CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212436Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 212436
Review #1

Drug Name/Dosage Form	IBRANCE® (palbociclib) tablets
Strength	75 mg, 100 mg and 125 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Pfizer
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	01/31/2019	DS, DP, Manufacturing, Biopharm.
Quality Amendment 0002	03/07/2019	DP/ Biopharm
Quality Amendment 0007	07/01/2019	DP/Biopharm
Quality Amendment 0008	07/24/2019	Manufacturing
Quality Amendment 0009	07/31/2019	DP

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	N/A	N/A
Drug Product	Tefsit Bekele	Anamitro Banerjee
Manufacturing	Steve Rhieu	Haitao Li
Microbiology	N/A	N/A
Biopharmaceutics	Gerlie Gieser	Banu S. Zolnik
Regulatory Business Process Manager	Kristine Leahy	
Application Technical Lead	Xiao Hong Chen	
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental	Tefsit Bekele	Anamitro Banerjee

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III	(b) (4)	(b) (4)	Adequate	9/30/2019	DMF has been reviewed and found acceptable for other approved drug products.
(b) (4)	Type III			Adequate	9/30/2019	DMF has been reviewed and found acceptable for other approved drug products.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	69324	Initial IND for palbociclib was submitted to DOP1 on 3/10/2004.
NDA	207103	IBRANCE® (palbociclib) capsules was approved on 2/3/2015.

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
OBP	N/A			
CBER	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The product quality review team (consisting of the following disciplines: API, drug product, manufacturing process/facility and biopharmaceutics) recommends Approval of this NDA. Complete CMC information has been submitted to NDA 212436 and found to be adequate upon completion of the review. No PAI (pre-approval inspection) was conducted for the NDA as all API and drug product facilities are found adequate upon review of the inspection history.

II. Summary of Quality Assessments

A. Product Overview

The NDA 207103 for IBRANCE® (palbociclib) capsules was approved for the treatment of Advanced Breast Cancer (ABC) on February 3, 2015. The current NDA (212436) seeks approval for IBRANCE® (palbociclib) tablet formulation for oral use in the same approved indications and dose. The tablet formulation will replace the current capsule formulation once approved. The dose for the currently marketed palbociclib capsules (75, 100, and 125 m) must be taken with food to achieve the consistent and desired bioavailability. The proposed tablet formulation will allow administration of palbociclib with or without food and concomitant administration of proton pump inhibitors (PPIs) under any food intake condition. Palbociclib is a kinases inhibitor indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant. CMC information for the drug substance is provided by referencing the applicant's NDA 207103. The proposed commercial palbociclib immediate release film-coated tablet is provided as the same strengths as those of NDA 207103, 75 mg, 100 mg and 125 mg strengths. (b) (4) Three batches for each strength of twelve-month stability data are provided. Pfizer conducted a BE study to demonstrate bioequivalence between the capsule and the tablet formulations. Pfizer requests waive the in vivo bioequivalence requirement for the 75 mg and 100 mg palbociclib film-coated tablets, which has been found acceptable by the biopharmaceutics reviewer.

Proposed Indication(s) including Intended Patient Population	IBRANCE is a kinase inhibitor indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with: • an aromatase inhibitor as initial endocrine based therapy in postmenopausal women; or • fulvestrant in women with disease progression following endocrine therapy.
Duration of Treatment	Until disease progression or unacceptable toxicity occurs

Maximum Daily Dose	IBRANCE tablets are taken orally in combination with an aromatase inhibitor or fulvestrant. • Recommended starting dose: 125 mg once daily taken with or without food for 21 days followed by 7 days off treatment. (2.1) • Dosing interruption and/or dose reductions are recommended based on individual safety and tolerability. (2.2)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

On January 01, 2019 Pfizer Inc. submitted an NDA 212436 for palbociclib (Ibrance®) tablets for oral use in the currently marketed indications for Ibrance® capsules. The commercial capsule formulation (NDA 207103, approved on 02/19/2019) is indicated for the treatment of hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant. Ibrance® capsule is for oral administration with food to reduce variability in drug absorption and to mitigate drug-drug interactions with gastric acid reducing agents. The proposed tablet formulation will allow the administration of Ibrance® tablet with or without food. Ibrance® tablets are formulated as immediate release film-coated tablet supplied in 75 mg, 100 mg, and 125 mg strength, same strength as the currently approved capsules. The tablets are packaged in (b) (4) blisters (b) (4) The packaged Ibrance® tablets are stored at 20–25°C and the applicant proposes a shelf life of 24 months, which is deem acceptable based on the review of stability data.

