CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209936Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 209936
Review #1

Drug Name/Dosage Form	Aliqopa for Injection
Strength	60 mg/vial
Route of Administration	IV
Rx/OTC Dispensed	R_x
Applicant	Bayer
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	21-Dec-16	All
Amendment (SD 9)	10-Jul-17	DP
Amendment (SD 9)	12-Jul-17	DP
Amendment (SD 10)	21-Jul-17	DP
Amendment (SD 7)	28-Jun-16	DP

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Sharron Kelly	Benjamin Stevens
Drug Product	Rajiv Agarwal	Anamitro Banerjee
Process	Diane Goll	Rakhi Shah
Microbiology	John Metcalfe	Christine Craig
Facility	Rebecca Dombrowski	Derek Smith
Biopharmaceutics	n/a	n/a
Regulatory Business Process Manager	Teshara Bouie	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)		
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 III	(b) (4)		N/A	No Review	Adequate information provided in the NDA
	Type III			N/A	No Review	Adequate information provided in the NDA
	Type V			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
N/A		

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 209936 for Aliqopa® (Copanlisib Hydrochloride) for Injection, 60 mg. As part of this action, OPQ grants a (b) (4) month re-test period for the drug substance when stored (b) (4) °C,a 36-month drug product expiration period when stored at 2°C to 8°C and a 24 hour in-use period for the reconstituted drug product when stored at 2°C to 8°C. There are no outstanding issues and no post-approval quality agreement to be conveyed to the applicant.

II. Summary of Quality Assessments

A. Product Overview

NDA 209936 was submitted for Aliquipa® (Copanlisib dihydrochloride) for Injection, 60 mg in accordance with section 505(b)(1) of the Food, Drug and Cosmetic Act. Copanlisib is a phosphatidylinositol 3-kinase (PI3K) inhibitor indicated for the treatment of patients with relapsed (b) (4) follicular lymphoma who have received at least two prior therapies. Copanlisib was originally investigated under INDs 103,240 and 115, 916. Copanlisib is an NME which received orphan designation for the treatment of patients with follicular lymphoma in February 2015. Copanlisib was granted Fast Track designation and priority review to address the unmet medical need for the treatment of follicular lymphoma (FL) in February 2016.

Copanlisib dihydrochloride drug substance is a small molecule that is produced as a non-stoichiometric (b) (4) The drug product is presented as a white to slightly yellow 60 mg (equivalent to 69.1 mg of the dihydrochloride) lyophilisate in a 6 mL colorless injection vial. The drug product is designed to be reconstituted with 4.4 mL of a 0.9%NaCl solution and is to be further diluted in 100 mL of 0.9% sodium chloride (NaCl) to prepare an infusion.
The dosing regimen for Copanlisib consists of an intermittent dosing schedule. The recommended dose of the drug product is 60 mg, administered as a weekly 1-hour IV infusion (3 weeks on/1week off) on days 1,8, and 15 of a 28-day cycle.

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 209936 and grants a (b) (4) month re-test period for the drug substance, a 36 month expiration period for the drug product when stored under refrigerated conditions (2°C to 8°C) in the commercial packaging and a 24 hour in-use period for the reconstituted drug product when stored at 2°C to 8°C.

Proposed Indication(s) including Intended Patient Population	Follicular Lymphoma (FL)
Duration of Treatment	undefined
Maximum Daily Dose	60 mg
Alternative Methods of Administration	IV

B. Quality Assessment Overview

Drug Substance

Copanlisib dihydrochloride drug substance is a non-hygroscopic, white to yellow powder. Copanlisib dihydrochloride is achiral and is manufacture in (b) (4) by Bayer Pharma AG of Germany.

The drug substance manufacturing process is described in a manner to clearly delineate how impurities are formed, how changes in the process could potentially affect the formation, fate, and purge of impurities and why the proposed control strategy is suitable for the drug substance manufacturing process. The drug substance was investigated for polymorphism and the data indicated that copanlisib dihydrochloride exists 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.

