CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213736Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 213736
Assessment #1

Drug Product Name	PEMAZYRE (pemigatinib)
Dosage Form	Tablets
Strength	4.5 mg, 9 mg and 13.5 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Incyte Corporation
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original NDA	09/30/2019	All
Quality Amendment	11/06/2019	OPMA
Quality Amendment	12/11/2019	OPMA
Labeling Amendment	12/20/2019	DP

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Raymond Frankewich	Suong Tran
Drug Product	Olen Stephens	Anamitro Banerjee
Manufacturing	Sridhar Thumma	Bogdan Kurtyka
Microbiology	Sridhar Thumma	Bogdan Kurtyka
Biopharmaceutics	Mei Ou	Banu Zolnik
Regulatory Business Process Manager	Shamika Brooks	
Application Technical Lead	Xing Wang	
Laboratory (OTR)	N/A	N/A
Environmental	James Laurenson	N/A

Xing Wang

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EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Complete CMC information has been submitted to NDA 213736 and found to be adequate upon completion of the review. All the facilities are approvable based on acceptable compliance history, no PAIs.

OPQ recommends **APPROVAL** of NDA 213736 for PEMAZYRE (pemigatinib) Tablets 4.5 mg, 9 mg and 13.5 mg. OPQ grants an 24-month expiration period for PEMAZYRE (pemigatinib) Tablets 4.5 mg, 9 mg and 13.5 mg, when stored at "(b) (4) room temperature: 20°C - 25°C (68°F – 77 °F); excursions permitted to 15-30 °C (59°F - 86°F) [See USP Controlled Room Temperature]". In addition, OPQ grants a (b) (4) month re-test period for the drug substance when stored (b) (4).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Pemigatinib is a kinase inhibitor indicated for the treatment of adults with previously treated, locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement as detected by an FDA-approved test. Pemigatinib drug substance is a free base, white to off-white solid, no chiral center, and not hygroscopic (b) (4) (b) (4). Pemigatinib drug product is supplied as immediate release uncoated tablets for oral administration in strengths of 4.5 mg, 9 mg and 13.5 mg. Drug load is (b) (4) %wt and the excipients are MCC (b) (4), sodium starch glycolate (b) (4), and magnesium stearate (b) (4) (b) (4). The manufacturing process is identical for all three tablet strengths and uses conventional pharmaceutical processes: (b) (4) (b) (4) (b) (4). Pemigatinib tablets are packaged in (b) (4) HDPE bottles, with 14 count per bottle. The drug product is stored at controlled room temperature. The recommended dose is 13.5 mg, QD.

Proposed Indication(s) including Intended Patient Population	For the treatment of adults with previously treated, locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement as detected by an FDA-approved test.
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	13.5 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

(b) (4)

(b) (4) Pemigatinib is manufactured (b) (4)

(b) (4)

Pemigatinib drug substance is controlled using a specification that contains tests for Identity by IR spectrum, Assay and impurities using HPLC, elemental impurities using ICP-MS, residual solvents, solid state form using XRPD, and particle size distribution. Pemigatinib drug substance is (b) (4)

(b) (4)

The retest period for pemigatinib drug substance is (b) (4) months, supported by real-time stability data with storage (b) (4) (b) (4) when the DS is stored (b) (4). Stress testing indicates that pemigatinib is not light sensitive.

Drug Product: Adequate

The drug product is available in three dosage strengths manufactured (b) (4) (b) (4) and are (b) (4). The formulation consists of the drug substance and excipients of compendial quality. The manufacturing process reviewer verified that though the formulation has a (b) (4) (b) (4) there are no manufacturability issues. The batch data demonstrates content uniformity is not a challenge with the given manufacturing process. The drug product specifications include the standard list of quality attributes with acceptance criteria in typical ranges for solid oral dosage forms. The biopharmaceutics reviewer indicated that the dissolution method and acceptance criteria are acceptable. Batch release and stability data indicate the formulation is stable, consistently manufactured at high quality levels, and support the requested shelf life request of 24 months when stored at "Controlled

room temperature: 20°C - 25°C (68°F – 77 °F); excursions permitted to 15-30 °C (59°F - 86°F) [See USP Controlled Room Temperature]".

Labeling: Adequate

All CMC comments/edits have been conveyed to OND and the applicant.

Manufacturing: Adequate

Pemigatinib tablets 4.5 mg, 9 mg and 13.5 mg (b) (4) (b) (4) are manufactured (b) (4). The manufacturing process involves (b) (4) (b) (4) (b) (4) The proposed (b) (4) process parameters are supported by development/ registration batches data. No scale up is proposed. The batch size proposed for validation/commercial manufacturing is (b) (4) (b) (4).

