

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217729Orig1s000

PRODUCT QUALITY REVIEW(S)



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	3		



Template Revision: 03

NDA Executive Summary

1. Application/Product Information

NDA Number.	217729
Applicant Name	Pfizer
Drug Product Name	Bosutinib capsules
Dosage Form.	Capsule
Proposed Strength(s)	50 mg, 100 mg* [REDACTED] (b) (4) [REDACTED]
Route of Administration	Oral
Maximum Daily Dose	600 mg
Rx/OTC Dispensed	Rx
Proposed Indication	- Indicated for adult and pediatric patients 1 year of age and older with chronic phase Ph+ chronic myelogenous leukemia (CML), newly-diagnosed or resistant or intolerant to prior therapy. - Indicated for adult patients with accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy.
Drug Product Description	Bosutinib capsules are supplied as 50 mg and 100 mg hard gelatin, opaque capsules. The 50 mg capsule is a size 2, white body/orange cap capsule, with "BOS 50" printed on the body and "Pfizer" printed on the cap. The 100 mg capsule is a size 0 white body/brownish-red cap capsule with "BOS 100" printed on the body and "Pfizer" printed on the cap. The drug product is packaged in high-density polyethylene (HDPE) bottles with heat induction seal liner and [REDACTED] (b) (4) closure.
Co-packaged product information	N/A
Device information:	N/A



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Storage Temperature/ Conditions	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Keep in original package.		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Kabir Shahjahan	Haripada Sarker
	<i>Drug Product/ Labeling</i>	Rajiv Agarwal	Shalini Anand/David Claffey
	<i>Manufacturing</i>	Yifan Wang	Zhaoyang Meng
	<i>Biopharmaceutics</i>	Min Sammie Kang	Anitha Govada
	<i>Other (specify):</i>	N/A	N/A
	<i>RBPM</i>	Dahlia Walters	
	<i>ATL</i>	Shalini Anand	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: An expiration dating period of **36 months** is granted for the drug product when stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

b. Additional Comments for Action: n/a

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends **APPROVAL** of NDA 217729 for the commercialization of bosutinib 50 mg and 100 mg capsules. Based on our evaluation of the available information, the Applicant



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provided sufficient information to support an approval recommendation from the drug product quality perspective. The Applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and quality of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

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

Recommendation by Subdiscipline:

- Drug Substance - Adequate**
- Drug Product - Adequate**
- Quality Labeling - Adequate**
- Manufacturing - Adequate**
- Biopharmaceutics - Adequate**
- Microbiology - N/A**

Environmental Assessment: Categorical Exclusion - Adequate

QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments:

Comparability Protocols (PACMP): No

Comments: N/A

Additional Lifecycle Comments:

The Applicant submitted a comparability protocol [REDACTED] (b) (4)

[REDACTED]. The proposal was found acceptable by the Office of Lifecycle Drug Product Review team.



Shalini
Anand

Digitally signed by Shalini Anand

Date: 8/31/2023 05:46:58PM

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CHAPTER IV: LABELING

For more details about the items in this template, please see [Chapter IV \(Labeling\) of the NDA IQA Guide](#)

1.0 PRESCRIBING INFORMATION (ONLY primary and secondary labels are needed to complete this review. Cut and paste section 11 and 16 too)

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s) ¹	Adequate	Bosutinib (Bosutinib monohydrate)
Route(s) of administration	Adequate	Oral
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	(b) (4), 50 mg and 100 mg capsules
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	Not applicable
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	Not applicable
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets:	N/A	Not applicable

¹ Established name = [Drug] [Route of Administration] [Dosage Form]

10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).		

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
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)	Adequate	Stability of open capsules on food: Use it immediately. (For patients who are unable to swallow capsules, the contents of (b) (4) applesauce or yogurt. Remove the required number of capsules from the container to prepare the dose as instructed and the amount of either room temperature applesauce or yogurt in a clean container. Carefully open each capsule, add the entire capsule content of each capsule into the applesauce or yogurt, then mix the entire dose into the applesauce or yogurt. Patients should immediately consume the full mixture in its entirety, without chewing. Do not store the mixture for later use. If the entire preparation is not swallowed do not take an additional dose. Wait until the next day to resume dosing.
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	Yes, see above

For parenteral products: include statement: <i>“Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit”</i>	N/A	Not applicable
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	Not applicable
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	Not applicable
For hazardous products, include the statement <i>“DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.^x”</i> with x numerical citation to <i>“OSHA Hazardous Drugs”</i>.	N/A	Not applicable

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Capsules
Strength(s) in metric system	Adequate	(b) (4) 50 mg, and 100 mg Capsules
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	Not applicable (Each strength reflects the equivalent amount of bosutinib (on anhydrous basis).
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	(b) (4) 50 mg bosutinib capsules: white body/orange cap with "BOS 50" printed on the body and "Pfizer" printed on the cap in black ink. 100 mg bosutinib capsules: white body/brownish-red cap with "BOS 100" printed on the body and "Pfizer" printed on the cap in black ink.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not applicable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	Not applicable

Section 11 (DESCRIPTION)



(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	BOSULIF® (bosutinib)
Dosage form(s) and route(s) of administration	Adequate	Capsule/oral
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP . For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	Not applicable
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	Yes
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	Not Applicable
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	Not Applicable
Sterility statement (if applicable)	N/A	Not Applicable
Pharmacological/Therapeutic class	Adequate	Yes (Kinase Inhibitor)
Chemical name, structural formula, molecular weight	Adequate	Yes (list the structure of Bosutinib monohydrate)
If radioactive, statement of important nuclear characteristics.	N/A	Not applicable
Other important chemical or physical properties (such as pKa or pH)	Adequate	Yes (lists pH dependent solubility)

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	Not applicable
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	Not applicable
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	Not applicable

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)



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Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	Capsules
Strength(s) in metric system	Adequate	(b) (4) 50 mg, and 100 mg
Available units (e.g., bottles of 100 tablets)	Adequate	(b) (4) 50 mg (30 counts), and 100 mg (150 counts)
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	(b) (4) 50 mg Capsule: Size 2 capsule, white body/orange cap with "BOS 50" printed on the body and "Pfizer" printed on the cap in black ink. 100 mg Capsules: Size 0 capsule, white body/brownish-red cap with "BOS 100" printed on the body and "Pfizer" printed on the cap in black ink.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not applicable
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	Not applicable

