

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**212327Orig1s000**

**PRODUCT QUALITY REVIEW(S)**

**Recommendation: APPROVAL**

**NDA 212327  
Review #1**

Drug Name/Dosage Form	INREBIC (fedratinib) Capsules
Strength	100 mg
Route of Administration	Oral
Rx/OTC Dispensed	R <sub>x</sub>
Applicant	Impact Biomedicines, Inc
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	03-Jan-19	All
Amendment (SD 0002)	23-Jan-19	DS
Amendment (SD 0005)	21-Feb-19	Process
Amendment (SD 0017)	12-Apr-19	Process

**Quality Review Team**

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Sharron Kelly	Su Tran
Drug Product	Xing Wang	Anamitro Banerjee
Process and Facility	Zhijin Chen	Rakhi Shah
Microbiology	n/a	n/a
Biopharmaceutics	Mei Ou	Banu Zolnik
Regulatory Business Process Manager	Melinda Bauerlien	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	James Laurenson	n/a

## ATTACHMENT I: Final Risk Assessment

### A. Final Risk Assessment – NDA 212327 for Inrebic (fedratinib hydrochloride) Capsules,

#### a) Drug Product

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 (API), stability	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Physical stability (solid state)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place.
Content uniformity	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	M	Assessed during Development and controlled via specs	Acceptable	Controls are in place.
Microbial Limits	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> </ul>	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Dissolution – BCS Class II & IV	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Exclude major ref ormulations</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	H	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval

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## 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)	n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	78286	Fedratinib development

**2. CONSULTS**

N/A

## Executive Summary

### I. Recommendations and Conclusion on Approvability

OPQ recommends APPROVAL of NDA 212327 for INREBIC (fedratinib) Capsules, 100 mg. As part of this action, OPQ grants a (b) (4)-month re-test period for the drug substance when stored between (b) (4) C and a 48-month expiration period for the drug product when stored at or below 30 C (86 F). There are no outstanding issues and no post-approval quality agreements to be conveyed to the applicant.

### II. Summary of Quality Assessments

#### A. Product Overview

NDA 212327 was submitted for INREBIC (fedratinib) Capsules, 100 mg in accordance with section 505(b)(1) of the Food, Drug and Cosmetic Act by Impact Biomedicines, Inc. Impact Biomedicines, Inc. is a Wholly-owned Subsidiary of Celgene Corporation. Fedratinib hydrochloride is an orally bioavailable, monotherapy, selective JAK2 inhibitor indicated for the treatment intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (b) (4). Fedratinib is an NME that was originally investigated under IND 78286. Fedratinib was granted orphan drug designation in May of 2009 but was denied Fast Track designation.

Fedratinib is a small achiral molecule that is (b) (4)

The drug product is an immediate release 100 mg oral dosage form. The drug product is presented as a hard gelatin capsules containing the active, silicified microcrystalline cellulose (SMCC) and sodium stearyl fumarate in a reddish-brown size 0 hard gelatin capsule. The capsule body is imprinted with “100 mg” in white ink and the capsule cap is imprinted with “FEDR”. The 100 mg dose is equivalent to 117.30 mg of the dichloride monohydrate.

The recommended dosing regimen for INREBIC Capsules is 400 mg orally once daily with or without food until disease progression or unacceptable toxicity.

Based on the information provided in this application (original submission and in responses to information requests), OPQ considers all review issues adequately addressed and potential risks to patient safety, product efficacy, and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 212327 and grants a (b) (4) month re-test period for the drug substance, a 48-month expiration period for the drug product when stored below 30 C (86 F) in the proposed commercial packaging.

<b>Proposed Indication(s) including Intended Patient Population</b>	Indicated for the treatment of intermediate- or high-risk primary or secondary (post-polycythemia vera or postessential thrombocythemia) myelofibrosis (MF) (b) (4)
<b>Duration of Treatment</b>	Until disease progression or unacceptable toxicity
<b>Maximum Daily Dose</b>	400 mg
<b>Alternative Methods of Administration</b>	None

**B. Quality Assessment Overview**

**Drug Substance**

Fedratinib is a small achiral molecule. It is a white to off- white non-hygroscopic crystalline solid that exhibits pH-dependent aqueous solubility. It is freely soluble in the acidic condition and practically insoluble in the neutral condition (pH 6.8). (b) (4)

The specifications for all (b) (4)

The controls for all CQAs are adequately described in the submission. (b) (4)

Over the course of drug development there appear to have been 3 different drug substance manufacturers: (b) (4) (b) (4) and (b) (4). The first toxicology and clinical batches were manufactured by (b) (4) from 2007 to 2009. From 2011 to 2013, batches of drug substance were manufactured at (b) (4). The drug substance manufacturing process is described in sufficient detail to clearly delineate how impurities are formed, how changes in the process could potentially affect the formation, fate, and purge of impurities and why the proposed control strategy is suitable for the drug substance manufacturing process.

