CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217003Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	217003
Applicant Name	Pharmacyclics LLC
Drug Product Name	IMBRUVICA® (ibrutinib)
Dosage Form.	Suspension
Proposed Strength(s)	70 mg/mL
Route of Administration	Oral
Maximum Daily Dose	240 mg/m^2 (420 mg)
Rx/OTC Dispensed	Rx
Proposed Indication	IMBRUVICA is indicated for the treatment of adult patients with: • Mantle cell lymphoma (MCL) who have received at least one prior therapy This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). • Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) • Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL) with 17p deletion • Waldenström's macroglobulinemia (WM) • Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy • IMBRUVICA is indicated for the treatment of adult and pediatric patients age 1 year and older with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy (b) (4)
Drug Product Description	Ibrutinib is an orally bioavailable, protein kinase inhibitor that was previously approved in a tablet dosage form under NDA

	205552 in 2013 and in a capsule dosage form under NDA 210563 in 2018. Ibrutinib has Orphan Drug Designation for each of the aforementioned indications and Breakthrough Designation for the treatment of cGVHD after failure of one or more lines of systemic therapy. The drug product for this application is a pediatric formulation that was developed with the following key requirements: dose flexibility, acceptability for a pediatric population, patient compliance (palatability and smell), physicochemical and microbiological stability, manufacturability, and bioavailability/bioequvalence. The drug product is presented as 108 mL of a white to almost white oral suspension in a 150 mL multi-dose, amber glass bottle. The bottle is fitted with a (b) (4) press in bottle adapter; closed with a child-resistant (b) (4) closure and co-packaged with two 3mL dosing syringes. There are no novel excipients or excipients of animal origin included in the drug product formulation; however, benzyl alcohol, which is used as a (b) (4) in the formulation, is known to have toxicity in young children. The applicant noted that based on the highest dose of ibrutinib oral suspension (e.g. 6.0 mL per day) the maximum amount of benzyl alcohol delivered to a pediatric patient is (b) (4) mg or (b) (4) mg/kg/day, which is well below the maximum daily exposure limit and acceptable daily limit. This concern was addressed in the drug product IQA.		
Co-packaged product information	Two 3-mL Dosing Syringes		
Device information:	N/A		
Storage Temperature/ Conditions	(b) (4) °C to 25°C ((b) (4) °F to 77°F). (b) (4) (b) (4)		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Paresma Patel	Paresma Patel
	Drug Product/ Labeling	Molly Lee	Tom Oliver
	Manufacturing	Jinong Jenn	Yiwei Li
	Biopharmaceutics	Kevin Wei	Kevin Wei

	Microbiology	Dionne Robinson	Denise Miller
	Other (specify):		
	RBPM	Dahlia Walters	
	ATL	Sherita McLamore	
Consults			

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: 24 months storage statement of "2°C to 25°C (36°F to 77°F). Do not freeze

b. Additional Comments for Action: n/a

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends APPROVAL of NDA 217003 for commercialization of IMBRUVICA® (ibrutinib) oral suspension, 70 mg/mL. Based on our evaluation of the available information, the applicant provided sufficient information to support an approval recommendation from the product quality perspective. The applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance - Adequate
Drug Product - Adequate

Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: N/A

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: The storage statement was updated during the review cycle to be in line with the current preferred language. No other recommendations were communicated during the review.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	**IMBRUVICA® (ibrutinib) oral suspension**	Adequate
Established name(s)		
Route(s) of administration		
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Oral suspension: 70 mg/mL (3)	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	n/a	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

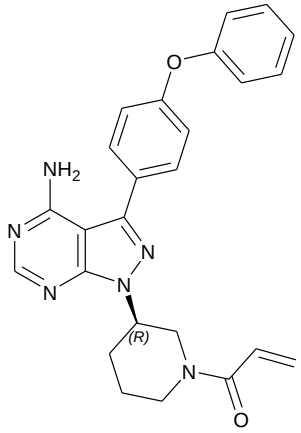
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted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

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Oral Suspension: 70 mg/mL, white to off-white suspension.	Adequate
Strength(s) in metric system	70 mg/mL	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	n/a	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	white to off-white suspension	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 labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	n/a	

