CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213217Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 213217
Review #1

Drug Name/Dosage Form	Zanubrutinib Capsules
Strength	80 mg
Route of Administration	Oral
Rx/OTC Dispensed	R_x
Applicant	BioGene USA, Inc
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Pre-Submission	04-Jun-19	Process/Facilities
Original Submission	27-Jun-19	All
Amendment (SD)	05-Sept-19	DP
Amendment (SD)	12-Sept-19	DP
Amendment (SD)	29-Jul-19	Process/facilities
Amendment (SD)	06-Sept-19	Process/Facilities

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Daniel Jansen	Su Tran
Drug Product	Anamitro Banerjee	Thomas Oliver
Process and Facilities	Yifan Wang	David Anderson
Microbiology	n/a	n/a
Biopharmaceutics	Zhuojun Zhao	Banu Zolnik
Regulatory Business Process Manager	Rabiya Laiq	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	Raanan Bloom	n/a

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type IV		(b) (4)	n/a	No Review	Adequate information provided in the NDA
	Type IV			n/a	No Review	Adequate information provided in the NDA
	Type IV			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
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type IV			n/a	No Review	Adequate information provided in the NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	125326	Zanubrutinib

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 213217 for Zanubrutinib Capsules, 80 mg. As part of this action, OPQ grants a (b) (4) re-test period for the drug substance when stored at (b) (4) and a 24-month expiration period for the drug product when stored at "20°C to 25°C (68°F to 77°F) excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]." 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 213217 was submitted for BRUKINSA (Zanubrutinib) Capsules, 80 mg in accordance with section 505(b)(1) of the Food, Drug and Cosmetic Act. Zanubrutinib is a once daily, orally bioavailable, Bruton's Tyrosine Kinase (BTK) inhibitor that is indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. Zanubrutinib is an NME that was granted Fast Track designation, Breakthrough Therapy Designation (January 2019) and Orphan Designation for the treatment of mantel cell lymphoma (MCL). (b) (4) (b) (4)

Zanubrutinib is a small chiral BCS 2 molecule that is manufactured as a single enantiomer by (b) (4) The drug product is supplied as an 80 mg, immediate-release, solid oral dosage form. It is presented as a size 0 white to off-white opaque capsules printed with "ZANU 80" in black ink containing white to off-white powder.

The recommended dose of BRUKINSA is 160 mg (two 80 mg capsules) taken orally approximately every twelve hours 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 213217 and grants a shelf life of 24 months for the drug product when stored in HDPE bottles at 20ºC to 25ºC (68ºF to 77ºF).

Proposed Indication(s) including Intended Patient Population	Indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.
Duration of Treatment	Duration of treatment is until disease progression or unacceptable toxicity

Maximum Daily Dose	320 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance

Zanubrutinib drug substance is a small chiral molecule that is synthesized as a single enantiomer. It is a BCS Class 2 drug, practically insoluble in water but is freely soluble in organic solvents such as methanol, acetone, DMSO and THF. It is a white to off-white, slightly hygroscopic solid that exhibits irregularly shaped, cohesive, (b) (4) particles with poor flow characteristics, and a tendency to agglomerate.

Zanubrutinib is manufactured (b) (4) as a single polymorph (Form A). The applicant included specifications and manufacturing schemes for each of the regulatory starting materials, a detail description of critical process parameters (CPPs) and in-process controls (IPCs). The Applicant included controls for the manufacturing process and details of the impurity fate and purge studies. Initial development of the synthetic process was completed by BeiGene. This early material was used to support IND-enabling toxicology and early clinical trials studies. (b) (4)

(b) (4)

The drug substance will be packaged in (b) (4)

(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.

Batch analyses were included from (b) (4) with batch sizes ranging from (b) (4)
The applicant included 12 months of long term (30°C/65%RH) and 6 months of accelerated (40°C/75%RH) stability data for three process performance qualification

(PPQ) lots that were manufactured at the proposed commercial scale (b) (4) at (b) (4) The three PPQ lots were designated as primary stability batches. The applicant requested a (b) (4) retest period for the drug substance when stored below (b) (4) No significant changes or trends were observed under either storage condition. The data provided is adequate to support the requested (b) (4) re-test for Zanubrutinib drug substance.

Drug Product

The drug product, Zanubrutinib, is presented as an 80 mg immediate-release solid oral dosage form. The drug product is presented as a size 0 white to off-white opaque capsule containing white to off-white powder. The capsules are printed with "ZANU 80" in black ink. The drug product formulation includes the active together with microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, colloidal silicon dioxide and magnesium stearate. The capsule shell ingredients include gelatin and titanium dioxide. The formulation contains no novel excipients and each of the excipients are below the maximum potency as reported in the IIG. A detailed description of the quantitative and qualitative drug product formulation are provided in the submission.

The drug product is manufactured by (b) (4) at a commercial batch size of *ca.* (b) (4) which corresponds to (b) (4) The drug product is manufactured with a (b) (4) remained unchanged from clinical development to the proposed commercial scale. 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 and is described in sufficient detail to support the approval of this NDA. While the manufacturing process and formulation remained unchanged from the first in human (FIH) study to the proposed commercial manufacturing process/formulation, 5 different manufacturing sites were used throughout development.

