CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210259Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 210259
Review #1

Drug Name/Dosage Form	Acalabrutinib Capsules
Strength	100 mg
Route of Administration	Oral
Rx/OTC Dispensed	R_x
Applicant	Acerta Pharma B.V.
US agent, if applicable	Yasameen Qazen

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	13-Jun-17	All
Amendment (SD 4)	13-Jul-17	Process
Amendment (SD 0014)	25-Aug-17	Facilities
Amendment (SD 0015)	25-Aug-17	Process, DS
Amendment (SD 0017)	30-Aug-17	DS, DP
Amendment (SD 0018)	08-Sept-17	DS

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Linsey Saunders and Paresma Patel	Anamitro Banerjee
Drug Product	Rajiv Agarwal	Anamitro Banerjee
Process	Quamrul Majumder	Rakhi Shah
Microbiology	n/a	n/a
Facility	Ruth Moore	Zhihao Peter Qiu
Biopharmaceutics	Yang Zhao	Okponanabofa Eradiri
Regulatory Business Process Manager	Rabiya Laiq	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	Rajiv Agarwal	Anamitro Banerjee

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type IV		(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
	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 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	118717	

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 210259 for Calquence (acalabrutinib) capsules, 100 mg. As part of this action, OPQ grants a (b)(4)-month re-test period for the drug substance when stored at or below (b)(4)°C, and a 24-month drug product expiration period when stored at stored at controlled room temperature (25°C/60% RH). 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 210259 was submitted for Calquence (acalabrutinib) capsules, 100 mg in accordance with section 505(b)(1) of the Food, Drug and Cosmetic Act. Acalabrutinib is an orally bioavailable, Bruton tyrosine kinase inhibitor (BTK) indicated for patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. Acalabrutinib is an NME which was originally investigated under IND 118717 and received orphan designation in September 2015.

Acalabrutinib is a small chiral molecule that is manufactured as a single enantiomer (S) in a linear manner. Acalabrutinib is a BCS class 2 compound that exhibits BCS class 1 characteristics under *in vivo* conditions. The drug product, Calquence (acalabrutinib) capsules, 100 mg, is presented as a (b)(4) hard gelatin capsule, with a blue cap and yellow body, printed with 'ACA 100mg' in black ink and containing 100 mg of acalabrutinib, microcrystalline cellulose, pregelatinized startch, sodium starch glycolate and magnesium stearate.

The dosing regimen for Calquence (acalabrutinib) capsules is 100 mg orally twice daily.

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 210259 and grants a (b)(4)-month re-test period for the drug substance and a 24 month expiration period for the drug product when stored at ICH controlled room temperature in the commercial packaging.

Proposed Indication(s) including Intended Patient Population	Indicated for the treatment of 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	200 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance

(b) (4)

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(b) (4)

Process

(b) (4)

Comparability protocol

This application includes a comparability protocol in which AstraZeneca, Sweden would be added as an alternate site for drug product manufacture, QC and stability testing. The applicant proposed to submit this change in the form of a CBE-30 supplement. The applicant indicates that the addition of this alternative site will ensure security and continuity of supply of the drug product. The comparability protocol was reviewed by the drug product, process and facility reviewers with input and guidance from OLDP (Dr. Ramesh Raghavachari BC, OLDP). The applicant was advised to amend the comparability protocol to include stability data on three batches in each packaging configuration. The applicant agreed and the comparability protocol was deemed acceptable by the review team.

Biopharmaceutics

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 was

assessed. The dissolution method included a USP Apparatus II (Paddle) at 50 rpm in 900 mL of 0.1 N HCl. The proposed dissolution acceptance criterion is Q= (b) (4)% in 20 minute. It is noted that the drug substance is a BCS class 2 compound and is highly soluble in acidic media up to pH 4. Both the proposed dissolution method and acceptance criterion were deemed acceptable and as such this application is recommended for approval from a biopharmaceutics perspective.

PBPK Model

The applicant proposed a Physiologically Based Pharmacokinetic (PBPK) model to support a particle size specification of D_{90} NMT (b) (4) µm for the drug substance. The information provided was incomplete and therefore does support the approval of the PBPK model. While the proposed PBPK model is not acceptable, this recommendation has no impact on the approvability of the NDA submission, because the newly proposed limit of D_{90}: NMT (b) (4) µm for the particle size of the drug substance is based on the actual D_{90} particle size limit of the drug product used in the pivotal clinical batches, which is acceptable.

Facilities

(b) (4)

(b) (4)

USE of CLINICAL BATCH for COMMERCIAL LAUNCH:

The sponsor submitted a proposal to ensure that acalabrutinib capsules would be available to meet a potential October 2017 approval. Specifically, the sponsor presented a supply option to meet this accelerated timeframe which included using material from the product validation campaign. During a Type A meeting teleconference held on August 17, 2017, the applicant requested the FDA's approval of API clinical batch C665/2 manufactured at AstraZeneca of the UK (FEI 3002850317) for use in one batch of commercial Acalabrutinib capsules in order to ensure availability of market launch supply upon approval of this application. To facilitate a risk assessment of the quality of batch C665/2 additional coverage was given to the manufacturing systems and records related to the C665 campaign manufactured at AstraZeneca. Review of the records for the production and testing operations, cleaning and qualification of facilities & equipment, and the resolution of deviations and investigations associated with the manufacture of the drug product batch C665/2 revealed no adverse findings that would pose a risk to use of the batch in drug product intended for commercial supply. Accordingly, the use of drug substance batch C665/2 for a commercial batch of capsules is acceptable. The corresponding commercial drug product batch number is L060511.

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).

The request for categorical exclusion is granted.

C. Special Product Quality Labeling Recommendations (NDA only)

n/a

D. Final Risk Assessment (see Attachment)

Appended at the end of the drug product review.