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	IMBRUVICA (ibrutinib) is available as immediate-release oral capsules, immediate-release oral tablets, and immediate-release oral suspension.	Adequate Immediate-release (IR) oral suspension description here is acceptable as the suspension is IR and the description matches the immediate-release description of the tablets and capsules.
Dosage form(s) and route(s) of administration		
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	n/a	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	IMBRUVICA (ibrutinib) oral suspension contains 70 mg/mL ibrutinib (active ingredient) and the following inactive ingredients: benzyl alcohol, citric acid monohydrate, disodium hydrogen phosphate, hypromellose, microcrystalline cellulose and carboxymethylcellulose sodium, purified water and sucralose.	Adequate Inactive ingredients are listed in alphabetical order
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	
Statement of being sterile (if applicable)	n/a	
Pharmacological/ therapeutic class	kinase inhibitor	Adequate
Chemical name, structural formula, molecular weight	The chemical name for ibrutinib is 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one and has the following structure:  empirical formula $C_{25}H_{24}N_6O_2$ and a molecular weight 440.50	Adequate
If radioactive, statement of important nuclear characteristics.		
Other important chemical or physical properties (such as pKa or pH)	white to off-white solid Ibrutinib is freely soluble in dimethyl sulfoxide, soluble in methanol and practically insoluble in water.	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	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	n/a	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Oral Suspension	Adequate
Strength(s) in metric system	Each mL contains 70 mg of ibrutinib	Adequate
Available units (e.g., bottles of 100 tablets)	108 mL in a 150 mL amber glass bottle with a pre-inserted bottle adapter and a child resistant closure.	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	white to off-white suspension NDC 57962-007-12	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	n/a	

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.)	Do not freeze	When the suspension was stored at -18 °C for 24 hours and then thawed at 5°C for 24 hours, large particles aggregated in the suspension. “Do not freeze.” Is listed in all labeling storage statements and is adequate.
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	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store the oral suspension bottle at 2°C to 25°C (36°F to 77°F). Do not freeze.	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	
Include information about child-resistant packaging	child resistant closure	Adequate

1.2.5 Other Sections of Labeling

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

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

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	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 and Marketed by: Pharmacyclics LLC South San Francisco, CA 94080 USA and Marketed by: Janssen Biotech, Inc. Horsham, PA 19044 USA Patent *http://www.imbruvica.com* IMBRUVICA® is a registered trademark owned by Pharmacyclics LLC	Adequate

2.0 PATIENT LABELING

(b) (4)

[redacted]

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

There were concerns from the team regarding incorrect dosing observed in the Human Factors studies, particularly during the shaking and bubble removal

steps. The applicant provided data to demonstrate than a consistent, accurate, and uniform dose of ibrutinib for the relatively small dose of 1.2 mL at different bottle fills can be delivered by following the Instructions for Use (IFU) and using the syringes provided. The data provided is sufficient to support the IFU Steps 3-7. We made the recommendation internally to DMEPA that any language on the carton/container regarding the instructions for use be bolded or underlined to ensure that the IFU is followed. Refer to the Drug Product Review for more information.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

3.2 Carton Labeling

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	(b) (4)	Adequate
Dosage strength		Adequate
Route of administration		Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	n/a	
Net contents (e.g. tablet count)	108 mL per Bottle	Adequate
"Rx only" displayed on the principal display	Rx only listed on carton and container label	Adequate
NDC number	NDC 57962-007-12 listed on carton and container label	NDC number matches number listed in PI
Lot number and expiration date	Space for Exp. And Lot.	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store between 36 ºF and 77 ºF (2 ºC and 25 ºC) Do not freeze Discard any unused portion 60 days after first opening. Discard Date:	"to" is the current preferred language instead of "and" **Comment to applicant:** Ensure that storage statements are consistent across all labeling, including prescribing information, instructions for use, patient labeling and container/carton.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	

Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Present	

Item	Information Provided in the NDA (b) (4)	Assessor’s Comments about Carton Labeling
Name of manufacturer/distributor		Meets requirements of 21 CFR 610.64
Medication Guide (if applicable)	n/a	
No text on Ferrule and Cap overseal	n/a	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	n/a	
And others, if space is available		

Assessment of Carton and Container Labeling: *Adequate*

Recommendation for Applicant:

Ensure that storage statements are consistent across all patient labeling, prescribing information, IFU and container/carton.

Overall Assessment and Recommendation:

Prescribing Information, Patient Labeling, Instructions for Use and Container/Carton Labeling is Adequate.

