CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208716Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 208716
Review #1

Drug Name/Dosage Form	Verzenio (abemacicilib) tablets
Strength	50 mg, 100 mg, 150 mg, 200 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Eli Lilly and Company
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA 0001	05/12/2017	DS/DP/Process/ (b) (4) Biopharm/Facility
Multiple Categories 0010	06/28/2017	DS/DP/Process/ Biopharm
Quality Amendment 0022	07/24/2017	Response to Office of Surveillance and Epidemiology
Quality Amendment 0020	07/26/2017	DP/Process
Quality Amendment 0024	08/08/2017	Process (b) (4)
Quality Amendment 0041	08/30/2017	Process
Quality Amendment 0042	09/01/2017	DP

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sithamalli Chandramouli	CDER/OPQ/ONDP/DNDAPI
Drug Product	Olen Stephens	CDER/OPQ/ONDP/DNDP1
Process	Ying Zhang	CDER/OPQ/OPF/DPA1
(b) (4)	Huiquan Wu	CDER/OPQ/OPF/DPA1
Facility	Krishnakali Ghosh	CDER/OPQ/OPF/DIA
Biopharmaceutics	Banu Zolnik, Okpo Eradiri	CDER/OPQ/ONDP/DB
Regulatory Business Process Manager	Kristine Leahy	CDER/OPQ/OPRO/DRBPMI

Application Technical Lead (ATL)	Xiao Hong Chen	CDER/OPQ/ONDP/DNDP1
Co-ATL, Emerging Technology Team	Rapti Madurawe	CDER/OPQ/OPF/DPA1
ORA	Paul Perdue Jr.	ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Analysis (EA)	James Laurenson	CDER/OPQ/ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	Adequate	No DMF review is needed.	Adequate info in the NDA
	Type III			Adequate	No DMF review is needed.	Adequate info in the NDA
	Type III			Adequate	No DMF review is needed.	Adequate info in the NDA
	Type III			Adequate	No DMF review is needed.	Adequate info in the NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	106100	Initial IND was submitted on 10/15/2009

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
RTD Model	N/A			Tom O'Connor

Executive Summary

I. Recommendations and Conclusion on Approvability

CMC information provided for Verzenio (abemacicilib) tablets in NDA 208716 has been review by the quality review team in the Office of Pharmaceutical Quality, and is found to be acceptable. The review team recommended approval for the NDA from the product quality standpoint.

A 24-month expiration date is granted for Verzenio (abemacicilib) tablets stored under at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

II. Summary of Quality Assessments

A. Product Overview

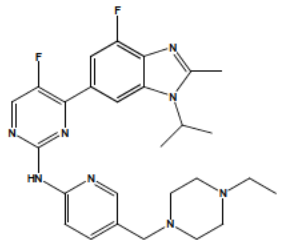
Proposed Indication(s) including Intended Patient Population	VERZENIO™ is a kinase inhibitor indicated: • in combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy. • as monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	Recommended dose: When used in combination with fulvestrant, the recommended dose of VERZENIO is 150 mg taken orally twice daily. When used as monotherapy, the recommended dose of VERZENIO is 200 mg taken orally twice daily.
Alternative Methods of Administration	None.

B. Quality Assessment Overview

Drug substance
- Chemical Name and Structure:

IUPAC Name: N-(5-((4-ethylpiperazin-1-yl)methyl)pyridin-2-yl)-5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)pyrimidin-2-amine

Structure:



Molecular Weight: 506.61

Abemaciclib (LY2835219) is an orally administered cyclin-dependent kinase (CDK / CDK4 & CDK6) inhibitor intended for the treatment of hormone receptor positive (HR+) / human epidermal growth factor 2 negative (HER2-) metastatic breast cancer (mBC).

Abemaciclib drug substance does not have a chiral center. It has multiple crystalline forms. (b) (4) was chosen for development and commercial manufacture of the drug product. (b) (4)

(b) (4)

The choice of starting materials has been adequately justified. The proposed controls for (b) (4) are appropriate to adequately ensure the quality of the drug substance. (b) (4) (b) (4) The specifications (b) (4) are appropriate to adequately ensure the quality of the drug substance. More than 10 batches of abemaciclib have been manufactured using the process that is representative of the final commercial synthesis in scales ranging from (b) (4) of the drug substance.

The drug substance has been adequately characterized. The analytical methods to control the quality of the drug substance are adequately described and validated to ensure quality control. The stability studies show the drug substance to be stable over the proposed retest period of (b) (4).

Comparability Protocol: The NDA included a comparability protocol for (b) (4) drug substance manufacture. (b) (4) The proposed comparability protocol is deemed acceptable.

Drug product

Product Background: Abemaciclib (LY2835219) is an orally administered, potent small-molecule cyclin-dependent kinase (CDK) inhibitor intended for the treatment of hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2−) metastatic breast cancer (mBC). CDKs play critical roles in regulating cell cycle progression. Alterations in CDK expression and modulation often result in dysregulated CDK activity leading to uncontrolled cancer cell growth. The mechanism of action for abemaciclib is distinct from that of endocrine therapies and traditional cytotoxic chemotherapies.