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.). For hazardous drugs, state “DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.^x” with x numerical citation to “OSHA Hazardous Drugs.”	Adequate	Sore and Dispense in Original Container

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

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Yes
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: “<i>Not made with natural rubber latex. Avoid statements such as “latex-free.”</i>”	N/A	Not applicable
Include information about child-resistant packaging	Adequate	Applicant is asked to add this information for both Tablet and capsule

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 review 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	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor , and/or packer	Adequate	Distributed by: Pfizer Labs Dision of Pfizer Inc. New York, NY 10001

2.0 PATIENT LABELING:

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ²	Adequate	Bosutinib
Special preparation instructions (if applicable)	Adequate	Yes
Storage and handling information (if applicable)	Adequate	Yes
If the product contains a desiccant , ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	Adequate	Applicant is asked to add this information for Tablet NDA
Active ingredient(s) (if applicable)	Adequate	Bosutinib
Alphabetical listing of inactive ingredients (if applicable)	Adequate	Yes
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	Pfizer Labs Dision of Pfizer Inc. New York, NY 10001

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels (Capsules)

(Copy/paste or refer to a representative example of a proposed container)

(b) (4)

² Established name = [Drug] [Route of Administration] [Dosage Form]

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QUALITY ASSESSMENT



APPEARS THIS WAY ON ORIGINAL

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ³ , (font size and prominence)	Adequate	Yes
Strength(s) in metric system	Adequate	Yes
Route(s) of administration	Adequate	Yes
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP .	N/A	Not Applicable
Net contents (e.g., tablet count, volume of liquid)	Adequate	Yes
“Rx only” displayed on the principal display	Adequate	Yes
NDC	Adequate	Yes
Lot number and expiration date	Adequate	Yes
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Yes
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, and these products require a “Not for direct infusion” statement.	N/A	Not Applicable
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	Not Applicable
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	Not applicable
Linear Bar code	Adequate	Yes

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/ distributor /packer	Adequate	Yes
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	Yes
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	Not applicable
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Not applicable
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	Not applicable
And others, if space is available.	N/A	Not applicable

- **Assessment of Carton and Container Labeling: {*Adequate* }**
- **Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."**

Proposed edits on PI and Labels were conveyed to the applicant and response are due on 8/17/2023 drug label.

Several CMC related edits were made after the labeling was sent to the applicant, and the following will be communicated to the applicant by OND.

1. *(b) (4) are recommended to be deleted from the PI and bottle labels for both Tablet and Capsule dosage forms.*
2. *Add "[USP Controlled Room Temperature]" statement in both How Supplied Section and on Bottle labels for Capsule NDA.*

Adequate

ITEMS FOR ADDITIONAL ASSESSMENT

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See [Carton/Container Labeling Specific Resources](#) for a presentation about inappropriate inconsistencies of product quality information between labeling. If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these as deficiencies in this section.

Overall Assessment and Recommendation:

- Adequate

Primary Labeling Assessor Name and Date: Rajiv Agarwal 8/15/2023

Secondary Assessor Name and Date: David Claffey, Ph.D 8/14/2023



Rajiv
Agarwal

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David
Claffey

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Memo

From: Rajiv Agarwal, Ph.D., Ph.D., FDA Expert Regulatory Review Scientist

Date 8/25/2023

IND: [NDA 217729 \(SDN # 0016 dated 8/04/2023 and SDN #17 dated 8/11/2023\)](#)

Re: Review of New CMC information, including Capsule container labels

Title: Review of the new CMC information (amended dissolution specifications), removal of (b) (4) from the Labelling (b) (4) and Capsule container labels for 50 and 100 mg strength.

Background: Via two amendments, at the request of Biopharmaceutics, the dissolution specifications are revised, and this review captures the changes. The acceptance criterion of $Q = (b) (4)\%$ at 15 minutes for the dissolution of bosutinib (b) (4), 50 mg and 100 mg capsules are suitable for immediate release capsules.

TM-9543A uses UV spectroscopy for end analysis determination of the dissolution of bosutinib capsules. This method has been validated in accordance with ICH Q2(R1) guidelines. Appropriate reference materials were used during this validation. Acceptable range, specificity, filter suitability, linearity, accuracy, precision, repeatability, and stability of analytical solutions were demonstrated. All release and long-term stability data have met this criterion.

Applicant decided to remove (b) (4) from the labels and labelling, and it is acceptable to OND.

Via Email dated 8/24/2023, applicant amended the Capsule bottle primary labels (50 and 100 mg), and they are adequate. (b) (4)

(b) (4)

(b) (4)

(b) (4)

Evaluation: CMC information submitted via Amendment SDN # 16 and 17 and Capsule container labels are reasonable from a CMC standpoint. Adequate

New Drug Product Specifications

(b) (4)

Table 3.2.P.5.1-1. Bosutinib Capsule Specification

Test/Method Type	Analytical Procedure Number	Acceptance Criteria
Physical characteristics:		
Appearance (Visual)	Visual inspection	(b) (4) 50 mg: White/Orange ^(b) capsule with BOS 50/Pfizer printed on capsule containing (b) (4) granules 100 mg: White/Brownish-red ^(c) capsule with BOS 100/Pfizer printed on capsule containing (b) (4) granules
Identification^(d):		
Identity (HPLC)	TM-9541A	Retention time of the main peak in the test chromatogram is comparable to that of reference standard
Identity (UV)	TM-9541A	UV spectrum of the main peak in the test chromatogram is comparable to that of the reference standard
Assay:		
Assay (HPLC)	TM-9541A	(b) (4) % of label claim
Degradation Products (HPLC)		
Unspecified Degradation Product	TM-9542A	NMT (b) (4) % each
Total Degradation Products	TM-9542A	NMT (b) (4) %
Dissolution (UV)		
Dissolution	TM-9543A	Q = (b) (4) % at 15 min Conforms to USP <711> requirements
Uniformity of Dosage Units (HPLC)^(d)		
Content Uniformity	TM-9541A	Meets USP <905>, Ph. Eur. 2.9.40 requirements
Microbial Limits:		
Total Aerobic Microbial Count	USP <61> Ph. Eur. 2.6.12	NMT (b) (4) CFU/g
Total Yeast and Mold Count	USP <61> Ph. Eur. 2.6.12	NMT (b) (4) CFU/g
<i>Escherichia coli</i> ^(d)	USP <62> Ph. Eur. 2.6.13	Absence of <i>E. coli</i> in (b) (4)

