CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213871Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: **July 19, 2021**
From: **Hamid Shafiei, Ph.D.**
Application Technical Lead, Branch IV
Division of New Drug Products 2
Office of New Drug Products

To: **To Executive Summary, IQA for Assessment # 1 of NDA 213871**

Subject: **Addition of 200mg Tablets to the approval recommendation**

In the original IQA review #1 dated March 9, 2021, in the Executive Summary section, it was stated that although the 200mg tablet dosage strength was reviewed and found to be adequate from the CMC perspective, based on the lack of adequate clinical information the 200mg tablets could not be approved for marketing and was to be removed from the prescribing information (PI). The applicant submitted a major amendment with additional clinical information in support of the approval of 200mg tablets on April 16, 2021. The CMC PI labeling and container/carton labels comments for all tablet strengths, including 200mg had been appropriately addressed prior to March 9, 2021.

Therefore, from the OPQ perspective, the 200mg tablets can be included in PI labeling and approved or marketing.

Application Technical Lead:
Hamid Shafiei, Ph.D.
Branch IV/DNDP 2/ONDP/OPQ

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/

HAMID R SHAFIEI
07/19/2021 11:23:00 AM

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 213871
Assessment # 1

Drug Product Name	CIBINQO® (abrocitinib)
Dosage Form	Tablet
Strength	50mg, 100mg, and 200mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Pfizer, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Pre-Submission Meeting	06/29/2020	Clinical
Original NDA Submission	08/25/2020	All
Quality Information Amendment	09/16/2020	ONDP and OPMA
Request for Proprietary Name	09/21/2020	All
Clinical Information Amendment	10/21/2020	Clinical
Clinical Study Report	10/30/2020	Clinical
Response to Quality Information Request	11/12/2020	ONDP
Clinical Study Report	11/23/2020	Clinical
Quality and Clinical Information Amendment	11/23/2020	OPMA and Clinical
Clinical Study Report	12/04/2020	Clinical
Clinical Study Report	12/10/2020	Clinical
Response to Quality Information Request	12/11/2020	ONDP
Quality and Clinical Information Amendment	12/21/2020	ONDP, OPMA, and Clinical
Response to Clinical Information Request	12/29/2020	Clinical

Response to Clinical Information Request	01/11/2021	Clinical
Multiple Categories - Clinical	01/14/2021	Clinical
Response to Clinical Information Request	02/03/2021	Clinical
Response to Clinical Information Request	02/09/2021	Clinical
Response to Quality Information Request	02/11/2021	ONDP-EA
Response to Quality and Clinical Information Request	02/22/2021	ONDP and Clinical
Container Labels	03/01/2021	ONDP and DMEPA
DMF LOAs and Late Cycle Meeting Follow-up Communication	03/08/2021	All

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Friedrich Burnett, Ph.D.	Sukhamaya Bain, Ph.D.
Drug Product	Michael Theodorakis, Ph.D.	Wendy Wilson-Lee, Ph.D.
Manufacturing	Mesfin Abdi, Ph.D. Yong Wu, Ph.D.	Yubing Tang, Ph.D. Sharmista Chatterjee, Ph.D.
Microbiology	Mesfin Abdi, Ph.D.	Yubing Tang, Ph.D. Sharmista Chatterjee, Ph.D.
Biopharmaceutics	Gia Yin, Ph.D.	Tapash Ghosh, Ph.D.
Regulatory Business Process Manager	Melinda Bauerlien, M.S.	
Application Technical Lead	Hamid Shafiei, Ph.D. Sharmista Chatterjee, Ph.D.	
Laboratory (OTR) Modeling Consultants	Geng Tian, Ph.D. Wei Tang, Ph.D. Scott Krull, Ph.D. Naresh Pavurala, Ph.D.	Thomas O'Connor, Ph.D.
Environmental	Michael Theodorakis, Ph.D.	Wendy Wilson-Lee, Ph.D.

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

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 substances, abrocitinib, and the drug product, CIBINQO (abrocitinib) Tablets, 50mg, 100mg, and 200mg intended for oral administration.
- Labels/labeling issues have been **satisfactorily** addressed.
- The Office of Pharmaceutical Manufacturing Assessment has made an overall "**Acceptable**" recommendation regarding the facilities involved in this NDA.
- The claim for categorical exclusion of the environmental assessment has been granted.

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

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Pfizer, Inc. has submitted this 505(b)(1) application for CIBINQO (abrocitinib) Tablets, 50mg, 100mg, and 200mg intended for oral administration. This drug product is indicated for the treatment of moderate-to-severe atopic dermatitis (b) (4)

The active ingredient, abrocitinib is a synthetic Janus Kinase 1 (JAK1) inhibitor. It is an orally bioavailable small molecule that reversibly and selectively inhibits JAK1 by blocking the ATP binding site. In a cell-free isolated enzyme assay, it has shown much higher biochemical selectivity for JAK1 over the other three isoforms, JAK2, JAK3, and TYK2 as well as broader kinome. This active ingredient has not been previously approved, and it is classified as a New Molecular Entity (NME).

All strengths of CIBINQO is manufactured by (b) (4) (b) (4) and only differ in size. 50mg strength is a pink film-coated oval-shaped tablet debossed on one side with "PFE" and on the other side with "ABR 50". 100mg strength is a pink film-coated round tablet debossed on one side with "PFE" and on the other side with

"ABR 100". 200mg strength is a pink-film coated tablet debossed on one side with "PFE" and on the side with "ABR 200".

All strengths of CIBINQO (abrocitinib) are to be packaged as 30 tablets in a 60-mL white high-density polyethylene (HDPE) bottles with a white (b) (4) closure.

Although, the information provided for the 200mg tablet strength has been reviewed and found adequate from the CMC perspective, 200mg tablets will not approved for marketing from the clinical perspective and is removed from the PI labeling.

Proposed Indication(s) including Intended Patient Population	Treatment of moderate-to-severe atopic dermatitis (b) (4)
Duration of Treatment	As prescribed by the healthcare provider
Maximum Daily Dose	200mg
Alternative Methods of Administration	Oral

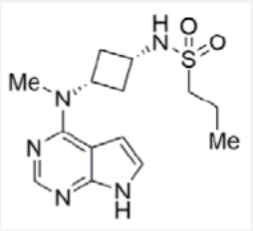
B. Quality Assessment Overview

Drug Substance: Adequate

Abrocitinib is a synthetic orally bioavailable small molecule that reversibly and selectively inhibits JAK1 by blocking the ATP binding site. It has not been previously approved, and therefore, it has been classified as a new molecular entity. Abrocitinib is the active ingredient of the drug product CIBINQO tablets.

Abrocitinib is a white to slightly colored crystalline powder. It is non-hygroscopic with a melting point of ~189ºC, pKa of 5.3, and LogP of 1.66. Polymorph screening of abrocitinib (b) (4) (b) (4) (b) (4). Abrocitinib is has shown a solubility of 12.7mg/mL in aqueous buffer at pH of 2.9 with drastic decease in solubility with increased pH. Solubility screening shows that abrocitinib is insoluble, sparingly, slightly soluble in most common organic solvents but very soluble in dimethyl sulfoxide and dimethyl formamide.

Abrocitinib has the chemical name, N-((1s,3s)-3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide, the molecular formula of $C_{14}H_{21}N_5O_2S$ with a molecular weight of 323.42g/mole, and the chemical structure presented below:



Abrocitinib is produced by (b) (4) (b) (4) (b) (4) Abrocitinib for this application is manufactured by Pfizer Ireland Pharmaceuticals, Ringaskiddy, Cork, Ireland in accordance to current good manufacturing practice. It is packaged (b) (4). (b) (4) (b) (4). It is tested and released according to a specification consistent with ICH Q3A, Q3C, and Q3D guidelines that assures the identity, strength, purity, and quality of the drug substance at release and throughout its assigned retest o (b) (4) months. The applicant has provided sufficient stability data in support of the proposed retest period.