The applicant included batch analyses for three validation batches (batches BXR70RW, BXR70X7 and BXR70X8). The batches were manufactured at commercial scale according to the process describe in this submission and packaged in (b) (4)

Twelve months of long term data, 6 months accelerated data and stress testing (thermal, oxidative and hydrolytic stress) are included for the validation batches. (b) (4)

(b) (4) there were no trends observed for any stability quality attributes in either packaging configurations. The stability data and stress testing supports the proposed (b) (4) month retest period with the following storage conditions: (b) (4)

Drug Product

The drug product is Copanlisib Lyophilisate 60 mg for Injection. The drug product is presented as a white to slightly yellow 60 mg (equivalent to 69.1 mg of the dihydrochloride) (b) (4) lyophilisate in a 6 mL colorless injection vial. The (b) (4) The strength designation is on the basis of the free base, which is consistent with the current salt nomenclature policy. The drug product is designed to be reconstituted with 4.4 mL of sterile isotonic (0.9%) sodium chloride (NaCl) solution and is to be further diluted in 100 mL of 0.9% NaCl to prepare the infusion solution. The recommended dose of the drug product is 60 mg, administered as a weekly 1-hour IV infusion on an intermittent schedule (3 weeks on/1week off) on Days 1,8, and 15 of a 28-day cycle

The drug product is manufactured, packaged and release tested by (b) (4) (commercial batch size (b) (4)). The drug product composition includes the active, citric acid and mannitol. The drug product formulation includes common compendial excipients and an overfill consistent with USP<1151> to ensure an extractable amount of 69.1 mg of the dihydrochloride which is equivalent to 60 mg of the free base. The container closure system for the drug product is a 6 mL colorless type 1 glass bottle for injection that is closed with a bromobutyl gray type 1 stopper for lyophilization. The stopper is fixed with a flanged closure with (b) (4) color coded for injection.

Batch analyses data were included for eight batches of the 60 mg drug product used in the clinical trial. It is noted that three different strengths of the drug product ((b) (4) 60 mg (b) (4) were used during development. Drug product specifications are consistent with ICH Q6A and provide adequate controls to ensure the quality of the drug product throughout the product expiry.

Based on the 30 months of stability data for three pilot-scale, registration batches of the drug product, Bayer HealthCare proposed and the FDA accepts the expiration dating period of **36 months** for the drug product when stored under refrigerated conditions (2°C to 8°C; 36°F to 46°F). When reconstituted as directed, both the reconstituted lyophilisates as well as the diluted infusion solutions are stable for up to 24 hours at 2-8 °C; however, the final diluted infusion solutions (in (b) (4) bags) should not be exposed to direct sunlight if not administered immediately after preparation.

The product reviewer has the following recommendations for Lifecycle management of this product:

(b) (4)

• *The solubility of copanlisib dihydrochloride in aqueous formulations is decreasing with increasing pH. Therefore, a change in pH will impact the solubility of the drug product.*

(b) (4)

Process

The drug product manufacturing process consists of the following steps:

(b) (4)

The following process steps were deemed critical in the manufacturing process:

(b) (4)

Process parameters for each of the individual processing steps were defined based on process knowledge and experience gained during development. The reviewer concluded that the applicant has provided adequate process parameters and in-process controls (IPC) for all critical steps.

This application also included a comparability protocol (CP) for generalized steps for facility (b) (4) and commercialization of the drug product including but not limited to batch size and formula, equipment additions (b) (4)

Bayer proposed a reduced reporting category for these changes (CBE 30). The CP was reviewed by the process and micro reviewers and the proposed reduced reporting category (CBE-30) was deemed acceptable.

Biopharmaceutics

No Biopharm reviewer assigned as this is a 505(b)(1) application and a liquid dosage form.

Quality Microbiology

The drug product is a lyophilized powder for solution, for intravenous (IV) administration after reconstitution. The product is sterilized by (b) (4)

(b) (4)

(b) (4) Deficiencies pertaining to the container closure integrity validation studies were identified and resolved during the review cycle. The validation information supporting the (b) (4) manufacturing demonstrates that the sterilization processes are controlled and are suitable for (b) (4) processing.

Facilities

Drug substance, copanlisib dihydrochloride, is manufactured by Bayer Pharma AG of Germany (FEI 3003229486). This facility had an acceptable inspection history and years of experience of manufacturing non-sterile APIs by chemical synthesis (CSN). This site has been the subject of several FDA inspections from 2005 to present, with the most recent being in April of 2017. Accordingly, a PAI was not requested and approval was based on capabilities and experience.

Drug product, Aliqopa® (Copanlisib Hydrochloride) for Injection, 60 mg, is manufactured by Bayer Pharma AG of Germany (FEI 3002808086). This site was considered high risk and had a history of findings/VAI. A pre-approval inspection (PAI) was requested and performed under this review due to lack of coverage and assessment of lyophilization operations. Based on this expedited PAI review, the compliance status of this firm and the demonstrated controls and capabilities of the quality unit in controlling and releasing manufactured product, this site is recommended for approval under this application.