Polymorph screenings revealed multiple crystalline forms and one amorphous form of the drug substance. These forms have been identified and characterized and are distinguishable by XRPD. (b) (4) is a highly persistent monohydrate in ambient conditions, is the (b) (4) form and was the form deemed most appropriate for the drug product manufacturing process. The applicant confirmed that (b) (4) remains unchanged during processing. A summary of the results of the polymorphic studies is included in the drug substance review. The risk (b) (4) is controlled in the drug substance specification.

The drug substance will be (b) (4) which meet the requirements of 21 CFR 177.1520 and EU Regulation 10/2011. (b) (4)

Specifications and acceptance criteria for the drug substance are consistent with ICH Q6A and are adequate to ensure the quality of the drug substance as it relates to the safety and efficacy of the drug product. All analytical methods are described in adequate detail and are appropriate for their intended use. All validation parameters (system suitability and system precision, specificity, linearity, range, precision, accuracy, ruggedness, robustness, and stability of solutions) are provided in the NDA and are adequate.

Registration stability studies were conducted on three batches of drug substance produced at (b) (4). The samples were manufactured according to the commercial manufacturing scheme and stored for up to (b) (4) months under long-term (b) (4) and (b) (4) months under accelerated conditions (b) (4). Stability studies were also initiated on three batches of drug substance manufactured at (b) (4). The samples were stored for up to (b) (4) months under long-term (b) (4) and accelerated conditions (b) (4). Both site manufactured batches ranging from (b) (4) kg scale and according to the commercial synthetic process and packaged in the aforementioned container closure system. The stability data for the registration batches demonstrated no notable changes after up to (b) (4) months under long term or accelerated storage conditions. The applicant requested (b) (4) month retest for drug substance when stored between (b) (4) °C. Based on the available long-term, accelerated, forced degradation and stress data, the proposed retest of (b) (4) months for the drug substance when stored at (b) (4) is acceptable.

NDA 212327 is recommended for approval from a drug substance perspective.

### **Drug Product**

The drug product, INREBIC Capsules, is presented as 100 mg, immediate-release hard gelatin capsule containing 117.30 mg of Fedratinib dihydrochloride, silicified microcrystalline cellulose (SMCC) and sodium stearyl fumarate in a reddish-brown size 0 hard gelatin capsule. The capsule body is imprinted with "100 mg" in white ink and the capsule cap is imprinted with "FEDR". All excipients are compendial, commonly used in solid oral dosage forms and demonstrate good compatibility with the drug substance.

The drug product is manufactured by (b) (4) at a commercial batch size (b) (4) kg which translates to (b) (4) capsules. The drug product is manufactured using a (b) (4)

(b) (4) The QTPP was defined and the CQAs were identified. The proposed process parameters and in-process

controls were described in sufficient detail and justified. The applicant demonstrated the suitability of the manufacturing process for the drug product at commercial scale. The description of the manufacturing process includes appropriate in-process controls and operating parameters.

The drug product will be packaged in 120 count 250 mL, white, round HDPE bottles with a 45 mm (b) (4). All packaging components comply with applicable FDA indirect food additive regulations (21CFR Parts 172-178)

The drug product specifications are consistent with ICH Q6A and are based on batch analyses and stability data. The drug product specifications included appearance, identification, assay, content uniformity, individual and total degradants, (b) (4) dissolution, and microbial limits. The proposed specification and acceptance criteria for the drug product, together with controls for impurities in the drug substance are adequate to ensure that the critical quality attributes of this product are well controlled.

(b) (4)

[Redacted text block]

The drug product specifications provide adequate controls to ensure the quality of the drug product throughout the product expiry.

Primary stability studies were conducted on three batches (C1021922, C1021924 and C1021925) of the unprinted drug product manufactured at approximately (b) (4) of the commercial scale (i.e. (b) (4) kg) at Sanofi Winthrop Industrie. Sanofi was the drug product manufacturer in 2010 for Phase 1/2/3 (formulations 1A1<sup>1</sup> and 1B1<sup>1</sup>). The Sanofi batches are stored for 48 months under long term (30°C/65% RH) and 6 months under accelerated (40°C/75% RH) conditions in the proposed commercial packaging configurations. Stability studies were also initiated on three batches of unprinted drug product manufactured at the commercial manufacturing site ( (b) (4) ). These batches were also manufactured at (b) (4) commercial scale, stored under long term (30°C/65% RH) and accelerated (40°C/75% RH) conditions and packaged in the proposed commercial packaging configurations. In addition to the long term and accelerated data, the applicant completed photostability and forced degradation studies for the drug product. All stability studies were executed in accordance with the ICH 1A and Q1B and no notable trends were observed under any storage condition

The available stability data shows consistency over time and support the proposed expiry. Based on the stability data provided, Impact proposed and the FDA accepts the expiration dating period of **48 months** for the drug product when stored at or below 30 C (86 F).