The drug product specifications include description, identification, uniformity of dosage units, assay, related substances, dissolution and (b) (4). The applicant included a risk assessment for elemental impurities as per ICH Q3D/USP <232> and justification (b) (4). The results of the risk assessment were acceptable and therefore a test for an elemental impurity in the drug product release specifications was not proposed and is not required. Only one (b) (4) was observed for the drug substance, which does not change during the drug product manufacturing process. (b) (4) are not used in the manufacture of the drug product. Accordingly, the omission of these tests (b) (4) is acceptable. The final drug product specifications are consistent with ICH Q6A and are based on batch analyses, manufacturing capability, and stability data. The drug product specifications are adequate to establish the drug product identity, potency and purity and provide adequate controls to ensure the quality of the drug product through the product expiry. 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.

In support of the proposed 24-month expiry, the applicant included 12 months of long term (25°C/60% RH) and 6 months of accelerated (40°C/75% RH) data for three primary registration batches (L0609229, L0609232, and L0609233). The primary stability batches were manufactured at the commercial site according to the proposed commercial manufacturing process and packaged separately in two commercial presentations (60 and 120 count bottles). In addition to the primary stability data, the Applicant included up to 36 months of supporting data for the 80 mg capsule packaged in various packaging configurations and manufactured at one of the five manufacturing sites used for clinical studies. These sites employed the same manufacturing process and formulation. Stability studies were executed in accordance with the ICH 1A and Q1B and the available stability data shows consistency over time and supports the proposed expiry. Therefore, based on the 12 months of stability data included in this application for Zanubrutinib Capsules, 80 mg, BeiGene USA, Inc. proposed and the FDA accepts the expiration dating period of **24 months** for the drug product when stored at stored at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

NDA 213217 is recommended for approval from a drug product and drug process perspective.

Biopharmaceutics

The drug substance is considered a BCS Class 2 molecule (low solubility, high permeability). The biopharmaceutics review focused on (1) the acceptability of the proposed in vitro dissolution method and acceptance criterion for the routine quality control testing of the proposed drug product at batch release and on stability and (2) bridging of the clinical and commercial formulations.

Dissolution Specification and Method: The original dissolution method included a USP Apparatus I (Baskets) at 100 RPM in 900 mL of 0.1 N HCl with 0.5% sodium lauryl sulfate (SLS) at 37°C. The proposed dissolution acceptance criterion was Q= (b) (4)% in 30 minutes. The method employing 0.5% SLS in 0.1 N HCl was selected after being shown to have superior discriminating power against changes in drug substance particle size; however, during development the Applicant was advised that a lower level of SDS and lower rotation speed may be more appropriate. In the original submission, the Applicant provided additional data to justify the surfactant level and rotation speed. Upon review of the additional data it was concluded that the dissolution method (including the SLS level and rotation speed) and acceptance criterion are acceptable as QC method for batch release and stability testing of the drug product.

Bridging of the Clinical Formulations: The manufacturing process and formulation of the drug product remained unchanged from the Phase I FIH study to the proposed commercial manufacturing process/formulation; however, 5 different manufacturing sites were used throughout development. The applicant indicated that equipment,

manufacturing process parameter, in-process control and historical release data are equivalent for each of the sites. The Applicant provided a comparison of drug product batches manufactured at each of the manufacturing sites and provided similarity factors (*f*2). Review of the data indicates that the comparative dissolution data supports the bridge between the proposed commercial site (b) (4) and the clinical manufacturing sites. The biopharmaceutics review team concluded that the bridge between the clinical and commercial formulations is established and additional *in vitro* or *in vivo* bridging studies are not required.

Based on the information provided (i.e. dissolution profile data for pivotal clinical batches and stability data), the proposed dissolution method and acceptance criterion are deemed acceptable for batch release and stability testing for the drug products and NDA 213217 is recommended for approval from a biopharmaceutics perspective.

Facilities

This application includes 4 sites and all sites were listed as ready for inspection:

- (b) (4) Manufacturing of Drug Substance, Packaging of Drug Substance, Release testing of Drug Substance (all test parameters), Stability testing of Drug Substance (XRPD only)
- **BeiGene (Suzhou) Co. Ltd. (FEI 3014150588)–** Stability testing of Drug Substance (all test parameters, except XRPD)
- (b) (4) – Drug Product Manufacturing; Batch Release Testing (all test parameters); Stability Testing (all test parameters) and Bulk Storage
- (b) (4) - Drug product: Labeling, primary packaging, secondary packaging and serialization and bulk and finished product storage.

At the conclusion of the review of NDA 213217, all facilities listed in were deemed acceptable for the responsibility listed in the application. This application is recommended for approval from the facilities perspective

Environmental Assessment

The applicant provided a claim for categorical exclusion and a statement of no extraordinary circumstances under 21 Code of Federal Regulations (CFR) Sections 25.31(b) and a statement of no extraordinary circumstances.

The request for categorical exclusion is granted.

C. Special Product Quality Labeling Recommendations (NDA only)

n/a

D. Final Risk Assessment (see Attachment)

Included at the beginning of the drug product review.

