eur.			
Edetate Disodium		USP/NF/Ph. Eur.			
Polyethylene Glycol 200		USP/NF			
Phenoxyethanol		USP/NF/Ph. Eur.			
Total				100%	60 g

* Conversion factor for phosphate salt to free base is (b) (4) (b) (4)

For 5 g tube:

Component	Function	Quality Standard	(b) (4)	1.5% Cream	
				wt%	g per 5 g tube
Ruxolitinib Phosphate*	Active	Incyte specification			
Propylene Glycol	(b) (4)	USP/NF/Ph. Eur.			
Methylparaben		USP/NF/Ph. Eur.			
Propylparaben		NF/Ph. Eur.			
Xanthan Gum		USP/NF/Ph. Eur.			
Light Mineral Oil		USP/NF/Ph. Eur.			
Glyceryl Stearate SE		Non-compendial			
Polysorbate 20		USP/NF/Ph. Eur.			
White Petrolatum		USP/NF/Ph. Eur.			
Cetyl Alcohol		USP/NF/Ph. Eur.			
Stearyl Alcohol		USP/NF/Ph. Eur.			
Dimethicone 350		USP/NF/Ph. Eur.			
Triglycerides, Medium Chain		USP/NF/Ph. Eur.			
Purified Water		USP/Ph. Eur.			
Edetate Disodium		USP/NF/Ph. Eur.			
Polyethylene Glycol 200		USP/NF			
Phenoxyethanol		USP/NF/Ph. Eur.			
Total				100%	5 g

* Conversion factor for phosphate salt to free base is (b) (4)
(b) (4)

- Description of Container Closure System:

Component	Description	Supplier
Tube	5 g or 60 g fill Aluminum tube with (b) (4) (b) (4) and (b) (4) crimp (b) (4)	(b) (4)
Cap	(b) (4) (5 g fill) white (b) (4) puncture cap or (b) (4) (60 g fill) white (b) (4) puncture cap	

Assessment: *Adequate*

The description of the drug product is adequate.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

(b) (4)

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Dustin Thomas

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Jesse Wells

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