The drug substance module of this application has been reviewed by the Drug Substance Reviewer Dr. Friedrich Burnett. Dr. Burnett has found the drug substance information provided in the application adequate to support the approval of this application from the drug substance perspective. Dr. Burnett's review is provided in the Drug Substance Chapter of the Integrated Quality assessment (IQA).

Drug Product: Adequate

The drug product, CIBINQO (abrocitinib) Tablets, 50mg, 100mg, and 200mg has been developed for the treatment of moderate-to-severe atopic dermatiti (b) (4). CIBINQO tablets are intended for once a day oral administration. All strengths of CIBINQO are packaged as 30 tablets in 60-mL white high-density polyethylene bottles with white (b) (4) closure.

CIBINQO tablets are film-coated tablets each containing 50mg, 100mg, or 200mg of abrocitinib depending of the strength as the active ingredient

and microcrystalline cellulose (NF), dibasic calcium phosphate anhydrous (USP), sodium starch glycolate (NF), magnesium stearate (NF) (b) (4) (b) (4) (b) (4) as inactive ingredients . Components used (b) (4) (b) (4) are all compendial materials. All strengths of the tablets are manufactured (b) (4) with identical quantitative composition and only differ in size.

CIBINQO tablets are manufactured in accordance to the current good manufacture practices by a continuous manufacturing process and the use of a new emerging technology by Pfizer Manufacturing Deutschland GmbH, Freiburg, Germany. The details of the continuous manufacturing process and the use of the specific emerging technology used in the manufacture of CIBINQO tablets are provided in Manufacturing Chapter of the IQA. It is tested and released against a specification consistent with ICH Q3B 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 applicant has submitted sufficient stability data in support of the proposed expiration dating period.

Although the information provided for the 200mg tablet strength has been found adequate from the CMC perspective, this strength of the tablets will not approved for marketing from the clinical perspective and is removed from the PI labeling.

The drug product module for this drug product has been reviewed by the Drug Product Reviewer, Dr. Michael Theodorakis. Dr. Theodorakis has found the drug product information provided in this application adequate to support the approval of this application from the drug product perspective. Dr. Theodorakis's review is provided in the Drug Product Chapter of the IQA.

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

Labeling: Adequate

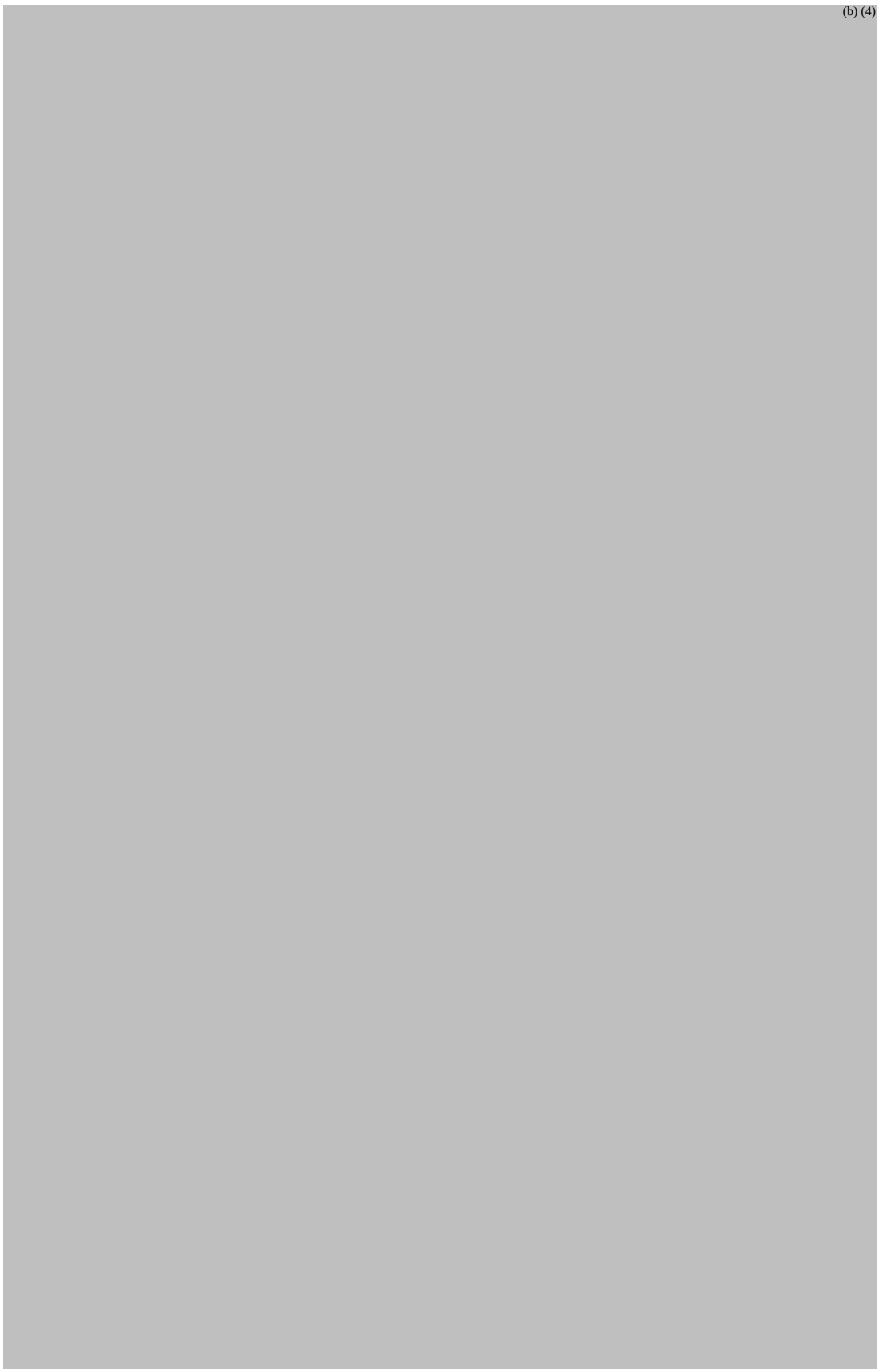
The CMC section of prescribing information (PI) labeling as well as the immediate container and carton labels have been reviewed by the Drug Product Reviewer, Dr. Michael Theodorakis. Dr. Theodorakis has identified multiple CMC labeling deficiencies in the PI as well as the immediate container and carton labels at the time of his labeling/labels review # 1. These labeling/labels deficiencies were communicate to the

applicant. The applicant agreed with the CMC labeling/labels recommendations and provided the revised labeling/labels on 03/01/2021 that have adequately addressed and resolved the deficiencies delineated in Review # 1. Therefore, Dr. Theodorakis has recommended the approval of this application from Labeling and labels perspective. Dr. Theodorakis's labeling/labels review # 1 and the addendum to his labeling review # 1 is provided in the Labeling Chapter of the IQA.

Manufacturing: Adequate

Abrocitinib is a film-coated tablet with strengths of 50, 100 and 200 mg. The three tablet strengths are prepared (b) (4)

(b) (4)


(b) (4)

(b) (4)

The drug product batch release is based on finish product testing of CQAs, i.e. appearance, identity, assay, degradation products, dissolution and uniformity of dosage units.

The drug substance manufacturer is recommended for approval based on compliance history, acceptable profile codes and experience in the proposed responsibilities.

For the drug product manufacturing site a 704(a)(4) based assessment was conducted in lieu of an onsite PAI. Based on the assessment of the records, the facility is recommended for approval for the stated function in this application.

Manufacturing assessment was jointly conducted by Drs. Mesfin Abdi and Yong Wu in OPMA. Dr. Abdi reviewed the continuous manufacturing process and associated control strategy. Dr. Wu conducted review of the (b) (4) method in context of its role within the control strategy. A consult was sought from the modeling group in OTR (Office of Testing and Research) to evaluate the (b) (4) model. Drs. Thomas O'Connor, Geng Tian, Wei Yang, Scott Krull, and Naresh Pavurala provided consult from OTR. They found that the (b) (4) model is valid under the proposed operating conditions. The detailed manufacturing assessment for this application is provided in the Manufacturing Chapter of the IQA.