(b) (4)

^(d) Tested at release only

**Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls**

1. **NDA Supplement Number: NDA-217229-Original-1**
2. **NDA Recommendation:** Approval Complete Response
NDA managed by: OPQ OND

2. **Submission(s) Being Reviewed:**

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original NDA	Type 3- New Dosage Form	03/30/2023	03/30/2023	04/27/2023	09/30/2023	08/31/2023

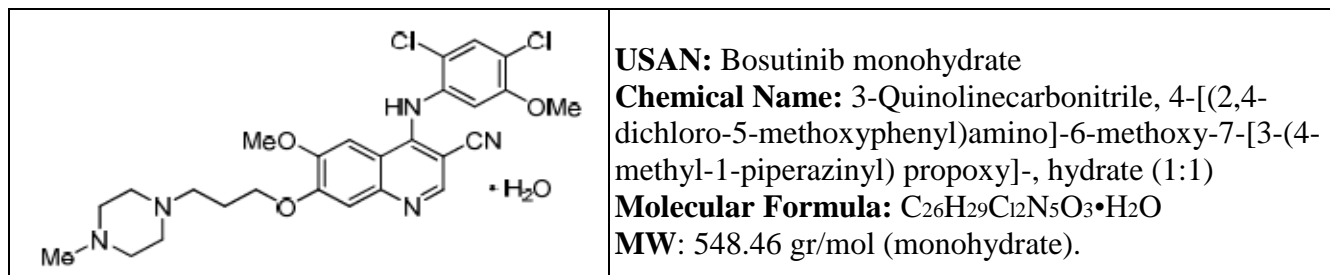
3. **Provides For:**
Post Approval Change Management Protocol (PACMP) for Drug Product Shelf-life Extension.
4. **Review #:** 1
5. **Clinical Review Division:**
Office of Oncologic Diseases (OOD) / Division of Hematologic Malignancies 1 (DHM1)

6. **Name and Address of Applicant:**
Aparna Srirangam, MS, PhD
Senior Manager
Global Regulatory Sciences – Oncology
Pfizer Inc
10646 Science Center Drive
San Diego, CA 92121
Tel: 858-568-5550
Fax: 860-686-5250
Email: aparna.srirangam@pfizer.com

7. **Drug Product:**

Drug Name	Dosage Form	Strength (mg)	Route of Admin.	Rx or OTC	Special Product	Orphan Designation
Bosulif® (Bosutinib monohydrate)	Capsules	(b) (4) 50 and 100.	Oral	Rx	Yes	08-2748

8. **Chemical Name and Structure of Drug Substance:**



9. Indication:

Bosulif® (Bosutinib, NDA-217729) is indicated for the treatment of pediatric patients greater than or equal to 1 year of age with newly diagnosed CP Ph+ CML and chronic phase, (b) (4) Ph+ CML with resistant or intolerant to prior therapy

10. Supporting/Relating Documents: N/A.

11. Consults: None

12. Executive Summary:

The applicant is submitting a New Drug Application (NDA) in electronic common technical document (eCTD) format for BOSULIF® (bosutinib) Capsules 50 mg, and 100 mg. Reference is made to the email correspondence on 22 June 2022 from CDER pre-assigning the NDA number (217729). The original NDA 203341 for BOSULIF® (bosutinib) 100 mg and 500 mg film-coated tablets received approval on 04 September 2012 in the US for the treatment of adult patients with chronic phase (CP), accelerated phase (AP), or blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML) with resistance/intolerance (R/I) to prior therapy. An additional supplemental approval was granted on 27 October 2017 for the use of 400 mg tablets in addition to the already approved 100 and 500 mg tablets. On 19 December 2017, bosutinib received approval for the treatment of adult patients with newly diagnosed CP Ph+ CML (1L indication). The approval was based on accelerated approval regulations based on molecular and cytogenetic response rates and was granted regular approval on 14 May 2021 based on continued clinical benefit on long-term follow-up. Bosutinib was granted orphan drug designation on 24 February 2009 therefore studies to be conducted under the Pediatric Research Equity Act (PREA) do not apply.

The applicant proposes to extend the shelf-life of bosutinib capsules (b) (4), 50 mg, and 100 mg) based on an extrapolation of the available primary stability data via Annual Report in alignment with the stability protocol in order to ensure continuous supply of the drug product. (b) (4)

(b) (4) Primary stability data for (b) (4), 50 mg and 100 mg capsules in the commercial package are provided in *Section 3.2.P.8.3 Stability Data* and are summarized in *Section 3.2.P.8.1 Stability Summary and Conclusion*. Data available through 24 months at the long-term storage condition demonstrates acceptable stability with no meaningful trends.

The applicant submitted the following documents to review for this original NDA application:

Module 1.1 Cover Letter

Module 1.2 Information for Reviewers

Module 1.3.1.4 Transfer of Obligations

Module 3.2.P.1. Description and Composition of the Drug Product

Module 3.2.P.8.1. Stability Summary and Conclusion

Module 3.2.P.8.2. Post-Approval Stability Protocol and Stability Commitment

Module 3.2.P.8.3. Stability Data (for PF-05208763 (b) (4) 50 mg and 100 mg sizes (b) (4) (b) (4) gelatin capsules)

Reviewer's Assessment for PACMP: Adequate

The applicant is proposing in 3.2.R. *Post Approval Change Management Protocol (PACMP)* in future to change the shelf-life extension from 24 months to 36 months in this submission for NDA-217729 original submission (low dose capsules for pediatric use). The applicant states in the cover letter this application has been prepared to support the registration of a new proposed dosage form: oral capsules for pediatric patients 1 year of age and older, available in 2 dosage strengths, 50 mg, and 100 mg. acceptable from CMC perspective. (b) (4)

The applicant provided stability data and post-approval stability protocol and stability commitment for 0, 6, 12, 24 months and annually through expiry of the drug product. Based on the provided information and proposed protocol and changes are less likely effect the quality of the product. Therefore, this NDA PAMCP is found adequate from CMC perspective.