Drug Substance

The drug substance, palbociclib (b) (4) which is also the form used in the commercial Ibrance® capsules (NDA 207103). There is no drug substance information needs to be reviewed since it is referenced to the applicant's approved NDA 207103.

Drug Product

The applicant provided satisfactory drug product information including adequate stability data for Ibrance® (Palbociclib) tablet. The proposed Ibrance® film-coated tablets for oral administration are supplied as 75 mg, 100 mg, and 125 mg in (b) (4) blisters (1 tablet per cell, 7 tablets in each blister pack and 21 tablets in each monthly box). Pfizer is not planning to continue to market Ibrance capsules post-approval (b) (4) Ibrance® tablet is formulated as immediate release, film coated tablets containing palbociclib and common pharmaceutical excipients. Unlike Ibrance® capsule that should be taken with food. (b) (4) (b) (4)

(b) (4)

(b) (4) The 12-months stability studies at long-term support the proposed storage temperature of 20–25°C with excursions permitted to 15–30°C for a shelf life of 24 month. No significant chemical or physical changes at accelerated storage conditions are observed. The drug product information is found acceptable.

Manufacturing

The manufacturing process of the drug product includes (b) (4)

(b) (4)

The status of all drug substance and drug product manufacturing and testing facilities is found CGMP compliant. No PAI is needed. The overall DP manufacturing process and facility information is deemed acceptable.

Biopharmaceutics

The Biopharmaceutics review is focused on the evaluation of the 1) proposed in vitro dissolution method and acceptance criterion, and (2) formulation bridging. Palbociclib has poor aqueous solubility in the physiological pH range (high solubility at low pH), and low permeability.

The proposed QC dissolution method (USP Apparatus 2 at 75 rpm) is discriminating (b) (4)

(b) (4)

(b) (4) (b) (4) the operating parameters of the dissolution method for the proposed drug product are the same as those approved for the IBRANCE® Capsules.

Bridging of the clinical to the To-Be-Marketed drug product has been demonstrated. The proposed commercial tablet (125 mg) has the same formulation, and is manufactured using the same drug product manufacturing process as the tablet evaluated in the Pivotal BE Study. Additionally, the proposed commercial tablets will be manufactured at a similar batch size as the lots used in registration stability and the pivotal BE studies.

The Applicant's request to waive the requirement to conduct an *in vivo* BA or BE study for the two lower strengths (75 mg and 100 mg) of the proposed commercial tablet is granted based on the evidence of (b) (4) and comparable *in vitro* dissolution profile data of the test and reference strengths, using the proposed QC dissolution method that was shown to be clinically relevant. Additionally, the Applicant noted that palbociclib PK are dose proportional across the (b) (4) dose range. The biopharmaceutical information is deemed acceptable.

Environmental Assessment

The applicant requested categorical exclusion from the requirement for environmental impact assessment per 21 CFR 25.31. Based on their knowledge, no extraordinary circumstances exist that would warrant the preparation of an environmental assessment based on 21 CFR 25.15(d). In addition, the proposed tablet formulation is to replace the currently marketed capsule formulation. There is no increased usage/production expected. It is acceptable.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	(b) (4)	L	(b) (4)
Physical stability (solid state)	• Formulation • Raw materials • Process parameters	M		L	

	• Scale/equipments • Site				(b) (4)
Content uniformity	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M	(b) (4)	M	
Microbial limits	• Formulation • Container closure • Process parameters • Scale/equipments • Site	L		L	(b) (4)
Dissolution – BCS Class II & IV	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M		L	