Biopharmaceutics: Adequate

This drug product is an immediate release tablet containing an active ingredient classified as BCS II. The biopharmaceutics review of this application was mainly focused on determination of the adequacy of formulation bridging between the pivotal clinical and the commercial batches, the suitability of the proposed dissolution method, and the evaluation of the biowaiver request for the 50mg and 100mg tablet strengths.

Since the 100mg tablet formulation used in the Phase 3 clinical trial is identical to the formulation used for the commercial 100mg tablets and that all commercial tablet strengths have identical formulation (b) (4) (b) (4) and 50mg and 100mg tablets strengths

have shown similar dissolution profile as the 200mg tablet, the biowaiver request has been found valid and is granted.

The proposed dissolution method and corresponding acceptance limits for all tablet strengths were also evaluated and found to be adequate.

The biopharmaceutics section of this application has been reviewed by the Biopharmaceutics Reviewer Dr. Gia Yin. Dr. Yin has found the overall information provided in this section the application adequate to support the approval of this application from the biopharmaceutics perspective. Dr. Yin's review is provided in the Biopharmaceutics Chapter of the IQA.

Microbiology : Adequate

Routine microbial limits testing for abrocitinib film-coated tablets has been omitted from the proposed DP specification based on ICH Q6A risk assessment and data collected during development and registration stability. The abrocitinib film-coated tablets in long term stability conditions have demonstrated water activity levels below (b) (4) minimizing contaminating organisms to proliferation and survival. Overall, microbiological control was found to be adequate by Dr. Mesfin Abdi. Dr. Abdi's review of the microbiological control is provided in the Manufacturing 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**
Tablet assay	Purity/assay of DS Change in properties of in-coming materials beyond what is investigated that can impact flow of materials through the system	High (b) (4)	(b) (4)	Low	(b) (4)

	(b) (4)		(b) (4)		(b) (4)
Impurities	Impurities in DS	Low	DS is fairly stable	Low	
Tablet CU (uniformity of dosage units)	(b) (4)	High	Refer to Assay comments	Low	Refer to Assay comments
Dissolution	DS is BCS Class II (b) (4)	Medium	(b) (4)	Low	(b) (4)

	(b) (4)		(b) (4)	
Appearance		Low	Low	To confirm that tablet appearance (this is a debossed tablet) remains unchanged (b) (4) (b) (4) (b) (4) via future submission
Identification		Low	Low	none
Microbial limits		Low	Low	none

	(b) (4)		Tablets in long term stability showed water activity levels below (b) (4)		

D. List of Deficiencies for Complete Response

None

Application Technical Co-Lead:
Hamid Shafiei, Ph.D.
Branch IV/DNDP 2/ONDP/OPQ

Application Technical Co-Lead:
Sharmista Chatterjee, Ph.D.
DPMII/OPMA/OPQ

Hamid Shafiei

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Sharmista Chatterjee

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Date: 3/03/2021 02:59:36PM
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U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	----------	----------	Sufficient information is provided in the NDA
	III			----------	----------	Sufficient information is provided in the NDA
	III			----------	----------	Sufficient information is provided in the NDA
	III			----------	----------	Sufficient information is provided in the NDA
	III			----------	----------	Sufficient information is provided in the NDA
	III			----------	----------	Sufficient information is provided in the NDA

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

Document	Application Number	Description
N/A		

2. CONSULTS

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

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

List of Submissions Reviewed and Discipline Reviews Cited:

Document Reviewed (eCTD #)	Date Received	
eCTD-0007 (SDN-7) (ORIG-1)	2020-11-12	Stability data child resistant closur (b) (4)s
eCTD-0005 (SDN-5) (ORIG-1)	2020-10-21	Investigator's brochure
eCTD-0004 (SDN-4) (TRIAGE-1)	2020-09-21	Proprietary name
eCTD-0002 (SDN-2) (ORIG-1)	2020-08-25	Labeling

1.0 PRESCRIBING INFORMATION

The quality related aspects of the prescribing information are provided in the submission listed above. DMEPA approved the proprietary name CIBINGO.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

1. TITLE:
CIBINGO (abrocitinib) tablets, for oral use.
Initial U.S. Approval: 20YY

2. DOSAGE FORMS AND STRENGTHS
CIBINGO tablets: 50 mg and 100 mg.

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights: Drug product name §201.57(a)(2)		
Proprietary name	CIBINGO	**Adequate**, it has been approved by DMEPA
Established name(s)	(abrocitinib) tablets for oral use	**Adequate**
Route(s) of administration	Oral	**Adequate**
Dosage Forms and Strengths Heading in Highlights (21 CFR §201.57(a)(8))		

Summary of the dosage form(s) and strength(s) in metric system.	Tablets: 100 mg and 50 mg.	**Adequate**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A The tablets are not 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	N/A

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

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

1.2.2. Section 3 (DOSAGE FORMS AND STRENGTHS)

Tablet 50 mg, 30 tablets, film coated, packaged in 60 cc white HDPE container with child resistant closure.
Tablet 100 mg, 30 tablets, film coated, packaged in 60 cc white HDPE container with child resistant closure.

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Tablet	**Adequate**
Strength(s) in metric system	Tablet 50 mg Tablet 100 mg API: abrocitinib	**Adequate**
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	It is not a salt. It is a free base	**Adequate**
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Tablets 50 mg are oval, pink film-coated, debossed with **PFE** on one side and **ABR 50** on the other side. Tablets 100 mg are oval, pink film-coated, debossed with **PFE** on one side and **ABR 100** on the other side.	**Adequate**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A Not scored	N/A
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include	N/A	N/A

pharmacy bulk package and imaging bulk package.		

1.2.1 Section 11 DESCRIPTION

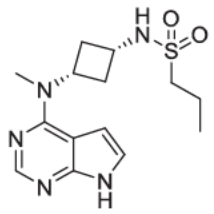
Section 11 Description in the PI should be revised to read as follows:

CIBINGO™ (abrocitinib) tablets are film coated tablets formulated with the free base of abrocitinib.

Abrocitinib is a white to pale colored powder with the following chemical name:
N ((1s,3s) 3 (methyl(7H pyrrolo[2,3-d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide

The solubility of abrocitinib in water is 0.04 mg/mL at 25°C.

Abrocitinib has a molecular weight of 323.42 Daltons and a molecular formula of $C_{14}H_{21}N_5O_2S$. The chemical structure of abrocitinib is:



CIBINGO is supplied for oral administration as a 50 mg or 100 mg immediate-release film-coated tablet. Each tablet of CIBINGO contains the following inactive ingredients: dibasic calcium phosphate anhydrous, hypromellose, iron oxide red, lactose monohydrate, Macrogol, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, titanium dioxide, and triacetin.

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	CIBINGO (abrocitinib) tablets	**Adequate**
Dosage form(s) and route(s) of administration	Tablets, oral	**Adequate**
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	N/A

List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Both the 50 mg and 100 mg tablets have the same inactive ingredients: dibasic calcium phosphate anhydrous, hypromellose, iron oxide red, lactose monohydrate, Macrogol, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, titanium dioxide, and triacetin.	**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	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/therapeutic class	Abrocitinib is a Janus kinase 1 inhibitor, known as JAK inhibitors, which are used to treat inflammatory diseases such as rheumatoid arthritis and various skin diseases such as atopic dermatitis	**Adequate**

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	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	N/A

Assessment of Section 11 (DESCRIPTION): Adequate

1.2.2 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Dosage Form	Strength	Description	Bottle Size (number of tablets)	NDC Number
Tablets	50 mg	Pink, oval table (b) (4) mm long an (b) (4) mm wide, debossed with "PFE on one side and "ABR 50" on the other.	30 count bottle	0069-0235-30
Tablets	100 mg	Pink, round table (b) (4) mm in diameter, debossed with "PFE" on one side and "ABR 100" on the other.	30 count bottle	0069-0335-30

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) [see USP Controlled Room Temperature]. Keep in original package.