Primary Labeling Assessor Name and Date: Molly Lee, Ph.D., Branch 2, ONDP Division of New Drug Products I, August 3, 2022

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

Thomas Oliver, Ph.D., ONDP Division of New Drug Products I, August 3, 2022

Molly Lee

Digitally signed by Molly Lee
Date: 8/03/2022 02:00:28PM
GUID: 5e2b04c70029e7c7580982b0a5cb16be

Thomas Oliver

Digitally signed by Thomas Oliver
Date: 8/03/2022 02:16:28PM
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BIOPHARMACEUTICS

NDA: 217003 [505(b)(1)]
Drug Product Name/Strength: IMBRUVICA® (ibrutinib) oral suspension, 70 mg/mL
Route of Administration: Oral
Proposed Indication: pediatric chronic graft versus host disease (cGVHD)
Applicant Name: Pharmacyclics LLC (AbbVie)
Submission Date: 02/24/2022
Primary Reviewer: Kevin Wei, Ph.D.
Secondary Reviewer: Kevin Wei, Ph.D.
Recommendation: Approval

EXECUTIVE SUMMARY

Pharmacyclics LLC submitted this NDA 217003 for IMBRUVICA® (ibrutinib) oral suspension, 70 mg/mL, indicated for the treatment of adult and pediatric patients aged 1 year and older with cGVHD after failure of one or more lines of systemic therapy cGVHD. Ibrutinib is an orally bioavailable, protein kinase inhibitor that was previously approved in a capsule dosage form under NDA 205552 in 2013 and in a tablet dosage form under NDA 210563 in 2018. The newly proposed oral suspension allows once-daily oral dosing for pediatric patients of 1 to 12 years old, with the proposed recommended pediatric equivalent dose (RPED) dose of 240 mg/m^2 based on body surface area (BSA). This Biopharmaceutics review focuses on the evaluation of the adequacy of the overall information and data supporting (i) the in vitro dissolution method and acceptance criterion as quality control (QC) test, and (ii) need for bridging between the clinical and To-Be-Marketed (TBM) drug products.

In vitro dissolution methods and acceptance criterion:

Ibrutinib is considered a low soluble drug substance as per the BCS criteria. The Applicant proposed to implement a dissolution method of USP Apparatus 2 (paddle) at 25 rpm in 900 mL of pH 6.8, 0.05M potassium phosphate with 1.5% w/v Tween 20, using 2 mL suspension samples, and set a dissolution acceptance criterion of Q= (b)(4)% in 15 minutes. The proposed dissolution method was deemed acceptable during the review of IND 102688. Based on the submitted dissolution data for the registration batches, and considering the discriminating ability of the proposed method towards the API particle size, the proposed acceptance criterion of Q= (b)(4)% in 15 minutes is deemed adequate.

Bridging:

Two ready-to-use suspension formulations (single-dose and multi-dose), 70 mg/mL, were used in clinical studies. The initial single-dose oral suspension was evaluated in a Phase 1 relative bioavailability (BA) Study CLL1015 for PK, palatability, and relative BA as compared to the approved Imbruvica® (ibrutinib) Capsule, 140 mg. The single-dose suspension was further developed to a multi-dose suspension with a main formulation

change of replacing (b) (4) (b) (4) The multi-dose suspension is used for the registration batches, proposed for the TBM product, and evaluated in the pivotal clinical studies in pediatric subjects. The Applicant has submitted comparability data (pH, viscosity, particle size distribution and in vitro dissolution) between the single-dose and multi-dose formulations and the submitted data indicated that the two formulations have similar pH, viscosity, particle size distribution and in vitro dissolution. From a Biopharmaceutics perspective, no further bridging is warranted to support this NDA.

RECOMMENDATION

From a Biopharmaceutics perspective, NDA 217003 for IMBRUVICA® (Ibrutinib) Oral Suspension, 70 mg/mL, is recommended for **Approval**. The following dissolution method and acceptance criterion are deemed acceptable as quality control (QC) test for the proposed drug product.