Abemaciclib is provided as 50-, 100-, 150-, and 200-mg tablets, supplied in blister (b) (4) packaging. These dose proportional formulations are based on a (b) (4) The recommended dose of abemaciclib tablets in combination with fulvestrant is 150 mg orally, twice daily and the recommended dose of abemaciclib as a single agent is 200 mg orally, twice daily.

The pivotal MONARCH 1 and MONARCH 2 clinical trials for abemaciclib were conducted using a third generation capsule formulation capsule dosage form manufactured (b) (4). A tablet dosage form was then developed and compared to the capsules in a bioequivalence study (I3Y-MC-JPCC). The tablets for the bioequivalence study were manufactured using the proposed commercial (b) (4) continuous manufacturing (CM) process and formulation.

Drug product review: The Critical Quality Attributes (CQAs) identified for the abemaciclib tablets are its description, identification, potency, purity, content uniformity, and in vitro release. Abemaciclib (b) (4) was selected because it (b) (4) was used in all of the clinical trials. At the highest dose strength (200 mg), abemaciclib (b) (4) is soluble in less than 250 mL across the pH range of 1 to 6.8. Therefore, for the prescribed doses, the drug substance is soluble in the volume of gastric fluid and solubility of the drug substance is not limiting in product development.

The commercial CM process includes [redacted] Release testing for all other quality attributes is conducted on the [redacted] tablets. The primary stability batches were manufactured at Lilly's Indianapolis CM2 GMP pilot plant over short run times. This CM module is stated to be identical to the commercial manufacturing site, CM3, in Puerto Rico. Therefore, the 12-month stability data from CM2 batches can be considered as primary stability data and are adequate to establish a shelf life. The applicant requests and is granted 24 months of shelf life when stored at USP controlled room temperature conditions based on 12 months of primary stability data. This application is recommended for approval from a drug product perspective. Labeling negotiations are proceeding through the clinical division with Lilly.

Drug Product Manufacturing Process – Emerging Technology Summary

Introduction: NDA 208716 for abemaciclib tablets was accepted into the CDER Emerging Technology Program as the tablets are made by a novel continuous manufacturing (CM) process. The process review is based on the information in the NDA and observations from the pre-approval site inspection (PAI).

Process Overview: [redacted] Insufficient manufacturing process information to permit review was a significant deficiency identified during the NDA review. The NDA was subsequently amended and the Master Batch Record submitted to capture relevant process details and in-process hold times.

Batch Definition: The proposal for a variable commercial batch size [redacted] was found acceptable as both the batch size and CM mass flow rate employed [redacted] are defined before the start of manufacture. The ability to manufacture at this scale was successfully demonstrated by 12 process validation batches. Future batch size increases are not anticipated, but would be achieved by an increase in run time. Risks from increased run time (i.e., scale-up) are mitigated as there are no changes to equipment and the mass flow rate, and the applicant will institute the change only after it is validated. For product recall decisions when multiple lots of raw materials are used in a batch, a problem with a single lot is considered to affect the entire batch even if that lot was used only for a portion of the batch.

Process Parameters: (b) (4)

(b) (4)

Although we do not agree with the applicant's identification of critical vs. non-critical parameters, it is concluded that all relevant process parameters are adequately identified, controlled and captured in the Master Batch Record for consistent manufacture.

In-Process Controls: (b) (4)

(b) (4)

CM Operation (System Startup/Shutdown, Product Collection and State of Control):

(b) (4)

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Facility: A PAI of Lilly Del Caribe, San Juan, PR (FEI# 2619243) was conducted from July 10-21, 2017. Initial facility risks identified included the lack of prior CM experience at the site and the paucity of commercial process information in the NDA. The PAI resulted in a nine item FDA 483 related to manufacturing process control, cleaning validation, proposed alternate strategy, batch record and Quality Assurance review of Abemaciclib tablet release and additional GMP deficiencies. The facility has subsequently implemented various plans and quality initiatives to address the FDA 483 deficiencies. Some of the evidence documents related to the corrective actions were submitted to FDA for review. The applicant has committed to address the pending corrective actions post approval and submit the evidence documents through San Juan district office for adequate closure of the FDA 483 observations. Observations related to the manufacturing process were addressed satisfactorily as discussed above. It is concluded that there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. the facility is acceptable.

Lifecycle Considerations: Please refer to the final risk assessment table.

Facility

Based on compliance history review and considering the proposed manufacturing to be conducted in at each site, the Drug Substance Manufacturing facility (b) (4)), the drug substance manufacturing and testing facility (FEI# 3002806888), final drug product packaging facility (FEI# 1819470) are deemed acceptable. Therefore, no Pre-approval inspection (PAI) is to be for the aforementioned three manufacturing sites. A PAI is recommended for the drug product manufacturing facility, Lilly Del Caribe site (FEI# 2619243).

PAI was conducted at the drug product manufacturing site at Lilly Del Caribe, PR (FEI# 2619243), and is described above under the Drug Product Manufacturing summary. Following a review of the application, compliance history of this manufacturing site and outcome from the recently conducted PAI at the Lilly Del Caribe, Inc. site in San Juan (FEI# 2619243) there are no significant, outstanding manufacturing or facility risks that prevent approval of this application. The manufacturing facilities for NDA 208716 are found to be acceptable.