Two additional sites were included in this NDA: (b) (4) and Bayer Healthcare LLC (FEI 224325) which is named as the distribution center for the finished product. (b) (4) (b) (4) The Bayer site was not further evaluated in this review.

Environmental Assessment

A categorical exclusion was submitted under 21 CFR § 25.31(b). The applicant states that to the applicant's knowledge, no extraordinary circumstances exist. The drug substance and intermediates are not derived from plants or animals taken from the wild. There is no information indicating that additional environmental information is warranted. The environmental assessment team has screened the categorical exclusion and concurs with these observations. The claim of categorical exclusion is acceptable. Accordingly, the request for categorical exclusion is granted.

C. Special Product Quality Labeling Recommendations (NDA only)

n/a

D. Final Risk Assessment (see Attachment)

see Attachment

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LABELING (NDA 209936)

R Regional Information

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section:

11 DESCRIPTION

ALIQOPA (copanlisib) is a kinase inhibitor [(b) (4)] for intravenous infusion. [(b) (4)] is a [(b) (4)] which exists as a non-stoichiometric hydrate and has the molecular formula of $C_{23}H_{28}N_8O_4 \cdot 2HCl$ and a molecular weight of 553.45 g/mol. The molecular formula and molecular weight are based on the anhydrous form. The chemical name 2-amino-N-{7-methoxy-8-[3-(morpholin-4-yl)propoxy]-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl}pyrimidine-5-carboxamide dihydrochloride. Copanlisib dihydrochloride has the following structural formula:

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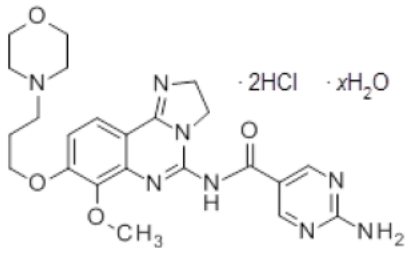

ALIQOPA is supplied in single-dose vials as a sterile lyophilized solid for reconstitution and further dilution for intravenous infusion. The product is white to slightly yellowish. After reconstitution, the solution is colorless to slightly yellowish. Each vial contains 60 mg copanlisib free base (equivalent to 69.1 mg copanlisib dihydrochloride). After reconstitution, each mL contains 15 mg/mL copanlisib free base (equivalent to 17.3 mg/mL copanlisib dihydrochloride).

Inactive ingredients: Citric acid anhydrous, mannitol, sodium hydroxide.

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

ALIQOPA is contained in a colorless glass vial closed with bromobutyl stopper with a flanged closure. Each vial of ALIQOPA contains copanlisib as a lyophilized solid.

NDC	Strength	Reconstituted Concentration
50419-385-01	60 mg (one single-dose vial per carton)	15 mg/mL

Storage and Handling

(b) (4)

Product as packaged for sale

ALIQOPA vials must be refrigerated at 2°C to 8°C (36°F to 46°F). (b) (4)

Product after reconstitution

Administer reconstituted solution immediately. If not, refrigerate at 2°C to 8°C (36°F to 46°F) and use within 24 hours. After refrigeration, allow the product to adapt to room temperature before use. (b) (4)

(b) (4) *[see Dosage and Administration (2)].*

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

The recommended dose of ALIQOPA is 60 mg administered as a 1-hour intravenous infusion on Days 1, 8, and 15 of a 28-day treatment cycle on an intermittent schedule (three weeks on one week off). Continue treatment until disease progression or unacceptable toxicity *[see Warnings and Precautions (5)]*.

2.1 Preparation and Administration

(b) (4)

For intravenous infusion only.

Administer ALIQOPA as a single agent, following reconstitution and dilution. (b) (4)

(b) (4)

Mix only with 0.9% sodium chloride (NaCl) solution. Do not mix or inject ALIQOPA with other drugs or other diluents.

2.2 Reconstitution Instructions

Reconstitute ALIQOPA with 4.4 mL of sterile 0.9% NaCl solution leading to a concentration of 15 mg/mL.