Suspension sample volume	2 mL
USP Apparatus	USP Apparatus 2 (paddle)
Rotation speed	25 rpm
Temperature	37 ± 0.5°C
Volume	900 mL
Dissolution medium	pH 6.8, 0.05 M potassium phosphate with 1.5% (w/v) Tween 20
Acceptance criterion	Q= (b) (4) % in 15 minutes

BIOPHARMACEUTICS REVIEW

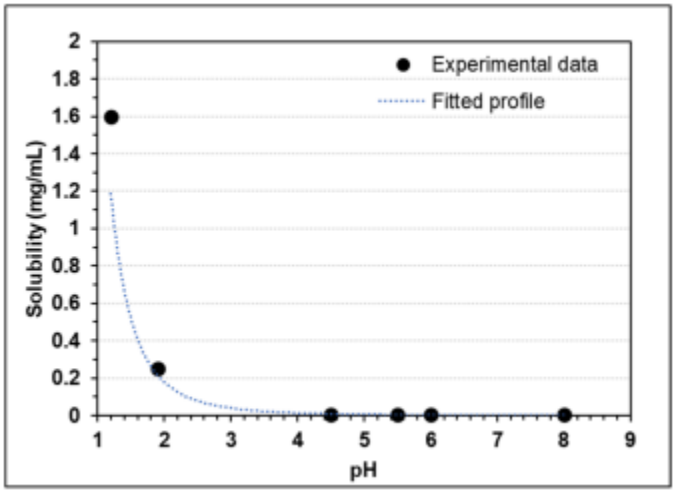
1. Drug Substance (DS) solubility and permeability

The solubility data of ibrutinib drug substance (37°C) were submitted as below.

Table 1. The solubility of ibrutinib at 37°C in aqueous media
(*3.2.P.2 Drug Product-Physicochemical and Biological Properties*, Table 2, Page 7)

Medium	pH	Solubility (mg/mL)	Amount of ibrutinib dissolved in 250 mL solution (mg)
0.1 N HCl	1.2	1.6	400
0.1 N Trifluoracetic acid	1.9	0.25	62.5
0.2% Formic Acid	3.0	0.06	15
10 mM Ammonium Acetate	4.5	0.003	0.75
Water	~ 5.5	0.003	0.75
10 mM Ammonium Acetate	6.0	0.003	0.75
10 mM Ammonium Acetate	8.0	0.003	0.75

Figure 1. The pH-solubility profile of ibrutinib drug substance at 37°C
(*3.2.P.2 Drug Product-Physicochemical and Biological Properties, Figure 1, Page 8*)



According to the Applicant, ibrutinib is a highly permeable drug substance based on the in-vitro permeability. The permeability studies have been cross-referenced to NDA 205552 (Imbruvica® (ibrutinib) Capsules).

Reviewer's Assessment:
Ibrutinib exhibits pH-dependent solubility (solubility decreases with an increase in pH) and the submitted data indicated that ibrutinib is a low soluble drug substance as per BCS criteria (based on the highest single therapeutic dose of 420 mg for pediatric cGvHD patients).

2. Evaluation of dissolution conditions

The proposed dissolution method [USP Apparatus 2 (paddle), 25 rpm, 900 mL of pH 6.8, 0.05 M Potassium Phosphate with 1.5% w/v Tween 20] has been reviewed under IND 102688. The preliminary dissolution method development data and information were submitted in SDNs 1486, 1588 and 1620 under IND 102688 and the Biopharmaceutics reviews for the submitted data and information under IND 102688 can be found in DARRTs as below.

Submitted dissolution method development reports assessed under IND 102688:

Document number	Date Received	Biopharmaceutics Review	Date Responded
SDN-1620 Biopharmaceutics IR response	12/06/21	COR-INDAD-02 (Advice /Information Request)[1]	12/23/21
SDN-1588 Dissolution Method Development Report	08/19/21	REV-QUALBIOPHARM-21 (Primary Review)[2]	11/29/21
SDN-1486 Pharmaceutical Development	08/12/20	REV-QUALBIOPHARM-21 (Primary Review)[3]	11/09/20

The proposed dissolution method in the NDA submission is the same as the method found acceptable during the IND review and the method was found acceptable based on the following findings:

(b) (4)

[redacted]

Reviewer's Assessment:

The proposed dissolution method in the NDA submission [USP Apparatus 2 (paddle) at 25 rpm in 900 mL of pH 6.8, 0.05 M Potassium Phosphate with 1.5%w/v Tween 20, 2mL suspension samples] is deemed adequate.