Summary of Facility Information for Drug substance:

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Risks Identified	Final Recommendation
[redacted] (b) (4)			Medium	Acceptable by file review
Eli Lilly S.A. - Ireland	3002806888	CSN: Drug Substance Manufacturing, [redacted] (b) (4) QC and stability testing	Medium	Acceptable by file review

Reviewer's Assessment: Adequate.

Initial Risk assessment:

Facility Name	FEI	Profile Code	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment
[redacted] (b) (4)			17	6	0	23
Eli Lilly S.A. - Irish Branch	3002806888	CSN	9	6	0	15

Summary of Drug Product Facility Information:

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Risks Identified	Final Recommendation
Lilly del Caribe, Inc. (San Juan)	2619243	Drug Product Manufacturing, Control and Stability Testing	High	Acceptable by PAI Inspection and responses to FDA 483 observations
Eli Lilly and Company (Indianapolis)	1819470	Final drug packaging only	Low	Acceptable by file review

Reviewer's Assessment: Adequate

Initial Risk assessment:

Facility Name	FEI	Profile Code	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment
Lilly del Caribe, Inc.	2619243	TCM	12	76	0	88
Eli Lilly and Company	1819470	TCM	4	0	0	4

Biopharmaceutics

The Biopharmaceutics review evaluated the overall dissolution data supporting; 1) The proposed dissolution method, 2) The proposed dissolution acceptance criterion, and 3) The Biowaiver Request for the 100 mg and 200 mg strengths.

1) Dissolution Method and Acceptance Criterion

The dissolution method (USP II, 0.01 N HCL, 75 rpm, 900 mL) and the acceptance criterion of Q= (b)(4)% in 15 minutes are acceptable. Abemaciclib exhibits high solubility in the physiological pH range at the highest strength.

USP Apparatus	Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criterion
USP II (paddle)	75 rpm	900 mL	37°C	0.01 N HCl	Q = (b)(4)% in 15 minutes

2) Biowaiver

The Applicant's biowaiver request for the 100 mg and 200 mg tablet strengths is granted based on the following reasons:

a) The Applicant conducted a BE study (I3Y-MC-JPCC) between the 50 mg capsules, 50 mg tablets and the 150 mg tablets. Results of the JPCC study was found acceptable by the Office of Clinical Pharmacology (OCP) in establishing *i)* bioequivalence between the capsule and tablet dosage forms, *ii)* dose proportionality between 50 mg tablets and 150 mg tablet strengths (refer to the Clinical Pharmacology review by Pierre V., Zheng N., Fourie Zirkelbach J., and Yu J.);

b) The 100 mg strength is bracketed between the 50 mg and 150 mg strengths;

c) The Applicant conducted a single dose ascending study with 200, 300, and 400 mg strengths of abemaciclib capsules. Therefore, 200 mg dose PK data are available;

d) The proposed strengths are compositionally proportional; and

e) The proposed strengths exhibit similar dissolution rate i.e. greater than (b)(4)% abemaciclib dissolved in 15 minutes.

3) Bridging the Formulations

The Phase 2 and Phase 3 clinical studies (Absolute bioavailability study-I3Y-MC-JPBS, Monarch 1 and Monarch 2 study) were conducted with a capsule dosage form (referred as C3 in the submission). A tablet, which will be the commercial dosage form, was developed (b) (4) The Applicant conducted a bioequivalence study (I3Y-MC-JPCC) between the 50 mg strength capsules, the 50 mg tablets and the 150 mg tablets. As stated in 2a above, the OCP Reviewer has confirmed that the tablets and capsules were bioequivalent. The to-be-marketed abemaciclib tablets have therefore been adequately bridged to the clinical trial capsule formulation.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A.

D. Final Risk Assessment (see Attachment)

Application Technical Lead Name and Date:

Rapti Madurawe, Ph.D.
Xiao Hong Chen, Ph.D.

25-Sept-2017

NDA 208716 Abemaciclib Tablets FDA Final Risk Assessment

Attribute/ CQA	Factors that can impact the CQA	FDA Initial Risk Ranking	Risk Mitigation Approach	FDA Final Risk Evaluation	Lifecycle Considerations/ Comments
Description	(b) (4)	LOW Risk (b) (4)	(b) (4)	LOW Risk Acceptable	None
Identification (ID)	(b) (4)	LOW Risk	(b) (4)	LOW Risk Acceptable	(b) (4) (b) (4)

Attribute/ CQA	Factors that can impact the CQA	FDA Initial Risk Ranking	Risk Mitigation Approach	FDA Final Risk Evaluation	Lifecycle Considerations/ Comments
Potency	Purity/assay of abemaciclib DS Change of supplier of incoming materials. (b) (4)	MEDIUM Risk (b) (4)	Incoming material attributes are controlled through specification; some excipient particle size controls are through in-house specification and not in the NDA. Change control procedures in place when material suppliers are changed. (b) (4)	LOW Risk Acceptable	(b) (4)

Attribute/ CQA	Factors that can impact the CQA	FDA Initial Risk Ranking	Risk Mitigation Approach	FDA Final Risk Evaluation	Lifecycle Considerations/ Comments
			(b) (4)		
Purity and Degradation Products	DS purity Purity of excipients Cross contamination (b) (4) hold times (b) (4)	LOW Risk (b) (4)	(b) (4)	LOW Risk Acceptable	(b) (4)
Uniformity of Dosage Units [Content Uniformity by RTRT]	Incoming material attributes and change of supplier (b) (4	MEDIUM RISK (b) (4)	Incoming material attributes are controlled through specification; some excipient particle size controls are through in-house specification and not in the NDA. Change control procedures in place when material suppliers are changed. (b) (4)	LOW risk Acceptable	(b) (4)

Attribute/ CQA	Factors that can impact the CQA	FDA Initial Risk Ranking	Risk Mitigation Approach	FDA Final Risk Evaluation	Lifecycle Considerations/ Comments
	(b) (4)	elevates risk	(b) (4)		(b) (4) Evaluate change management activities if new DS or excipient suppliers are used.