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	BRUKINSA	Adequate
Established name(s)	Zanubrutinib	Adequate
Route(s) of administration	Capsules, for Oral	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Capsules: 80 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally 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.	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)	The recommended dose of BRUKINSA is 160 mg (b) (4)) taken orally (b) (4) until disease progression or unacceptable toxicity. BRUKINSA can be taken with or without food. Advise patients to swallow capsules whole with water. Advise patients not to open, break or chew the capsules. If a dose of BRUKINSA is missed, it should be taken as soon as possible on the same day with a return to the normal schedule the following day.	Acceptable

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)	Capsules	Acceptable
Strength(s) in metric system	80 mg	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	NA	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Not provided in the original submission. Updated during the labeling negotiations	Acceptable
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	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	

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	BRUKINSA (zanubrutinib)	Acceptable
Dosage form(s) and route(s) of administration	Capsule for oral use	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	NA	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	The applicant included all the ingredients as listed in the section 3.2.P.1	Acceptable
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.	NA	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	
Statement of being sterile (if applicable)	NA	
Pharmacological/ Therapeutic class	Specific and irreversible Burton's tyrosine kinase inhibitor	Acceptable
Chemical name, structural formula, molecular weight	Provided as indicated in the section 3.2.S.1	Acceptable
If radioactive, statement of important nuclear characteristics.	NA	
Other important chemical or physical properties (such as pKa or pH)	Not included in the original submission. Updated during labeling negotiations.	Acceptable

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	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)	Capsules	Acceptable
Strength(s) in metric system	80 mg	Acceptable
Available units (e.g., bottles of 100 tablets)	Bottles of 120 counts	Acceptable. P1 also say 60 counts in 150 mL bottle in P1 not included in the label. The applicant confirmed that this is a physician's sample; hence need not be included in the USPI.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	The applicant description as listed in the section 3.2.P.1	Did not include "in black ink" for markings in the original submission. Updated during labeling negotiations. Acceptable
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally 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.	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.)	NA	Acceptable
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."	Desiccant not used	Acceptable
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	USP controlled room temperature	Acceptable
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."	NA	
Include information about child-resistant packaging	Provided	Acceptable

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	Not included in the original submission. Updated during labeling negotiations.	Acceptable

2.0 PATIENT LABELING

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

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

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Appears prominently in the label	Acceptable
Dosage strength	80 mg	Acceptable
Route of administration	Not listed	Acceptable
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	NA	
Net contents (e.g. tablet count)	120 tablets	Acceptable
"Rx only" displayed on the principal display	Yes	Acceptable
NDC number	Yes	Acceptable
Lot number and expiration date	Not included, space provided	Acceptable
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Provided.	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	
Bar code	Provided	Acceptable

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Included	Acceptable
Medication Guide (if applicable)	NA	
No text on Ferrule and Cap overseal	NA	
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	
And others, if space is available	NA	

Assessment of Carton and Container Labeling: ***Adequate***

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

ITEMS FOR ADDITIONAL ASSESSMENT

Overall Assessment and Recommendation:

Acceptable

Primary Labeling Assessor Name and Date: Anamitro Banerjee, PhD, September 20, 2019

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

Anamitro Banerjee

Digitally signed by Anamitro Banerjee
Date: 9/24/2019 10:28:21AM
GUID: 5075764700003844b7bc89632228509f

Thomas Oliver

Digitally signed by Thomas Oliver
Date: 9/24/2019 10:33:47AM
GUID: 508da71f00029ed4697700cee3d31ca0
Comments: Just signed labeling review

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	213217
Assessment Cycle Number	# 1
Drug Product Name/ Strength	Zanubrutinib Immediate Release Capsules, 80 mg
Route of Administration	Oral
Applicant Name	BeiGene USA, Inc.
Therapeutic Classification/OND Division	Lymphoma/DHP
RLD/RS Number	NA
Proposed Indication	Treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy
Primary Assessors	*Zhuojun Joan Zhao, Ph.D.*
Secondary Assessors	*Banu Zolnik, Ph.D.*
Assessment	**Adequate**
Recommendation	Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 213217 for Zanubrutinib IR Capsules, 80 mg, is recommended for **APPROVAL**.

Assessment Summary:

The Applicant's dissolution method development report was reviewed in IND 125326. This review evaluates the additional data supporting the proposed dissolution method, acceptance criterion justification as well as the bridging between the commercial DP manufacturing site (b) (4) and the clinical batches manufacturing sites.

Dissolution method and Acceptance Criterion:

During the IND stage (IND 125326), FDA recommended the Applicant to the use lower level of SDS and lower rotation speed [1]. In the NDA submission, the Applicant provided additional data to justify the amount of surfactant and rotation speed of the proposed dissolution method. Based on the provided data, the following dissolution method and acceptance criterion are acceptable as QC method for release and stability:

USP Apparatus	Rotation Speed	Medium	Volume	Cumulative % of Drug Dissolved (Label Claim)
USP I (Basket)	100 RPM	0.5% SLS in 0.1 N HCl	900 mL	Q= (b) (4)% in 30 minutes

[1] DARRTS: IND 125326 REV-QUALBIOPHARM-21 (Primary Review), final date 12/06/2018

Bridging Formulations:
The Applicant provided adequate dissolution data to support the bridging between the commercial DP manufacturing site (b) (4) and the clinical batches manufacturing sites (BeiGene-Beijing, BeiGene-Suzhou and (b) (4)).

List Submissions being assessed:

Document(s) Assessed	Date Received
0001 (2)	**June 27, 2019**

Highlight Key Issues from Last Cycle and Their Resolution: NA

Concise Description of Outstanding Issues): None

B.1 BACKGROUND

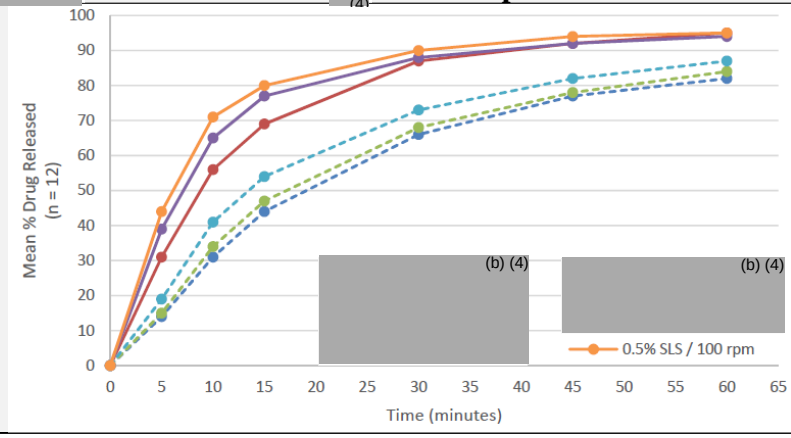
The Applicant is proposing a New Drug Application for zanubrutinib, an oral Bruton's tyrosine kinase (BTK) inhibitor for the indication of (b) (4) The proposed commercial presentation is an immediate-release, hard gelatin capsule for oral administration of the 80 mg strength. The drug product formulation for the 80 mg capsule was introduced in Phase 1 clinical trials and has remained unchanged throughout development.

The Applicant found that drug substance Zanubrutinib has poor aqueous solubility. The Applicant's dissolution method development report was reviewed in IND 125326[1]. The selection of apparatus (USP I Basket), dissolution medium (0.1 N HCl) and dissolution medium volume (900 mL) were found acceptable. However, additional data were requested in Advice/Information Request letter dated December 18, 2018[2] to justify the rotation speed (100 RPM) and the amount of surfactant used in the proposed dissolution medium (0.5% SLS in 0.1 N HCl).

B.2 NDA SUBMISSION

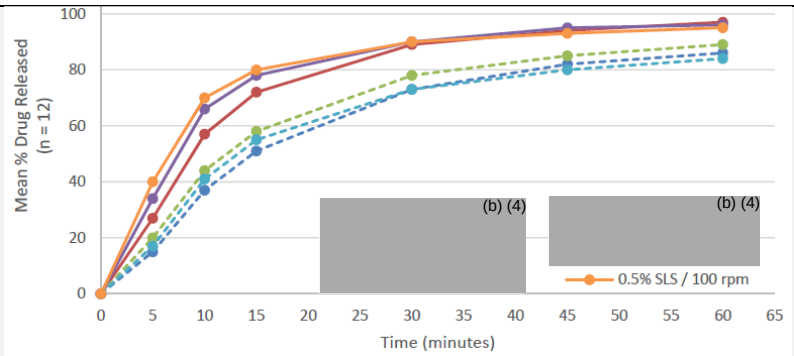
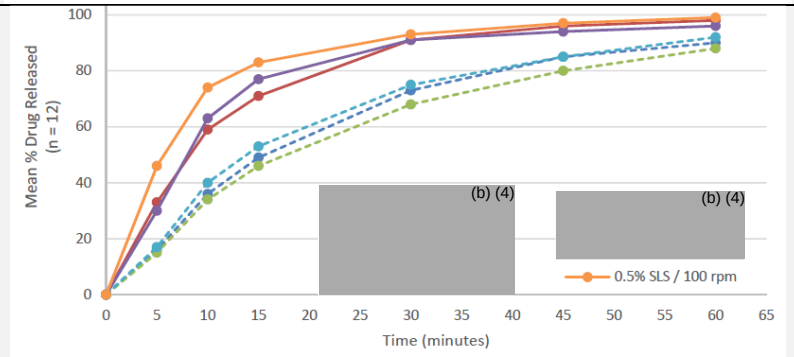
In the NDA submission[3], the Applicant provided the following additional evaluation study on rotation speed and surfactant:

Table 1: Dissolution Profiles Using USP I (Basket) with 900 mL 0.1 N HCl with (b) (4) and 0.5% SLS at (b) (4) and 100 rpm

Beijing Batch 3111080038 (n=12)	

[2] DARRTS: IND 125326 COR-INDAD-02 (Advice/Information Request), final date 12/18/2018

[3] \\cdsesub1\evsprod\nda213217\0001\m3\32-body-data\32p-drug-prod\zanubrutinib\32p2-pharm-dev\drug-prod.pdf

(b) (4) Batch L0602203 (n=12)	
Suzhou Batch 171102A1 (n=12)	

Based on the above data, the dissolution profiles with rotation speed of (b) (4) rpm showed incomplete release (Appendix 1). With rotation speed of 100 rpm, the dissolution profiles are comparable with (b) (4) and 0.5% SLS in the dissolution medium.

Discriminating Ability of the Method:
The Applicant evaluated the discriminating power of the proposed dissolution method with various surfactant levels on the following critical material attributes (CMA) and critical process parameters (CPP):

Drug Substance Particle Size Distribution:
The Applicant manufactured 5 batches of Zanubrutinib capsules with drugs substance of different PSD (**Table 2**).

Table 2: PSD Data of DS Batches Used in Discriminating Power Evaluation

DP Batch No.	DS Batch No.	DS Particle Size		
		D_{10} (µm)	D_{50} (µm)	D_{90} (µm)
D-1608FP1919-01	A02489-025D2	(b) (4)		
1612FP1788-01	PH-BEI-BGB-3111-0-B(FP)-3			
D-1611FP1788-01	PH-BEI-BGB-3111-GMP-0-A(FP)-2			
D-1611FP1788-03	A03151-022A2			
D-1611FP1788-02	A02489-083A16			

Note: Batch D-1608FP1919-01 was set as a reference batch, for its D90, D50 and D10 are all within the proposed PSD specification.

The Applicant generated similarity factor f_2 (Table 4) to compare the dissolution profiles (Table 3). The similarity factor calculation was confirmed by this Reviewer's own analysis.