13. Conclusions & Recommendations:

This original NDA PACMP submission is found adequate.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer:

Mustafa Guzel, Ph.D., CMC reviewer, Branch 1, DPMA I, OLDP, OPQ.

Note: Electronic signatures are appended at the end of this document.



Mustafa
Guzel

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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	NDA 217729—505(b)(1)
Submission History	3/30/2023: Original Submission 5/10/2023 (SDN-9): Response to the Biopharmaceutics IR #1 6/12/2023 (SDN-13): Response to the Biopharmaceutics IR #2 7/12/2023 (SDN-14): Response to the Biopharmaceutics IR #3 8/4/2023 (SDN-16): Response to the Biopharmaceutics IR #4
Drug Product Name/ Strength	Bosulif® (bosutinib) Capsules, (b) (4), 50 mg and 100 mg
Route of Administration	Oral
Applicant Name	Pfizer Inc.
Therapeutic Classification/ OND Division	DHM1
Proposed Indication	Bosulif® is indicated for treatment of pediatric patients 1 year of age and older with newly diagnosed Ph+ chronic myelogenous leukemia (CML), as well as chronic (CP), (b) (4) Ph+ CML with resistance, or intolerance to prior therapy
Primary Reviewer	Min Kang, PharmD, MS.
Secondary Reviewer	Anitha Govada, PhD.
Tertiary Reviewer	Angelica Dorantes, PhD.
Assessment Recommendation	Adequate

EXECUTIVE SUMMARY:

The Applicant submitted 505(b)(1) NDA 217729-ORIG-1 for Bosulif® (Bosutinib) Capsules, (b) (4), 50 mg, and 100 mg, indicated for treatment of pediatric patients 1 year of age and older with newly diagnosed (ND) Ph+ chronic myelogenous leukemia (CML), as well as chronic (CP), (b) (4) Ph+ CML with resistance, or intolerance to prior therapy. It is noted that the proposed drug substance/Active Pharmaceutical Ingredients (API) considered in this application has been approved in a different dosage form (Tablet¹), and therefore, this application does not contain a New Chemical Entity (NCE) or New Molecular Entity (NME).

This application seeks to provide a new age-appropriate bosutinib capsule dosage form² for pediatric patients 1 year of age and older with ND or R/I prior therapy Ph+ CML, developed as part of the Pediatric Written Request for supplementing approved NDA

¹ FDA approved NDA 203341 for Bosulif® (Bosutinib) Tablets, 100 mg, 400 mg, and 500 mg, for the treatment of **adult** patients with newly diagnosed Ph+ chronic myelogenous leukemia (CML), as well as chronic (CP), accelerated (AP), or blast phase (BP) Ph+ CML with resistance, or intolerance to prior therapy.

² Capsule dosage form is designed to be taken intact or opened and content mixed with either applesauce or yogurt for administration

203341³ for pediatric indication, and is based on efficacy and safety study results of BCHILD study⁴ (ITCC-054/ B187-WI202099) as well as the bioequivalence and relative bioavailability bridging studies⁵ B1871061, B1871062, and B1871063.

Assessment Summary:

This Biopharmaceutics Review focuses on evaluating (1) the in vitro dissolution method and acceptance criterion as a quality control (QC) test, and (2) the bridging between the clinical and the proposed to-be-marketed drug product manufacturing sites.

- **In Vitro Dissolution Method and Acceptance Criterion:**

The Applicant developed an in-house dissolution method and submitted a Dissolution Method Development Report investigating the selection of each testing parameter. Based on the dissolution data and information submitted, the following dissolution method and acceptance criterion are finalized for the Quality Control (QC) test of Bosulif® (Bosutinib) Capsules, (b) (4), 50 mg, and 100 mg, at batch release and on stability:

Table 1: Approved Dissolution Method and Acceptance Criterion for Bosulif® (bosutinib) Capsules, (b) (4) 50 mg, and 100 mg

Approved Dissolution Method and Acceptance Criterion for Bosulif® (bosutinib) Capsules, (b) (4), 50 mg, and 100 mg					
Apparatus		Speed	Volume/Temp	Medium	Acceptance Criterion
USP (Paddle)	II	50 rpm	900 mL/ 37 °C	0.1 N HCl (pH 1.2)	Q = (b) (4) % of bosutinib dissolved in 15 minutes

Table 2: Risk Assessment

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment	Comments
Dissolution	Medium	Bosutinib monohydrate drug substance has pH-dependent solubility	Low	(1) Dissolution Method with limited discriminating capability (2) Tightened dissolution acceptance criterion

³ The applicant is seeking a concurrent approval of NDA 203341-SUPP-25 for the proposed new indication for the treatment of **pediatric** patients 1 year of age and older with ND CP Ph+ CML (b) (4) with resistance or intolerance to prior therapy, which was submitted in parallel to NDA 217729, based on the results from a Phase 1/2 BCHILD Study (ITCC-054/ B187-WI202099)

⁴ The pivotal BCHILD Study included the approved 100 mg and 500 mg Bosutinib Tablets and (b) (4) 25 mg and 50 mg Bosutinib Capsules. The results from this study were submitted as part of NDA 203341-SUPP-25.

⁵ Study B1871061 was the pivotal BE study to support the bridging of the approved immediate-release film-coated tablet (100 mg Bosutinib Tablet) to the age-appropriate capsule dosage form (100 mg Bosutinib Capsule) in healthy participants. And B1871062 and B1871063 were conducted to characterize the effect of food, vehicle, and capsule strength on bosutinib PK for the capsule drug product.