(b) (4)

Assessment of Section 16 HOW SUPPLIED/STORAGE AND HANDLING: Not Adequate

The Applicant has submitted stability data for abrocitinib tablet [redacted] The Applicant should revise Section 16 of the PI [redacted]

NDC numbers should be provided including information about the primary containe [redacted]

Additionally, the Applicant should provide information about the design of the carton container and carton labels.

Section in 3.2.P.7 should be revised accordingly.

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Pink oval tablet debossed with "**PFE**" on one side and "**ABR 50**" on the other. Pink, round tablet debossed with **"PFE"** on one side and **"ABR 100**" on the other	**Adequate**
Strength(s) in metric system	Tablets: 50 mg and 100 mg.	**Adequate**
Available units (e.g., bottles of 100 tablets)	In 60 cc HDPE bottles of 30 tablets.	**Adequate**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Pink, oval table (b) (4) mm long an (b) (4) mm wide, debossed with **"PFE"** on one side and **"ABR 50"** on the other. **NDC 0069-0235-30** Pink, round table (b) (4) mm in diameter, debossed with **"PFE"** on one side and **"ABR 100"** on the other. **NDC 0069-0335-30**	**Adequate**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	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	N/A

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

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	N/A	N/A
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	The storage statement "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) (b) (4) [redacted]"	**Adequate**
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	N/A

Include information about child-resistant packaging.	Initially the Applicant stated in Section 2.3.P.7 container that the commercial packaging configuration(s) does meet Consumer Product Safety Commissions (CPSC) standards under 16 CFR §1700. Section §1700.15 is about Child resistant packaging. On 11/12/2020 the Applicant included information about the child resistant packaging (b) (4) (b) (4)	**Not Adequate** The Applicant should revise the section 2.3.P.7. Container Closure System by providing adequate information about the (b) (4) container and in general provide the DMFs that cover the composition, specifications, and manufacturing of the packaging materials"

Assessment of Section 16 (How Supplied/Storage and Handling): {Not Adequate}

See page 7 and 8 above.

Also, the Applicant should revise the Section 2.3.P.7. Container Closure System by providing adequate information about the (b) (4) container and in general provide the DMFs that cover the composition, specifications, and manufacturing of the packaging materials"

Relevant sections of PI, PII and Medication Guide should be revised accordingly.

1.2.3 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 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.

Assessment: Adequate
CIBINGO (abrocitinib) tablets do not contain any of the ingredients listed in Section 1.2.3. above.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Distributed by Pfizer Labs Division of Pfizer Inc. NY, NY 10017	**Not adequate** The Applicant should provide the street address per 21 CFR §201.1(i)

Assessment: Not Adequate

1. Per 21 CFR §201.1(i) the Applicant should add the street address and name of city of the Distributor Pfizer Labs.

2.0 PATIENT LABELING:

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions (PII) for Use): Not Adequate

1. On page 4, of Medication Guide, Section "How Should I store CIBINGO" add the statement "The package is child resistant".

2. Per 21 CFR §201.1(i) provide the street address of the Distributor Pfizer Labs.

3.0 CARTON and CONTAINER LABELING

3.1. Primary Container (60 cc HDPE bottle) Label

The primary container is a 60 cc HDPE bottle.
The packaging configurations are as follows:

Samples:
14 count tablets in 60 cc HDPE bottles for each the 50 mg and 100 mg CIBINGO tablets.

Prescription:
30 count tablets in 60 cc HDPE bottles for each the 50 mg and 100 mg CIBINGO tablets.

Note:
The clinical division decided not to allow marketing of the 200 mg CIBINGO tablets

(b) (4)

4 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

3.2 Secondary (Carton) Container Label

No carton labels were submitted

Assessment { Not adequate}

1. The bottle labels for samples, 14 count tablets containers should have a linear barcode for the NDC numbers as follows:
   NDC 63539-236-14 for 14 count 50 mg samples
   NDC 63539-336-14 for 14 count 100 mg samples

2. Provide labels with the trade name CIBINGO.

3. Clarify whether or not secondary (carton) containers will be used to package the primary containers, 60 cc HDPE bottles, for the prescription and samples of CIBINGO.

4. Provide information about the [redacted] (b) (4) labels, NDC numbers, etc.

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence [21 CFR § 210.10(g)(2).	CIBINGO (abrocitinib) tablets	**Adequate**
Dosage strength	50 mg tablets 100 mg tablets.	**Adequate**
Route of administration	Oral	**Adequate**
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	N/A
Net contents (e.g. tablet count)	14 tablets in samples containers 30 tablets in prescription containers	**Adequate**
"Rx only" displayed on the principal display	It is displayed on the principal display panel	**Adequate**
NDC number	Prescription (60 cc HDPE bottles): NDC 63539-0235-30 for 50 mg NDC 63539-0335-30 for 100 mg Samples (60 cc HDPE bottles): NDC 63539-236-14 for 50 mg NDC 63539-336-14 for 100 mg	**Not Adequate** NDC numbers were not provided (b) (4) (b) (4)
Lot number and expiration date	Lot number and expiration date appear on the labels of the 60 cc HDPE bottles.	**Adequate**
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	N/A
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A

Bar code: 21 CFR 201.25(c)(2)	A linear barcode that contains the National Drug Code (NDC) has been added to the immediate container, 60 cc HDPE bottle for the prescription drug product.	**Not Adequate**: The container labels for samples must include a linear barcode for NDC number

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/ distributor	Distributed by Pfizer Labs Division of Pfizer Inc. NY, NY 10017	**Not Adequate** Per 21 CFR §201.1(i) it should include the street address and name of the city, state and zip code
Medication Guide (if applicable)	The package insert has a medication guide	**Adequate**
No text on Ferrule and Cap overseal	N/A	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	N/A
And others, if space is available	N/A	N/A

ITEMS FOR ADDITIONAL ASSESSMENT ITEMS FOR ADDITIONAL ASSESSMENT

PRESCRIPTION INFORMATION

1. Include in Section 16 of the package insert the statement: "The container closure system of HDPE bottles is child resistant."

2. Per 21 CFR §201.1(i) provide the street address and name of the city of the Distributor Pfizer Labs.

3. The bottle labels for the samples, 14 count tablets containers should include a linear barcode for the NDC numbers for the 50 mg and 100 mg tablet samples.

4. Provide container labels with the proprietary name CIBINGO.

5. Clarify whether or not secondary (carton) containers will be used to package the primary containers, 60 cc HDPE bottles, for the prescription and samples of CIBINGO tablets and provide copies of the design of the secondary (carton) container and labels.

6. Revise Section 16 of the P [redacted] (b) (4)

7. Revise the section in 3.2.P.7 to include information [redacted] (b) (4)

8. On page 4, of the Medication Guide, Section "How Should I store CIBINGO" add the statement "The HDPE bottle package is child resistant".

9. Provide information about th [redacted] (b) (4) labels, NDC numbers, etc.

Overall Assessment and Recommendation:

Primary Labeling Assessor's Name and Date:

Michael C. Theodorakis, Ph.D. Date: December 10, 2020
Chemistry Reviewer
Branch IV/DNDP II/ONDP

As of this review, NDA 213871 is deemed not ready for approval per 21 CFR §314.125(b)(6) from the CMC labeling perspective. The CMC labeling and other deficiencies listed above should be transmitted to the Applicant rectified.

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

Wendy I Wilson-Lee, Ph.D. Date:
Division Director
CDER/OPQ/ONDP/DNDPII

Memorandum DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: **2/24/2021**

From: **Michael C.** Theodorakis, Ph.D.
Drug Product Reviewer
Branch IV Division of New Drug Products II
Office of New Drug Products

Through: **Wendy I Wendy-Lee, Ph.D.**
Director
Division of New Drug Products II
Office of New Drug Products

To: Labeling Review #1 of NDA 213871 CIBINQO (abrocitinib) Tablets, 50 mg and 100 mg.