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LABELING (NDA 210259)

R Regional Information

1.14 Labeling

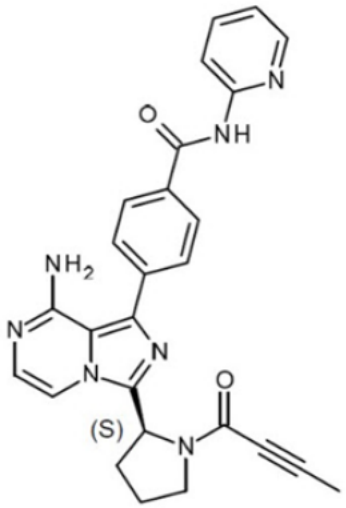
Labeling & Package Insert

DESCRIPTION section:

11 DESCRIPTION

TRADENAME (acalabrutinib) is an inhibitor of Bruton tyrosine kinase (BTK). The molecular formula for acalabrutinib is $C_{26}H_{23}N_7O_2$, and the molecular weight is 465.51. The chemical name is 4-{8-amino-3-[(2S)-1-(but-2-ynoyl)pyrrolidin-2-yl]imidazo[1,5-a]pyrazin-1-yl)}-N-(pyridine-2-yl)benzamide.

The chemical structure of acalabrutinib is shown below:



Acalabrutinib is a white to (b) (4) powder with pH-dependent solubility. It is freely soluble in water at pH values below 3 and practically insoluble at pH values above 6.

TRADENAME capsules for oral administration contains 100 mg acalabrutinib and the following inactive ingredients: microcrystalline cellulose, (b) (4) partially pregelatinized starch, magnesium stearate, and sodium starch glycolate. The capsule shell contains gelatin, titanium dioxide, yellow iron oxide, FD&C Blue 2 and is imprinted with edible black ink.

Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

HOW SUPPLIED section:

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Pack Size	Contents	NDC Number
		(b) (4)
60-count bottle	Bottle containing 60 capsules 100 mg, hard gelatin capsules with yellow body and blue cap, marked in black ink with 'ACA 100 mg'	0310-YYYY-ZZ

Storage

Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59° - 86°F) [see USP Controlled Room Temperature].

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of TRADENAME is 100 mg taken orally approximately every twelve hours until disease progression or unacceptable toxicity.

Advise patients to swallow whole with water. Advise patients not to open, break or chew the capsules. TRADENAME may be taken with or without food. If a dose of TRADENAME is missed by more than 3 hours, it should be skipped and the next dose should be taken at its regularly scheduled time. Extra capsules of TRADENAME should not be taken to make up for a missed dose.

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)?

☒ Yes ☐ No ☐ N/A

If "No," explain.

Reviewer's Assessment:

The PI label is modified and the comments will be communicated to the applicant via OND PM. The applicant has not responded yet. ***Pending***

Immediate Container Label (100mg: (b) (4) 60 counts)

(b) (4)

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Reviewer's Assessment:

The following comments were communicated to the applicant on 14-SEP-2017 by DMEP. The applicant has not responsed to deficiencies yet. ***Responses pending***

1) Replace the term "TRADENAME" with the conditionally acceptable proprietary name.

2) Relocate the net quantity statement (60 capsules) away from the product strength (100 mg), such as to the bottom of the principal display panel. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. Draft Guidance: Container and Carton, April 2013 (lines 461-463).

3) As currently presented, there is no space allotted for the lot number and expiration. The lot number statement is required on the container and carton labeling when there is sufficient space per 21 CFR 201.10(i)(1). Please ensure the lot number is clearly differentiated from the expiration date. In addition, please ensure that there are no other numbers located in close proximity to the expiration date where it can be mistaken as the expiration date.

4) Update the NDC numbers in the PI and Container Closure labels.

A separate memo will be filed in Panorama, once the Agency received an agreed upon labeling and labels. ***Pending***

Conclusion: *Labels and Labeling are not adequate from a CMC stand point.*

Primary Labeling Reviewer Name and Date:

Rajiv Agarwal, Ph.D, 14-SEP-2017

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

Anamitro Banerjee, PhD, Acting BC, September 15, 2017

Rajiv Agarwal

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Anamitro Banerjee

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BIOPHARMACEUTICS

NDA: 210259-ORIG-1

Drug Product Name/Strength: Acalabrutinib Capsules, 100 mg

Route of Administration: Oral

Applicant Name: Acerta Pharma B.V.

Product Background:

Acalabrutinib is a kinase inhibitor indicated for the treatment of patients with Mantle Cell Lymphoma (MCL) who have received at least one prior therapy. The recommended dose is 100 mg orally twice daily taken with or without food.

The proposed drug product is presented as a (b) (4) hard gelatin capsule, with a blue cap and yellow body, printed with 'ACA 100 mg' in black ink and containing 100 mg of acalabrutinib.

REVIEW SUMMARY:

Submission: Acerta Pharma B.V. submitted this NDA seeking approval for Acalabrutinib Capsules 100 mg under section 505 (b)(1) of the Federal Food, Drug, and Cosmetic Act.

Reviewer's Assessment: The Biopharmaceutics Review evaluates the adequacy of the proposed dissolution method and acceptance criterion for the routine QC testing of the proposed drug product at batch release and on stability.

The following dissolution method and acceptance criterion for the proposed Acalabrutinib Capsules 100 mg are acceptable:

Apparatus:	USP Apparatus II (Paddle)
Speed:	50 rpm
Medium:	0.1 N HCl
Volume:	900 mL
Temperature:	37 °C
Dissolution acceptance criterion:	Q = (b) (4) % in 20 minutes.

Recommendation: From the Biopharmaceutics perspective, NDA-210259 for Acalabrutinib Capsules, 100 mg, is recommended for **APPROVAL**.

List of submissions being reviewed: Original NDA-210259 submitted on June 13, 2017.

Highlight of key outstanding issues from last cycle: None.

Concise description of outstanding issues: None.

REVIEW:

1. BCS Designation:

The Applicant reported that acalabrutinib is a BCS class 2 compound (low solubility and high permeability). The Applicant reported that the drug substance is highly soluble in acidic media up to pH 4.