- **Product Bridging:**

Two out of the three registration batches were used in clinical PK studies (100 mg [191292492 {BE study#: B1871061}, 201293130 {BA Study#: B1871062}, 201292672); thus, no bridging was necessary between the clinical and registration batches. However, it was noted that the drug product's manufacturing site was changed from (b) (4) where the clinical and registration/primary stability batches were produced, to Germany (Pfizer, Freiburg) where the to-be-marketed products will be produced. Thus, the two sites were bridged using comparative in vitro dissolution data and was observed to be comparatively similar with a very rapid dissolution of $\geq 90\%$ within 15 minutes (see Figure 8-10 and Appendix II). There were no other changes (e.g., formulation, manufacturing process) between the clinical products, registration batches, and TBM products.

Table 3: List of Submissions Being Assessed:

IND/NDA	eCTD sequence #	Date of submission	Document
NDA	0001	3/30/2023	Original Submission
NDA	0009	5/10/2023	Quality/Response to the Biopharmaceutics IR #1 ⁶
NDA	0013	6/12/2023	Quality/Response to the Biopharmaceutics IR #2 ⁷
NDA	0014	7/12/2023	Quality/Response to the Biopharmaceutics IR #3 ⁸
NDA	0016	8/4/2023	Quality/Response to the Biopharmaceutics IR #4 ⁹

Concise Description of Outstanding Issues (list bullet points with key information and update as needed): None.

Overall Biopharmaceutics Recommendation:

From the Biopharmaceutics perspective, NDA 217729-ORIG-1 for Bosulif® (Bosutinib) Capsules, (b) (4), 50 mg, and 100 mg, is **Adequate** and recommended for Approval.

⁶ SDN-9 (M.1.11.1): \\CDSESUB1\EVSPROD\nda217729\0009\m1\us\response-28-apr-23-query-dissolution.pdf

⁷ SDN-13 (M.1.11.1): \\CDSESUB1\EVSPROD\nda217729\0013\m1\us\responses-fda-rfi-16-may-2023-query.pdf

⁸ SDN-14 (M.1.11.1): \\CDSESUB1\EVSPROD\nda217729\0014\m1\us\resp-22jun2023-ir-dissolution-method.pdf

⁹ SDN-16 (M.1.11.1): \\CDSESUB1\EVSPROD\nda217729\0014\m1\us\response-fda-rfi-01aug2023-dissolution-spec.pdf

BIOPHARMACEUTICS ASSESSMENT

B.1 BCS DESIGNATION

Assessment: N/A

Solubility: The Applicant has submitted the solubility of Bosutinib monohydrate as shown in Table 1 below.

Table 4: Solubility (mg/mL) of Bosutinib monohydrate at 37°C

Media and pH	Solubility (mg/mL)
0.1M Hydrochloric Acid (pH 1.0)	11.03
0.01M Hydrochloric Acid (pH 2.0)	9.4
pH 4.5 USP Buffer	6.1
pH 5.0 USP Buffer	2.7
pH 6.8 USP Buffer	0.02
pH 8.0 USP Buffer	0.053

Reviewer's comments:

A BCS designation is not requested by the Applicant, nor required by the FDA. Based on the submitted solubility data which demonstrates a pH-dependent solubility across the physiologic pH (pH 1-6.8), this Reviewer considers Bosutinib monohydrate to be a low solubility drug substance. The proposed drug product is an immediate release (IR) capsule (b) (4)

(b) (4)