NDA 212327 is recommended for approval from a drug product and process perspective.

### **Biopharmaceutics**

The biopharmaceutics review focused on (1) the acceptability of the proposed dissolution method and acceptance criterion for the routine QC testing of the proposed drug product at batch release and on stability and (2) bridging of the between the clinical and commercial formulations.

**Dissolution Specification and Method:** The dissolution method includes a USP Apparatus 1 (Baskets) at 50 rpm in 900 mL of 0.1N HCl. The proposed dissolution acceptance criterion is  $Q = \frac{(b)}{(4)}\%$  in 20 minutes While the proposed dissolution method was not discriminatory, the drug product demonstrated rapid and consistent dissolution behavior of under multi-media and different dissolution conditions. Accordingly, the proposed dissolution method and acceptance criteria were deemed acceptable for batch release and stability testing for the drug product.

**Bridging of the Clinical Formulations:** The reviewer notes that the Phase 1/2/3 clinical formulations and commercial formulation only differ in the presence of ink difference in ink for the commercial product and the lack of ink for the clinical formulation and have very rapid and comparable dissolution profiles. The reviewer further notes that the dissolution profiles for batches produced at Sanofi were comparable to profiles the for batches manufactured at (b) (4). For these reasons, it was concluded that the bridge between the clinical and commercial formulations is established and no additional *in vitro* or *in vivo* bridging studies were required.

This application is recommended for approval from a biopharmaceutics perspective.

### **Facilities**

There were 5 facilities included in this application:

- **Celgene International Sarl (FEI 3006323509)** – Drug product packaging and labeling

All facilities listed in NDA 212327 were deemed acceptable for the responsibility listed in the application. Accordingly, this application is recommended for approval from a compliance perspective.

**Environmental Assessment**

(b) (4)

**C. Special Product Quality Labeling Recommendations (NDA only)****n/a****D. Final Risk Assessment (see Attachment)****Attached.**



Sherita  
McLamore

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**LABELING**

**I. Package Insert**

**1. Highlights of Prescribing Information**

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	INREBIC (fedratinib)
Dosage form, route of administration	Capsules, for oral use
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Capsules: 100 mg

**2. Section 2 Dosage and Administration**

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	N/A

**3. Section 3 Dosage Forms and Strengths**

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Capsules
Strengths: in metric system	100 mg
Active moiety expression of strength with equivalence statement (if applicable)	refer to Section 11
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	reddish brown, opaque size 0, printed with "FEDR 100 mg" in white ink

**4. Section 11 Description**

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	INREBIC (fedratinib)
Dosage form and route of administration	oral administration
Active moiety expression of strength with equivalence statement (if applicable)	100-mg (equivalent to 117.3 mg of fedratinib dihydrochloride monohydrate)
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Each capsule contains inactive ingredients of silicified microcrystalline cellulose and sodium stearyl fumarate. The capsule shell contains gelatin, red iron oxide, titanium dioxide and white ink.
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	Kinase inhibitor
Chemical name, structural formula, molecular weight	chemical name N-tert-butyl-3-[(5-methyl-2-{{4-(2-pyrrolidin-1-ylethoxy)phenyl}amino}pyrimidin-4-yl)amino]benzenesulfonamide dihydrochloride monohydrate. Its empirical formula is C <sub>27</sub> H <sub>36</sub> N <sub>6</sub> O <sub>3</sub> S·2HCl·H <sub>2</sub> O and a molecular weight of 615.62.
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	Fedratinib exhibits pH-dependent aqueous solubility; it is freely soluble in the acidic condition (>100 mg/mL at pH 1) and practically insoluble in the neutral condition (4 mcg/mL at pH 7.4).

**5. Section 16 How Supplied/Storage and Handling**

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(17))
Strength of dosage form	100 mg capsules
Available units (e.g., bottles of 100 tablets)	Bottles of 120 capsules (NDC 59572-720-12)
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Reddish brown, opaque size 0 capsule, printed with "FEDR 100 mg" in white ink.
Special handling (e.g., protect from light)	N/A
Storage conditions	Store below 86°F (30°C)
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured for and marketed by: Celgene Corporation Street address needed Summit, NJ 07901

**Reviewer's Assessment of Package Insert: Adequate**  
*Adequate after above edits shaded in yellow color. The edits will be done during labeling review meeting.*

**II. Labels:**

**1. Container Labels**



(b) (4)

Item	Information provided in the container label
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	INERBIC (fedratinib) capsules
Dosage strength	100 mg
Net contents	120 capsules
“Rx only” displayed prominently on the main panel	displayed
NDC number (21 CFR 207.35(b)(3)(i))	NDC 59572-720-12
Lot number and expiration date (21 CFR 201.17)	yes
Storage conditions	Store below 86°F (30°C).
Bar code (21CFR 201.25)	yes
Name of manufacturer/distributor	yes
And others, if space is available	Salt equivalent statement revised to (equivalent to 117.3 mg fedratinib dihydrochloride monohydrate)