E. Signature

Application Technical Lead Name and Date:
Xiao Hong Chen, Ph.D.
15-October-2019

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Ibrance	Adequate
Established name(s)	palbociclib	Adequate
Route(s) of administration	For oral use	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Tablets: 125 mg, 100 mg, 75 mg	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)	Tablets	Adequate
Strength(s) in metric system	125 mg, 100 mg, 75 mg	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	125 mg tablets: Oval, light purple, film-coated tablets debossed with "Pfizer" on one side and "PBC 125" on the other side. 100 mg tablets: Oval, green, film-coated tablets debossed with "Pfizer" on one side and "PBC 100" on the other side. 75 mg tablets: Round, light purple, film-coated tablets debossed with "Pfizer" on one side and "PBC 75" on the other side.	Tablets: 125 mg palbociclib, oval, light purple, film-coated tablets debossed with "Pfizer" on one side and "PBC 125" on the other side. Tablets: 100 mg palbociclib, oval, green, film-coated tablets debossed with "Pfizer" on one side and "PBC 100" on the other side. Tablets: 75 mg palbociclib, round, light purple, film-coated tablets debossed with "Pfizer" on one side and "PBC 75" on the other side.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
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)	Ibrance and palbociclib	Adequate
Dosage form(s) and route(s) of administration	Tablets for oral administration	Adequate
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.	Inactive ingredients: Microcrystalline cellulose,….	Adequate. The applicant provided a list of all the ingredients
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	**Chemical name**: 6-acetyl-8-cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl)pyridin-2-yl]amino}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one **Structural**: provided **Molecular weight**: 447.54 daltons	Adequate

If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Palbociclib is a yellow to orange powder with pKa of 7.4 (b) (4) [redacted] At or below pH 4, palbociclib behaves as a high-solubility compound. Above pH 4, the solubility of the drug substance reduces significantly.	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)	Tablet	
Strength(s) in metric system	125 mg, 100 mg, 75 mg	
Available units (e.g., bottles of 100 tablets)	Monthly box containing 3 weekly blister packs of 7 tablets each (21 tablets total)	Info provided for all presentations. Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Oval, light purple, film-coated tablets debossed with "Pfizer" on one side and "PBC 125" on the other side. Oval, green, film-coated tablets debossed with "Pfizer" on one side and "PBC 100" on the other side. Round, light purple, film-coated tablets debossed with "Pfizer" on one side and "PBC 75" 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	
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.)	Store in the original blister pack	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 at 20 °C to 25 °C (68 °F to 77 °F); excursions permitted between 15 °C to 30 °C (59 °F to 86 °F)	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	Not relevant for oral dosage forms
Include information about child-resistant packaging	not provided	This is not required but the applicant can choose to include this information

1.2.5 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	Adequate

2.0 PATIENT LABELING

Assessment patient Labeling: Patient Labeling is adequate from the product quality perspective.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

The applicant provided labeling information for wallet card and dose pack, but they communicated to DMEPA that only the wallet card is to be used for commercial. Under weekly card, information for sample and trade were provided. The only difference between the wallet card weekly sample and wallet card weekly trade is that the wallet card weekly sample has the statement "PROFESSIONAL SAMPLE - NOT FOR SALE". The NDC numbers are also different.

Representative example of wallet card weekly sample

Representative example of wallet card weekly trade

3.2 Carton Labeling

The only difference between the wallet carton monthly sample and wallet carton monthly trade is that the wallet carton monthly sample has the statement “PROFESSIONAL SAMPLE - NOT FOR SALE”. The NDC numbers are also different.

Representative example of wallet carton monthly sample

Representative example of wallet carton monthly trade

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Provided	Adequate
Dosage strength	Provided	Adequate
Route of administration	Not provided	This is not a requirement
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	Provided	Adequate
"Rx only" displayed on the principal display	Provided	Adequate
NDC number	Provided for each strength if samples and trade	Adequate
Lot number and expiration date	Provided both on the container and carton	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Storage conditions provided	Adequate
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	Provided both on the container and carton	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Provided	Adequate
Medication Guide (if applicable)	"how should I take" is part of the container label	Adequate
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

Overall Assessment and Recommendation:

The container and carton labels as well as the prescribing information complies with all regulatory requirements from a CMC perspective pending revision of what are noted in the Assessor's Comments column for prescribing information.