Table 1. Solubility of acalabrutinib in different pH media at 37 °C (Page 44, Module 2.7.1)

pH	Solubility mg/mL	USP solubility description	BCS solubility description	Dose of acalabrutinib soluble in 250 mL (mg)
1	>100	Freely soluble	High	>25000
2	>100	Freely soluble	High	>25000
3	>100	Freely soluble	High	>25000
4	3.9	Slightly soluble	High	975
5	0.34	Very slightly soluble	Low	85
6	0.077	Practically insoluble	Low	19.3
7	0.051	Practically insoluble	Low	12.8
8	0.048	Practically insoluble	Low	12

The Applicant also measured the equilibrium solubility of acalabrutinib in Fasted State Simulated Intestinal Fluid (FaSSIF, pH=6.5, 0.12 mg/mL), and in Fed State Simulated Intestinal Fluid (FeSSIF, pH=5.0, 0.67 mg/mL).

2. Dissolution method:

The proposed dissolution method for Acalabrutinib capsules 100 mg is as follows:

Apparatus:	USP apparatus II (Paddle)
Paddle Speed:	50 rpm
Medium:	0.1 N HCl
Volume:	900 mL
Temperature:	37 ºC

(b) (4)

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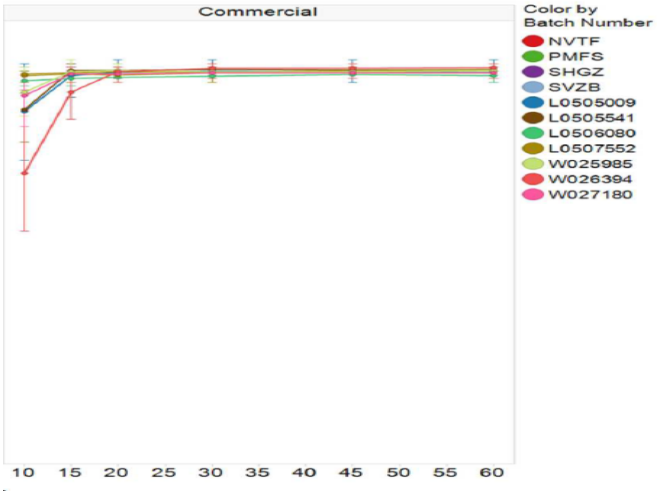
(b) (4)

4. Dissolution data and proposed dissolution acceptance criterion for the Acalabrutinib capsules, 100 mg:

The Applicant provided the dissolution profile data for different batches used in clinical studies (refer to Table 3 for more batch information) using the proposed dissolution method (Figure 10).

Figure 10. Dissolution profiles of the proposed Acalabrutinib capsules, 100 mg, using the proposed dissolution method



Reviewer's Assessment of the Proposed Dissolution Acceptance Criterion: Based on the dissolution data, the Applicant's proposed dissolution acceptance criterion of Q = (b) (4) % dissolved in 20 minutes for Acalabrutinib capsules 100 mg is acceptable.

5. Stability data:

The Applicant provided stability data for Batches L0505009, L0505541, L0506080 L0508305, L0508623, and L0508625 packaged in bulk pack, or in 60 mL HDPE bottle, or in 110 mL HDPE bottle under 25°C/60% RH up to 18 months, 30°C/75% RH up to 18 months, and 40°C/75% RH up to 6 months. The stability dissolution data indicate that these batches meet the dissolution acceptance criterion of Q = (b) (4) % in 20 minutes in different storage conditions.

Reviewer's Assessment: The Applicant provided the stability dissolution data at 12 months using the proposed dissolution method and all samples passed the dissolution acceptance criterion at Stage 1. Therefore, the proposed drug product is stable with regards to dissolution for at least 12 months under long term storage conditions.

6. Bridging between the (b) (4) capsules and planned commercial products:

The (b) (4) capsule formulations were used in some pivotal clinical studies and supportive studies (Table 3). The (b) (4) capsule formulations contain (b) (4)

Figure 11 below demonstrates that the (b) (4)

.

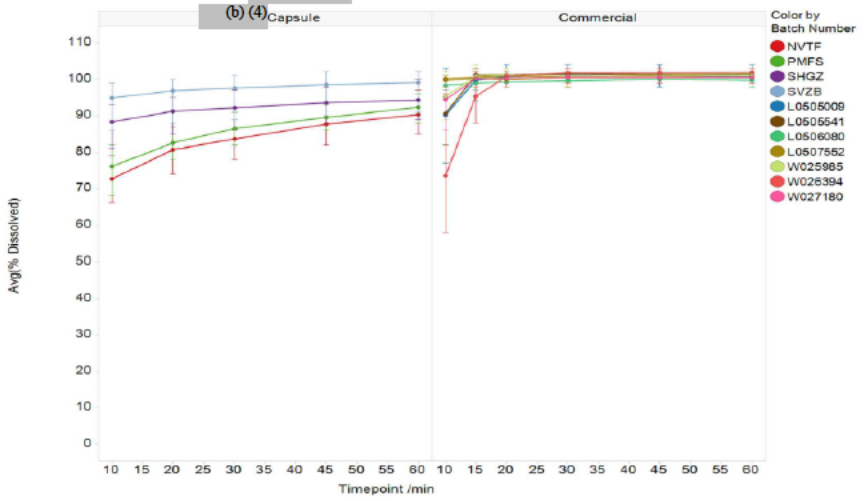
In addition, the Applicant reported that the pharmacokinetic (PK) exposure was generally similar between 100 mg acalabrutinib in either (b) (4) capsule or the intended commercial formulation in healthy subjects and on Cycle 1 Day 1 in patients.