**Reviewer’s Assessment of Labels: Adequate**

*After above edits, the labels will comply with all regulatory requirements from a CMC perspective. The edits have been made during labeling review meeting.*

*List of Deficiencies: None*

*Overall Assessment and Recommendation: Adequate from a CMC perspective*

**Primary Labeling Reviewer Name and Date:**

***Xing Wang, Ph.D., Reviewer, ONDP/DNDPI/NDPBII***

**Secondary Reviewer Name and Date (and Secondary Summary, as needed):**

***Anamitro Banerjee, Ph.D., Branch Chief, ONDP/DNDPI/NDPBII***



Xing  
Wang

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Anamitro  
Banerjee

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**BIOPHARMACEUTICS**

**Application No:** NDA 211327 [505(b)(1)]  
**Drug Product Name:** Inrebic™ (Fedratinib Hydrochloride) Capsules,  
**Strength:** 100 mg  
**Route of Administration:** Oral  
**Applicant Name:** Impact Biomedicines, Inc., a Wholly-owned Subsidiary of Celgene Corporation  
**Proposed Indication:** Treatment of intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (b) (4)  
**Submission Dates:** 01/04/2019  
**Primary Reviewer:** Mei Ou, Ph.D.  
**Secondary Reviewer:** Banu Zolnik, Ph.D.

**EXECUTIVE SUMMARY**

The proposed drug product, Inrebic (Fedratinib Hydrochloride) Capsules, 100 mg, is an immediate release hard gelatin capsule for oral administration. The proposed dosing regimen is 400 mg orally once daily.

In the preliminary comments of a Type B (pre-NDA) CMC meeting cross reference to IND 078286 dated 10/12/2018, the Applicant provided: (i) the summarized in vitro dissolution method development report, (ii) the summarized dissolution data of clinical and primary registration stability (commercial) batches. Therefore, the Division of Biopharmaceutics: (a) considered the proposed dissolution method appeared reasonable during IND stage; (b) conveyed detailed requirement of setting dissolution acceptance criterion<sup>1</sup>.

In current NDA 212327 submitted dated on 01/04/2019, the Biopharmaceutics Review focuses on the evaluation of: i) the in vitro dissolution method and acceptance criterion of the proposed drug product, ii) the need of in vitro bridging between the clinical and commercial formulations.

**In Vitro Dissolution Testing of the Finished Product:**

Although the proposed dissolution method showed very limited discriminating ability, because of the very rapid and consistent dissolution behavior of the drug product under multi-media and different dissolution conditions, the proposed dissolution method is acceptable as a quality control (QC) test of the finished drug product for batch release and stability testing.

<sup>1</sup> IND 078286, a Type B (pre-NDA) CMC meeting, preliminary comments dated 10/12/2018:  
<https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af804bcda3>

The final approved *in vitro* dissolution method and acceptance criterion for the finished drug product are presented below:

USP Apparatus	I (Basket)
Rotation Speed	50 rpm
Medium and Volume	0.1 M HCl, 900 mL
Temperature	37 ± 0.5°C
Acceptance Criterion	Q = <sup>(b)</sup> <sub>(4)</sub> % in 20 minutes

**Formulation Bridging:**

Because (a) the Phase 1/2/3 clinical formulations and commercial formulation (only difference in ink) have very rapid then comparable dissolution data/profiles, (b) the dissolution data/profiles of batches produced from two manufacturing sites (Sanofi vs. <sup>(b)</sup><sub>(4)</sub>) are comparable, the bridge between the clinical and commercial formulations is established; therefore, no additional *in vitro* or *in vivo* bridging studies are needed.

**RECOMMENDATION**

From the Biopharmaceutics perspective, NDA 212327 for the proposed Inrebic (Fedratinib Hydrochloride) Capsules, 100 mg, is recommended for **APPROVAL**.

**BIOPHARMACEUTICS REVIEW****1. Drug Substance Solubility and Permeability**

The drug substance, fedratinib dihydrochloride monohydrate (a weak base, with two pKa values, 6.3 pyrimidine group, and 9.5 pyrrolidine group) has low solubility from pH 6.8 and pH 7.4, as presented in Table 1 below.

Table 1: Aqueous Solubility of Fedratinib Drug Substance in Different pHs at 37°C

Medium	Solubility (mg/mL)	Measured pH at 24 hours
0.1 N HCl (pH 1)	112	1.1
50 mM Sodium Acetate (pH 4.5)	≥ 30 <sup>1</sup>	4.3
50 mM Sodium Phosphate (pH 6.8)	0.02	6.8
50 mM Sodium Phosphate (pH 7.4)	0.004	7.2

<sup>1</sup> Saturation was not achieved because adding drug substance to pH 4.5 acetate buffer will lower the pH and thus increase its solubility.