The DS and DP manufacturing facilities are approvable based on acceptable compliance history, District file review and Final ORA recommendation. No PAIs were recommended/performed for these facilities. Three DS testing facilities were listed in the application which are approvable based on profile. A DP secondary packaging facility was also listed which does not require evaluation.

Biopharmaceutics: Adequate

Biopharmaceutics Review focuses on the evaluation of (i) the in vitro dissolution method and acceptance criterion as a quality control (QC) test for the proposed drug product, (ii) biowaiver request, (iii) the need of in vitro formulation bridging studies between the clinical formulation and the commercial formulation:

(i)The proposed dissolution method showed an acceptable discriminating ability (b) (4), therefore, the proposed dissolution method is acceptable as a quality control (QC) test for the propose drug product for batch release and stability testing. The dissolution data support the proposed dissolution acceptance criterion.

(ii)The proposed three strengths products have proportional composition in both active and inactive ingredients, have same immediate release dosage form, have the linearity in pharmacokinetics from 1-20 mg dose used in clinical studies, have comparative in vitro dissolution profiles in QC medium and in multi-pH media, have same manufacturing process and are produced from same manufacturing site. Therefore, the biowaiver request of the proposed two higher strengths products, Pemigatinib Tablets, 9 mg and 13.5 mg, can be granted per 21 CFR 320.22(d)(2).

(iii)For the proposed three strengths of pemigatinib tablets, the 4.5 mg products have been used in clinical studies, but the 9 mg and 13.5 mg products have not been used in clinical studies. The 4.5 mg tablets used in clinical studies have

same formulation with the commercial formulation, only debossing configuration is applied to the final product image, (b) (4) (b) (4). All three strengths tablets (4.5 mg, 9 mg, and 13.5 mg) are (b) (4) using the same manufacturing process and are produced from same manufacturing site. Therefore, no additional in vitro bridging studies are needed to bridge the clinical and the commercial formulations for the proposed drug products.

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**
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	**L**	(b) (4)	**L**	
Physical Stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	**M**		**L**	
Content Uniformity	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	**M**		**L**	
Dissolution – BCS Class II	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	**L**		**L**	

Application Technical Lead Name and Date: Xing Wang, Ph.D.

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U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	Adequate	12/3/2019	DMFs not reviewed per MAPP 5015.5 (Rev. 1).
	III			Adequate		
	III			Adequate		

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

Document	Application Number	Description
IND	124358	Drug development

2. CONSULTS None

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate pending changes communicated through clinical division.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Pemazyre	Approved by DMEPA
Established name(s)	Pemigatinib	Adequate; consistent with USAN
Route(s) of administration	Oral Use	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Tablets: 4.5 mg, 9 mg, 13.5 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	No scoring	NA
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.	Not injectable	NA

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)	Pemazyre can be taken with or without food. Do not crush, chew, split or dissolve tablets	Adequate.

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	4.5 mg, 9 mg, 13.5 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Not a salt	NA
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Color, shape, and debossing defined	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
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.	NA	NA

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Pemazyre (pemigatinib) tablets	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.	Not a salt	NA
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Qualitative formulation provided	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.	Not an injectable	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	No alcohol present	NA
Statement of being sterile (if applicable)	Not a sterile product	NA
Pharmacological/ therapeutic class	FGFR 1, 2 and 3 inhibitor	Adequate
Chemical name, structural formula, molecular weight	Added during labeling review	Pending
If radioactive, statement of important nuclear characteristics.	Not radioactive	NA
Other important chemical or physical properties (such as pKa or pH)	Added during labeling review	Pending

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	No such statements included	NA
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	No such statements included	NA

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)	Tablets	Adequate
Strength(s) in metric system	4.5 mg, 9 mg, 13.5 mg	Adequate
Available units (e.g., bottles of 100 tablets)	Bottles of 14	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Tablet shape, color, and debossing included	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not scored	NA
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.	No injectable	NA

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.)	No special handling required; not photolabile; freeze-thaw study indicated robustness; (b) (4) (b) (4) limits do not impact dissolution or chemical stability.	NA
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."	No desiccant included	NA
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store PEMAZYRE bottles at room temperature 20-25^{O}C (68-77^{O}F); excursions permitted to 15-30^{O}C (59-86^{O}F)	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."	No latex statement needed	NA
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	Manufactured for: Incyte Corporation Wilmington, DE 19803	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): The medication guide includes information regarding storage, inactive ingredients, and administration.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