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERION

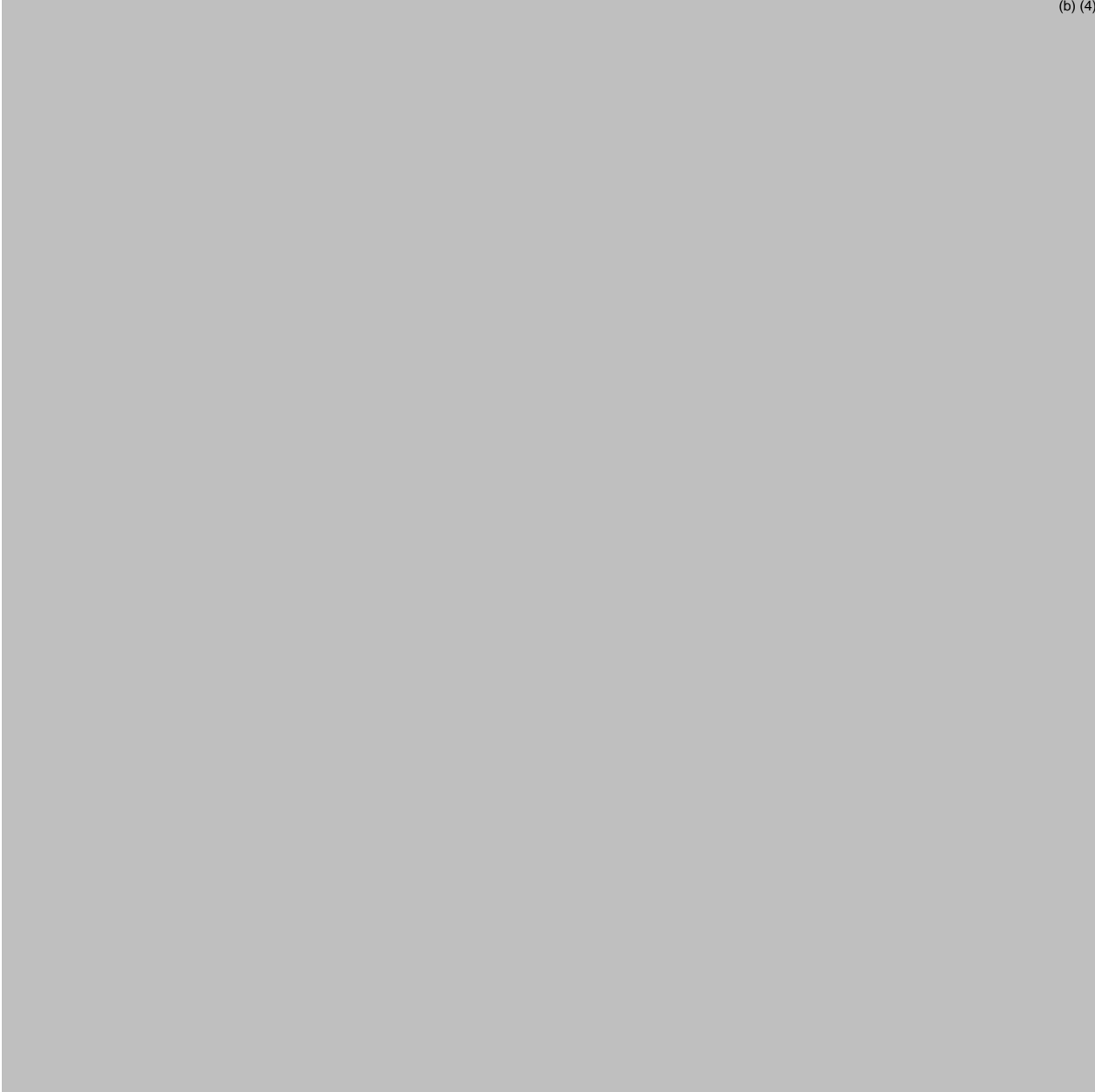
Assessment: Adequate

Table 5: Applicant's proposed/FDA's accepted dissolution method and final acceptance criterion for Bosulif® (bosutinib) Capsule, (b) (4), 50 mg, and 100 mg

Apparatus	Speed	Volume/ Temp	Medium	Acceptance Criterion
USP II (Paddle)	50 rpm	900 mL/ 37 °C	0.1N HCl (pH 1.2)	Q = (b) (4) % in 15 minutes

B. 2.1. Selection of dissolution medium and agitation speed: (b) (4)

phosphate) at paddle speed of 50 rpm and 75 rpm. The results are presented in Figure 1 below.



B. 2.3. Evaluation of dissolution method's discriminating ability: The Applicant investigated the dissolution method's discriminating ability against the following Critical Bioavailability Attributes [CBAs]: (i) Critical Formulation Attributes [CFVs] such as variant formulation compositions, and (ii) Critical Material Attributes [CMAs] such as the cross-linking of the gelatin capsule. The results are presented in Figures 2 to 4 below.

Table 6: CFV—Variant formulation compositions

Name of Ingredients	Reference (%)	Variant A (%)	Variant B (%)	Variant C (%)
(b) (4)				

Figure 2: Dissolution Profile of 100 mg Bosutinib Capsule vs. Variant Lot A and B containing different excipient composition (using QC dissolution method)

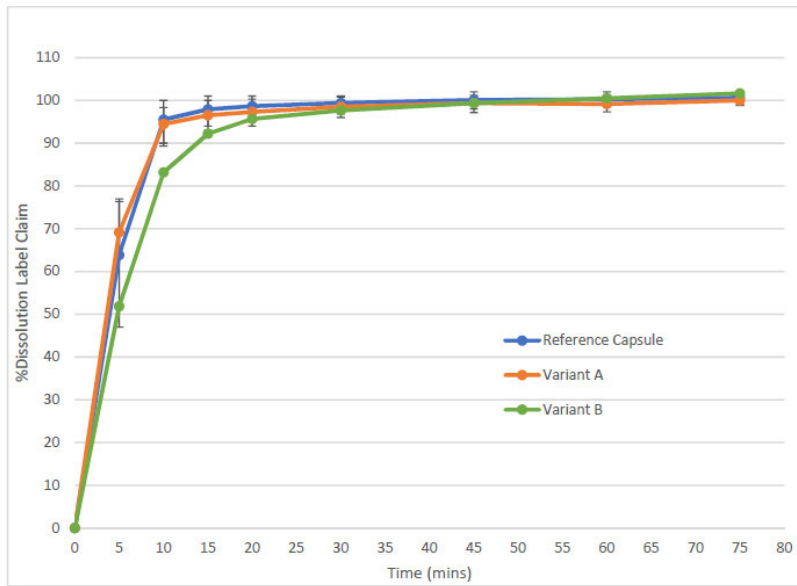


Figure 3: Dissolution Profile of 100 mg Bosutinib Capsule vs. Variant Lot C containing different excipient composition (using QC dissolution method)

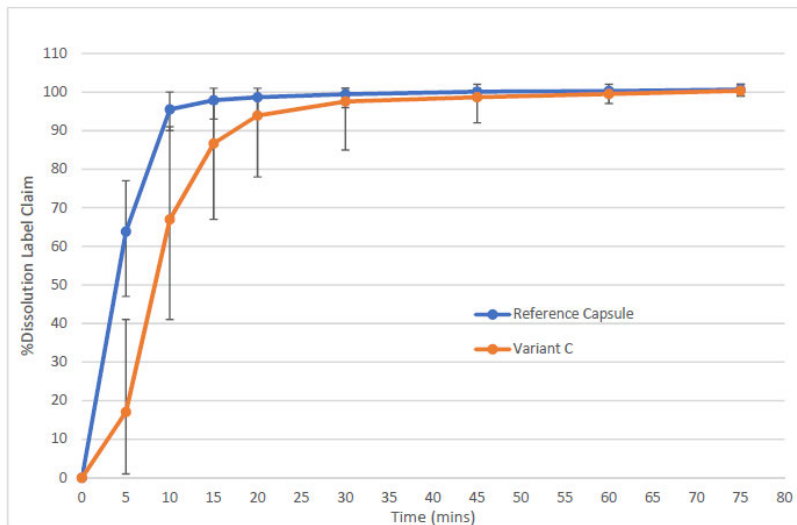
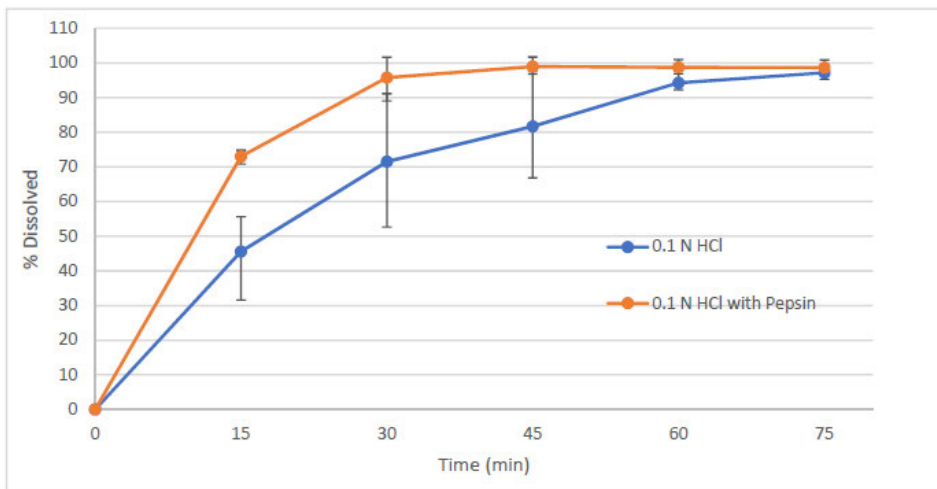