The drug substance, Fedratinib, has pH and concentration dependent permeability. At the initial concentration of 20 µM, Fedratinib exhibited low permeability in both apical pH 6.5 and 7.4, although Fedratinib has a relatively higher permeability at pH 7.4. The permeability of Fedratinib is increased when its initial concentration is increased but the permeability is reached to a plateau at a concentration of approximately 40 µM (concentration tested in the 20 -190 µM range). The permeability of Fedratinib was saturated at concentrations ≥ 100 µM. However, Fedratinib still has low permeability at at 100 µM compared to the high permeability reference drug testosterone. Fedratinib is also a P-gp substrate. The representative in vitro permeability data are presented in Table 2 below, while the detailed data are submitted in Study AIV0208.

Per the Applicant, data from the human mass balance study (Report BEX12257) showed estimated absorption of fedratinib at approximately 77%, which claimed that absorption of fedratinib is not limited by its solubility or permeability. *Note, no BCS classification request of the drug substance and drug product is submitted for review.*

**Table 2: Permeability Coefficient, Concentration Dependence and pH effect of Fedratinib Drug Substance**

Test Article (batch No.): SAR302503A (TG101348)		Study Number: AIV0208
Test System: Caco-2/TC7 cells		Location: (b) (4)
Permeability coefficient		
Experimental conditions: kinetic study; pH 6.5 or pH 7.4; BSA 0.5 % (donor chamber) / pH 7.4; BSA 5 % (receiver chamber)		Sampling times: 0, 15, 30, 45 and 60 min for SAR302503A (TG101348) 120 min for reference compound
Compound	Concentration	Apical to basal transport $P_{app} \times 10^{-7} \text{ (cm.s}^{-1}\text{)} \pm \text{SD}$
SAR302503A (TG101348) Apical pH = 6.5	20 $\mu\text{M}$ (10500 ng/mL)	BLQ
SAR302503A (TG101348) Apical pH = 7.4	20 $\mu\text{M}$ (10500 ng/mL)	44.1 $\pm$ 4.4
Low permeability reference: D-[1- <sup>14</sup> C]-mannitol	20 $\mu\text{M}$	0.9 $\pm$ 0.1
High permeability reference: [4- <sup>14</sup> C]-testosterone	20 $\mu\text{M}$	152.3 $\pm$ 4.5
Additional information: $P_{app}$ calculation: $P_{app} = \frac{dQ}{dt} \frac{1}{A \cdot C_0}$ $dQ/dt$ is the amount of SAR302503A (TG101348) or reference compound transported per unit time. $dQ/dt$ is determined by linear regression and expressed as $\text{pmol.s}^{-1}$ . $A$ is the filter area equal to 0.31 $\text{cm}^2$ , and $C_0$ , expressed in $\text{pmol.mL}^{-1}$ is the initial concentration of the compound in the donor chamber. Threshold for a high permeability compound: $P_{app} > 20 \times 10^{-7} \text{ cm.s}^{-1}$ BLQ: Below the Limit of Quantification		

Permeability coefficient : concentration dependence and pH effect				
Experimental conditions: transport study in the presence of concentration gradient of SAR302503A (TG101348), pH 6.5 or pH 7.4, BSA 0.5 % (donor chamber) / pH 7.4, BSA 5 % (receiver chamber)				Sampling times: 120 minutes
Compound	Concentration	$P_{app} \times 10^{-7} \text{ (cm.s}^{-1}\text{)} \pm \text{SD}$		
		Apical pH 6.5	Apical pH 7.4	
Test compound	SAR302503A (TG101348) 20 $\mu\text{M}$ (10500 ng/mL))	BLQ	44.1 $\pm$ 2.7	
	SAR302503A (TG101348) 40 $\mu\text{M}$ (21000 ng/mL)	2.1 $\pm$ 0.2	143.9 $\pm$ 8.5	
	SAR302503A (TG101348) 100 $\mu\text{M}$ (52500 ng/mL)	27.6 $\pm$ 2.1	178.4 $\pm$ 5.1	
	SAR302503A (TG101348) 180 $\mu\text{M}$ (99700 ng/mL)	30.0 $\pm$ 2.3	164.1 $\pm$ 4.5	
Low permeability reference: D-[1- <sup>14</sup> C]-mannitol	20 $\mu\text{M}$	3.5 $\pm$ 0.5	N.D.	
High permeability reference: [4- <sup>14</sup> C]-testosterone	20 $\mu\text{M}$	214.8 $\pm$ 3.9	N.D.	