Table 3: Effect of Zanubrutinib Drug Substance PSD on Dissolution (n=12)

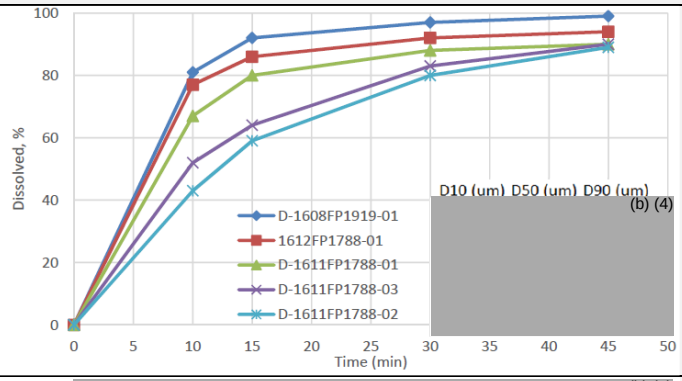
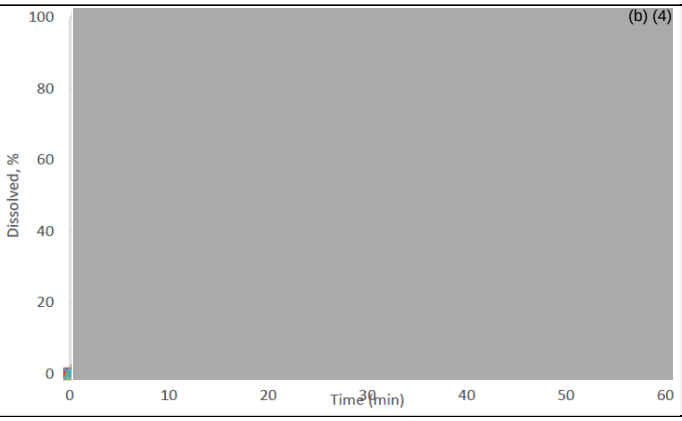
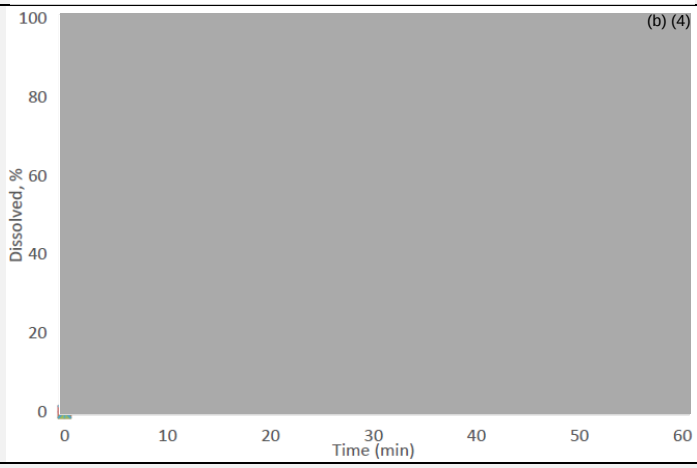
0.5% SLS	
(b) (4) % SLS	
(b) (4) % SLS	

Table 4: Similarity Factors (*f*2) of *Dissolutions*: USP I (Basket) at 100 rpm with Different Surfactant Levels

Reference Batch	SLS Level	1612FP1788-01	D-1611FP1788-	D-1611FP1788-	D-1611FP1788-
		(b) (4)			
D-1608FP1919-01 (D_{50} = (b) (4) D_{90} =	0.5%	$f_2 = 66$	$f_2 = 46$	$f_2 = 33$	$f_2 = 28$
		(b) (4)			

The Applicant concluded that all 3 methods (0.5%, (b) (4) SLS) demonstrated discriminating power for zanubrutinib drug substance particle size changes, while the 0.5% SLS method is slightly more sensitive to particle size change than the (b) (4) SLS methods based on the calculated *f*2 values.

Excipients:
The Applicant found that none of the excipients studied, including SLS, croscarmellose sodium, and magnesium stearate have an impact on zanubrutinib capsules, 80 mg dissolution profiles using the proposed dissolution method (i.e. USP I (Basket) 0.5% SLS in 0.1 N HCl at (b) (4) rpm).

Critical Process Parameters:
In the process development DOE studies, the Applicant evaluated the (b) (4) and found it had no impact on dissolution. The identified critical process parameters including (b) (4) are known to have no impact on dissolution, as well.

Assessment: *{Adequate}*
Based on the provided information, the selected rotation speed (100 rpm) and SDS level (0.5% SLS) are adequately justified.

Therefore, the proposed dissolution method is acceptable for the QC dissolution testing of the proposed drug product. The proposed dissolution method could discriminate variation of drug substance particle size distribution only.

B.3 DISSOLUTION ACCEPTANCE CRITERION

The Applicant proposed a dissolution acceptance criterion of Q= (b) (4)% in 30 minutes based on dissolution profile data from the clinical batches (e.g. 1703FF1788-01, 1704FP1788-01, 170901A, 171101A, 171102A, 110901A, etc.) and primary registration batches (3.2.P.8.3).