3.2 Carton Labeling

No carton used in the container closure

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Pemazyre (pemigatinib) tablets	Adequate
Dosage strength	4.5 mg, 9 mg, 13.5 mg	Adequate
Route of administration	Not specified, but not required	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not a salt	NA
Net contents (e.g. tablet count)	14-tablets	Adequate
"Rx only" displayed on the principal display	Provided	Adequate
NDC number	Included	Adequate
Lot number and expiration date	Space included	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at room temperature 20^{O}C to 25^{O}C (68^{O}F to 86^{O}F) [See USP Controlled Room Temperature]	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Not an injectable	NA
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	No packaging alternatives proposed	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Contains no alcohol	NA
Bar code	Provided	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured for: Incyte Corporation Wilmington, DE 19803	Adequate
Medication Guide (if applicable)	Provided	Adequate
No text on Ferrule and Cap overseal	Complies	Adequate
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.	NA	NA
And others, if space is available	None	NA

Assessment of Carton and Container Labeling: Adequate; not comments necessary for the container label

ITEMS FOR ADDITIONAL ASSESSMENT

1. **None**

Overall Assessment and Recommendation:

Adequate pending revision following information request. At the time of this review, preliminary comments have been communicated to update section 11 of the package insert for additional description of the drug substance. Labeling review will continue in collaboration with the clinical division and the final label included in the action package.

Primary Labeling Assessor Name and Date: Olen Stephens, 1/24/2020

Secondary Assessor Name and Date: Anamitro Banerjee, 1/24/2020

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BIOPHARMACEUTICS

NDA: 213736 [505(b)(1)]
Drug Product Name/Strength: Pemazyre™ (Pemigatinib) Tablets, 4.5 mg, 9 mg and 13.5 mg
Route of Administration: Oral
Proposed Indication: For the treatment of adults with previously treated, locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement as detected by an FDA-approved test.
Applicant Name: Incyte Corporation
Submission Date: 09/30/2019
Primary Reviewer: Mei Ou, Ph.D.
Secondary Reviewer: Banu Zolnik, Ph.D.

EXECUTIVE SUMMARY

Pemigatinib is a small molecule inhibitor of the fibroblast growth factor receptor (FGFR) family 1, 2 and 3 for the treatment of adults with previously treated, locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement. Pemigatinib free base is selected as the drug substance (DS) to manufacture the drug product. The proposed drug product, Pemigatinib Tablets, 4.5 mg, 9 mg and 13.5 mg, are the immediate release uncoated tablets, while the proposed dose is 13.5 mg taken orally once daily for 14 days followed by 7 days off therapy.

In the current NDA 213736 submission, the Biopharmaceutics Review focuses on the evaluation of (i) the in vitro dissolution method and acceptance criterion as a quality control (QC) test for the proposed drug product, (ii) biowaiver request, (iii) the need of in vitro formulation bridging studies between the clinical formulation and the commercial formulation.

In Vitro Dissolution Testing of the Finished Product:
The dissolution parameters have been evaluated. The proposed dissolution method showed an acceptable discriminating ability with regards to tablet hardness and disintegrant in the formation, therefore, the proposed dissolution method is **acceptable** as a quality control (QC) test for the propose drug product for batch release and stability testing. The dissolution data support the proposed dissolution acceptance criterion.

The final approved in vitro dissolution method and acceptance criterion for the proposed Pemigatinib Tablets, 4.5 mg, 9 mg and 13.5 mg are presented below:

USP Apparatus	I (Basket)
Rotation Speed	50 rpm
Dissolution Medium	500 mL of 0.01 N HCl
Temperature	37°C±0.5°C
Sampling Time	10, 15, 20, 30, 45, 60 minutes
Acceptance Criterion	Q= (b) (4)% in 30 minutes

The In Vitro Formulation Bridging:
For the proposed three strengths of pemigatinib tablets 4.5 mg, 9 mg, and 13.5 mg. The 4.5 mg strength has been used in clinical studies when 9 mg and 13.5 mg doses (as 4.5 mg X 2 or 4.5 mg X 3) are used in the clinical trials. However, the 9 mg and 13.5 mg strengths have not been used in the clinical studies. The 4.5 mg tablets used in clinical studies have same formulation as the commercial formulation, (b) (4) (b) (4) (b) (4). All three strengths tablets (4.5 mg, 9 mg, and 13.5 mg) are (b) (4) using the same manufacturing process and are produced from same manufacturing site. Therefore, no additional in vitro bridging studies are needed to bridge the clinical and the commercial formulations for the proposed drug products.

Biowaiver:
The proposed three strengths products have proportional composition in both active and inactive ingredients, have same immediate release dosage form, have the linearity in pharmacokinetics from 1-20 mg dose used in clinical studies, have comparative in vitro dissolution profiles in QC medium and in multi-pH media, have same manufacturing process and are produced from same manufacturing site. Therefore, the biowaiver request of the proposed two higher strengths products, Pemigatinib Tablets, 9 mg and 13.5 mg, is granted per 21 CFR 320.22(d)(2).