Table 3. Different Acalabrutinib formulations used in clinical studies. The "Capsule" in the column labeled "Brief Description" is the intended commercial formulation

Drug Product Bulk Lot	Study	Brief Description[a]	Strength (mg)	Manufacturing Facility
NCZP	ACE-HV-001	(b) (4) capsule	2.5	(b) (4)
NCZS	ACE-HV-001	capsule	25	
NVTF	ACE-HV-004	capsule	100	
L0505009	ACE-HV-005	capsule	100	
STGY	ACE-HV-007	(b) (4) capsule	15	
NCZS	ACE-HV-008	capsule	25	
L0505009	ACE-HV-009	capsule	100	
(b) (4)	ACE-HV-009	[^{14}C]acalabrutinib oral solution	1.0 mg/mL (~10 nCi/mL)	
	ACE-HV-009	[^{14}C]acalabrutinib IV solution	1.64 µg/mL (~200 nCi/mL)	
STGY	ACE-HV-111	(b) (4) capsule	15	
L0505009	ACE-HV-112	capsule	100	
W026394	ACE-HV-113	capsule	100	
NZCP	ACE-HI-001	(b) (4) capsule	25	
NFYY	ACE-CL-001	capsule	25	
NVTF	ACE-CL-001	capsule	100	
PMFS	ACE-CL-001	capsule	100	
SHGZ	ACE-CL-001	capsule	100	
SVZB	ACE-CL-001	capsule	100	
W025985	ACE-CL-001	capsule	100	
W026394	ACE-CL-001	capsule	100	
W027180	ACE-CL-001	capsule	100	
W032242	ACE-CL-001	capsule	100	
L0505009	ACE-CL-001	capsule	100	
L0505541	ACE-CL-001	capsule	100	
L0506080	ACE-CL-001	capsule	100	
L0507552	ACE-CL-001	capsule	100	
L0508306	ACE-CL-001	capsule	100	
NVTF	ACE-LY-002	(b) (4) capsule	100	
PMFS	ACE-LY-002	capsule	100	
SHGZ	ACE-LY-002	capsule	100	
W025985	ACE-LY-002	capsule	100	
W026394	ACE-LY-002	capsule	100	
L0505009	ACE-LY-002	capsule	100	
L0505541	ACE-LY-002	capsule	100	
L0506080	ACE-LY-002	capsule	100	
L0507552	ACE-LY-002	capsule	100	
PMFS	ACE-LY-003	(b) (4) capsule	100	
SHGZ	ACE-LY-003	capsule	100	

					(b) (4)
W025985	ACE-LY-003	capsule		100	
W026394	ACE-LY-003	capsule		100	
W027180	ACE-LY-003	capsule		100	
L0505009	ACE-LY-003	capsule		100	
L0505541	ACE-LY-003	capsule		100	
L0506080	ACE-LY-003	capsule		100	
L0507552	ACE-LY-003	capsule		100	
L0508306	ACE-LY-003	capsule		100	
SHGZ	ACE-LY-004	(b) (4)	capsule	100	
SVZB	ACE-LY-004		capsule	100	
W025985	ACE-LY-004	capsule		100	
W026394	ACE-LY-004	capsule		100	
W027180	ACE-LY-004	capsule		100	
W032242	ACE-LY-004	capsule		100	
L0505009	ACE-LY-004	capsule		100	
L0505541	ACE-LY-004	capsule		100	
L0506080	ACE-LY-004	capsule		100	
L0507552	ACE-LY-004	capsule		100	
L0508306	ACE-LY-004	capsule		100	
NVTF	ACE-WM-001	(b) (4)	capsule	100	
PMFS	ACE-WM-001		capsule	100	
SHGZ	ACE-WM-001		capsule	100	
SVZB	ACE-WM-001		capsule	100	
W025985	ACE-WM-001	capsule		100	
W026394	ACE-WM-001	capsule		100	
W027180	ACE-WM-001	capsule		100	
W032242	ACE-WM-001	capsule		100	
L0505009	ACE-WM-001	capsule		100	
L0505541	ACE-WM-001	capsule		100	
L0506080	ACE-WM-001	capsule		100	
L0507552	ACE-WM-001	capsule		100	
L0508306	ACE-WM-001	capsule		100	
PMFS	ACE-MY-001	(b) (4)	capsule	100	
SHGZ	ACE-MY-001		capsule	100	
W025985	ACE-MY-001	capsule		100	
W026394	ACE-MY-001	capsule		100	
W027180	ACE-MY-001	capsule		100	
L0505009	ACE-MY-001	capsule		100	
L0505541	ACE-MY-001	capsule		100	
NVTF	15-H-0016	(b) (4)	capsule	100	
PMFS	15-H-0016		capsule	100	
SHGZ	15-H-0016		capsule	100	
SVZB	15-H-0016		capsule	100	
W025985	15-H-0016	capsule		100	
W026394	15-H-0016	capsule		100	
L0505009	15-H-0016	capsule		100	
L0505541	15-H-0016	capsule		100	
L0506080	15-H-0016	capsule		100	
L0507552	15-H-0016	capsule		100	
L0508306	15-H-0016	capsule		100	

Figure 11. Dissolution profiles of (b) (4) capsule batches and the proposed commercial batches

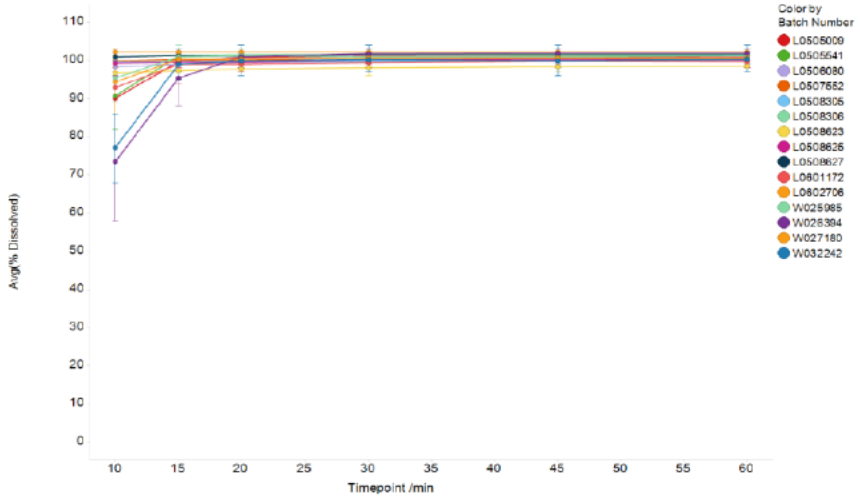


7. Bridging between the capsules manufactured at different sites:

Acalabrutinib Capsules manufactured at the development site (b) (4) and the commercial manufacturing facility (b) (4) were used in clinical studies (Table 3). The Applicant reported that the clinical formulations and the intended commercial products are (b) (4)

More than 85% was dissolved for all formulations using the proposed dissolution method (Figure 12). Therefore, similar comparative dissolution profiles were demonstrated for the proposed drug product batches manufactured at different sites.