BLQ: Below the Limit of Quantification  
 N.D.: Not Determined

**2. In Vitro Dissolution Method**

The proposed dissolution method and acceptance criterion as a quality control (QC) test for the drug product batch release and stability testing are summarized as below:

USP Apparatus	I (Basket)
Rotation Speed	50 rpm
Medium and Volume	0.1 M HCl, 900 mL
Temperature	37°C $\pm$ 0.5°C
Acceptance Criterion	Q = $\frac{(b)}{(4)}$ % in 20 minutes

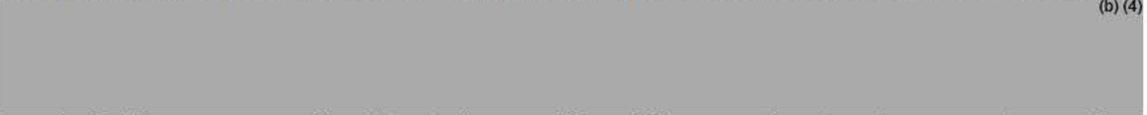
Note: 0.1 M HCl (presented in dissolution analytical procedure) is equal to 0.1 N HCl (presented in dissolution method development report), although the units of concentration are different.

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The following parameters have been evaluated during the method development, listed as:



initially developed, however, the Applicant continued the development with Dissolution Method 2 (*USP apparatus I basket, 50 rpm, 900 mL of 0.1 N HCl*) because of the better adaptation for capsule testing. The Applicant proposed Dissolution Method 3 which has



method. The representative dissolution profiles of drug product batches manufactured from Sanofi are presented in Figure 1 below, showing very rapid dissolution in multi-media.



(b) (4)

The following variables were used to evaluate the discriminating ability of the proposed dissolution method, summarized as:

	Parameter	Evaluated Range	Discrimination Observed
Material Attribute	(b) (4)		No
Formulation Variant			No
Process Variant			No

- Drug substance particle size: as profiles presented in Figure 2 below, the lot with larger drug substance particle size distribution (PSD) and the lot with target drug substance PSD have comparable and very rapid dissolution profiles.

Figure 2: Dissolution Profiles of Drug Product Lots with larger and target API particle size distribution, generated by the proposed dissolution QC method



Note: PD01-631 Batch 1 ( (b) (4) ) and PD01-649 Batch 1 ( (b) (4) ) were generated from same API lot (batch BF17602M-STEP1.5) containing larger API PSD (D50 (b) (4) ) than the target lot W039165 containing target API PSD (D50 (b) (4) ). Proposed API PSD (D50 NMT (b) (4)  $\mu$ m, D90 NMT (b) (4)  $\mu$ m).

To further understand the impact of (b) (4) drug substance, a (b) (4) biorelevant dissolution experiment was performed using 1000 mL of gastro-intestinal media at pH 1.1 (simulated gastric fluid, SGF) and pH 6.5 (fasted state simulated intestinal fluid, FaSSIF), with (b) (4) at 50 rpm (information presented in Table 3). As shown in Figure 3, all three tested batches showed greater than (b) (4)% dissolution under gastric media. After 30 minutes, with addition of the intestinal medium, the medium was supersaturated, and a rapid precipitation of the drug substance was observed from all the batches, which might due to the decreased drug substance solubility. The results indicated that the drug substance with different particle sizes showed no significant difference in dissolution.

Table 3: Drug substance used in the biorelevant dissolution study

Batch #	Size
MGL 1000-56	(b) (4)
T1010994	(b) (4)
VAC.VJH.1.10	(b) (4)

<sup>a</sup> Particle size data for this batch is not available but the material meets the proposed particle size acceptance criteria for (b) (4)

Figure 3: Dissolution profiles for drug substance batches with different size and shape



eq = equivalent.

\* Typographical error: T1011994 in this figure is technical batch T1010994.

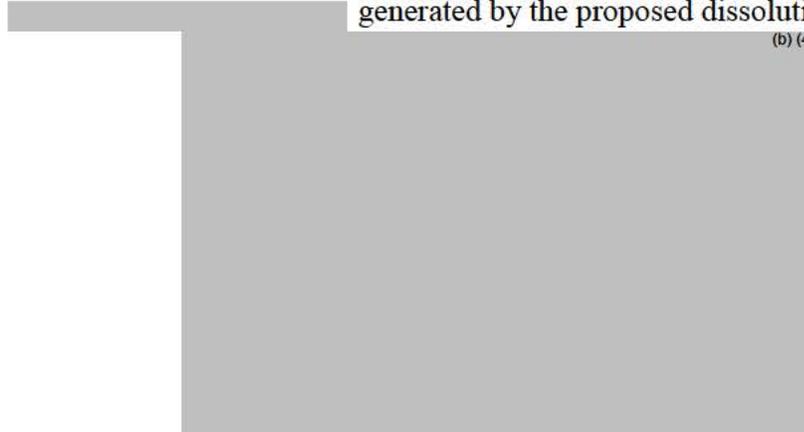
- Variation in excipient composition: as profiles presented in Figure 4 below, the two batches containing different levels of (b) (4) have comparable and very rapid dissolution profiles.