Subject: Finalized label/labeling of CMC Sections; Addendum to Labeling Review #1.

At the time when labeling review of this application was completed (12/10/2020), this NDA was not recommended for approval due to unresolved CMC label/labeling issues. On 03/02/2021, the Applicant submitted revised labels and labeling which satisfactorily addressed all CMC label/labeling issues that have been identified (see **Attachment** below).

Recommendation:
The outstanding CMC label/labeling issues have been resolved, and therefore, this application is now recommended for **approval** from the labeling perspective.

Michael C. Theodorakis, Ph.D.
Drug Product Reviewer
Branch IV, Division II, ONDP

Wendy I. Wilson-Lee, Ph.D.
Director
Division II, ONDP

Attachment:
The following comments were included in my labeling review dated 1/4/2021:

Comment 1
Include in Section 16 of the package insert the statement: "The container closure system of HDPE bottles is child resistant."

Reviewer's Response:
I have entered the statement in Section 16 of the Prescription Information (PI) on the SharePoint Drive of the Division of Dermatological and Dental Drug Products (DDDP).

Comment 2
Per 21 CFR §201.1(i) provide the street address and name of the city of the Distributor Pfizer Labs.

Reviewer's Response:
I have entered the request in the Prescription Information (PI) on the SharePoint Drive of the Division of Dermatological and Dental Drug Products (DDDP).

Comment 3
The bottle labels for the physician samples, 14 count tablet containers should include a linear barcode for the NDC numbers for the 50 mg and 100 mg tablet samples.

Applicant's Response
On February 23, 2021, the Applicant confirmed that will include linear barcodes for the HDPE bottle labels for the physician samples. See response in DARRTS ora_ias@fdslv96017.fda.gov .

Comment 4
Provide container labels with the proprietary name CIBINQO.

Applicant's Response
On February 23, 2021, the Applicant confirmed that change the TRADENAME with CIBINQO throughout the labeling. See response in DARRTS ora_ias@fdslv96017.fda.gov .

Comment 5
Clarify whether or not secondary (carton) containers will be used to package the primary containers, 60 cc HDPE bottles, for the prescription and samples of CIBINQO tablets and provide copies of the design of the secondary (carton) container and labels.

Applicant's Response
On February 23, 2021, the Applicant confirmed that will address the secondary (carton) container. . See response in DARRTS ora_ias@fdslv96017.fda.gov .

Comment 6
Revise Section 16 of the P [redacted]

Applicant's Response
The Applicant confirmed that has no intention to commercialize tablets [redacted]. See eCTD-0020 (SDN-20) (ORIG-1) 2021-02-22.

Comment 7
Revise the section in 3.2.P.7 to include information [redacted]

Applicant's Response
No intention to commercialize tablets [redacted]
See eCTD-0020 (SDN-20) (ORIG-1) 2021-02-22.

Comment 8
On page 4, of the Medication Guide, Section "How Should I store CIBINQO" add the statement "The HDPE bottle package is child resistant".

Reviewer's Response
The statement "The HDPE bottle package is child resistant" has been inserted in the Medication Guide, Section "How Should I store CIBINQO" on the SharePoint Drive of the Division of Dermatological and Dental Drug Products (DDDP).

Comment 9
Provide information about th [redacted] labels, NDC numbers, etc.

Applicant's Response
No intention to commercialize tablet [redacted]
See eCTD-0020 (SDN-20) (ORIG-1) 2021-02-22.

Michael Theodorakis

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Date: 2/26/2021 10:53:22AM
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Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 2/26/2021 11:00:27AM
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BIOPHARMACEUTICS

NDA: 213871 (associated IND 123554)
Submission Type: 505(b)(1)
Drug Product Name / Strength: Cibinqo® Abrocitinib Tablet/50 mg, 100 mg, 200 mg
Dosage Form: Immediate Release Tablet
Route of Administration: Oral
Applicant: Pfizer, Inc
Indication: Moderate to severe atopic dermatitis
Submission Date: 6/29/2020 part 1, 8/25/2020 part 2
Primary Reviewer: Jia Yin, Ph.D.
Secondary Reviewer: Tapash Ghosh, Ph.D.

Background: The Applicant seeks approval for Cibinqo® (Abrocitinib) via 505(b)(1) pathway for the treatment of moderate to severe atopic dermatitis (b) (4) (b) (4) Abrocitinib is considered as a new molecular entity (NME) and the NDA is under priority review. Abrocitinib tablet is a film-coated, immediate-release (IR) tablet with three strengths: 50 mg, 100 mg, and 200 mg. The recommended daily dose is 100 mg or 200 mg. The 50 mg strength is developed to facilitate the appropriate dosing in special population and for management of drug-drug interactions. The three commercial strengths are prepared (b) (4) with the only difference in film coating and tablet debossing.

The commercial manufacturing process for the abrocitinib tablet (b) (4)
(b) (4)

(b) (4)
(b) (4)
(b) (4). The Applicant conducted a pivotal bioequivalence (BE) study on the 100 mg Phase 3 tablet and the 200 mg commercial tablet and submitted a biowaiver request for the lower commercial strengths: 50 mg and 100 mg.

REVIEW SUMMARY

The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting **1)** formulation bridging between the pivotal clinical batch and

the commercial batch, **2)** the proposed dissolution method and acceptance criterion, and **3)** the biowaiver request for the 50 mg and 100 mg strengths. The key review findings are summarized as follows:

Formulation Bridging: Adequate

As the (b) (4) formulation of the Phase 3 tablet (100 mg) is identical to that of the commercial 100 mg tablet and the formulation of all three commercial strengths (50 mg, 100 mg, and 200 mg) is proportional, no in vivo formulation bridging study is needed.

Dissolution Method: Acceptable

The Applicant performed a series experiments to select the dissolution medium, apparatus, rotation speed, and vessel. The selection of the dissolution parameters is reasonable. The Applicant evaluated the discriminatory ability of the proposed dissolution method against tablet hardness, API particle size, and a (b) (4) variant (b) (4) (b) (4) The Applicant claimed the method is discriminatory against API particle size and th (b) (4) variant. However, due to the fast dissolution of the drug product (b) (4), the proposed dissolution method is not considered as discriminatory. Nevertheless, as the Applicant has implemented an integrated strategy to control drug product dissolution, (b) (4) (b) (4) the risk of drug product dissolution is mitigated. The proposed dissolution method is acceptable.

Dissolution Acceptance Criterion: Acceptable

The Applicant used a (b) (4) approach and the dissolution data of the clinical and stability batches to support the originally proposed dissolution acceptance criterion of Q = (b) (4)% in (b) (4) minutes. The (b) (4) approach is deemed inadequate. Based on the provided dissolution data, the Agency recommended a dissolution acceptance criterion of Q = (b) (4)% in 15 minutes in an information request dated 11/27/2020. In response, the Applicant revised the dissolution acceptance criterion to Q (b) (4)% in 15 minutes (b) (4) (b) (4). Due to the very fast dissolution of the proposed drug product, further tightening the dissolution acceptance criterion is not likely to have significant clinical impact. Further, the revised dissolution acceptance criterion is able to reject the (b) (4) variant batch. The revised dissolution acceptance criterion Q = (b) (4)% in 15 minutes is acceptable.

Biowaiver: Granted

Per 21 CFR 22(d)(2), the biowaiver for the 50 mg and 100 mg abrocitinib tablets can be granted for the following reasons:

1) The in vivo PK of the 200 mg abrocitinib tablet has been measured

2) The 50 mg and 100 mg abrocitinib tablets are in the same dosage form as the 200 mg abrocitinib tablet.
3) The formulation of 50 mg and 100 mg abrocitinib tablets are proportionally similar to that of the 200 mg abrocitinib [redacted] (b) (4)
4) The in vitro dissolution of the 50 mg and 100 mg abrocitinib tablets is similar to that of the 200 mg abrocitinib.