Withdraw 4.4 mL of sterile 0.9% NaCl solution by using a 5 mL sterile syringe with needle. Inject the measured volume through the disinfected stopper surface into the vial of ALIQOPA. Dissolve the lyophilized solid by gently shaking the injection vial for 30 seconds. Allow to stand for one minute to let bubbles rise to the surface. Check if any undissolved substance is still seen. If yes, repeat the gentle shaking and settling procedure.

Inspect visually for discoloration and particulate matter. After reconstitution, the solution should be colorless to slightly yellowish. Once the solution is free of visible particles, withdraw the reconstituted solution for further dilution.

2.3 Dilution Instructions for Intravenous Use

Further dilute the reconstituted solution in 100 mL sterile 0.9% NaCl solution for injection. With a sterile syringe, withdraw the required amount of the reconstituted solution for the desired dosage:

60 mg: Withdraw 4 mL of the reconstituted solution with a sterile syringe.

45 mg: Withdraw 3 mL of the reconstituted solution with a sterile syringe.

30 mg: Withdraw 2 mL of the reconstituted solution with a sterile syringe.

Inject the contents of the syringe into the patient infusion bag of 100 mL sterile 0.9% NaCl solution. Mix the dose well by inverting.

Discard any unused reconstituted or diluted solution appropriately.

Use reconstituted and diluted ALIQOPA immediately or store the reconstituted solution in the vial or diluted solution in the infusion bag at 2°C to 8°C (36°F to 46°F) for up to 24 hours before use . Avoid exposure of the diluted solution to direct sunlight. Allow the product to adapt to room temperature before use following refrigeration.

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

☒ Yes ☐ No ☐ N/A

If "No," explain.

R Regional Information

1.14 Labeling

Immediate Container Label (60 mg)

(b) (4)

[redacted]

Reviewer's Assessment: *The applicant responsed to deficiencies and revised the label as recommended. Adequate.*

Carton Labeling (60 mg):

(b) (4)

[redacted]

Reviewer's Assessment:

The PI label is modified and will be communicated to the applicant via OND PM. The following deficiencies on immediate container and carton were identified and communicated to the applicant by DMEPA on 18-JUL-2017.

1) We recommend relocating and increasing the prominence of the strength of the drug to appear under the drug name in the primary display panel (PDP). As currently presented, the strength of the product is not prominent. In addition, we suggest revising the strength from "60 mg/vial (equivalent to 69.1 mg copanlisib dihydrochloride)" to read "60 mg*" and include asterisk information separately. Please see below for our suggested revision:

Aliqopa

(copanlisib) for injection

60 mg*

***Equivalent to 69.1 mg copanlisib dihydrochloride**

2) Consider revising the statement (b) (4) to read "Single dose vial – discard unused portion" to (b) (4) (b) (4)

3) Increase prominence of statements "For Intravenous Infusion Only" as currently presented it is difficult to read.

The applicant responded satisfactorily to the deficiencies on 2-AUG-2017 and 3-AUG-2017.

The container labeling is now adequate.

Conclusion: *Labels and Labeling are adequate from a CMC stand point.*

Primary Labeling Reviewer Name and Date:

Rajiv Agarwal, Ph.D, 9-AUG-2017

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

Anamitro Banerjee, PhD, 9-AUG-2017

Rajiv Agarwal

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Anamitro Banerjee

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MICROBIOLOGY

IQA Review Guide Reference

Product Background:

NDA: 209936

Drug Product Name / Strength: ALIQOPA (Copanlisib lyophilisate, 60 mg).

Route of Administration: Injection solution

Applicant Name: Bayer HealthCare Pharmaceuticals Inc.

Manufacturing Site: Bayer Pharma AG, Muellerstrasse4 170-178, 13353 Berlin, Germany.

Method of Sterilization: (b) (4)

Review Recommendation: Recommended for Approval

Review Summary: The drug product is (b) (4)

List Submissions Being Reviewed: 3/16/2017

Highlight Key Outstanding Issues from Last Cycle: NA

Remarks: The drug product is indicated for the treatment of relapsed (b) (4) follicular lymphoma.

Concise Description Outstanding Issues Remaining: None.

Supporting Documents: The type V DMF (b) (4) was referenced for the (b) (4) of the primary packaging material ((b) (4) stoppers) and was reviewed and deemed adequate on November 6, 2015 ((b) (4) mic8.doc).

S Drug Substance

The drug product is sterilized [redacted] (b) (4) and the drug substance is not assessed in this review.