Figure 4: Dissolution Profiles of Drug Product Lots with different levels of (b) (4), generated by the proposed dissolution QC method



- Variation in (b) (4): as profiles presented in Figure 5 below, the (b) (4) does not affect the very rapid dissolution behavior of the drug product.

Figure 5: Dissolution Profiles of Drug Product Lots produced from (b) (4) generated by the proposed dissolution QC method

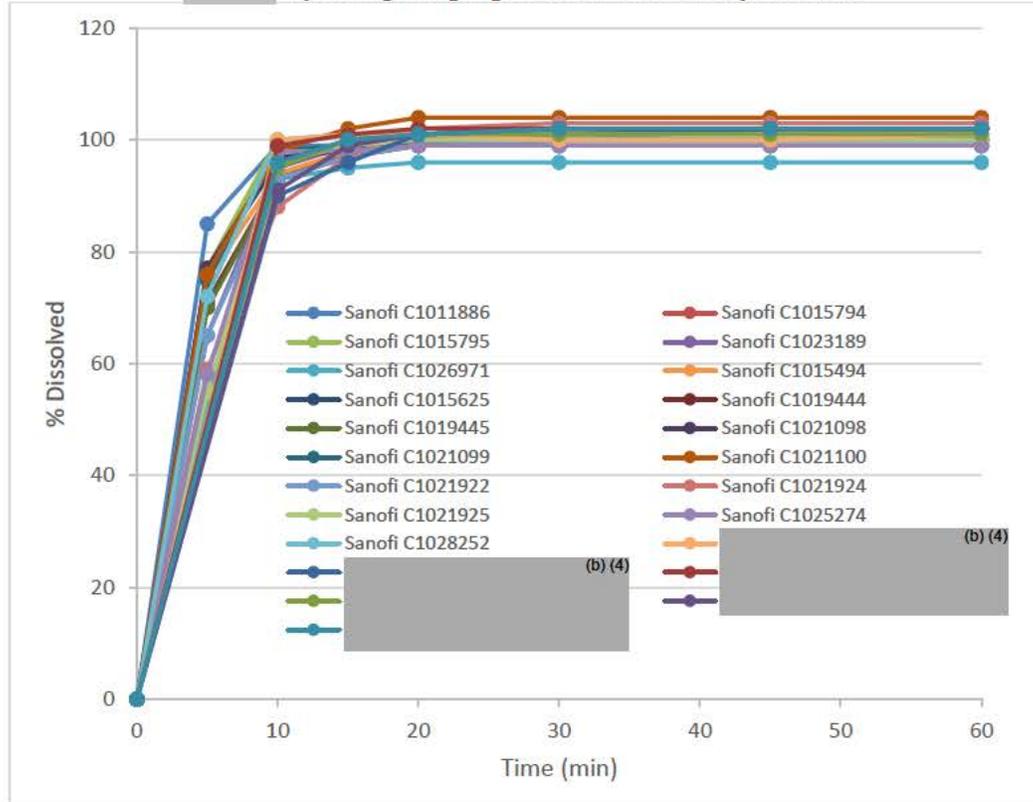


Although the propose dissolution method has very limited discriminating ability, because of the very rapid dissolution behavior, the proposed dissolution method (USP apparatus I basket, 50 rpm, 900 mL of 0.1 N HCl) is **acceptable** as a QC method for the propose drug product.

### **3. In Vitro Dissolution Data and Acceptance Criterion**

The drug product batches for pivotal clinical studies and a primary stability study were produced by Sanofi. The proposed commercial site, (b) (4) used a manufacturing process comparable to the one employed by Sanofi. The dissolution data of the drug product batches from Sanofi (b) (4) are provided and plotted in Figure 6 below. From the data, the proposed drug product has very rapid dissolution profiles (> (b) (4) % dissolution in (b) (4) minutes) then comparable dissolution profiles between the two manufacturing sites. Therefore, the similarity factor ( $f_2$ ) calculation from the batches between the two manufacturing sites is not needed.

Figure 6: Dissolution Profiles of the proposed Drug Product produced from Sanofi and (b) (4) by using the proposed dissolution QC method



The dissolution data of commercial batches produced from (b) (4) under long-term stability condition (30°C/65%RH) up to 12 months are also provided. The overall data support the proposed dissolution acceptance criterion of “Q = (b) (4)% in 20 minutes”.