Attribute/ CQA	Factors that can impact the CQA	FDA Initial Risk Ranking	Risk Mitigation Approach	FDA Final Risk Evaluation	Lifecycle Considerations/ Comments
Dissolution	DS particle size distribution and polymorphic form (b) (4)	MEDIUM risk	Highest strength is highly soluble and therefore lowers dissolution risk. DS particle size and polymorphic form are controlled via DS specification (b) (4) Although dissolution is only tested at release, stratified dissolution data were obtained during process validation.	LOW risk Acceptable	Evaluate the risk to dissolution if the following changes occur: • Addition of a higher strength tablet • Change in DS particle size • (b) (4) • Change in equipment • Change in processing conditions, (b) (4)
Microbial limits (test not included in drug product specification and not conducted at release or stability)	Quality of input materials (b) (4)	MEDIUM risk (b) (4)	(b) (4)	LOW risk Acceptable	(b) (4)

Attribute/ CQA	Factors that can impact the CQA	FDA Initial Risk Ranking	Risk Mitigation Approach	FDA Final Risk Evaluation	Lifecycle Considerations/ Comments
					(b) (4)
Elemental impurities (test not included in drug product specification)	Quality of incoming raw materials Equipment wear and tear (b) (4)	LOW risk	Incoming material quality is controlled via specification (b) (4)	LOW risk	

(b) (4)

Xiao Chen

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Rapti Madurawe

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QUALITY ASSESSMENT

BIOPHARMACEUTICS

NDA: 208716

Drug Product Name / Strength: Verzenio® tablets (abemaciclib), 50 mg, 100 mg, 150 mg and 200 mg.

Route of Administration: Oral

Applicant Name: Eli Lilly and Company

List Submissions being reviewed:
Seq.0000 dated 05/05/2017
Seq.0010 dated 06/28/2017

Background:
Eli Lilly and Company is seeking approval for abemaciclib tablets, 50 mg, 100 mg, 150 mg and 200 mg for the treatment of metastatic breast cancer under section 505 (b) (1) of the Federal Food, Drug and Cosmetic Act (FDCA).

The Application received Breakthrough Therapy, Fast Track and a Priority Review Designations due to unmet medical need in the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer. The submission includes 15 clinical studies. The Applicant conducted the pivotal Phase 2 MONARCH 1 and Phase 3 MONARCH 2 safety and efficacy studies to support approval of the proposed drug product. In addition, the Applicant conducted a Phase 2 study of single agent abemaciclib in mantle cell lymphoma and 11 clinical pharmacology studies.

The Applicant stated that the recommended starting dose is 150 mg twice daily when used in combination with fulvestrant and 200 mg twice daily when used as monotherapy. It is also recommended that dosing interruption and/or dose reduction may be required based on individual safety and tolerability.

Review Summary:

This Biopharmaceutics Review evaluated the overall dissolution data supporting; **1)** The proposed dissolution method, **2)** The proposed dissolution acceptance criterion, and **3)** Biowaiver Request for the 100 mg and 200 mg strengths.

1) **Dissolution Method and Acceptance Criterion**

The dissolution method (USP II, 0.01 N HCL, 75 rpm, 900 mL) and the acceptance criterion of Q= (b) (4)% in 15 minutes are acceptable. Abemaciclib exhibits high solubility in the physiological pH range at the highest strength.

USP Apparatus	Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criterion
USP II (paddle)	75 rpm	900 mL	37°C	0.01 N HCl	Q = (b) (4)% in 15 minutes

2) **Biowaiver**

The Applicant's biowaiver request for the 100 mg and 200 mg tablet strengths is granted based on the following reasons:

a) The Applicant conducted a BE study (I3Y-MC-JPCC) between the 50 mg capsules, 50 mg tablets and the 150 mg tablets. Results of the JPCC study was found acceptable by the Office of Clinical Pharmacology (OCP) in establishing *i)* bioequivalence between the capsule and tablet dosage forms, *ii)* dose proportionality between 50 mg tablets and 150 mg tablet strengths (refer to the Clinical Pharmacology review by Pierre V., Zheng N., Fourie Zirkelbach J., and Yu J.);
b) The 100 mg strength is bracketed between the 50 mg and 150 mg strengths;
c) The Applicant conducted a single dose ascending study with 200, 300, and 400 mg strengths of abemaciclib capsules. Therefore, 200 mg dose PK data are available;
d) The proposed strengths are compositionally proportional; and
e) The proposed strengths exhibit similar dissolution rate i.e. greater than (b) (4)% abemaciclib dissolved in 15 minutes.