[1] https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806362ba
[2] https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8062ce04
[3] https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805ab738

3. Evaluation of dissolution acceptance criterion

The Applicant proposed a dissolution acceptance criterion of Q= (b) (4) % in 15 minutes for batch release and at stability. The dissolution profile data for the clinical and registration batches were submitted as below:

Table 2. Batch summary of Ibrutinib Oral Suspension, 70 mg/mL
(*3.2.P.4.5 Batch Analysis*, Table 1, Page 3)

Batch Number	Batch Size (L)	Intended Use	Manufacturing Site	Manufacturing Date	Drug Substance Batch Number	Formulation / Process
20087	(b) (4)	Clinical / Primary Stability	(b) (4)	Mar 2020	171332	Multi-dose (b) (4)
20086		Clinical / Primary Stability		Mar 2020	181339	Multi-dose
20085		Clinical / Primary Stability		Mar 2020	181339	Multi-dose
19312		Clinical / Stability		Oct 2019	171333	Multi-dose
19125		Clinical		Jun 2019	171333	Multi-dose
19078		Clinical / Stability		May 2019	171333	Multi-dose
19046		Clinical / Stability		Mar 2019	171333	Multi-dose

Table 3. Dissolution profile data for Ibrutinib Oral Suspension, 70 mg/mL
(*3.2.P.4.5 Batch Analysis*, Table 6, Page 10)

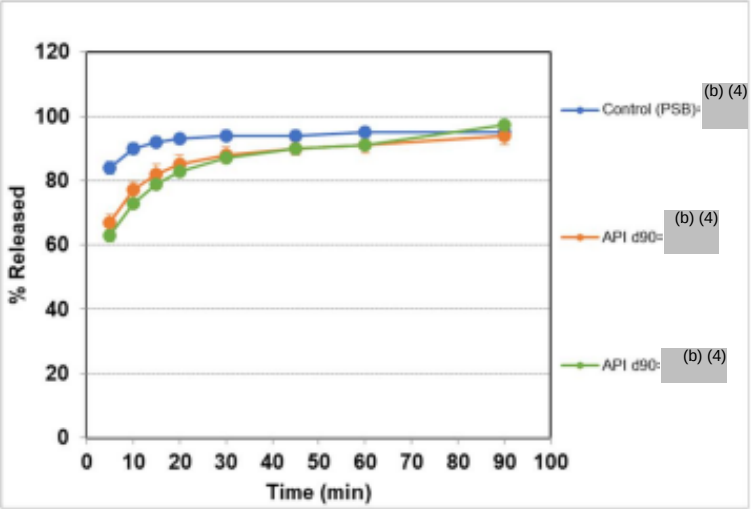
	Dissolution (% Labeled Amount)							
	5 minutes		10 minutes		15 minutes		20 minutes	
Batch Number	Individual	Mean	Individual	Mean	Individual	Mean	Individual	Mean
20087	(b) (4)	93	(b) (4)	96	(b) (4)	97	(b) (4)	97
20086		95		97		98		98
20085		94		96		97		97
19312		93		95		95		95
19125		96		99		99		100
19078		96		98		98		99
19046		95		97		98		98

In the NDA, the Applicant submitted complete dissolution profile data up to 12 months for the registration/clinical batches (n=12, sampling time points: 5, 10, 15, 20, 30, 45, and 60 minutes) and no Out-of-Specification (OOS) on dissolution was identified.

Reviewer's Assessment:

The submitted dissolution profile data for the registration and clinical batches showed very rapid dissolution and no significant trend in dissolution during the stability studies. The submitted data support the proposed acceptance criterion of Q= (b) (4) % in 15 minutes, which is generally set for the very rapid dissolving drug product. In addition, the submitted data showed that the proposed dissolution method is discriminating towards API particle size at 15 minutes (see Figure 2 below). Therefore, based on the totality of provided dissolution data and information, the proposed dissolution acceptance criterion of Q= (b) (4) % in 15 minutes is deemed adequate.

Figure 2. Dissolution profiles of Ibrutinib OS with different drug substance particle sizes using USP 2 (paddle) at 25 rpm in pH 6.8 buffer containing 1.5% Tween 20 (*3.2.P.2 Drug Product-Physicochemical and Biological Properties, Figure 12, Page 24*)



4. Bridging

Two ready-to-use suspension formulations (single-dose and multi-dose), 70 mg/mL, were used in clinical studies. The initial single-dose oral suspension was evaluated in a Phase 1 relative bioavailability (BA) Study CLL1015 for PK, palatability, and relative BA as compared to the approved Imbruvica® (ibrutinib) Capsule, 140 mg. The single-dose suspension was further developed to a multi-dose suspension that is used for the registration batches, proposed for the TBM products, and evaluated in the pivotal clinical studies in pediatric subjects.