Figure 12. Comparative dissolution profiles for different Acalabrutinib Capsule formulations used in clinical studies using the proposed dissolution method



REVIEWER'S OVERALL ASSESSMENT:

Dissolution Method: The proposed dissolution method [USP apparatus II (Paddle)/50 rpm/900 mL of 0.1 N HCl] is acceptable for the quality control of the proposed immediate release drug product, Acalabrutinib capsules, 100 mg, as part of the batch release and stability testing.

Dissolution Acceptance Criterion: The proposed dissolution acceptance criterion of NLT (b) (4)% (Q) of the labeled amount of acalabrutinib dissolved in 20 minutes for the proposed Acalabrutinib Capsules 100 mg is acceptable.

RECOMMENDATION:

From the Biopharmaceutics perspective, NDA 210259 for Acalabrutinib Capsules, 100 mg, is recommended for **APPROVAL**.

Primary Biopharmaceutics Reviewer:
Yang Zhao, Ph.D. 9/28/2017
Division of Biopharmaceutics
Office of New Drug Products/OPQ

Secondary Biopharmaceutics Reviewer:
I concur with Dr. Yang Zhao's assessment and **APPROVAL** recommendation.

Okpo Eradiri, Ph.D. 10/2/2017
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products/OPQ

Yang Zhao

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Okponanabofa Eradiri

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ADDENDUM TO ORIGINAL BIOPHARMACEUTICS REVIEW	
Application No.:	NDA 210259; 505(b)(1)
Applicant/Sponsor:	Acerta Pharma B.V.
Product Name:	Acalabrutinib Capsules, 100 mg
Primary Reviewer:	Yang Zhao, Ph.D.
Secondary Reviewer:	Fang Wu, Ph.D.
Tertiary Reviewer:	Okpo Eradiri, Ph.D.
Biopharmaceutics Branch Chief:	Angelica Dorantes, Ph.D., Kimberly Raines, Ph.D.
Recommendation:	**NOT ACCEPTABLE**

Biopharmaceutics Evaluation of the Physiologically Based Pharmacokinetic Model Supporting Proposed Particle Size Limit for Acalabrutinib Drug Substance.

REVIEW SUMMARY:

Background: This Addendum to the Original Biopharmaceutics Review Chapter, provides the specific details on the Biopharmaceutics evaluation of the proposed Physiologically Based Pharmacokinetic (PBPK) model for the proposed particle size limit for Acalabrutinib drug substance.

Submission: This NDA submission provided a PBPK model, which was developed with the objective of supporting the setting of the particle size limit (D_{90}: NMT (b) (4) µm) of the drug substance used in the manufacture of the proposed Acalabrutinib Capsules, 100 mg.

Review: The focus of this Biopharmaceutics review was to evaluate the PBPK model and provide a recommendation on the model's acceptability to be used to support the proposed particle size limit of D_{90}: NMT (b) (4) µm for acalabrutinib drug substance.

Conclusion and Recommendation: The provided information/data was incomplete and therefore, did not fully support the approval of the PBPK model. Although the proposed PBPK model was not acceptable, it is noted that this recommendation does not have an impact on the approvability of the NDA submission, because the newly proposed limit of D_{90}: NMT (b) (4) µm for the particle size of the drug substance is based on the actual D_{90} particle size limit of the drug product used in the pivotal clinical batches, which is acceptable.

Primary Biopharmaceutics Reviewer:
Yang Zhao, PhD 10/6/2017

Secondary and Tertiary Biopharmaceutics Reviewers:
Fang Wu, PhD 10/7/2017
Okpo Eradiri, PhD 10/10/2017

PROPOSED PBPK MODEL:

Purpose of the Model: to support a proposed acalabrutinib drug substance particle size specification of D_{90} of NMT (b) (4) µm.

List of submissions being reviewed related to the PBPK model:

Submitted Date	Description	Reviewed data
6/13/2017	Original submission	3.2.P.2 Pharmaceutical Development -P.2 Pharmaceutical Development-Attachment 2: In Silico Models Development
7/31/2017	Response to Information Request	1.11.1 Quality Information Amendment-Response to Questions-Quality-July 2017
8/2/2017	Response to Information Request	PBPK model data included in 3.2.P.2 Pharmaceutical Development
9/13/2017	Response to Information Request	1.11.1 Quality Information Amendment-Response to Questions-Quality-September 2017
9/20/2017	Response to Information Request	PBPK model data included in 3.2.P.2 Pharmaceutical Development
10/5/2017	Cover Letter	1.2 Cover Letters— Response to FDA CMC Information Request dated October 3, 2017

1. Introduction:

The proposed Acalabrutinib Capsules is presented as a (b) (4) hard gelatin capsule, with a blue cap and yellow body, printed with 'ACA 100 mg' in black ink and containing 100 mg of acalabrutinib (Table 1).

Table 1: Composition of Acalabrutinib Capsules 100 mg

Components	Quantity (mg/capsule)	Function	Standard
Acalabrutinib	100	Drug substance	In-house specification
Silicified microcrystalline cellulose	(b) (4)		NF
Partially pregelatinised starch			USP
Sodium starch glycolate			NF
Magnesium stearate			USP/NF
(b) (4)			
Hard gelatin capsule shell[a,b]			
Imprinting ink[b]			
Total filled capsule weight	316		

[a] (b) (4) yellow and blue, opaque hard gelatin capsule.
[b] See Table 2 for full composition of gelatin capsules and imprinting ink.
[c] This value represents an approximate average capsule shell weight.