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** The drug product is a sterile, white to yellow, lyophilized solid, in a 6 mL clear vial.
- **Drug product composition –** The drug product composition is displayed in the applicant table below (Module 3.2.P.1, Composition of the Drug Product-P.1.02#012873292, pg. 2).

Each vial contains:

Composition	Reference to standard	Function	Nominal amount [mg]	Filled amount [a, b] [mg]
Drug substance				
Copanlisib dihydrochloride	specification	drug substance	69.1 [c]	(b) (4)
Excipients				
Citric acid anhydrous	Ph. Eur., USP, Ph. Jap.	(b) (4)		
Mannitol	Ph. Eur., USP, Ph. Jap.			
Sodium hydroxide [e]	Ph. Eur., USP, Ph. Jap.			

a (b) (4)

b

c equivalent to 60 mg copanlisib (free base)

d (b) (4)

e (b) (4)

- **Description of container closure system –** The primary container closure system includes a 6 mL colorless type I glass injection bottle closed with a (b) (4) gray type I bromobutyl lyophilization stopper (3.2.P.7, Packaging Materials, pg. 2). The manufacturer and product number of the 6 mL glass vial, used in the drug product primary container closure system, were not provided.

The following information request was sent to the applicant on June 28, 2017:

We acknowledge the information provided in section 3.2.P.7 which states that a 6 mL colorless glass type 1 vial is used for the primary container closure system. Please provide the manufacturer and a product identification number of the 6 mL glass vial proposed for the container closure system of Copanlisib lyophilisate, 60 mg.

Applicant Response: The 6 mL vials used for the primary container closure system are purchased from [redacted] (b) (4) The product numbers are not provided; however, DMF (b) (4) and DMF (b) (4) are referenced.

Adequate

Reviewer's Assessment: The applicant provided an adequate description of the drug product composition and container closure system.

- Growth promotion testing should yield positive results.

Adequate

Reviewer's Assessment: The applicant has met regulatory expectations for the performance of process simulations in support of the (b) (4) manufacture of Copanlisib lyophilisate, 60 mg.

Actions Concerning Product (b) (4)

In the event that acceptance criteria are not met, the following actions are taken:

(b) (4)

Adequate

Reviewer's Assessment: The applicant provided an acceptable course of action for (b) (4) failures.

P.5 Control of Drug Product

P. 5.1 Specification

(3.2.P.5.1, Release Specifications-P.5.1.01#012773102)

Test	Test Method	Acceptance Criteria
Bacterial Endotoxins	USP <85>	< (b) (4) EU/mg
Sterility	Equivalent to USP <71>	No growth

Adequate

Reviewer's Assessment: The applicant provided equivalent sterility and endotoxin test methods to USP methods.

P.5.2 Analytical Procedures

(3.2.P.5.2, Test Procedure –P -5.2.01#012773104)

Bacterial Endotoxins Testing

The bacterial endotoxins test method is stated to be equivalent to USP <85>.

Sterility
The sterility test method conforms to the harmonized pharmacopoeial Ph. Eur. 2.6.1 and is stated to be equivalent to USP <71>.

P.5.3 Validation of Analytical Procedures

Endotoxins
(3.2.P.5.3, Validation of Test for Endotoxins)

Validation data were provided for the endotoxin Limulus Amebocyte Lysate (LAL) gel clot method. The drug product is administered as a one hour intravenous infusion delivering a maximum dose of 60 mg of drug product at a concentration of 15 mg/mL. The maximum endotoxin exposure complies with the USP <85> recommendation of (b) (4) EU/kg/hr for injection products (calculation below).

(b) (4) /kg/hr

The maximum valid dilution is calculated as (b) (4) (calculation below).

MVD = (b) (4)

An enhancement inhibition study was performed using three batches of the drug product (KM500M7, KM500M8 and KM500M9). The test was performed on samples with and (b) (4) proposed for endotoxins testing of the drug product.

Adequate
Reviewer's Assessment: The applicant has met regulatory expectations with regard to the test method, acceptance criteria and verification of the suitability of use of the bacterial endotoxins test that will be performed on the drug product at release and stability.