**4. Formulation Bridging**

The historical overview and batch information of clinical formulations (Initial, 1A1, 1B1) and the commercial formulation (1C2) are summarized in the following Table 4 to 6:

**Table 4: Historical Overview of Fedratinib Capsule Formulation Changes**

Dosage Strengths	Formulation	Change	Effect of Changes (if any)
10, 40, 200 mg	Initial <sup>1</sup>	Not Applicable	Not Applicable
50, 100 mg	1A1	New dosage strengths. Fill compositions equivalent and dose proportional to the 200 mg strength	No effect on dissolution rate using method effective at the time
100 mg	1B1	Addition of (b) (4) step for drug substance to ensure batch to batch consistency for particle size distribution	<ul style="list-style-type: none"> <li>No effect on dissolution rate using the proposed commercial QC method</li> <li>No effect on dissolution rate in simulated gastro-intestinal media</li> <li>No effect on in vivo absorption through cross-over study conducted in Pentagastrin-treated dogs</li> </ul>
100 mg	1C2	Commercial image: white ink printing on cap and body. Tech transfer to new clinical/commercial site (b) (4)	<ul style="list-style-type: none"> <li>No effect on dissolution rate using the proposed commercial QC method</li> <li>No change in dissolution rate between Sanofi and (b) (4) batches at pH 1, pH 4.5 and pH 6.8</li> </ul>

**Table 5: A Side by Side Comparison of Formulations used in Clinical Development (Initial, 1A1 and 1B1)**

Components	Initial Formulation (Phase 1)	Formulation 1A1 (Phase 1/2)		Formulation 1B1 (Phase 1/2/3)	
		(b) (4)		(b) (4)	
		100 mg		100 mg	
		mg/unit	% w/w	mg/unit	% w/w
Drug substance <sup>1</sup>		117.30	(b) (4)	117.30	(b) (4)
SMCC (b) (4)		(b) (4)		(b) (4)	
SSF <sup>3</sup>					
Total capsule fill weight	(b) (4)	(b) (4)			
Opaque hard capsule	(b) (4)	Reddish brown, size 0 <sup>2</sup>		Reddish brown, size 0 <sup>2</sup>	

<sup>1</sup> 1.173 mg fedratinib dihydrochloride monohydrate equivalent to 1.0 mg free base

<sup>2</sup> Silicified microcrystalline cellulose (b) (4)

<sup>3</sup> Sodium stearyl fumarate (b) (4)

<sup>2</sup> Composed of gelatin, titanium dioxide, and red iron oxide

**Table 6: Compositions of Pivotal Clinical Formulation (1B1) and Commercial Formulation (1C2)**

Components	Formulation 1B1 (100 mg)		Formulation 1C2 (100 mg)	
	mg/unit	% w/w	mg/unit	% w/w
Fedratinib dihydrochloride monohydrate	117.30	(b) (4)	117.30	(b) (4)
Silicified microcrystalline cellulose high density 90 µm	(b) (4)		(b) (4)	
Sodium stearyl fumarate				
Total capsule fill weight	(b) (4)			
Hard gelatin capsule	Reddish brown, size 0 <sup>2</sup>		Reddish brown, size 0 <sup>2</sup> , imprinted with white ink	

<sup>1</sup> 1.173 mg fedratinib dihydrochloride monohydrate equivalent to 1.0 mg free base

<sup>2</sup> Composed of gelatin, titanium dioxide, and red iron oxide

*Note: The only difference between commercial formulation 1C2 and the pivotal formulation 1B1 is the ink print, which is considered a Level 1 change per FDA SUPAC-IR guidance.*

The comparative dissolution profiles among the clinical formulations (Initial, 1A1, 1B1) and the commercial formulation (1C2) are presented in the following Figure 7 to 9.

Figure 7: Dissolution Profile Comparison for Fedratinib Capsules, 200 mg (Initial Formulation) and 100 mg (Formulation 1A1)



Figure 8: Comparison of Fedratinib 100 mg Capsule Formulation, 1A1 and 1B1



Figure 9: Comparison of Dissolution Profiles Between Clinical Formulation 1B1 and Commercial Formulation 1C2



From the data profiles presented from Figure 6 to 9, this Reviewer considered that (a) the dissolution data/profiles between Phase 1/2/3 clinical formulation 1B1 and commercial formulation 1C2 (similar formulation with white ink) are comparable, while all formulations showed very rapid dissolution; (b) the dissolution data/profiles between clinical batches (produced from Sanofi) and commercial batches (produced from (b) (4)) are comparable. Therefore, the bridge between the clinical formulations and the commercial formulation is established, so that no additional *in vitro* or *in vivo* bridging studies are needed.



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**ATTACHMENT I: Final Risk Assessment**

A. Final Risk Assessment – NDA 212327 for Inrebic (fedratinib hydrochloride) Capsules,

a) Drug Product

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 (API), stability	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Physical stability (solid state)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place.
Content uniformity	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	M	Assessed during Development and controlled via specs	Acceptable	Controls are in place.
Microbial Limits	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> </ul>	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Dissolution – BCS Class II & IV	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Exclude major ref ormulations</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	H	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval

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Sherita  
McLamore

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