2. Pharmacokinetic Data:

Observed individual plasma pharmacokinetic profiles from studies ACE-HV-009, ACE-HV-004, and ACE-HV-112 were used in the PBPK modelling.

Study ACE-HV-009 is an absolute bioavailability study conducted for cohort 1 (healthy volunteers) receiving an oral dose of 100 mg acalabrutinib capsule (Batch No.: L0505009) and a micro-dose of 7.9 mg acalabrutinib solution infused intravenously over 2 minutes at t=58 min following oral dosing. Study ACE-HV-004 is a phase 1, 2-period, 3-part study to evaluate the interaction of calcium carbonate, omeprazole, or rifampin on acalabrutinib in healthy adult subjects. Study ACE-HV-112 is a phase 1, 4-period, 3-part study in healthy adult subjects to evaluate the effect of an acidic formulation of acalabrutinib [acidic formulation of acalabrutinib is to increase the acidic microenvironment for the acalabrutinib capsule by adding L-tartaric acid and alginic acid (acid diluents)], acidic beverage, or grapefruit juice on the pharmacokinetics of acalabrutinib alone and co-administered with omeprazole.

The proposed PBPK model was analyzed using GastroPlus v9.0 (CA) software package. The objective of the GastroPlus model was to justify an acceptable limit for drug substance particle size.

3. Solubility and Permeability Data:

The Applicant reported that acalabrutinib could be classified as a BCS class 2 compound (high permeability and low solubility). Acalabrutinib exhibits pH-dependent solubility across the physiological pH range. In acidic conditions up to pH 4, acalabrutinib demonstrates high solubility (Table 2), and therefore, the Applicant stated that 100 mg acalabrutinib solid oral dosage forms behave as a non-precipitating solution, with low biopharmaceutical risk similar to highly soluble, highly permeable BCS class 1 compounds.

The Applicant also measured the equilibrium solubility of acalabrutinib in Fasted State Simulated Intestinal Fluid (FaSSIF, pH=6.5, 0.12 mg/mL), and in Fed State Simulated Intestinal Fluid (FeSSIF, pH=5.0, 0.67 mg/mL).

Table 2: Solubility of acalabrutinib in different pH media at 37 °C

pH	Solubility mg/mL	USP solubility description	BCS solubility description	Dose of acalabrutinib soluble in 250 mL (mg)
1	>100	Freely soluble	High	>25000
2	>100	Freely soluble	High	>25000
3	>100	Freely soluble	High	>25000
4	3.9	Slightly soluble	High	975
5	0.34	Very slightly soluble	Low	85
6	0.077	Practically insoluble	Low	19.3
7	0.051	Practically insoluble	Low	12.8
8	0.048	Practically insoluble	Low	12

The Applicant assessed acalabrutinib permeability using the in vitro MDCK cell assay and pharmacokinetic data from human study ACE-HV-004.

The passive permeability (Papp) from MDCK cell line was assessed at 23.4×10^{-6} cm/s which was scaled to a human jejunal effective permeability (Peff) of 4.61×10^{-4} cm/s using the reference correlation (Drug Metabolism & Disposition 2010; 38(7): 1147-1158).

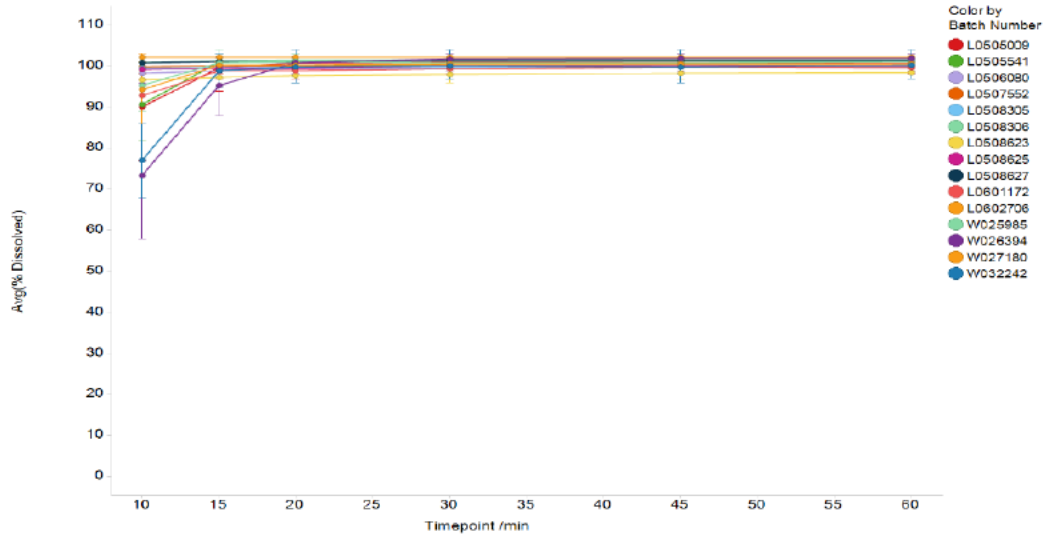
Individual pharmacokinetic profiles from study ACE-HV-004 were fitted using a multi-fractional dose, 2 compartment PK model. In vivo absorption rates were transformed to effective permeability values. For n=64 evaluable subjects the average effective permeability value was found to be $6.8\pm2.6\times10^{-4}$ cm/s with min and max values of 1.8×10^{-4} and 10×10^{-4} cm/s, respectively, and a median value of 6.7×10^{-4} cm/s.

The Applicant stated that the data from MDCK and human pharmacokinetic profiles support high permeability of acalabrutinib.