The applicant is also requested to remove the labeling information for the dose pack. The following information request was sent to the applicant on 9/17/2019.

You propose to package commercial Ibrance® tablets in (b) (4) *blisters with* (b) (4) *(wallet card configuration). Remove* (b) (4) (b) (4)

Primary Labeling Assessor Name and Date: Tefsit Bekele 9/18/2019

Secondary Assessor Name and Date: Anamitro Banerjee 09/23/2019

TEFSIT BEKELE

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Anamitro Banerjee

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	NDA-212436-ORIG-1
Assessment Cycle Number	Original/ 505(b)(1)
Drug Product Name/ Strength	IBRANCE® (palbociclib) Tablets / 75 mg, 100 mg, and 125 mg
Route of Administration	(Immediate Release) Oral
Applicant Name	Pfizer, Inc.
Therapeutic Classification/ OND Division	Anti-Cancer/Kinase Inhibitor, DOP1
RLD/RS Number	Not Applicable
Proposed Indication & Dosage	(Same as approved for the IBRANCE Capsules) For the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with: an aromatase inhibitor as initial endocrine based therapy in postmenopausal women; or fulvestrant in women with disease progression following endocrine therapy. ➢ 125 mg once daily for 21 days with (or without) food followed by 7 days off treatment in each 28-day treatment cycle
Primary Reviewer:	Gerlie Gieser, Ph.D.
Secondary Reviewer:	Banu Zolnik, Ph.D.
Assesment Recommendation	ADEQUATE

Assessment Summary:

The proposed dissolution method and acceptance criterion (as tabulated below) are adequate for the routine quality control (QC) testing of IBRANCE® (palbociclib) tablets.

Adequate bridging data were provided to support the approval of the proposed to-be-marketed drug product.

USP Apparatus	Speed	Medium	Volume	Acceptance criterion
2 (paddle)	75 rpm	0.1N HCl, 37 ± 0.5°C	900 mL	NLT (b) (4) (Q) of the label claim is dissolved in 30 min

List of Submissions Assessed:

Document(s)	Date Received
Original NDA	1/31/2019
Response to Quality Information (SDN-2)	3/7/2019
Response to Quality Information (SDN-9)	7/31/2019

Concise Description of Outstanding Issues:
None

B.1 BCS DESIGNATION

Note that the proposed drug product IBRANCE® (palbociclib) **Tablets** uses the same active pharmaceutical ingredient (API, anhydrous palbociclib (b) (4) as the already approved IBRANCE® **Capsules**.

Assessment:

Solubility: *Low*
Palbociclib exhibits pH-dependent solubility, and low solubility per BCS criteria. The approved labeling of IBRANCE® Capsules indicates that the solubility of the drug substance is high at or below pH 4, and is reduced significantly above pH 4. For the pH-solubility profile of palbociclib, refer to either Figure 13 of 2.7.1. Biopharmaceutics Studies Summary of the current NDA or page 16 of the Biopharmaceutics Review of NDA 207103 for the approved IBRANCE® Capsules.

Permeability: *Low*
The approved labeling of IBRANCE® Capsules states that the mean absolute bioavailability of orally administered IBRANCE® 125 mg is 46%.

Dissolution: *Rapid to Very Rapid Dissolution in Low pH Media; Incomplete Dissolution in High pH Media*
The proposed drug product exhibits (b) (4) dissolution (i.e., at least (b) (4) % mean dissolution at 30 min) in 900 mL volumes of 0.1N HCl and pH (b) (4) buffer medium. (b) (4) (b) (4) See Figure 3.2.P.2.2-17 to Figure 3.2.P.2.2-20.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: *ADEQUATE*

Dissolution Method: *ADEQUATE*

(b) (4)

Table 1. Palbociclib Tablets Dissolution Parameters (TM-8440A)

Apparatus	II (paddles)
Medium	0.1 N hydrochloric acid
Volume	900 mL
Temperature	37 ± 0.5 °C

Agitation rate	75 rpm
Analytical Wavelength	UV-Vis at (b) (4) nm

Justification for Chosen Method Parameters:

(b) (4)

Discriminating Power:

The proposed QC dissolution method is discriminating for (b) (4)

(b) (4)

Analytical Method Validation:

UV-Vis is used for the quantification of drug in the dissolution samples. The analytical method was validated for range, specificity, (b) (4) suitability, linearity, accuracy,

system precision, repeatability (method precision), solution stability [redacted] and robustness with respect to dissolution method parameters. The dissolution method was shown to be robust with respect to paddle speed (75 [redacted] rpm), HCl concentration (0.1 [redacted] 1 N), medium volume (900 [redacted] mL) and temperature (37 [redacted] °C). Per the Drug Product Reviewer (Dr. Tefsit Bekele) the analytical methods validation including that for dissolution testing is adequate.

Dissolution Acceptance Criterion: *ADEQUATE*

The proposed dissolution acceptance criterion (Q = [redacted]% in 30 min) was based on the release and stability data of registration stability and clinical batches, as well as developmental batches of the commercial formulation.

Based on the dissolution profile data of the tablet batch (S78147/17-002158) that was reported by the Applicant to be bioequivalent (BE) to the approved reference capsule, [redacted] this Reviewer finds the proposed dissolution acceptance criterion acceptable for routine QC testing of all three strengths of the proposed drug product. Note that the Clinical Pharmacology Reviewer (Dr. Wentao Fu) confirmed the BE findings of Study 1042.

Note that the following quality attributes (at the studied ranges) did not significantly influence in vitro dissolution profiles of the tablet: [redacted]

Dissolution on Stability

Per the Applicant, there were no significant changes in the mean dissolution values at 30 minutes for tablets packaged in [redacted] blisters and stored under long term (25 °C/60% RH and 30 °C/75% RH for 12 months) and accelerated (40 °C/75% RH for 6 months) conditions. All results met the specification criterion. For the regression plots of the dissolution data (mean % dissolved at 30 minutes) for blister packaged samples stored up to 12 months at the long-term condition 30 °C/75% RH, refer to Figure 3.2.P.8.1-8 to Figure 3.2.P.8.1-10. Note that based on the 12 months

stability data, the proposed expiration period is 24 months when stored at controlled room temperature for product packaged in (b) (4) blisters.

The Applicant noted however that in the registration and developmental stability studies, trends of (b) (4)

(b) (4)

(b) (4)

(b) (4)

B.12 BRIDGING OF FORMULATIONS

Assessment: *ADEQUATE*

Bridging of the Clinical to the Final To-Be-Marketed Drug Product

The proposed commercial tablet (125 mg) has the same appearance, and will be manufactured using the same formulation, drug product manufacturing process (b) (4) and API manufacturing site (b) (4)

(b) (4) as the tablet evaluated in the Pivotal BE Study (A5481081; vs. IBRANCE® Capsule 125 mg/fed), the DDI Study with PPI/A5481091, as well as the target/reference tablet drug product used in Relative BA Study A5481042. Additionally, the proposed commercial tablets will be manufactured at a similar batch size as the lots used in registration stability lots and the pivotal BE and DDI studies lots (b) (4) Note that the pivotal BE batch (S78147/17-002158) is also a registration (stability) lot (S78147/17-002158, blisters), and like this clinical/registration (stability) lot, the commercial scale lots (at batch release) conform to the Applicant's proposed/ FDA's recommended dissolution acceptance criterion.

Of note, the proposed commercial packaging is (b) (4) blisters with (b) (4) whereas the clinical PK study materials were supplied to the clinical research unit in HDPE bottles (b) (4) (for dispensing of the pharmacy into unit dose containers [per the study reports of Studies 1091 and 1042]). As indicated in the paragraph above, there is proof that the drug product in its proposed commercial packaging configuration (b) (4) were able to meet the proposed dissolution acceptance criterion over 12 months of long-term storage and 6 months of accelerated storage. Based on the established "clinical safe space" and clinically relevant dissolution specification as shown in Figure 2 above, any palbociclib tablet lot that conforms to the proposed/approved dissolution acceptance criterion (i.e., achieves at least (b) (4) % dissolution at 30 min) is anticipated to be bioequivalent to the (target) palbociclib tablet drug product that was tested in the pivotal BE study (1081 vs. the IBRANCE Capsules) and the relative BA study (1042).