RECOMMENDATION:

Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 213871 for Cibinqo® (Abrocitinib) Immediate Release Tablet is deemed adequate for approval.

BIOPHARMACEUTICS ASSESSMENT

List Submissions Being Reviewed

Received Date	Submission
8/25/2020	Original submission
12/11/2020	Response to Biopharmaceutics IR dated 11/27/2020

BCS Designation

Reviewer's Assessment:

Based on provided solubility data, abrocitinib has pH-dependent solubility. The highest strength (also the highest single dose) of abrocitinib tablet, 200 mg, is insoluble in 250 mL aqueous medium above pH 4 (tested pH range 2.9 – 12.0). Per BCS criterion, abrocitinib has low solubility. The determined absolute bioavailability of abrocitinib (greater tha (b) (4) %) from study B7451008 suggests high permeability of abrocitinib. Low solubility and high permeability of abrocitinib support BCS II designation of the drug substance.

Solubility:

The Applicant provided aqueous solubility data for abrocitinib over pH 2.9 – 12.0 (**Table 1**). As shown, the drug substance (abrocitinib) has pH-dependent solubility. When pH is above 4, the highest strength (200 mg) is no longer able to dissolve in less than 250 mL aqueous medium.

Table 1 Aqueous Solubility of Abrocitinib at 25°C[1]

Aqueous media	Solubility at 25 °C (mg /mL)
pH 2.9	12.7
pH 3.3	3.7
pH 3.5	2.0
pH 3.7	1.5
pH 3.7	1.4
pH 3.9	0.9
pH 4.0	0.8
pH 4.3	0.4
pH 4.8	0.13
pH 5.1	0.08
pH 6.0	0.03
pH 7.0	0.02
pH 8.0	0.02
pH 8.9	0.02
pH 10.0	0.02
pH 10.7	0.03
pH 12.0	0.13
Water (unbuffered)	0.04

[1] \\CDSESUB1\evsprod\nda213871\0002\m2\23-qos\drug-substance-geninfo.pdf

Permeability:

The Applicant conducted a clinical study B7451008 to determine the absolute bioavailability of abrocitinib. The results showed the fraction of dose absorbed is greater tha (b) (4) %. The Applicant concluded that abrocitinib is a highly permeable compound.

Formulation Bridging

Reviewer's Assessment: ***Adequate***

As the (b) (4) formulation of the Phase 3 tablet (100 mg) is identical to that of the commercial 100 mg tablet and the formulation of all three commercial strengths (50 mg, 100 mg, and 200 mg) is proportional, no in vivo formulation bridging study is needed.

The formulation of the 100 mg tablet used in Phase 3 clinical study and the proposed commercial formulation are identical, except for the color coating. In addition, the formulation of 50 mg, 100 mg, and 200 mg strengths are proportionally simila (b) (4) (b) (4)

Table 2 Formulation used in Phase 3 Trials and Commercial Formulation[2]

Tablet Strength		100 mg	50 mg	100 mg	200 mg [b]
Uses		Phase 3, Clinical	Registration Stability (Commercial Formulations)		
Formulation ID		D1700147	DP-000627	D1800023	D1800025
Name of Ingredients	% Composition	Unit Formula (mg/tablet)			
Abrocitinib (PF-04965842) [b]	(b) (4)	100.00	50.00	100.00	200.00
Microcrystalline Cellulose [c]					
Dibasic Calcium Phosphate, Anhydrous[d]					
Sodium Starch Glycolate					
Magnesium Stearate [e]					
(b) (4)					
Final Coated Tablet Weight		(b) (4)			
Tablet Color			Pink	Pink	Pink
Tablet Shape		Round	Oval	Round	Oval
Tablet Debossing		(b) (4)	"ABR 50" on one side "PFE" on another side	"ABR 100" on one side "PFE" on another side	"ABR 200" on one side "PFE" on another side

Dissolution Method and Acceptance Criteria

Reviewer's Assessment:

Dissolution Method: ***Adequate***

The selection of the dissolution parameters is reasonable. The Applicant evaluated the discriminatory ability of the proposed dissolution method against tablet hardness, API particle size, and (b) (4) varian (b) (4)

The Applicant claimed the method is discriminatory against API particle size and the (b) (4) variant. However, the dissolution of the commercial batch and the (b) (4) particle size batch both reached more than (b) (4) % in 15 minutes for all strengths. Therefore, the

[2] \\CDSESUB1\evsprod\nda213871\0002\m3\32-body-data\32p-drug-prod\abrocitinib-tablet\32p2-pharm-dev\pharma-dev-drug-product.pdf

proposed dissolution method is not considered as discriminatory against API particle size. In terms of the (b) (4) variant (b) (4), the proposed dissolution method is not considered as discriminatory against the (b) (4) variant either. Overall, the proposed dissolution method is not discriminating. However, as the Applicant has implemented (b) (4), the risk of drug product dissolution is mitigated. The proposed dissolution method is acceptable.

Dissolution Acceptance Criterion *(Acceptable)*

The Applicant intended to use a (b) (4) approach and the dissolution data of the clinical and stability batches to support the originally proposed dissolution acceptance criterion of Q = (b) (4)% in (b) (4) minutes. The (b) (4) approach is to establish in vivo bioequivalence (BE) between the (b) (4) variant and the commercial tablet, so that the dissolution acceptance criterion could be set based on the dissolution of the (b) (4) variant. However, due to multiple deficiencies (b) (4) dissolution acceptance criterion is not justified. Based on the provided dissolution data, the Agency recommended a dissolution acceptance criterion of Q (b) (4)% in 15 minutes in an information request dated 11/27/2020.

In response, the Applicant provided explanations to the deficiencies, which are satisfactory. The Applicant also agreed that the BE between th (b) (4) variant and the Phase 3 tablet is not fully demonstrated. Therefore, the Applicant revised the dissolution acceptance criterion to Q (b) (4)% in 15 minute (b) (4)

The revised dissolution acceptance criterion is wider than what was recommended by the Agency. However, due to the very fast dissolution of the proposed drug product, further tightening the dissolution acceptance criterion is not likely to have significant clinical impact. Further, the revised dissolution acceptance criterion is able to reject the (b) (4) variant batch. The revised dissolution acceptance criterion Q (b) (4)% in 15 minutes is acceptable.

Proposed Dissolution Method

Table 3 Proposed dissolution method

Apparatus	Paddles with peak vessels
Medium	Citrate-phosphate buffer, pH 3.5
Medium Volume	900 mL
Agitation Rate	55 rpm
Analytical End Analysis	UV at 289 nm

Proposed Dissolution Acceptance Criterion

Originally proposed: For all strengths, $Q = $ (b) (4) $\% \; i$ (b) (4) min for all strengths

Proposed in response to Biopharmaceutics IR dated 11/27/2020: $Q =$ (b) (4) $\% \; in \; 15 \; min$ for all strengths

Variant Formulations

(b) (4)

Dissolution Method Development

(b) (4)