4. Dissolution Data:

The proposed dissolution acceptance criterion of "Q = (b) (4)% at 20 minutes" is acceptable, indicating that dissolution is not rate limiting with respect to in vivo absorption (Figure 1).

Figure 1: Comparative dissolution profiles for different Acalabrutinib Capsules 100 mg formulations used in clinical studies using the proposed dissolution method [USP apparatus II (Paddle) at 50 rpm, 900 mL of 0.1 N HCl at 37 °C]



5. Simulated Particle Size:

(b) (4)

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Yang Zhao

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Fang Wu

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Okponanabofa Eradiri

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – NDA 210259 Calquence (acalabrutinib) 100 mg 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, stability At release and stability)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Physical Stability (solid state)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Content Uniformity	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Justification is provided, refer to OPF review.
Dissolution – BCS Class II & IV	• Formulation • Raw Materials • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval, refer to BioPharm review.

Rajiv Agarwal

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Anamitro Banerjee

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Sherita McLamore

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U.S. FOOD & DRUG ADMINISTRATION

METHOD VERIFICATION
MATERIALS RECEIVED

NDA 210259

August 25, 2017

Yasameen Qazen
yasameen.qazen@acerta-pharma.com
Acerta Pharma B.V.
2200 Bridge Parkway Ste. 101
Redwood City, CA 94065

Dear Yasameen::

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Acalabrutinib 100 mg capsules and to our August 1, 2017, letter requesting sample materials for method verification testing.

We acknowledge receipt on August 25, 2017, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3811), FAX (314-539-2113), or email (michael.hadwiger@fda.hhs.gov).

Sincerely,

Michael E. Hadwiger -S

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Date: 2017.08.25 09:31:07 -05'00'

Michael E. Hadwiger, Ph.D.
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

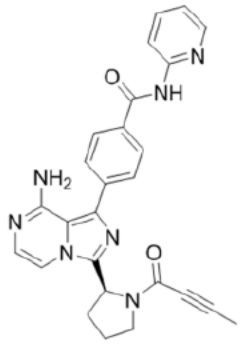
NDA 210259 Summary

This NDA was submitted as a 505(b)(1) NDA under the Federal Food, Drug and Cosmetic Act. The drug product, acalabrutinib capsules is indicated for the treatment of patients with mantel cell lymphoma (MCL) who have received at least one prior therapy Acalabrutinib orally bioavailable, Bruton tyrosine kinase inhibitor (BTK). Acalabrutinib is an NME that was granted orphan designation (Sept 2015). The applicant has requested a priority review of this application.

Pharmaceutical Information

Reference Listed Drug Name:	**n/a**
Innovator Company Name:	n/a
Established Product Name:	Pending
Applicant Name:	Acerta Pharma B.V.
Drug Substance:	Acalabrutinib
Strength(s):	100 mg
Route of Administration:	Oral
Dosage Form:	Immediate Release Hard Shell Capsules

Drug Substance:



Chemical Abstracts Service (CAS) Index Name	4-[8-amino-3-[(2*S*)-1-(1-oxo-2-butyn-1-yl)-2-pyrrolidinyl]imidazo[1,5-*a*]pyrazin-1-yl]-*N*-2-pyridinylbenzamide
CAS Registry Number	1420477-60-6
Molecular Formula	$C_{26}H_{23}N_7O_2$
Molecular Weight	465.51

Acalabrutinib was originally investigated under IND 118717.

Acalabrutinib is a small chiral molecule that is manufactured as a single enantiomer (S) in a linear manner by AstraZeneca of the UK. The sponsor states that Acalabrutinib is classified as BCS class 2 (high permeability low solubility) but assert that it has BCS class 1 characteristics. It is manufactured at a commercial batch size of (b) (4) kg according to the synthetic scheme below. The applicant includes specifications and suppliers fo (b) (4)

Drug substance batches for clinical use have been manufactured at 5 different sites including the proposed commercial site (b) (4).

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Test procedure	Acceptance criteria	Method reference
Description	A white to (b) (4) powder	Visual inspection
Identification	Conforms with reference spectrum	Identification by IR spectroscopy
Assay (on water and solvent free basis)	98% to 102% w/w	Assay by LC
Organic impurities:		Organic impurities by LC
(b) (4)	NMT (b) (4) % w/w NMT % w/w NMT % w/w NMT % w/w NMT % w/w NMT % w/w NMT % w/w	
Any individual unspecified impurity	NMT (b) (4) % w/w	
Total impurities	NMT (b) (4) % w/w	
Mutagenic impurities		(b) (4) content by LC-MS
(b) (4)	NMT (b) ppm	
Enantiomeric purity	NLT (b) (4) %	Enantiomeric purity by LC
Residual solvents:		Residual solvents by headspace GC
(b) (4)	NMT (b) (4) % w/w NMT % w/w	
Residual (b) (4)	NMT (b) (4) % w/w	Residual (b) (4) by LC
(b) (4)	For information only	USP
		(b) (4)
Particle size distribution ($D_{(v, 0.9)}$)	NMT (b) (4) µm	Laser diffraction
(b) (4)	NMT ppm	(b) (4) content by ICP-OES
Residue on ignition/sulphated ash	NMT (b) (4) % w/w	USP

NLT Not more than
NMT Not less than

Additional Specs to consider: Second identification test Microbiological quality??

The applicant includes 12 months primary stability data and requests a (b) (4) month retest period

Drug Product:
The drug product is presented as a (b) (4) hard gelatin capsule, with a blue cap and yellow body, printed with 'ACA 100mg' in black ink and containing 100 mg of acalabrutinib, microcrystalline cellulose, pregelatinized startch, sodium starch glycolate and magnesium stearate. The qualitative and quantitative composition of the drug product is included in the table below. The drug product formulation contains no novel excipient. All excipients are compendial and commonly used in solid oral dosage forms. MDD 200 mg.