Sterility
(3.2.P.5.3, Validation of Test for Sterility)

Sterility testing is performed in accordance with USP <71> using the closed Millipore Steritest System. Validation was carried out using the same method proposed for testing of the drug product during commercial production. A total of (b) (4) of viable microorganisms (*Staphylococcus aureus* ATCC 6538, *Bacillus subtilis* ATCC 6633, *Pseudomonas aeruginosa* ATCC 9027, *Clostridium sporogenes* ATCC 11437, *Candida albicans* ATCC 10231 and *Aspergillus brasiliensis* ATCC 16404). Soybean casein digest medium (CSB) or fluid thioglycollate (THIO) medium were added to the vessels that were then incubated for three days. Results of the study are displayed in the applicant table below (3.2.P.5.3, Validation of Test for Sterility, pg. 4). Clearly visible growth of microorganisms was detected at a maximum of 3 days. The positive controls were positive and the negative controls were negative.

4.1 Millipore-Steritest-System

Type of microorganism	KM501RY Growth within x days		Inoculum [CFU]	KM501U3 Growth within x days		Inoculum [CFU]	KM501NB Growth within x days		Inoculum [CFU]
	CSB	THIO		CSB	THIO		CSB	THIO	
S. aureus ATCC 6538	n.d.	2	76	n.d.	2	76	n.d.	2	76
Control vessel	n.d.	2	76	n.d.	2	76	n.d.	2	76
B. subtilis ATCC 6633	2	n.d.	80	2	n.d.	80	2	n.d.	80
Control vessel	2	n.d.	80	2	n.d.	80	2	n.d.	80
P. aeruginosa ATCC 9027	n.d.	2	57	n.d.	2	33	n.d.	2	57
Control vessel	n.d.	2	57	n.d.	2	33	n.d.	2	57
C. sporogenes ATCC 11437	n.d.	2	84	n.d.	2	84	n.d.	2	84
Control vessel	n.d.	2	84	n.d.	2	84	n.d.	2	84
C. albicans ATCC 10231	3	n.d.	68	3	n.d.	68	3	n.d.	68
Control vessel	3	n.d.	68	3	n.d.	68	3	n.d.	68
A. brasiliensis ATCC 16404	3	n.d.	23	3	n.d.	23	3	n.d.	23
Control vessel	3	n.d.	23	3	n.d.	23	3	n.d.	23

Adequate

Reviewer's Assessment: The applicant has met regulatory expectations with regard to the test method, acceptance criteria and verification of the suitability of use of the sterility test that will be performed on the drug product prior to its release.

P.7 Container Closure

See P.1

P.8 Stability

P. 8.1 Stability Summary and Conclusion

The stability program is summarized in the table below (3.2.P.8.1, Stability Summary-P.8.1.01#012780231, pg. 5). Sterility and endotoxins testing are performed initially and at 12 month intervals.

Table 2: Stability schedule for pivotal study

Storage condition	Test stations [months]								
	Initial	1	3	6	9	12	18	24	36
2–8 °C/-- [a]	x	--	x	x	x[b]	x	x[b]	x	x
25 °C/60 % RH	x	--	x[b]	x[b]	x[b]	x	x[b]	x	x
30 °C/75 % RH	x	--	x[b]	x[b]	x[b]	x	(x)[b]	(x)	(x)
40 °C/75 % RH	x	x[b]	x[b]	x	--	--	--	--	--

-- not required/not scheduled
x required
(x) optional
a uncontrolled humidity
b particulate matter, water, endotoxins and sterility are tested only in 12-months intervals

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

Storage at a temperature greater than [redacted] (b) (4) of the drug product. Based on the available data, it was determined that 25°C is representative of accelerated conditions. The proposed testing conditions in the post approval protocol are displayed in the table below (3.2.P.8.2, Post-Approval Stability Protocol and Stability Commitment-P.8.2.01#0128733, pg. 3).

[redacted] (b) (4)

P.8.3 Stability Data

(3.2.P.8.3, Stability Data-P.8.3.01#012780260)

Sterility and endotoxins data were provided for three batches of drug product out to 24 months. All microbiology acceptance criteria were met.

Adequate

Reviewer's Assessment: The applicant has met regulatory expectations with regard to the design of the stability testing program to support the drug product's microbiological quality throughout its shelf life. In addition, the stability data

John Metcalfe

Digitally signed by John Metcalfe
Date: 7/20/2017 01:02:20PM
GUID: 503451f000004f68b7145543c615dbba
Comments: I concur.