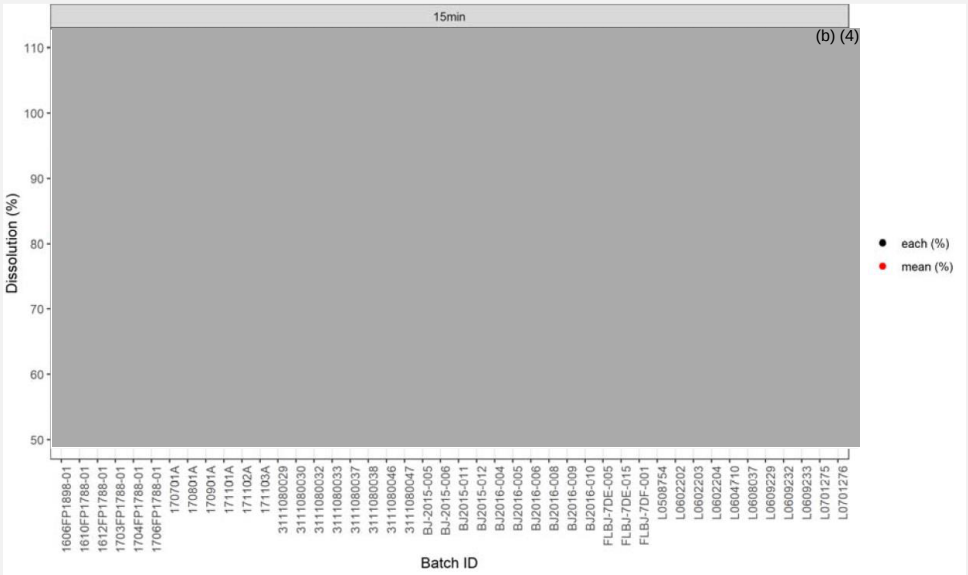
Table 5: Summary of Range Observed – Dissolution

Data Source		Number of Batches[a]	Range Mean %Dissolved at 30 min
Acceptance Criteria		NA	Q = (b) (4)% Label Claim at 30 minutes
Release (All sites)		44	88%–100%
Release (b) (4)		11	90%–99%
Stability (All Sites all packaging configurations)	Long Term (25°C/60%RH)	50	85%–100%
	Intermediate (30°C/65%RH)	50	86%–100%
	Accelerated (40°C/75%RH)	50	87%–100%
Stability (Primary Stability Batches, 60 ct)	Long Term (25°C/60%RH)	3	94%–96%
	Intermediate (30°C/65%RH)	3	91%-96%
	Accelerated (40°C/75%RH)	3	91%–96%
Stability (Primary Stability Batches, 120 ct)	Long Term (25°C/60%RH)	3	91%–96%
	Intermediate (30°C/65%RH)	3	91%–96%
	Accelerated (40°C/75%RH)	3	91%–96%

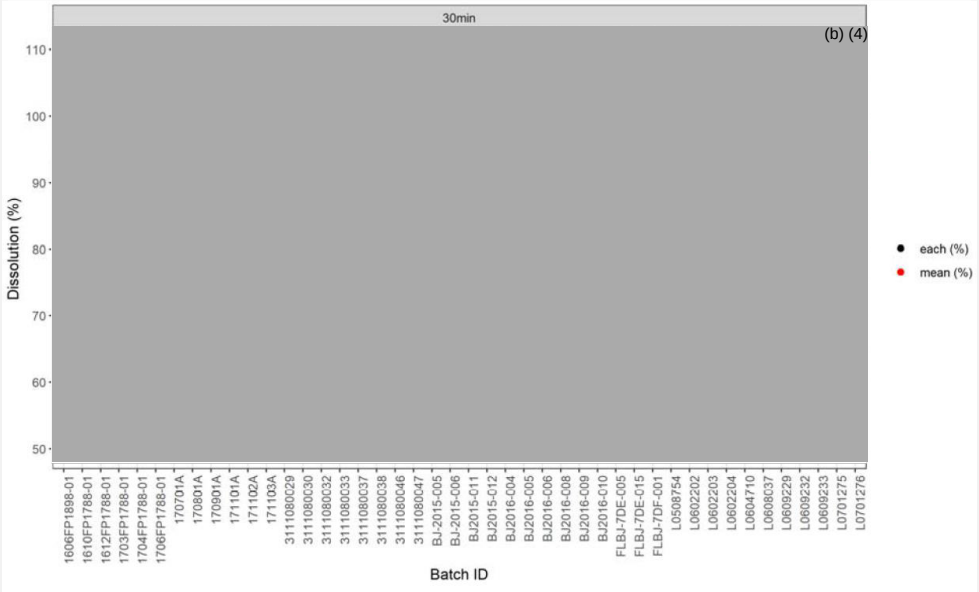
Note: ct = count; NA = not applicable; RH = relative humidity
[a] The number of batches are from bulk drug product for release and packaged drug product for stability.

Table 6: Dissolution Data at Release

At 15 minutes



At 30 minutes



Assessment: ***{Adequate}***
The proposed dissolution acceptance criterion is acceptable.

B.4 BRIDGING OF FORMULATIONS

The proposed commercial presentation is an immediate-release, hard gelatin capsule for oral administration of the 80 mg strength. The drug product formulation for the 80 mg capsule was introduced in Phase 1 clinical trials and has remained unchanged throughout development. The proposed commercial manufacturing process for the 80 mg capsules is (b) (4) remained unchanged from clinical to the proposed commercial scale. The Applicant states that equipment, manufacturing process parameter, in-process control and historical release data are equivalent at all clinical

supply manufacturing sites. The proposed DP commercial manufacturing site is (b) (4), (b) (4) while Zanubrutinib capsules from 4 manufacturers were used during the conduct of the pivotal Phase 1 Study BGB-3111-AU-003 and Phase 2 Study BGB-3111-206 (**Table 7**).