Components	Quantity (mg/capsule)	Function	Standard
Acalabrutinib	100	Drug substance	In-house specification
Silicified microcrystalline cellulose	(b) (4)		NF
Partially pregelatinised starch			USP
Sodium starch glycolate			NF
Magnesium stearate			USP/NF
(b) (4)			
Hard gelatin capsule shell[a,b]			
Imprinting ink[b]			
Total filled capsule weight	316		

[a] (b) (4) yellow and blue, opaque hard gelatin capsule.
[b] See Table 2 for full composition of gelatin capsules and imprinting ink.
[c] This value represents an approximate average capsule shell weight.

The drug product is manufactured by (b) (4) at a commercial batch size of either (b) (4) or (b) (4) kg (??) which correspond to (b) (4) and (b) (4) capsules, respectively. (b) (4)

At the agency's request, drug product comparability data was provided to demonstrate the equivalency of drug substances manufactured at (b) (4) AstraZeneca (UK). The applicant claims that the data demonstrate consistent quality of drug product batches made from the three drug substance sources.

The commercial container closure system for the drug product is a white, HDPE bottle with a white (b) (4) screw cap. The two packaging options are:

- (b) (4)
- 110 mL HDPE bottle with a 33 mm PP cap containing 60 capsules

The bulk container closure system is a (b) (4).

Table: Drug Product Specification

Test procedure	Acceptance criteria	Method reference
Description	(b) (4) hard capsule with a blue opaque cap and a yellow opaque body printed with "ACA 100mg" in black ink	Visual inspection
Identification	Consistent with the retention time and UV spectrum of the reference standard	UHPLC or HPLC
Assay	90% to 110% of label claim	UHPLC or HPLC
Degradation products:		UHPLC or HPLC
(b) (4)	NMT (b) (4)% w/w	
	NMT % w/w	
Individual unspecified degradation products	NMT % w/w	
Total degradation products	NMT (b) (4)% w/w	
Dissolution	Shall comply with the requirements of USP<711> Q= (b) (4)% at 20 minutes	USP apparatus 2 UV or HPLC
Uniformity of dosage units	Shall comply with the requirements of USP<905>	Weight variation

NMT Not more than.

*justification for no microbial testing included??

Stability:

Six drug product batches (3 ink-printed and 3 non-inked) in the 60 mL bottle and 3 batches of ink printed drug product in the 110 mL bottle have been placed on stability. The non-inked capsules are identical to the commercial product but devoid of the commercial print. All capsules were manufactured at commercial scale at the proposed commercial manufacturing facility. The applicant included 12 months of long term and intermediate data and 6 months of accelerated data and proposes a 24 month expiry (also 10 month holding time). There were some changes noted under accelerated conditions. As such the applicant includes a statistical analysis of the long term data to support the proposed expiry.

Facilities

(b) (4)

NDA 210259 Risk Assessment Table

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	CHANGES & VARIATIONS	FAILURE MODE	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN
Assay, Stability	• Formulation • Container closure • Process parameters • Scale/equipments • Site	(b) (4)	4	2	Release (1)	8
					Stability (3)	24
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site		Crystalline (3)	3	4	36
Content Uniformity	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site		High Loading Dose (2)	2	4	16
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipments • Site		1	2	5	10
Dissolution – BCS Class II & IV	• Formulation • Raw Materials • Process parameters • Scale/equipments • Site		4	2	4	32

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Sherita McLamore

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U.S. FOOD & DRUG ADMINISTRATION

REQUEST FOR METHOD VERIFICATION MATERIALS

NDA 210259

August 1, 2017

Yasameen Qazen
yasameen.qazen@acerta-pharma.com
Acerta Pharma B.V.
2200 Bridge Parkway Ste. 101
Redwood City, CA 94065

Dear Yasameen:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Acalabrutinib 100 mg capsules.

We will be performing method verification studies on Acalabrutinib 100 mg capsules as described in NDA 210259.

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials as well as impurities if available.

In order to perform the necessary testing, we request the following sample materials and equipment:

Method, current version

1) Drug Substance: Analytical Procedure for Assay by LC (3.2.S.4.2)
2) Drug Substance: Analytical Procedure for Organic Impurities by LC (3.2.S.4.2)
3) Drug Substance: Analytical Procedure for (b) (4) Content by LC-MS (3.2.S.4.2)
4) Drug Substance: Analytical Procedure for Enantiomeric Purity by LC (3.2.S.4.2)
5) Drug Product: Assay by UHPLC (3.2.P.5.2)
6) Drug Product: Assay by HPLC (3.2.P.5.2)
7) Degradation products: UHPLC (3.2.P.5.2)
8) Degradation products: HPLC (3.2.P.5.2)

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Comments/Clarifications/Questions

1. DPA recognizes that the availability of some impurities may be problematic and the amounts requested are negotiable.
2. The pH of ammonium acetate buffers can vary between pH 2.8 and pH 11, is the pH of the ammonium acetate buffer controlled? If the ammonium acetate buffer pH is controlled, at what pH should the buffer be prepared and how is this accomplished?
3. In the Organic Impurities by (U)HPLC methods (both DS and DP), instructions state to prepare (b) (4) and (b) (4) at a "detectable level". Please specify the concentration at which it is desirable to prepare these impurities.
4. If sample and/or reference standard solutions are unstable at room temperature (i.e. 22°C ± 3°C), please specify the time and/or temperature (after preparation) these solutions are suitable for analysis.
5. We encourage you to share with us any special techniques or "tricks" not specified in your written procedures to help us successfully replicate your analytical methods.
6. Note: If temperature logging is required during sample shipment, DPA personnel are NOT allowed to connect unapproved USB devices (i.e. temperature logging devices) to our computers, please plan appropriately to recover temperature data.

Equipment

(b) (4)

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
NDA 210259
645 S. Newstead Avenue
St. Louis, MO 63110

Please notify me upon receipt of this email. You may contact me by telephone (314-539-3811), FAX (314-539-2113), or email (michael.hadwiger@fda.hhs.gov).

Sincerely,

Michael E. Hadwiger -S

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Michael E. Hadwiger, Ph.D.
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research