3) **Bridging the Formulations**

The Phase 2 and Phase 3 clinical studies (Absolute bioavailability study-I3Y-MC-JPBS, Monarch 1 and Monarch 2 study) were conducted with a capsule dosage form (referred as C3 in the submission). A tablet, which will be the commercial dosage form, was developed (b) (4) The Applicant conducted a bioequivalence study (I3Y-MC-JPCC) between the 50 mg strength capsules, the 50 mg tablets and the

150 mg tablets. As stated in 2a above, the OCP Reviewer has confirmed that the tablets and capsules were bioequivalent. The to-be-marketed abemaciclib tablets have therefore been adequately bridged to the clinical trial capsule formulation.

- ***OVERALL REVIEW RECOMMENDATION***

From the Biopharmaceutics perspective, NDA 208716 for Abemaciclib Tablets, 50 mg, 100 mg, 150 mg, and 200 mg is recommended for APPROVAL.

- ***SIGNATURES***

Primary Biopharmaceutics Reviewer Name and Date:

Banu S. Zolnik, PhD ***09/15/2017***
Biopharmaceutics Reviewer
Division of Biopharmaceutics-Branch 1
Office of New Drug Products

Secondary Reviewer Name and Date:

Okpo Eradiri, PhD ***09/15/2017***
Acting Biopharmaceutics Lead
Division of Biopharmaceutics-Branch 1
Office of New Drug Products

BIOPHARMACEUTICS ASSESSMENT

➢ DRUG SUBSTANCE

Abemaciclib (also referred as LY2835219 throughout the submission) is a crystalline compound; (b) (4) Abemaciclib is a tri-basic compound with pKa values of 7.95, 4.48, and 3.80. The solubility of abemaciclib across the physiological pH range is shown in Table 1. The highest dose strength, 200 mg, is soluble in less than 250 mL across the pH range of 1 to 6.8, i.e. solubility of abemaciclib in the pH range 1-6.8 is greater than 0.8 mg/mL, therefore abemaciclib is considered highly soluble. The Applicant stated that in vitro MDCK line studies indicate that abemaciclib has moderate permeability, and could be considered as a BCS Class 3 substance.

Table 1. The solubility of abemaciclib Across the Physiological pH Range at 37°C

Table P.2.3.6.1-2 Solubility of Abemaciclib Across the Physiological pH Range at 37°C

Testing Media	Abemaciclib Solubility (mg/mL) Mean ± Standard Deviation	Final pH
0.1N HCl	75.520 ± 5.653	6.79
0.01N HCl	12.779 ± 0.266	6.83
pH 6.0 Phosphate Buffer (USP)	6.889 ± 0.055	6.49
pH 6.8 Phosphate Buffer (USP)	1.577 ± 0.133	6.82
pH 7.6 Phosphate Buffer (USP)	0.002 ± 0.000	7.64
Water	0.053 ± 0.005	7.02
mSGF (Modified Simulated Gastric Fluid)[1]	10.381 ± 0.281	7.20
FaSSIF (Fasted State Simulating Intestinal Fluid)[2]	5.353 ± 0.165	6.93
FeSSIF (Fed State Simulating Intestinal Fluid)[3]	31.124 ± 2.078	7.14

[1] 0.01N HCl/Na lauryl sulfate 0.05%/NaCl 0.2% (pH~2).
[2] NaH_2PO_4 28.66 mM, Na taurocholate 3 mM/lecithin 0.75 mM/NaCl 105.8 mM (pH 6.5).
[3] Acetic acid 144.04 mM/Na taurocholate, 15 mM/lecithin 3.75 mM/NaCl 203.17 mM (pH 5.0).

Reviewer's Comment:

Abemaciclib is a weak base and exhibits pH-dependent solubility where the solubility is 1.577 mg/mL at pH 6.8 in aqueous media, 5 mg/mL at pH 4.0, and the highest solubility of 63.18 mg/mL in 0.1 N HCl. Therefore, abemaciclib is considered highly soluble.

The Applicant submitted the mechanistic absorption modeling approach to support the selection of particle size. However, the modeling approach is not reviewed here due to the high solubility of the drug compound (at the 200 mg strength), and the particle size will not be

critical to dissolution. Nonetheless, the Applicant controls API particle size in the drug substance specification (b) (4) The absorption model may be assessed if a future higher strength with limited solubility in 250 mL pH buffers is developed.

- **DRUG PRODUCT**

The proposed drug product is an immediate release tablet. The composition of the drug product is shown in Appendix 1. All the strengths (50 mg, 100 mg, 150 mg and 200 mg) of the proposed drug product are (b) (4)

Abemaciclib tablets are manufactured using a (b) (4)

- **DISSOLUTION METHOD**

The dissolution method proposed as a quality control tool for the proposed drug product is summarized below.