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 213736 for the proposed Pemazyre™ (Pemigatinib) Tablets, 4.5 mg, 9 mg and 13.5 mg, is recommended for **APPROVAL.**

BIOPHARMACEUTICS REVIEW

1. Drug substance solubility and permeability

Per the Applicant, pemigatinib is a BCS II compound. Pemigatinib (pK_as 3.1 and 5.7) has pH dependent solubility in aqueous buffers with pH range of 1.2 to 7.4. As solubility data presented in Table 1 below, pemigatinib has decreased solubility with increasing pH. Pemigatinib exhibits concentration dependent permeability in Caco-2 monolayer cells. As permeability data presented in Table 2 below, the apparent permeability ($P_{app\ A\ to\ B}$) range of pemigatinibe is $5.8x10^{-6}$ to $21x10^{-6}$ cm/sec from 0.01 to 30 µM, while the P_{app} of nadolol (low permeability marker) is $0.22x10^{-6}$ cm/sec and P_{app} of metolprolol (high permeability marker) is $15x10^{-6}$ cm/sec.

Table 1: Solubility of pemigatinib over the physiological pH range at 37°C
(*data from table 1 in M.3.2.S.1.3*)

pH	Buffer/Solution Type	Solubility (mg/mL)	Solubility (mg/250 mL)
1.2	HCl	> 0.71	> 177.6
2.0	HCl	0.65	162.7
3.3	Phosphate	0.20	50.5
4.3	Acetate	0.03	6.7
5.3	Acetate	< 0.001	< 0.001
6.5	Phosphate	< 0.001	< 0.001
7.4	Phosphate	< 0.001	< 0.001
1.2	SGF	13.98	3496
6.8	SIF	0.003	0.88
6.5	FaSSIF	0.008	2.00
5.0	FeSSIF	0.219	54.8

SGF = simulated gastric fluid; SIF = simulated intestinal fluid; FaSSIF = fasted-state simulated intestinal fluid; FeSSIF = fed-state simulated intestinal fluid.

Table 2: Bidirectional transport of INCB054828 (pemigatibib) across caco-2 monolayers
(*data from table 1 in study INCYTE-DMB-14.61.1 in M.5.3.2.3*)

Concentration (µM)	Inhibitor		Papp A-B[a] (× 10^{-6} cm/s)	Papp B-A[a] (× 10^{-6} cm/s)	Efflux Ratio (B-A/A-B)[a]
	Compound	Concentration (µM)			
0.01	NA	NA	5.8 ± 0.87	23 ± 1.0	**4.0 ± 0.63**
	CSA	5	15 ± 0.89	14 ± 1.8	**0.93 ± 0.10**
0.1	NA	NA	6.7 ± 1.9	22 ± 5.8	**3.3 ± 1.0**
	CSA	5	9.7 ± 0.65	14 ± 4.0	**1.4 ± 0.23**
1	NA	NA	7.3 ± 1.6	11 ± 0.95	**1.5 ± 0.35**
	CSA	5	12 ± 2.3	9.0 ± 1.8	**0.73 ± 0.17**
10	NA	NA	15 ± 0.58	13 ± 0.99	**0.89 ± 0.08**
	CSA	5	16 ± 1.0	16 ± 4.9	**1.0 ± 0.15**
30	NA	NA	21 ± 1.1	13 ± 1.6	**0.64 ± 0.07**
	CSA	5	18 ± 0.75	12 ± 1.3	**0.63 ± 0.07**

NA = not applicable.
[a] N = 3-6.

Per the Applicant, more than (b) (4) % of radiolabeled pemigatinib was absorbed following an oral dose of 13.5 mg from a mass balance and metabolism study conducted in healthy volunteers with 14C-pemigatinib (Study INCB 54828-105).

Therefore, the (b) (4) oral absorption of pemigatinib mitigate the risk of the impact of drug substance low solubility and low permeability on the drug product dissolution.

2. In vitro dissolution method

Dissolution is one of the critical quality attributes (CQAs) of the proposed drug product. The proposed dissolution method and acceptance criterion are listed as below, while the dissolution method development report is submitted in M.3.2.P.2. (b) (4)

(b) (4)

USP Apparatus	I (Basket)
Rotation Speed	50 rpm
Dissolution Medium	500 mL of 0.01 N HCl
Temperature	37ºC±0.5ºC
Sampling Time	10, 15, 20, 30, 45, 60 minutes
Acceptance Criterion	Q= (b) (4) % in 30 minutes

The following parameters have been evaluated for determining the dissolution method, summarized as:

(b) (4)

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(b) (4)

Overall, this Reviewer considers that the proposed dissolution method (USP Apparatus I Basket, 50 rpm, 500 mL of 0.01 N HCl) showed acceptable discriminating ability (b) (4) (b) (4), therefore, the proposed dissolution method is acceptable as a quality control (QC) test for the proposed drug product.