Table 7: Manufacturing Sites and Associated Clinical Studies

Site Name	Site Name Abbreviation	Address	Used in the Following Clinical Studies
(b) (4)			BGB-3111-AU-003 BGB-3111-1002
BeiGene (Beijing) Co., Ltd.	BeiGene-Beijing	No.30 Science Park Road Zhong-Guan-Cun Life Science Park Changping District Beijing, 102206 P.R. China	BGB-3111-103 BGB-3111-104 BGB-3111-105 BGB-3111-106 BGB-3111-AU-003 BGB-3111-1002
BeiGene (Suzhou) Co., Ltd	BeiGene-Suzhou	9 Building, 218 Sangtian Street Suzhou Industrial Park Jiangsu Province, 215025 P.R. China	BGB-3111-107 BGB-3111-108 BGB-3111-AU-003 BGB-3111-205 BGB-3111-206 BGB-3111-210 BGB-3111-1002
(b) (4)			BGB-3111-AU-003 BGB-3111-205 BGB-3111-206 BGB-3111-210
			(b) (4)
(b) (4)			

The Applicant compared DP batches manufactured at all manufacturing sites (Appendix 2) and (b) (4) (b) (4) and those manufactured by (b) (4), BeiGene-Suzhou, and BeiGene-Beijing.

Table 8: Similarity Factor f2 (using 0.1 N HCl with 0.5% SLS)[4]

(b) (4) Batch No.	BeiGene-Beijing		
	3111080030	3111080033	3111080038
L0602203	71	78	82
L0602204	63	77	71
L0604710	63	89	74

(b) (4) Batch No.	BeiGene Suzhou		
	171101A1	171102A1	171103A1
L0602203	72	68	92
L0602204	64	61	77
L0604710	65	61	75

(b) (4) Batch No.	(b) (4)		
	1610FP1788-01	1703FP1788-01	1704FP1788-01
L0602203	98	81	70
L0602204	83	70	62
L0604710	80	69	62

Assessment: ***{Adequate}***

The comparative dissolution data ($f2>50$) support the bridge between the proposed commercial site (b) (4) and the clinical batches manufacturing sites (BeiGene-Beijing, BeiGene-Suzhou and (b) (4)

B. 5 BIOWAIVER REQUEST

Assessment: ***N/A***

The Applicant is seeking approval for only one dosage strength (80 mg) and thus biowaiver request is not applicable for the application.

R. REGIONAL INFORMATION

Comparability Protocols: N/A

Post-Approval Commitments: N/A

Lifecycle Management Considerations: N/A

[4] \\cdsesub1\evsprod\nda213217\0001\m3\32-body-data\32p-drug-prod\zanubrutinib\32p2-pharm-dev\process-development.pdf

APPENDIX 1: Additional *Dissolution Data Comparing Agitation Speeds (USP I with 900 ml 0.1 N HCl with* (b) (4) *and 0.5% SLS)*

Summary Dissolution Data for BeiGene – Beijing Batch 3111080038 (n=12)

Agitation Speed	Dissolution Medium		5 min	10 min	15 min	30 min	45 min	60 min
(b) (4)	(b) (4)	Avg.%						(b) (4)
		SD.%						
		Min.%						
		Max.%						
		Avg.%						
		SD.%						
		Min.%						
		Max.%						
	0.5% SLS in 0.1 N HCl	Avg.%						
		SD.%						
		Min.%						
		Max.%						
100 RPM	(b) (4)	Avg.%						
		SD.%						
		Min.%						
		Max.%						
		Avg.%						
		SD.%						
		Min.%						
		Max.%						
	0.5 % SLS in 0.1N HCl	Avg.%	**44**	**71**	**80**	***90***	**94**	**95**
		SD.%	6	4	2	2	2	2
		Min.%	(b) (4)					
		Max.%						

Summary Dissolution Data for (b) (4) Batch L0602203 (n=12)

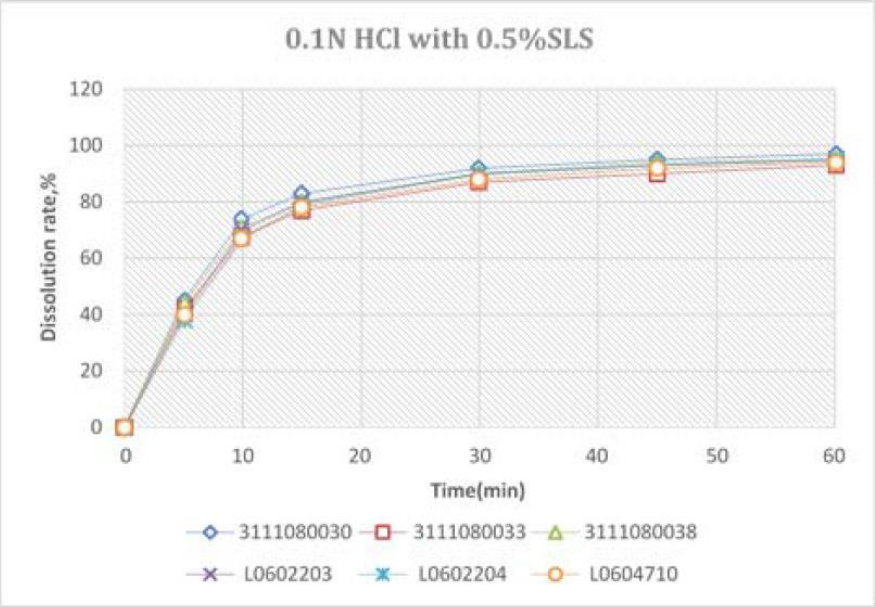
Agitation Speed	Dissolution Medium		5 min	10 min	15 min	30 min	45 min	60 min
(b) (4)	(b) (4)	Avg.%						(b) (4)
		SD.%						
		Min.%						
		Max.%						
		Avg.%						
		SD.%						
		Min.%						
		Max.%						
	0.5% SLS in 0.1 N HCl	Avg.%						
		SD.%						
		Min.%						
		Max.%						
100 RPM	(b) (4)	Avg.%						
		SD.%						
		Min.%						
		Max.%						
		Avg.%						
		SD.%						
		Min.%						
		Max.%						
	0.5 % SLS in 0.1N HCl	Avg.%	**40**	**70**	**80**	***90***	**93**	**95**
		SD.%	6	6	5	3	2	2
		Min.%	(b) (4)					
		Max.%						