The multi-dose suspension differs from the single-dose suspension with respects to the following formulation changes:

(b) (4)

Table 4. Composition of Ibrutinib Oral Suspension, 70 mg/mL
(*3.2.P.2.2.1 Drug Product - Formulation Development, Table 1, Page 5*)

Component	Function	Clinical Formulation (Single-Dose) [a] (mg/mL)	Clinical, Primary Stability, and Proposed Commercial Formulation (Multi-Dose) [b] (mg/mL)
Ibrutinib	Drug Substance	70.00	70.00
Microcrystalline Cellulose and Carboxymethylcellulose Sodium			(b) (4)
Hypromellose [c]			
Disodium Hydrogen Phosphate (b) (4)			
Citric Acid Monohydrate			
Sucralose			
(b) (4)			
Benzyl Alcohol			
(b) (4)			
Purified Water			

a. Used in relative BA study (CLL1015), Part A of PCYC-1146-IM (iMAGINE) study, and Part 1 of LYM3003 (SPARKLE) study.

b. Used in Parts A and B of iMAGINE study, Part 2 of SPARKLE study. (b) (4)

(b) (4)

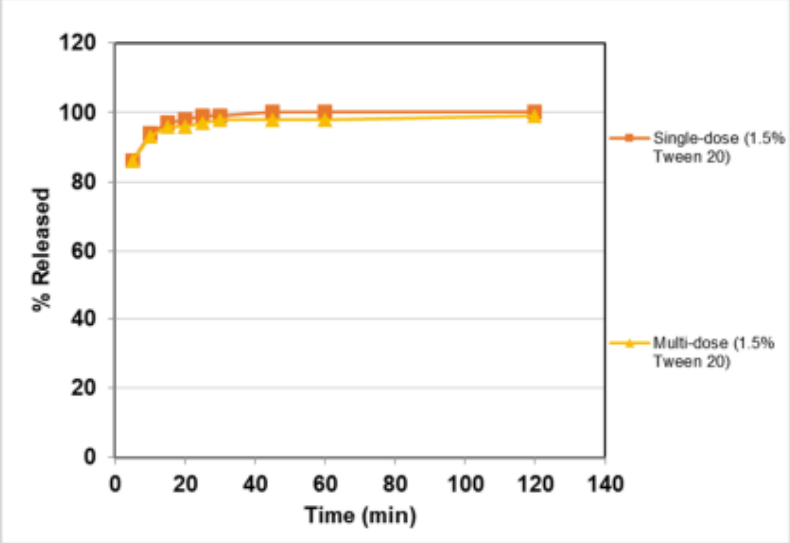
To establish the formulation bridging between the single-dose and multi-dose suspensions, the Applicant submitted the physicochemical properties comparison and comparative dissolution data using the proposed dissolution method.

Table 5. Physicochemical property comparison of single-dose and multi-dose Ibrutinib Oral Suspension (70 mg/mL)
(*3.2.P.2.2.1 Drug Product - Formulation Development, Table 4, Page 18*)

Batch Number	Date of Manufacture	Drug Substance Batch Number	pH	Viscosity (mPa*s) at 20°C	Particle Size Distribution (µm) [a]		
					d_{10}	d_{50}	d_{90}
Single-Dose							(b) (4)
18-0028	Mar 2018	171328	6.0	19			
18-0077	Jul 2018	171328	6.0	21			
18-0168	Jan 2019	171333	6.0	19			
19-0141	Jul 2019	181339	6.0	19			
Multi-Dose							
19046	Mar 2019	171333	6.1	17			
19078	May 2019	171333	6.1	18			
19125	Jun 2019	171333	6.1	18			
19312	Oct 2019	171333	6.0	19			
20085	Mar 2020	181339	6.0	22			

(b) (4)

Figure 3. Dissolution profiles of single-dose and multi-dose Ibrutinib Oral Suspension (USP 2 (paddle), 25 rpm, 900 mL of pH 6.8 Buffer with 1.5% Tween 20)
(*3.2.P.2.2.1 Drug Product - Formulation Development, Figure 1, Page 19*)