3. Dissolution data and acceptance criterion

The dissolution data of the proposed Pemigatinib Tablets, 4.5 mg, 9 mg and 13.5 mg evaluated during dissolution method development are presented in Figure 6 above. The dissolution data of primary stability/registration batches are provided in M.3.2.P.5.4, which are summarized in the Table 5 below. From the totality of the data, all three strengths products showed very rapid and complete dissolution (> (b) (4)% dissolution in 15 minutes), therefore, similarity factor (*f2*) calculation among the three strengths products is not needed while the three strengths products have similar dissolution profiles.

Table 5: Dissolution data of the proposed pemigatinib tablets, 4.5 mg, 9 mg and 13.5 mg

Batch Number		180006	180010	180014
Dosage Strength (mg)		4.5	4.5	4.5
Date of Manufacture		17 Jan 2018	23 Jan 2018	08 Feb 2018
Batch Size (Theoretical # of tablets)		(b) (4)		
Drug Substance Lot		CA17-1186	CA17-1186	CA17-1187
Use		Primary Stability	Primary Stability	Primary Stability
Test	Acceptance Criterion	Result		
Dissolution at Release	≥ (b) (4)% (Q) of the Label Claim dissolved in 30 minutes as defined in USP <711>	(b) (4)		
Dissolution for Retain Sample (additional time points tested)[a]	≥ (b) (4)% (Q) of the Label Claim dissolved in 30 minutes as defined in USP <711>			

[a] Additional testing was performed for dissolution only using retain samples and is provided here to demonstrate the inclusion of the 10 and 20 minute time points in the commercial method

Batch Number		180007	180011	180015
Dosage Strength (mg)		9	9	9
Date of Manufacture		17 Jan 2018	23 Jan 2018	08 Feb 2018
Batch Size (Theoretical # of tablets)		(b) (4)		
Drug Substance Lot		CA17-1186	CA17-1186	CA17-1187
Use		Primary Stability	Primary Stability	Primary Stability
Test	Acceptance Criterion	Result		
Dissolution At Release	≥ (b) (4)% (Q) of the Label Claim dissolved in 30 minutes as defined in USP <711>	(b) (4)		
Dissolution for Retain Sample (additional time points tested)[a]	≥ (b) (4)% (Q) of the Label Claim dissolved in 30 minutes as defined in USP <711>			

[a] Additional testing was performed for dissolution only using retain samples and is provided here to demonstrate the inclusion of the 10 and 20 minute time points in the commercial method

Batch Number		180008	180012	180016
Dosage Strength (mg)		13.5	13.5	13.5
Date of Manufacture		17 Jan 2018	23 Jan 2018	08 Feb 2018
Batch Size (Theoretical # of tablets)		(b) (4)		
Drug Substance Lot		CA17-1186	CA17-1186	CA17-1187
Use		Primary Stability	Primary Stability	Primary Stability
Dissolution	≥ (b) (4)% (Q) of the Label Claim dissolved in 30 minutes as defined in USP <711>	(b) (4)		
Dissolution for Retain Sample (additional time points tested)[a]	≥ (b) (4)% (Q) of the Label Claim dissolved in 30 minutes as defined in USP <711>			

[a] Additional testing was performed for dissolution only using retain samples and is provided here to demonstrate the inclusion of the 10 and 20 minute time points in the commercial method

The dissolution data of the registration batches under long-term stability conditions (25°C/60% RH) at initial, 1, 3, 6, 9, 12, and 17 months are provided in M.3.2.P.5.4, while the dissolution data collected at 17 months are summarized in the following Table 6. All registration batches have (b) (4) dissolution (b) (4) in 30 minutes for up to 17 months with no trend observed.

Table 6: Mean dissolution data of registration batches under long-term stability condition at 17 months (n=6)

	Time (min)					
	10	15	20	30	45	60
4.5 mg (Batch 180006) 17 months	103	103	103	103	104	104
4.5 mg (Batch 180010) 17 months	105	105	105	105	105	105
4.5 mg (Batch 180014) 17 months	103	104	104	104	104	104
9 mg (Batch 180007) 17 months	95	99	100	100	100	100
9 mg (Batch 180011) 17 months	94	98	100	100	100	100
9 mg (Batch 180015) 17 months	95	99	100	100	100	100
13.5 mg (Batch 180008) 17 months	85	92	97	99	100	100
13.5 mg (Batch 180012) 17 months	90	98	101	102	102	102
13.5 mg (Batch 180016) 17 months	86	94	99	102	102	102

Overall, this Reviewer considers the proposed dissolution acceptance criterion of "Q= (b) (4)% in 30 minutes" is supported by the data then is acceptable.