Figure 4: Dissolution Profile of 100 mg Bosutinib Capsule exhibiting cross-linking (60 months on stability) tested in QC dissolution media vs. with the addition of Pepsin



Reviewer’s comments:

To assess the suitability of dissolution method for the proposed product, the Applicant provided data to demonstrate discriminating ability of the selected dissolution method. Given the low solubility of the Bosutinib and to mitigate the risk, it was important that the Applicant’s proposed dissolution method is capable of showing discriminating ability towards changes in most relevant Critical Bioavailability Attributes [CBAs]. The Applicant identified the following CBAs: (i) Critical Formulation Attributes [CFVs] such as variant formulation compositions, and (ii) Critical Material Attributes [CMAs] such as the cross-linking of the gelatin capsule. As shown in Figure 2, 3, and 4, the proposed dissolution method was not sensitive to detect changes in the different amounts of (b) (4).

However, the method was sensitive to changes in CMAs, i.e. the cross-linked gelatin capsule [from 60 months stability batch] (Figure 4). Therefore, dissolution method can be used as stability indicating QC test to detect batches with lower quality.

With regards to the deemed risk, given that this is an immediate-release (IR) capsule (b) (4) the risk of drug release and bioavailability from this IR product (b) (4) is deemed to be mitigated by setting suitable controls for QC testing and tighter acceptance criterion to ensure rapid dissolution. (See section B.2.4. below).

B.2.4. Dissolution Data and Acceptance Criterion:

Table 6: Registration/ Primary Stability Batches of Bosutinib Capsules, (b) (4), 50 mg, and 100 mg

Batch No.	Manufacturing Site	Manufacture Date	Theoretical Batch Size (Capsules)	Testing Date	Dissolution Test Method Effective Date ^(d)	Drug Substance Lot ^(c)	Drug Product Final (b) (4) Lot	Formulation Identifier / Strength	Batch Use
191292402	(b) (4) BE study#: B1871061	Nov 2019	(b) (4)	May 2020	Apr 2020	18-005 ^(a) / E010019728 ^(b)	191292328	(b) (4)	Primary Stability
191292436								D1900093/50 mg	Primary Stability
191292492								D1900094/100 mg	Primary Stability/Clinical
201292632		Jan 2020		17-003 ^(a) / E010018542 ^(b)	201292568	(b) (4)	Primary Stability		
201292648						D1900093/50 mg	Primary Stability		
201292672						D1900094/100 mg	Primary Stability		
201293088		Mar 2020		19-004 ^(a) / E010019801 ^(b)	201293015	(b) (4)	Primary Stability/Clinical		
201293089						D1900093/50 mg	Primary Stability		
201293130						D1900094/100 mg	Primary Stability/Clinical		

Figure 5: Dissolution Profile of Bosutinib Capsule, 100 mg (The Pivotal BE Batch: 191292492)

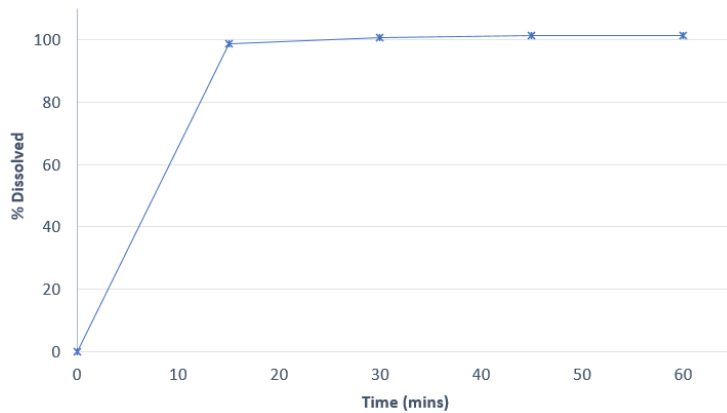
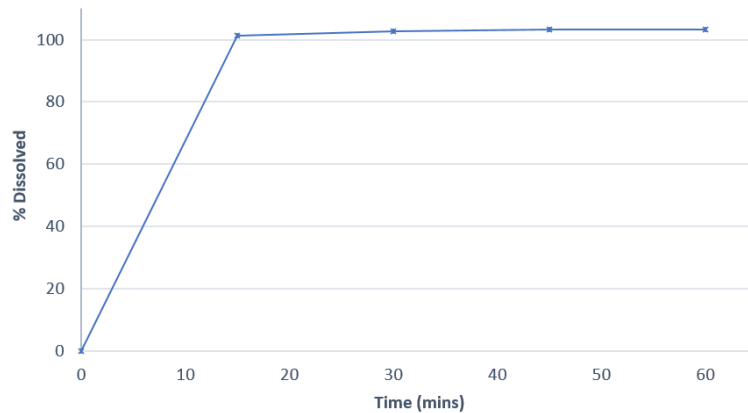


Figure 6: Dissolution Profile of Bosutinib Capsule, 50 mg (Representative Batch: 201293089)



Reviewer's Comments:

The Applicant initially proposed a dissolution acceptance criterion of “Q = (b) (4) % in (b) (4) minutes”. However, based on the totality of data submitted and to further mitigate the risk, FDA requested the Applicant to revise the acceptance criterion from “Q = (b) (4) % in (b) (4) minutes” to “Q = (b) (4) % in 15 minutes”, via Information Request #4 (dated 8/1/23) and in response (dated 8/4/23), the Applicant accepted FDA’s recommendation and updated the drug product’s specification for the dissolution test for batch release and stability with revised acceptance criterion.