Reviewer's Assessment:

Two ready-to-use suspension formulations (single-dose and multi-dose), 70 mg/mL, were used in clinical studies, and the multi-dose suspension is used for the registration batches, proposed for the TBM products, and currently evaluated in the pivotal clinical studies in pediatric subjects. Based on the provided information, the multi-dose suspension differs from the single-dose suspension with (b) (4) (b) (4) (b) (4) *The proposed formulation changes are unlikely to have any negative impact on formulation quality and in vivo performance. The Applicant has submitted comparability data (pH, viscosity, particle size distribution and in vitro dissolution) and the submitted data indicated that the single-dose and multi-dose formulations have similar pH, viscosity, particle size distribution and in vitro dissolution, indicating changes in formulation composition (e.g.,* (b) (4) *) between the single-dose and multi-dose suspensions are not expected to impact bioavailability[4]. Therefore, based on the overall risk assessment, no further bridging data and information is warranted to support this NDA.*

[4] https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805f5a74

Kevin Wei

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VII: MICROBIOLOGY

IQA ANDA Assessment Guide Reference

Product Information	Nonsterile solution indicated for use in patients with chronic graft versus host disease. Filled as a 108mL in a 150mL amber (b) (4) glass bottle; multiple-dose. Drug product is co-packaged with 2 3mL dosing syringes.
NDA Number	217003
Assessment Cycle Number	1
Drug Product Name / Strength	Ibrutinib, 70mg/mL Oral Suspension
Route of Administration	Oral Solution
Applicant Name	Pharmacyclics LLC
Manufacturing Site	AbbVie Inc. 1 N Waukegan Rd. North Chicago, IL 60064, USA
Method of Sterilization	Nonsterile Solution

Assessment Recommendation: **Adequate**

Theme:

☒ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: *view justification statements found at:* **Justification Statements**

N/A
Other (Requires Division Director Approval) – *Assessor writes-in justification here if "other" selected as theme.*

Assessment Summary: The submission is an original NDA submission for nonsterile, aqueous drug product, Ibrutinib, 70mg/mL Oral Suspension, packaged as a 108mL fill in a 150mL glass vial. The drug product co-packaged with 2 3mL dosing syringes. The oral suspension contains a (b) (4) and data are provided to demonstrate (b) (4) Information pertaining to the manufacturing process and method suitability data for controls for release and stability are provided and supportive of the manufacturing process. Therefore, submission **is recommended** for approval on the basis of sterility assurance.

List Submissions Being Assessed (table):

Date Submitted to FDA	Date Received by FDA	Date Assigned to Reviewer
07/28/2020	07/29/2020	08/10/2020

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

Remarks: The submission is in e-CTD format

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): N/A

Supporting Documents: N/A

Select Number of Approved Comparability Protocols: 0

S DRUG SUBSTANCE

S.2. MANUFACTURE

S.2.1 MANUFACTURERS

Assessment:

As the drug product is nonsterile, the drug substance will not be reviewed by microbiology.

Adequate

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –**

Nonsterile, white to almost white solution filled as a 108mL fill into a 150mL amber/ (b) (4) glass bottle, closed with a 24mm (b) (4) press-in bottle adaptor, and capped with (b) (4) child-resistant caps with a (b) (4) liner. Ibrutinib, 70mg/mL Oral Suspension is indicated use in patients with chronic graft versus host disease; multiple-dose bottle.

Drug product composition

Ingredient	Function	Quantity (mg/mL)
Ibrutinib	API	70.00
Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF	(b) (4)	
Hypromellose (b) (4) USP		
Disodium Hydrogen Phosphate, (b) (4) USP		
Citric Acid Monohydrate, USP		
Sucralose, NF		
Benzyl Alcohol, NF		
Purified Water, USP		

Exhibit Batch:

(b) (4)

Proposed Commercial Batch: The commercial batch size is (b) (4) the same as the exhibit batch sizes

- **Description of container closure system –**

Component	Material Code No.	Description	Manufacturer
Bottle	(b) (4)		
Closure			
Cap			
Syringe[1]			

[1]Drug package is co-packaged with 2 3mL dosing syringes.

Assessment:

Adequate

P.2 PHARMACEUTICAL DEVELOPMENT

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Denise Miller

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Dahlia A. Walters

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