4. In vitro formulation bridging studies

Although three early development pemigatinib tablets (0.5 mg, 2 mg and 4.5 mg) were used in some early clinical studies, the proposed 4.5 mg, 9 mg and 13.5 mg tablets are the final commercial drug products.

Among the proposed three strengths tablets, 4.5 mg tablets have been used in clinical studies, but the 9 mg and 13.5 mg tablets have not been used in clinical studies. The 4.5 mg tablet used in clinical studies have same formulation with the commercial formulation, only debossing configuration is applied to the final product image, (b) (4) (b) (4). All three strengths tablets (4.5 mg, 9 mg, and 13.5 mg) (b) (4) are produced from same manufacturing site.

Therefore, this Reviewer considers that no additional in vitro bridging studies are needed to bridge the clinical and the commercial formulations.

5. Biowaiver

Based on the meeting minutes of the Type B, End of Phase 2 (EOP2), CMC meeting scheduled on 04/05/2018 cross reference to IND 138179[1], FDA recommended the following the required information and data if a biowaiver request of the proposed Pemigatinib Tablets, 9 mg and 13.5 mg, will be requested, as:

- Inclusion of a biowaiver request in the NDA submission;
- All strengths are the same dosage form;
- There are bioavailability data for the 4.5 mg strength;
- Both the 9 and 13.5 mg strengths are proportionally similar in their active and inactive ingredients to the 4.5 mg strength;
- The two higher strengths are within the dose range studied in clinical trials;
- Linear pharmacokinetics have been demonstrated over the proposed dose range (note that the data submitted will be assessed by FDA to confirm linear pharmacokinetics); and
- Dissolution profile comparisons between the highest and lower strengths in three different media meet the *f*2 similarity requirements.

In current NDA submission, the Applicant submitted a formal biowaiver request for the proposed Pemigatinib Tablets, 9 mg and 13.5 mg, in M.1.12.15. In addition, the Applicant provided the supportive data information to support the biowaiver request, summarized as below.

(i) As the drug product composition information presented in Table 7 below, the proposed Pemigatinib Tablets, 4.5 mg, 9 mg, and 13.5 mg have proportional composition in both active and inactive ingredients. All three strengths products have same immediate release tablet dosage form.

[1] https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af80491a31&_afrRedirect=3518352982553227

Table 7: Composition of Pemigatinib Tablets

Component	wt%	4.5 mg Formulation 54828-004-00	9 mg Formulation 54828-004-01	13.5 mg Formulation 54828-004-02
		mg/tab	mg/tab	mg/tab
Pemigatinib	(b) (4)	4.50	9.00	13.50
Microcrystalline Cellulose		(b) (4)		
Sodium Starch Glycolate				
Magnesium Stearate				
Total	100.0			
Tablet Size and Shape				
Tablet Debossing		"I" on one side and "4.5"on the other side	"I" on one side and "9"on the other side	"I" on one side and "13.5"on the other side

(ii) The pharmacokinetics (PK) and bioavailability studies of the proposed 4.5 mg tablets have been studied in (a) a Phase I study (INCB 54828-104, DMB-18.64.1, submitted in M.5.3.3.4), (b) a Phase 1/2 study (INCB 54828-101, DMB-19.58.1, submitted in M.5.3.3.2). The proposed 9 mg and 13.5 mg tablets are within the dose range (1-20 mg) used in clinical studies. All PK and bioavailability results are under purview of the Office of Clinical Pharmacology (OCP).

(iii) The linear PK in the dose range of 1 to 20 mg was evaluated in a Phase 1 study (INCB 54828-101, DMB-19.116.1, submitted in M.5.3.3.4). The results are summarized in the following Table 8 and Figures 12 and 13.

Table 8: Summary of pemigatinib pharmacokinetic parameters for pemigatinib administered as monotherapy (part 1 and 2) in C1D8/C1D14 (steady state) of study INCB 54828-101

Dose	Participant(s)	$C_{max,ss}$ (nM)	$AUC_{ss,0\text{-}24}$ (h*nM)
1 mg	1002	26.2	208
2 mg	1004	22.9	322
4 mg	1008	103	1380
6 mg	N = 4	86.1 ± 38.0 78.8 (54.3)	1080 ± 301 1050 (27.6)
9 mg	N = 18	196 ± 123 162 (72.0)	2180 ± 1630 1670 (95.1)
13.5 mg	N = 57	271 ± 151 236 (56.4)	3010 ± 1890 2620 (54.1)
20 mg	N = 13	449 ± 172 421 (38.7)	4350 ± 1480 4150 (32.1)
P-values from a 1-Factor ANOVA of log-transformed, dose-normalized data (factor = dose)			
Dose		0.632	0.943
Pairwise p-values from a 1-factor ANOVA of log-transformed, dose-normalized data (factor = dose)			
6 mg vs 9 mg		0.2841	0.8577
6 mg vs 13.5 mg		0.3042	0.7238
6 mg vs 20 mg		0.1259	0.5923
9 mg vs 13.5 mg		0.8214	0.7634
9 mg vs 20 mg		0.4315	0.5749
13.5 mg vs 20 mg		0.2595	0.6877

Note: values are presented in the format of mean ± SD and geometric mean (CV%).