USP Apparatus	Rotation Speed	Medium Volume	Temperature	Medium
USP II (paddle)	75 rpm	900 mL	37°C	0.01 N HCl

(b) (4)

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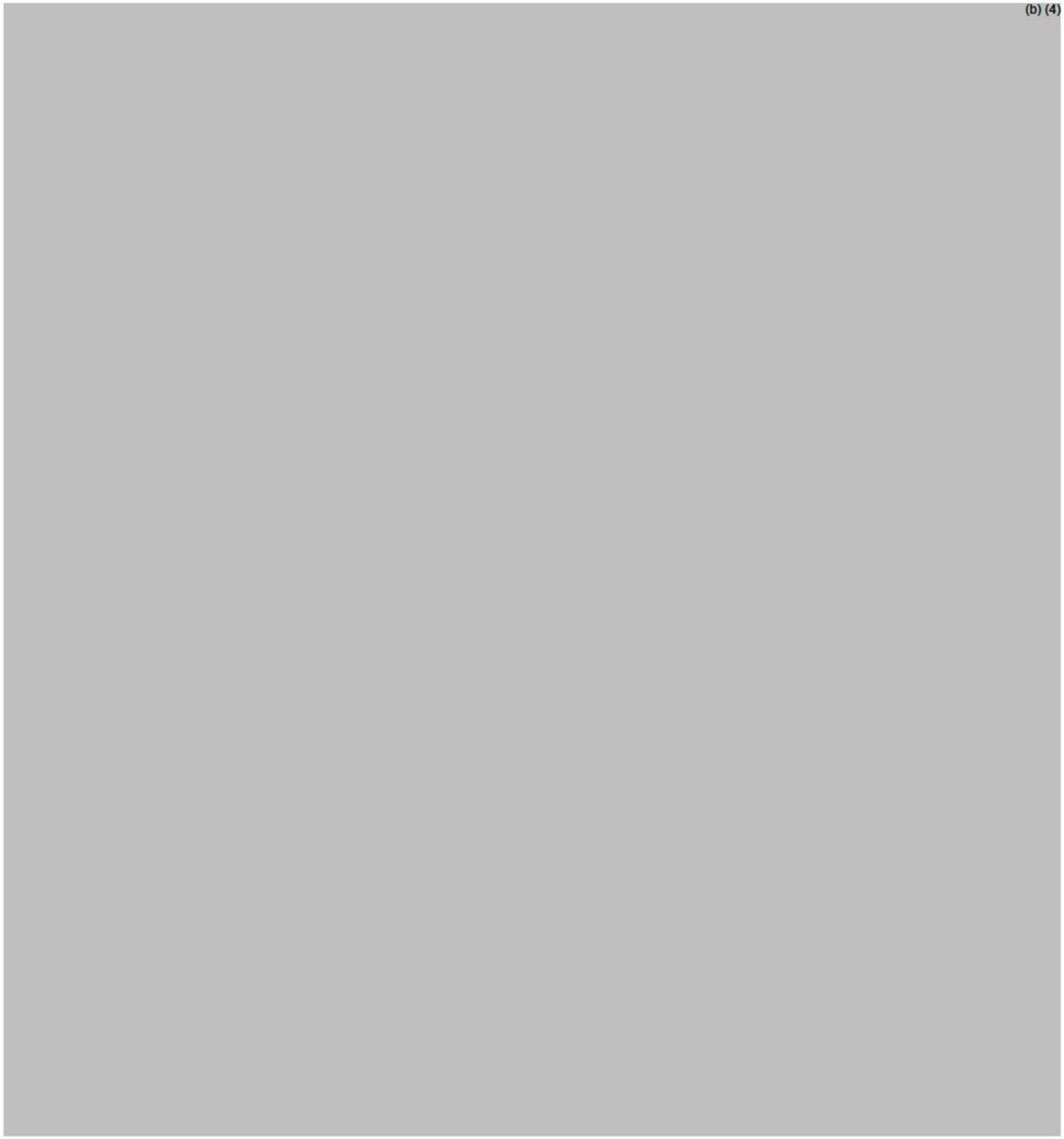
(b) (4)



➢ ***PROPOSED DISSOLUTION ACCEPTANCE CRITERIA:***

The Applicant proposed the following dissolution acceptance criterion.

Proposed Acceptance Criterion
Q = (b) (4)% in 15 minutes

Reviewer's Assessment:

Based on the dissolution data, the Applicant's proposed dissolution acceptance criterion is acceptable.

- ***BIOWAIVER REQUEST***

The Applicant requested biowaiver between the 100- and 200 mg strength tablets and the 50 mg strength capsules per 21 CFR 320.22.

The Applicant's biowaiver request for the 100 mg and 200 mg tablet strengths is granted based on the following reasons:

a) The Applicant conducted a BE study (I3Y-MC-JPCC) between the 50 mg capsules, 50 mg tablets and the 150 mg tablets. Results of the JPCC study was found acceptable by the OCP in establishing *i)* bioequivalence between the capsule and tablet dosage forms, *ii)* dose proportionality between 50 mg tablets and 150 mg tablet strengths (refer to the Clinical Pharmacology review by Pierre V., Zheng N., Fourie Zirkelbach J., and Yu J.);
b) The 100 mg strength is bracketed between the 50 mg and 150 mg strengths;
c) The Applicant conducted a single dose ascending study with 200, 300, and 400 mg strengths of abemaciclib capsules. Therefore, 200 mg dose PK data are available;
d) The proposed strengths are compositionally proportional; and
e) The proposed strengths exhibit similar dissolution rate i.e. greater than (b) (4)% abemaciclib dissolved in 15 minutes.