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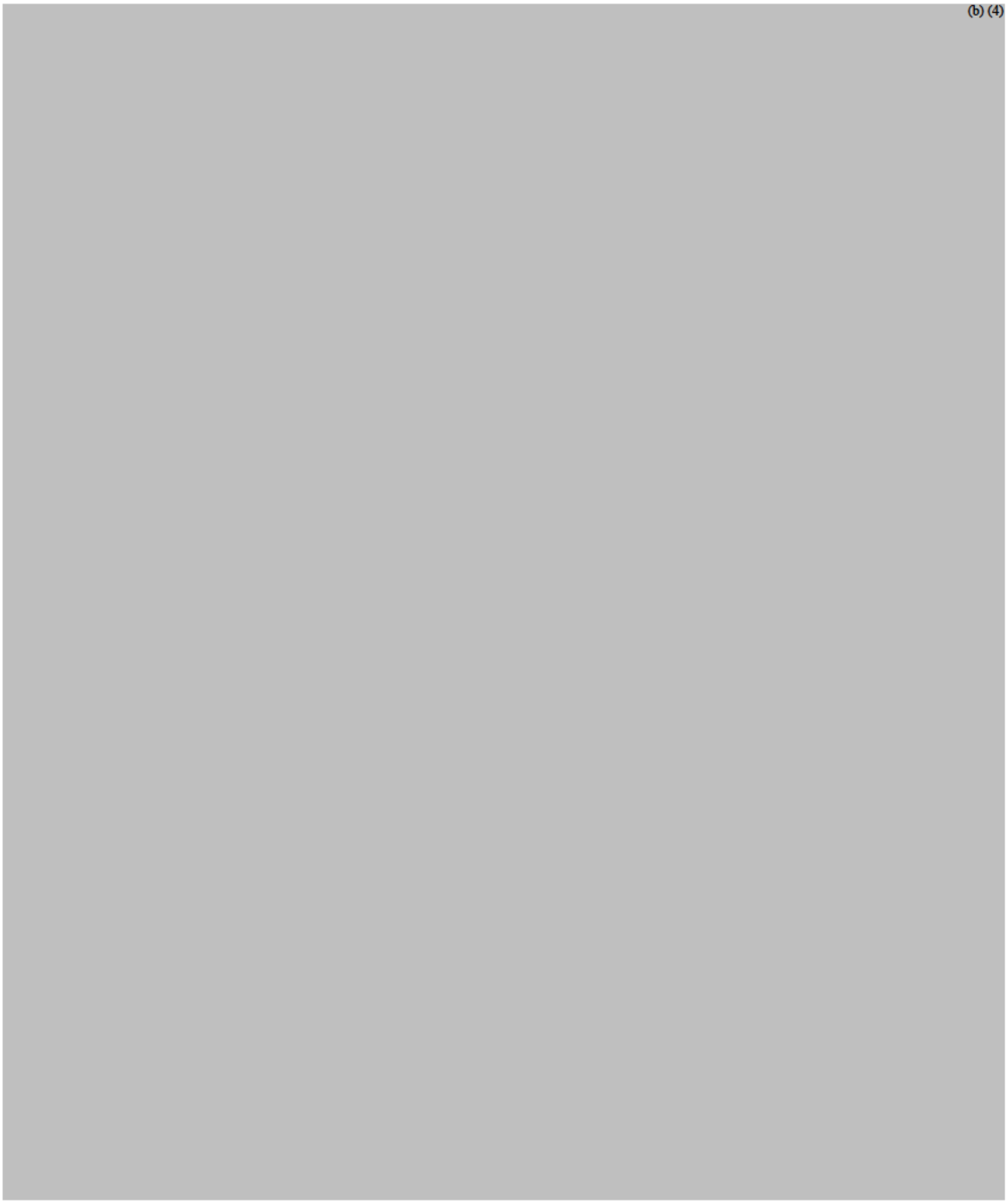


Justification for Dissolution Acceptance Criterion

1) Dissolution Data of Stability and Clinical Batches

The proposed dissolution acceptance criterion is Q = (b) (4)% in (b) (4) min. The Applicant summarized the dissolution data obtained using the proposed dissolution method at the (b) (4) minute timepoint for registration stability and clinical batches. According to the Applicant, the proposed dissolution method was not available at the time of release testing for most of Phase 3 clinical batches and the registration stability batches. For those batches, the dissolution test was performed on retained samples that had either

been stored in inventory and/or ambient laboratory conditions or performed on stability samples stored at 5 °C. As shown in **Table 8**, the dissolution of all samples a (b)(4) minutes is above 95%.

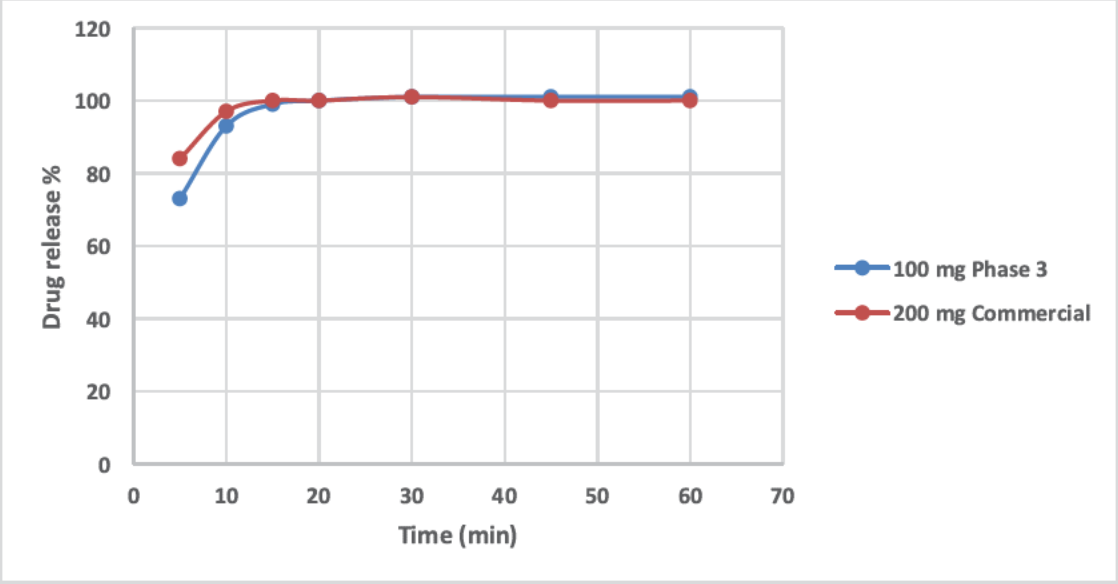
Table 8 Summary of Dissolution Data a (b)(4)-minute Timepoint for Registration Stability and Clinical Batches

Specification	Not less than (b)(4)% (Q) in (b)(4) minutes			
Method	TM-8831A			
		% Dissolved at (b)(4) Minutes (50 mg)	% Dissolved at (b)(4) Minutes (100 mg)	% Dissolved at (b)(4) Minutes (200 mg)
Range[a]	Release	NT	99 - 101	NT
	Retained Samples[b]	100	100 - 102	101
	Stability in Bottle			
	5 °C[c]	98 - 101	99 - 101	99 - 101
	25 °C/60% RH[d]	98 - 101	98 - 101	99 - 101
	30 °C/75% RH[d]	98 - 101	98 - 101	98 - 101
	40 °C/75% RH[e]	97 - 101	NT	NT
	Stability in Blister			
	5 °C[c]	98 - 99	100 - 101	100 - 101
	25 °C/60% RH[d]	97 - 101	99 - 100	100 - 101
	30 °C/75% RH[d]	97 - 100	99 - 101	99 - 101
	40 °C/75% RH[e]	97 - 101	NT	NT

a. Ranges provided represent mean dissolution results
b. Samples tested as shown in Table 3.2.P.5.6-12, Table 3.2.P.5.6-3 and Table 3.2.P.5.6-14
c. 5 °C sample tested at 6 months for 50 mg and at 9 months for 100 and 200 mg and data included in Table 3.2.P.5.6-12, Table 3.2.P.5.6-3 and Table 3.2.P.5.6-14
d. Includes results at 4.5 and 6 months for 50 mg, and 9 and 12 months for 100 and 200 mg
e. Includes results at 4.5 and 6 months for 50 mg
NT = Not Tested

Per Agency's current practice, the dissolution acceptance criterion for immediate release dosage forms is set based on USP <711> stage 2 dissolution testing of pivotal clinical batches and registration batches and at time point where Q = (b)(4)% dissolution occurs. This reviewer plotted the dissolution data of the two clinical batches (100 mg Phase 3 tablet and 200 mg commercial tablet) used in the pivotal BE study B7451032. As shown (**Figure 16**), the dissolution of both batches is over 90% in 10 minutes. Due to the deficiency in (b)(4) (the other support for the dissolution acceptance criterion), the Agency recommended a dissolution acceptance criterion of Q = (b)(4)% in 15 minutes based on the dissolution data.