Figure 12: Relationship of dose and pemigatinib plasma $C_{max,ss}$ in individual participants receiving QD dosing of pemigatinib in study INCB 54828-101

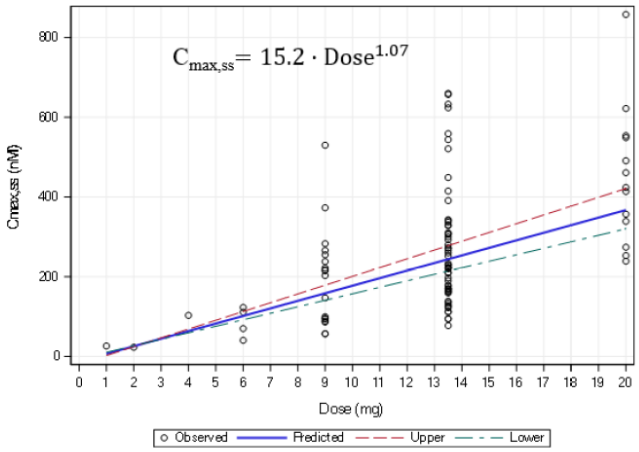
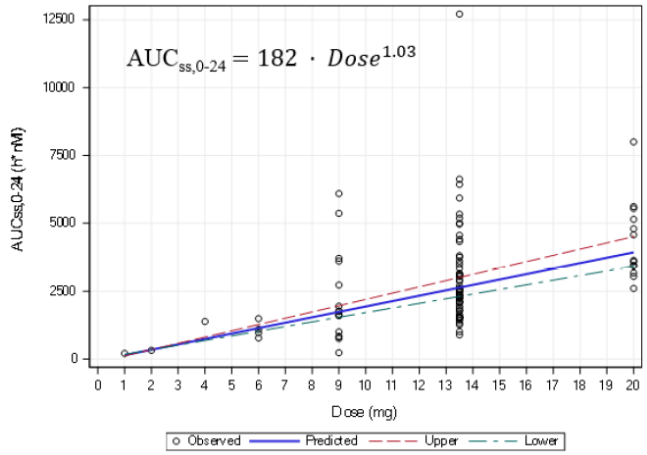


Figure 13: Relationship of dose and pemigatinib plasma $AUC_{ss,0-24}$ in individual participants receiving QD dosing of pemigatinib in study INCB 54828-101



Dr. Robert Schuck OCP reviewer confirmed that the slopes of C_{max} and AUC are not statistically significantly different from 1 based on the power-function regression analysis, therefore, OCP concludes that C_{max} and AUC of pemigatinib showed linearity in pharmacokinetics from 1 to 20 mg dosage range.

(iv) The comparative dissolution data profiles of the proposed Pemigatinib Tablets, 4.5 mg, 9 mg, and 13.5 mg in 0.01 N HCl (QC dissolution medium), 0.1N HCl, pH 4.5 and pH 6.8 media are provided. The dissolution profiles are plotted by this Reviewer in the following Figures 14 to 17. From the results, the proposed three strengths tablets have comparable dissolution in all media. In addition, all three strengths tablets (4.5 mg, 9 mg, and 13.5 mg) are [redacted] (b) (4) produced from same manufacturing site.

Table 14: Comparative dissolution profiles of the proposed Pemigatinib Tablets, 4.5 mg, 9 mg, and 13.5 in 0.01 N HCl

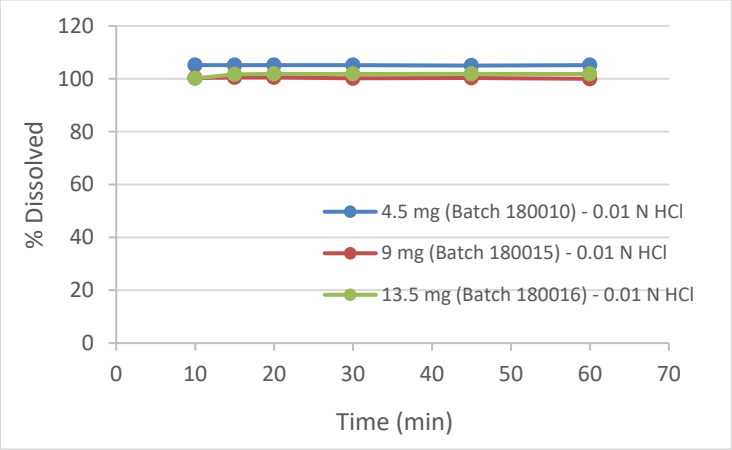


Table 15: Comparative dissolution profiles of the proposed Pemigatinib Tablets, 4.5 mg, 9 mg, and 13.5 in 0.1 N HCl