B.3. PRODUCT BRIDGING

Assessment: Adequate

Two out of the three registration batches were used in the clinical PK studies (100 mg [191292492 {BE study#: B1871061}, 201293130 {BA Study#: B1871062}, 201292672); thus, no bridging was necessary between the clinical and registration batches. However, it was noted that the drug product’s manufacturing site was changed from (b) (4) where the clinical and registration/primary stability batches were produced, to Germany (Pfizer, Freiburg) where the to-be-marketed products will be produced. Thus, the two sites were bridged using comparative in vitro dissolution data and was observed that the profiles are comparatively similar with a very rapid dissolution of $\geq 90\%$ within 15 minutes (see Figure 8-10 and Appendix II). There were no other changes (e.g., formulation, manufacturing process) between the clinical products, registration batches and TBM products.

Figure 9: Comparative Dissolution Profiles of 50 mg Bosutinib Capsules manufactured in (b) (4) vs Germany (Pfizer) using the QC dissolution method

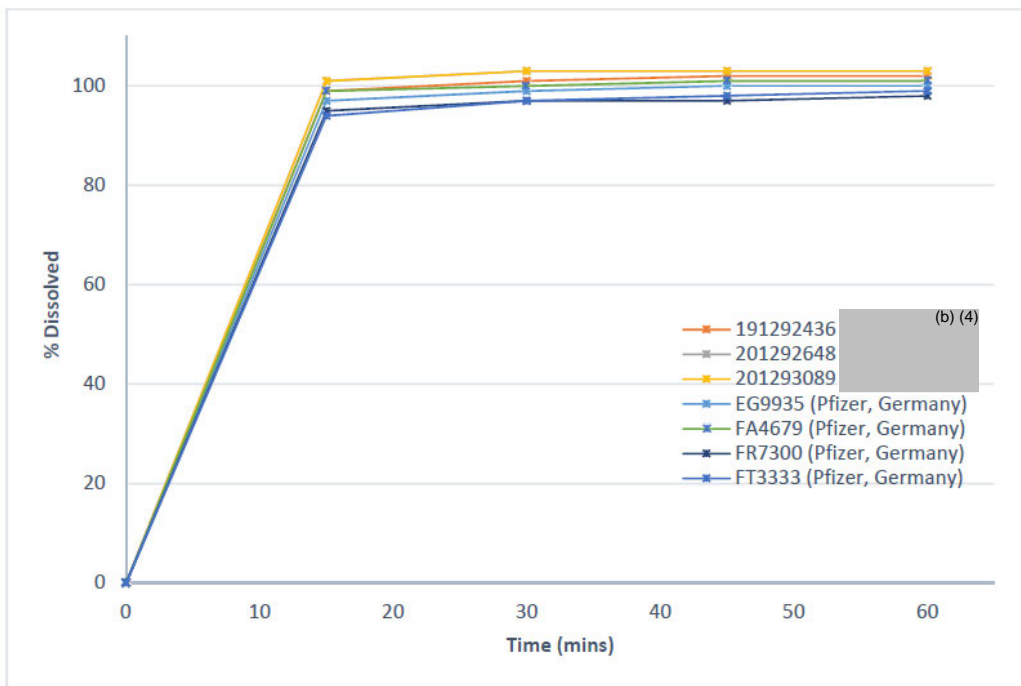
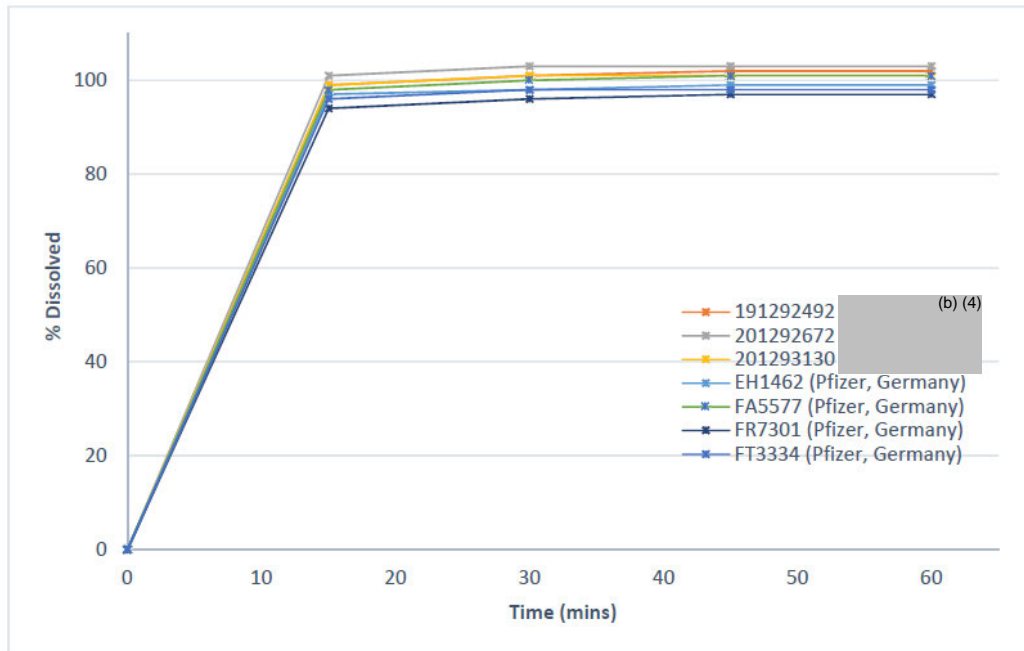


Figure 10: Comparative Dissolution Profiles of 100 mg Bosutinib Capsules manufactured in (b) (4) vs Germany (Pfizer) using QC dissolution method



B.4. BIOWAIVER REQUEST

Assessment: Not Applicable

The NDA does not contain a biowaiver request. The (b) (4) (b) (4) 50 mg) were evaluated in the pivotal clinical PK study BCHILDS Phase 1/2; ITCC-954/ B187—WI202099, and this study is reviewed by the Office of Clinical Pharmacology. Therefore, a biowaiver was not requested in this application.

BIOPHARMACEUTICS DEFICIENCIES PENDING:

None

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Dorantes

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