Figure 16 Dissolution Profiles of Clinical Batches in Pivotal BE Study B7451032 (prepared by this reviewer)



In response, the Applicant agreed that the [(b) (4)] approach is not adequately justified and revised the dissolution acceptance criterion to Q = [(b) (4)]% in 15 minute [(b) (4)] [(b) (4)] The revised dissolution acceptance criterion is wider what the Agency recommended Q = [(b) (4)]% in 15 minutes. However, based on the very fast dissolution of the proposed drug product, further tightening the dissolution acceptance criterion is not likely to have significant clinical impact. Further, the revised dissolution acceptance criterion is able to reject the [(b) (4)] variant batch. The revised dissolution acceptance criterion Q = [(b) (4)]% in 15 minutes is acceptable.

2 [(b) (4)]

In addition to the dissolution data, the Applicant tried to establish [(b) (4)] for the proposed drug product to support the proposed dissolution acceptance criterion.

[(b) (4)]

(b) (4)

[redacted] (b) (4) Therefore, the justification for using [redacted] (b) (4) to support the dissolution acceptance criterion is inadequate.

Table 9 Summary of PK Parameters in Clinical Study B7451032 (Part A)

(b) (4)

Table 10 Summary of Cmax and Tmax Across Different Studies

(b) (4)

Figure 17 Mean Plasma Concentration Profiles from Different Studies

(b) (4)

Biowaiver Request

Reviewer's Assessment: ***Granted***

Per 21 CFR 22(d)(2), the biowaiver for the 50 mg and 100 mg abrocitinib tablets can be granted for the following reasons:

1) The in vivo PK of the 200 mg abrocitinib tablet has been measured
2) The 50 mg and 100 mg abrocitinib tablets are in the same dosage form as the 200 mg abrocitinib tablet.

3) The formulation of 50 mg and 100 mg abrocitinib tablets are proportionally similar to that of the 200 mg abrocitinib (b) (4) (b) (4)
4) The in vitro dissolution of the 50 mg and 100 mg abrocitinib tablets is similar to that of the 200 mg abrocitinib.

As shown in **Figure 18**, the Applicant conducted a pivotal BE study on the highest strength 200 mg and submitted a biowaiver request for the lower strengths 50 mg and 100 mg. The justifications for the biowaiver request include: 1) formulations are proportionally similar across all three strengths (**Table 2**), 2) dissolution profiles are similar for all three strengths (**Figure 19**), and 3) linear PK over dose range 30 – 400 mg (study B7451001).

Figure 18 Bioequivalence Strategy for Abrocitinib Commercial Tablets

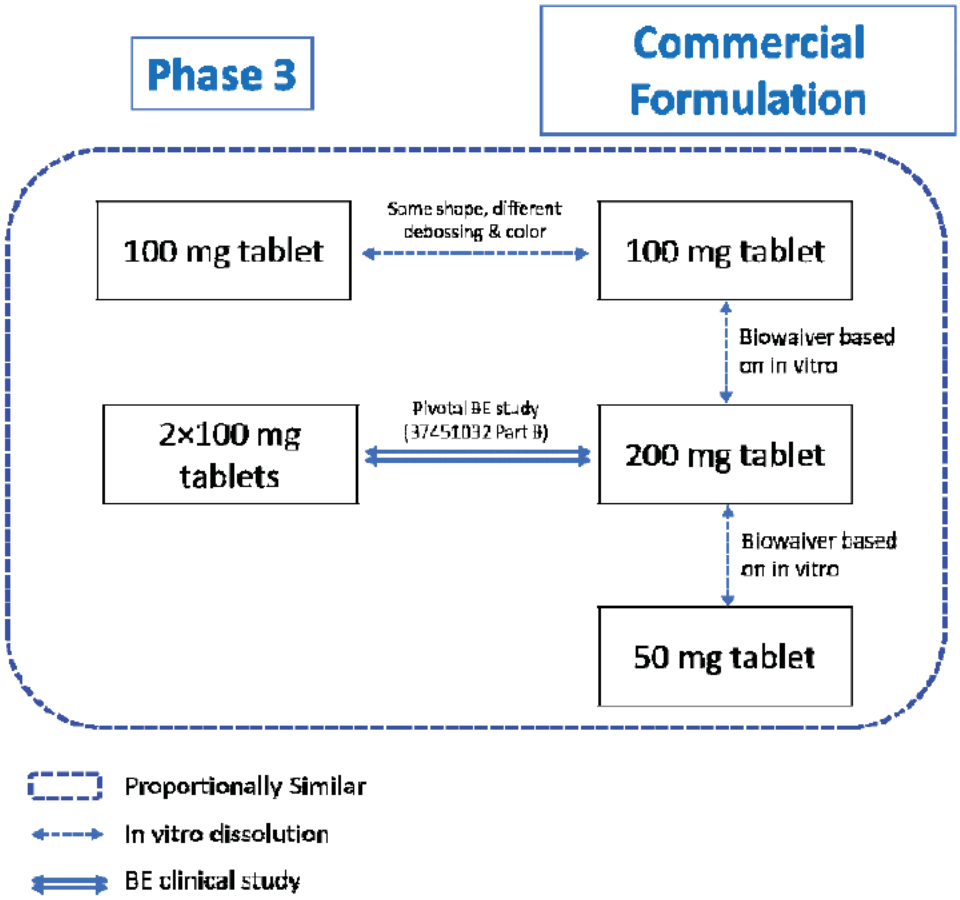
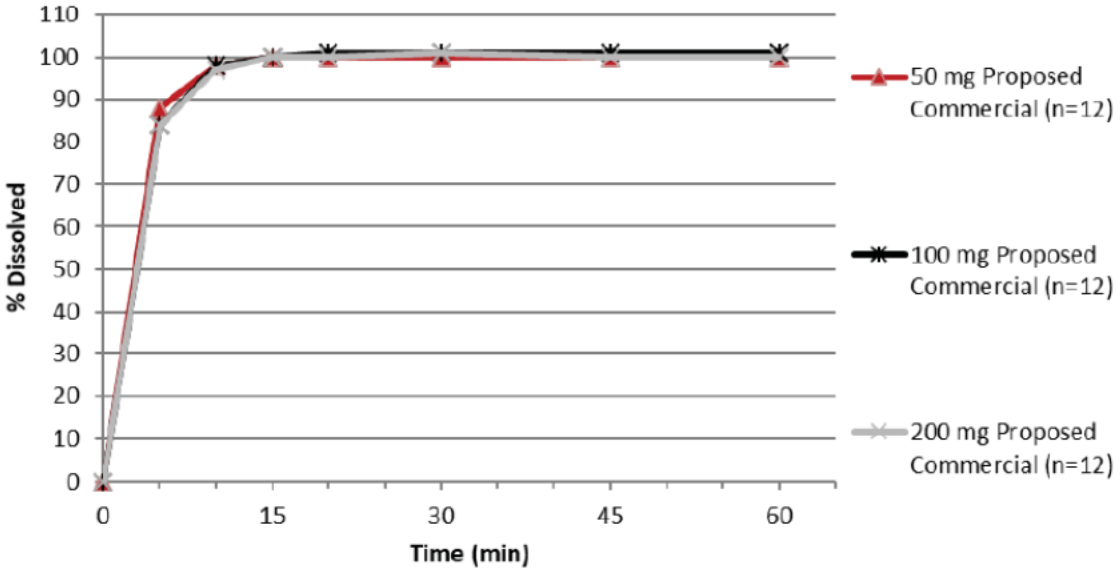


Figure 19 Dissolution Profiles for Abrocitinib Commercial Tablets Using the Proposed Dissolution Method



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