REVIEWER NOTE:
Scientific Bridging of the Proposed Drug Product (IBRANCE® Tablets) to the Approved IBRANCE® Capsules

This NDA for the IBRANCE® Tablets relies on the FDA's findings of clinical efficacy and safety for the approved IBRANCE® Capsules.

The Applicant's overall strategy to establish bioequivalence between the final to-be-marketed *tablet* to the commercial *capsule* is illustrated in Figure 2.3.P.2-2 of the NDA. Based on the results of Study A5481081, the Applicant concluded (and the Clinical Pharmacology Reviewer confirmed) that the proposed commercial palbociclib tablet (125 mg) is bioequivalent to the commercial capsule under fasted and fed conditions.

B. 13 BIOWAIVER REQUEST

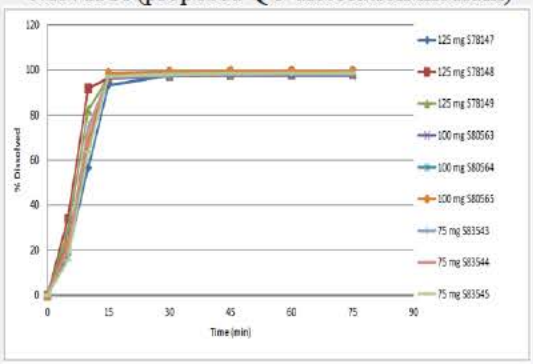
Assessment: *GRANTED*

The Applicant's request to waive the requirement to conduct an *in vivo* BA or BE study for the two lower strengths (75 mg and 100 mg) of the proposed commercial tablet is granted based on evidence of (b) (4) and comparable *in vitro* dissolution profile data of the test and reference strengths in 900 mL volumes

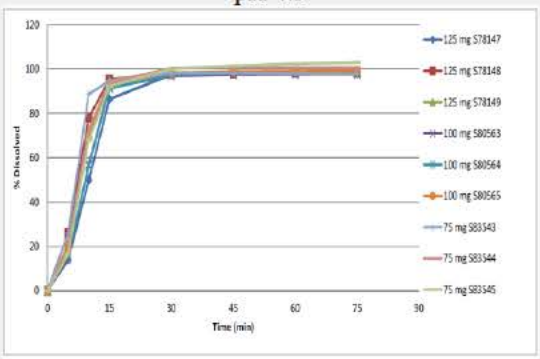
of various pH media, using the operating parameters of the proposed QC dissolution method (USP Apparatus 2 at 75 rpm; Figure 3) that was shown to be clinically relevant. Additionally, the Applicant noted that palbociclib PK are dose proportional across the (b) (4) mg dose range.

Figure 3. Comparative *In Vitro* Dissolution Profiles of Bio-Strength and Non-Bio-Strengths of the Proposed Commercial Palbociclib Tablets in Various pH Buffer Media (n=12; Paddles at 75 rpm)

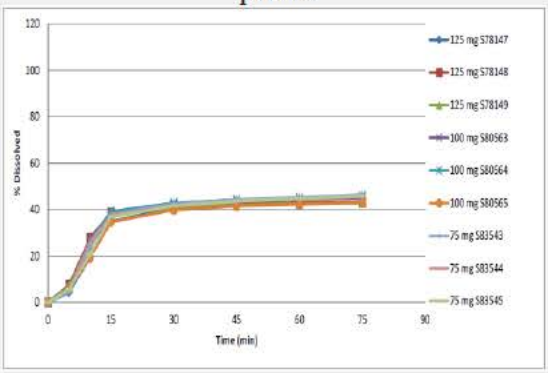
0.1N HCl (proposed QC dissolution medium)



pH 4.5



pH 6.8



Source: Figures 1 to 3 of 3.2.R Biowaiver Request
Note: The 125 mg Lot S78147 was used as the target/reference drug product in the Pivotal BE Study A5481081 and is one of the registration/stability lots.

Gerlie Gieser

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/s/

XIAOHONG CHEN
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