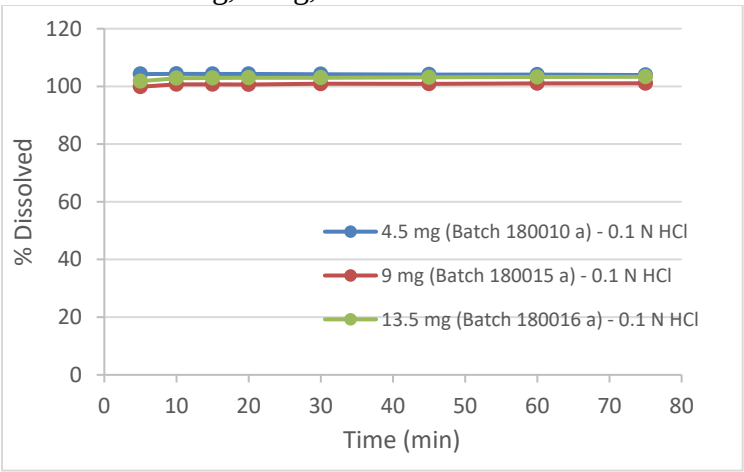


Table 16: Comparative dissolution profiles of the proposed Pemigatinib Tablets, 4.5 mg, 9 mg, and 13.5 in pH 4.5 acetate buffer

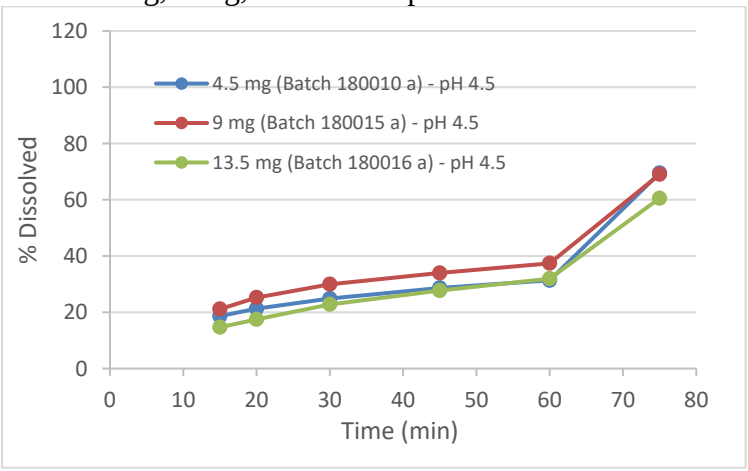
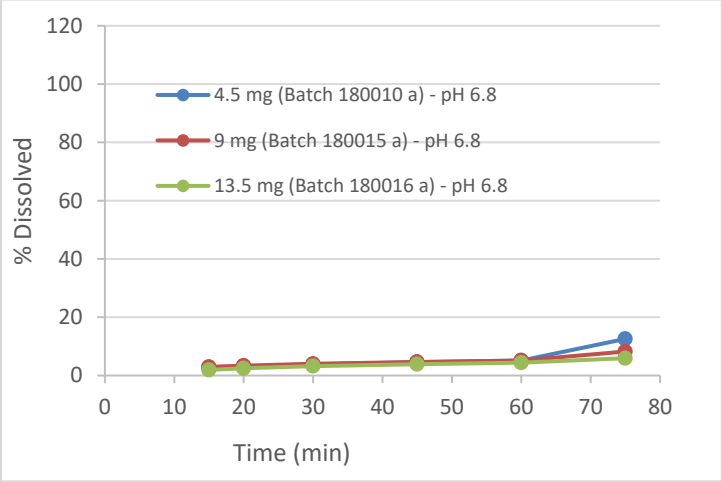


Table 17: Comparative dissolution profiles of the proposed Pemigatinib Tablets, 4.5 mg, 9 mg, and 13.5 in pH 6.8 phosphate buffer



Overall, this Reviewer considers that all the above data information support the biowaiver request of the proposed Pemigatinib Tablets, 9 mg and 13.5 mg. Therefore, the biowaiver request is granted per 21 CFR 320.22(d)(2).

Mei Ou

Digitally signed by Mei Ou
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Banu Zolnik

Digitally signed by Banu Zolnik
Date: 2/19/2020 11:39:30AM
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/s/

XING WANG
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