- ***BRIDGING OF FORMULATIONS***

The Phase 2 and Phase 3 clinical studies (Absolute bioavailability study-I3Y-MC-JPBS, Monarch 1 and Monarch 2 study) were conducted with a capsule dosage form (referred as C3 in the submission). A tablet, which will be the commercial dosage form, was developed (b) (4) The Applicant conducted a bioequivalence study (I3Y-MC-JPCC) between the 50 mg strength capsules, the 50 mg tablets and the 150 mg tablets. As stated Biowaiver Request section above, the OCP Reviewer has confirmed that the tablets and capsules were bioequivalent. The to-be-marketed abemaciclib tablets have therefore been adequately bridged to the clinical trial capsule formulation.

APPENDIX 1.

Quantitative Composition Information of Abemaciclib, 50 mg, 100 mg, 150 mg and 200 mg

Ingredient	Quantity (mg/tablet)				Function	Reference to Standards
	50 mg	100 mg	150 mg	200 mg		
Active Ingredient						
Abemaciclib[1]	50.00	100.0	150.0	200.0	Active	In-House
Other Ingredients						
Microcrystalline Cellulose 102	(b) (4)					USP-NF; Ph. Eur.; JP
Microcrystalline Cellulose 101						USP-NF; Ph. Eur.; JP
Lactose Monohydrate; (b) (4) (b) (4)						USP-NF; Ph. Eur.; JP
Croscarmellose Sodium						USP-NF; Ph. Eur.; JP
Silicon Dioxide; (b) (4) (b) (4)						USP-NF; Ph. Eur.; JPE
Sodium Stearyl Fumarate						USP-NF; Ph. Eur.; JPE
						(b) (4)
Color Mixture Beige	(b) (4)					(b) (4)
Color Mixture White						
Color Mixture Yellow (b) (4)						
						(b) (4)

Quantitative Composition Information of Abemaciclib, C2 and C3 capsule formulation

Table P.2.2.1-1 Abemaciclib C2 and C3 Formulation Comparison

(b) (4)

Banu Zolnik

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FDA/CDER/OPQ/OTR
Division of Pharmaceutical Analysis
645 S. Newstead Ave.
St. Louis MO 63110
P: 314.539.2135

METHOD VERIFICATION
REPORT SUMMARY

Date: August 31, 2017

To: Olen Stephens, Drug Product Reviewer
Sithamalli Chandramouli, Drug Substance Reviewer
Xiao Hong Chen, CMC Application Lead

Through: Jason D. Rodriguez, Ph.D., Lab Chief, Branch I, CDER/OPQ/OTR/DPA

From: Priyanka Chitranshi, Chemist, CDER/OPQ/OTR/DPA
Laura Pogue, Ph.D., Method Verification Coordinator, CDER/OPQ/OTR/DPA

Subject: Method Verification for NDA 208716: Abemaciclib, 200 mg tablets

The following methods were evaluated and are <u>acceptable with modifications</u> for quality control and regulatory purposes:

1. G1794, Ver. 0, Seq. 8: Determination of assay and impurities in Abemaciclib (LY2835219) drug substance by HPLC
2. G1796, Ver. 0, Seq. 6: Determination of (b) (4) in Abemaciclib (LY2835219) drug substance by HPLC

The following method was evaluated and <u>acceptability is pending review team assessment of data</u> included in the report:

3. G1929, Ver. 0, Seq. 4: Analytical procedure: Assay and degradation products for the

T
to

(b) (4)

N

(b) (4)

2.

3. (b) (4)

im (b) (4) (b) (4)

4. M

a) (b) (4)

b

c)

d) (b) (4)

e) Please see Summary of Analysis for further description of results.

Summary of Analysis

1. **Method G1794: Determination of assay and impurities in Abemaciclib (LY2835219) drug substance by HPLC**

(b) (4)			

(b) (4)

Table 2. Summary of results of the G1796 method for the determination of (b) (4) in Abemaciclib.

Test	Data	Acceptance criteria	Results
(b) (4)			

a) (b) (4)

3.

(b) (4)

N

R

1. (b) (4)

2

3

4

(b) (4)

Original analyst worksheets can be viewed using this ECMS link:
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f8814556a5

LABELING

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	VERZENIO (abemaciclib) tablets
Dosage form, route of administration	Tablets, for oral use
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Tablets: 50 mg, 100 mg, 150 mg, and 200 mg

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	None

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Tablets for oral use
Strengths: in metric system	50 mg, 100 mg, 150 mg, and 200 mg
Active moiety expression of strength with equivalence statement (if applicable)	Not applicable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Adequate: description includes oval shape of tablets, three distinguishable colors for each strength, “Lilly” debossing on one side, “50”, “100”, “150”, or “200” debossed on the other side

4. *Section 11 Description*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	With edits: VERZENIO (abemaciclib) tablets
Dosage form and route of administration	Stated with the drug substance: "for oral administration"
Active moiety expression of strength with equivalence statement (if applicable)	No equivalence statement needed; no salt form
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Not Applicable
Statement of being sterile (if applicable)	Not Applicable
Pharmacological/ therapeutic class	Kinase inhibitor
Chemical name, structural formula, molecular weight	Provided
If radioactive, statement of important nuclear characteristics.	Not Applicable
Other important chemical or physical properties (such as pKa or pH)	Not Applicable

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

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Provided for all configurations
Available units (e.g., bottles of 100 tablets)	[blister] Packs with quantity defined
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Tablet descriptions provided for each strength as in Section 3; NDC numbers provided for each configuration.
Special handling (e.g., protect from light)	None necessary; carton container (b) (4) provide protection from light; also stability data demonstrates drug product is not impacted by light exposure
Storage conditions	Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F)
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA

Reviewer's Assessment of Package Insert: Adequate with minor edits to Sections 3, 11 and 16. The edits will be communicated through the clinical division.