Summary Dissolution Data for BeiGene –Suzhou Batch 171102A1 (n=12)

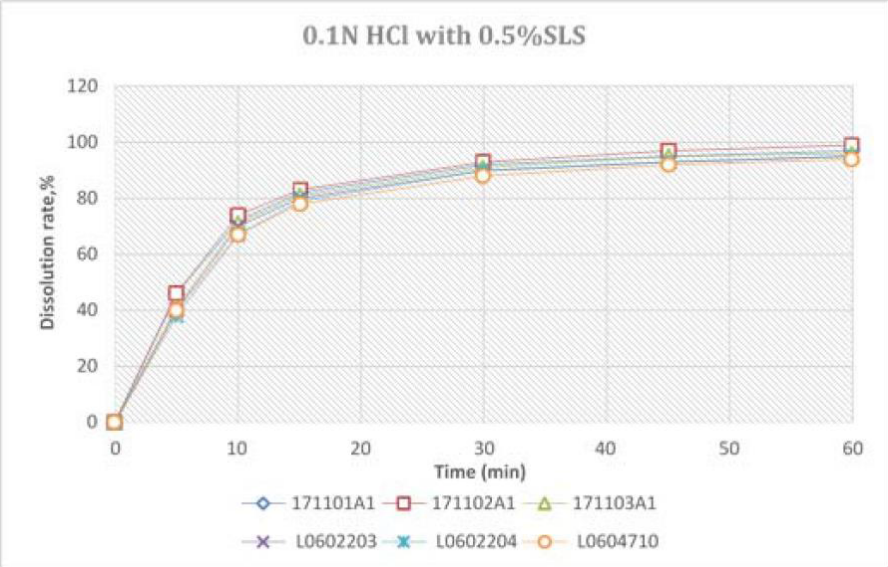
Agitation Speed	Dissolution Medium		5 min	10 min	15 min	30 min	45 min	60 min
(b) (4)	(b) (4)	Avg.%	(b) (4)					
		SD.%						
		Min.%						
		Max.%						
		Avg.%						
		SD.%						
		Min.%						
		Max.%						
	0.5% SLS in 0.1 N HCl	Avg.%						
		SD.%						
		Min.%						
		Max.%						
100 RPM	(b) (4)	Avg.%						
		SD.%						
		Min.%						
		Max.%						
		Avg.%						
		SD.%						
		Min.%						
		Max.%						
	0.5% SLS in 0.1 N HCl	Avg.%	**46**	**74**	**83**	***93***	**97**	**99**
		SD.%	5	5	3	2	2	2
		Min.%	(b) (4)					
		Max.%						

APPENDIX 2: *Dissolution Profiles*[4]

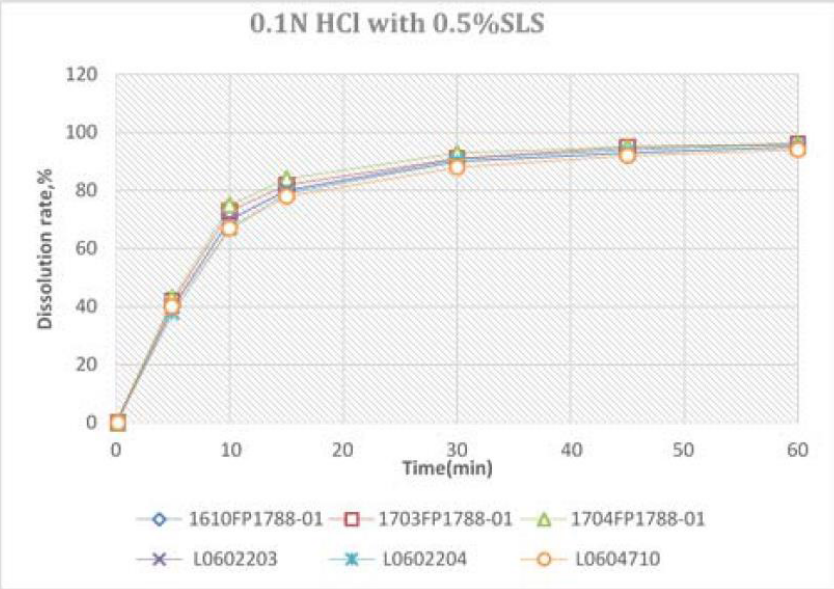
Dissolution Profiles ((b) (4) and BeiGene-Beijing)



3: Dissolution Profiles ((b) (4) and BeiGene-Suzhou)



Dissolution Profiles [redacted] (b) (4)



Zhuojun Zhao

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Banu Zolnik

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Sherita McLamore

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