"In Section 11, modify the description of VERZENIO to: 'VERZENIO (abemaciclib) tablets (b) (4) are provided (b) (4) as…'".

"**In Section 3, 11, and 16, the tablets are described as** (b) (4) **oval shaped. Justify the need for the work** (b) (4) **to distinguish this product for its visual description."**

II. Labels:

1. ***Container and Carton Labels: The container closure system is a single integrated blister card integrated into its carton container.***

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information provided in the container label
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Verzenio (abemaciclib) tablets; adequate size and prominence
Dosage strength	50 mg, 100 mg, 150 mg, or 200 mg
Net contents	Stated as 14-, (b) (4) -tablets
"Rx only" displayed prominently on the main panel	Yes
NDC number (21 CFR 207.35(b)(3)(i))	Provided
Lot number and expiration date (21 CFR 201.17)	Placeholder space designated
Storage conditions	Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F)
Bar code (21CFR 201.25)	Placeholder space designated
Name of manufacturer/distributor	Provided as "Marketed by : Lilly USA, LLC"
And others, if space is available	Designated as "Product of Ireland"

Reviewer's Assessment of Labels: ***{Adequate/Inadequate}***

{Assess if the labels comply with all regulatory requirements from a CMC perspective}

- ***Any deficiencies should be listed at the end in the "List of Deficiencies"***

List of Deficiencies: None

Overall Assessment and Recommendation: Adequate for approval with minor edits to be communicated through the clinical division.

Primary Labeling Reviewer Name and Date: Olen Stephens 28-Jul-17

Secondary Reviewer Name and Date: Anamitro Banerjee 17-Aug-17

Olen Stephens

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Anamitro Banerjee

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OFFICE OF PHARMACEUTICAL QUALITY

NDA FILING REVIEW

Application #: 208716	**Established/Proper Name: Abemaciclib**
Applicant: Eli Lilly	**Dosage Form: tablet**
Submission Type:505b1	**Strength(s): 50, 100, 150, 200 mg**
Chemical Type:small molecule	**Cross Referenced Applications: IND 106100**

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			N/A
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?		X	

B. OVERVIEW OF CRITICAL PRODUCT QUALITY REVIEW CONSIDERATIONS

Abemaciclib is a NME, selective, and potent small-molecule cyclin-dependent kinase inhibitor intended for the treatment of hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2–) metastatic breast cancer. Abemaciclib received both fast track and breakthrough therapy designations. Data from the nonclinical and clinical studies appear to demonstrate a favorable benefit-risk profile for the proposed indications. The recommended dose of abemaciclib in combination with fulvestrant is 150 mg orally, twice daily and the recommended dose of abemaciclib as a single agent is 200 mg orally, twice daily. Abemaciclib is

(b) (4)

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
	GENERAL/ADMINISTRATIVE				
1.	Has an environmental assessment report (NME, API with estrogenic, androgenic, or thyroid activity; API derived from plants and animals) or appropriate categorical exclusion (21 CFR 25.31 **AND** 25.15(d) been provided?	X			
2.	For DMFs, are DMF #'s identified and authorization letter(s) from the US agent provided in the application and referenced DMF?	X			
3.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the QOS to conduct a review?	X			
	FACILITY INFORMATION				
4.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet with complete identifying information?	X			
5.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	X			
	DRUG SUBSTANCE INFORMATION				
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in this section to conduct a review?	X			
	DRUG PRODUCT INFORMATION				
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in this section to conduct a review?	X			
	BIOPHARMACEUTICS				

C. FILING CONSIDERATIONS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?		X		The Office of Clinical Pharmacology will review the bridging BE study –JPCC comparing the 3X 50 mg (150 mg) C3 (capsule) formulation vs. the 150 mg T1 (tablet) formulationvs. 3X 50 mg (150 mg) T1 (tablet) formulation. This study also assessed the effect of high fat food on the PK of abemaciclib.
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)*	X			Refer to Comment for Q8.
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	X			The Applicant is requesting a biowaiver per 21 CFR 320.22.(d) (2) for the 100 mg and 200 mg tablets.
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?			X	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?			X	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?		X		There is no request for BCS 1 or 3 designation. However, the Applicant stated that abemaciclib may be considered a BCS Class III compound.
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?			X	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	X			
16.	If applicable, is the required information provided in 3.2.A for Biotech Products?			X	
17.	For Biotech Products, is sufficient information provided in compoliance with 21 CFR 610.9 and 601.2(a)?			X	

Document History	
Author: Integrated Quality Assessment Team, and Don Henry.	
Clearance Statement: This document is sponsored by the Integrated Quality Assessment Team. Jorge Rondon (OPRO/OE), Don Henry (OPRP/OE), and the Integrated Quality Assessment Team have cleared this template for use.	This process (CDER OPQ Integrated Quality Assessment Template) will be reviewed at the following intervals and changes to the work aid will be captured as needed: **This process will be reviewed approximately 150 days from date issued (May 24, 2016).**
Version	**Summary of Changes** **Date Issued**
01	Initial 05/24/2016