Christine Craig

Digitally signed by Christine Craig
Date: 7/20/2017 01:01:45PM
GUID: 57ced2690109ab449e84a49141df01f8

ATTACHMENT I: Final Risk Assessments

IQA Review Guide Reference

A. Final Risk Assessment – NDA 209936 Aliqopa for Injection/60 mg, Bayer

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**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipments • Site	H	Sterility testing, in-process controls, validation of (b) (4) manufacturing processes.	Acceptable to microbiologist	Controls are in place and continue stability monitoring post approval
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipments • Site	M	Endotoxin testing, inprocess controls, validation of (b) (4) manufacturing processes.	Acceptable to microbiologist	Controls are in place and continue stability monitoring post approval
Assay (API), 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) Lyophilized small molecule products	• 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
Uniformity of Dose (Fill Volume/deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipments • Site	L	Assessed during Development and controlled via specs	Acceptable	Solid cake and not a solution therefore CU is monitored. Controls are in place, continue stability monitoring post approval
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipments	L	Assessed during Development	Acceptable	(b) (4)

	• Site				
pH- (Low)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Controlled via specs during stability	Acceptable	Controls are in place during stability testing. Continue stability monitoring post approval
Particulate matter (non aggregate for solution only)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M	Controlled via specs during stability	Acceptable	Controls are in place. Continue stability monitoring post approval
Leachable extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	USP testes are performed and conforms	Acceptable	Controlled via DMF
Moisture Content (lyophilized)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	Controlled via specs during stability	Acceptable	Controls are in place. Continue stability monitoring post approval
Appearance (cake)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L	Controlled via specs during stability	Acceptable	Controls are in place. Continue stability monitoring post approval

Note: The method validation package is submitted to the OTR lab in St Loius. The lab

(b) (4)

[redacted]

(b) (4)

The applicant may submit this information via Annual report or via CBE supplement after the approval.

Rajiv Agarwal

Digitally signed by Rajiv Agarwal
Date: 7/21/2017 08:44:46AM
GUID: 504fa29c0000100b83d3aaa4905783c1

Anamitro Banerjee

Digitally signed by Anamitro Banerjee
Date: 7/21/2017 08:47:24AM
GUID: 5075764700003844b7bc89632228509f

Sherita McLamore

Digitally signed by Sherita McLamore
Date: 8/10/2017 11:17:33AM
GUID: 50325795000041575549 2db5bb8b1a5c

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: July 20, 2017

To: Rajiv Agarwal, Drug Product Reviewer
Sharon Kelly, Drug Substance Reviewer
Sherita McLamore-Hines, CMC Lead
Teshara Bouie, RBPM

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

From: Cindy Diem Ngo, Chemist, CDER/OPQ/OTR/DPA
Laura Pogue, Ph.D., Method Verification Coordinator, CDER/OPQ/OTR/DPA

Subject: Method Verification for NDA 209936: Aliqopa (copanlisib) Injection, 60mg

The following methods were evaluated and are *acceptable* for quality control and regulatory purposes:

1. S.4.2.01-02: [redacted] (b) (4) any unspecified impurity and sum of all organic impurities of drug substance by HPLC, pages 15-23.

2. P.5.2.01-01: [redacted] (b) (4) Any Unspecified Degradation Products, Sum of all Degradation Products and Assay by HPLC, pages 8-20.

Note: The correspondence from the Bayer regarding upcoming changes to their method have been shared with reviewers and uploaded to the document section in Panorama. DPA does not see any issue with these changes.

Original analyst worksheets can be viewed on ECMS:
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f8813178df

Summary of Analysis **NDA 209936**

Drug Substance, S.4.2.01-02:

% Assay:

	Assay i.d.s. of copanlisib dihydrochloride	Average Assay i.d.s. of copanlisib dihydrochloride	Limits
Sample 1	(b) (4) %	(b) (4) **%**	(b) (4) %, **PASS**
Sample 2	%		

% Impurity:

	RT	RRT	Impurity Name	% Impurity	Average % Impurity	Limits
Sample 1	(b) (4)		(b) (4)	(b) (4) %	(b) (4) **%**	NMT (b) (4) %, **PASS**
Sample 2				%	LT (b) (4) % not reporting	

No other impurities were detected above the (b) (4) % reporting limit.

Sum of all organic impurities (b) (4) **%,** NMT (b) (4) %, **PASS.**

Drug Product, P.5.2.01-01:

Assay:

Copanlisib	Sample 1	Sample 2	Average	Limits
mg/bottle	(b) (4)			Between (b) (4) **PASS**

Degradation product:

Components	Degradation product	Limits
(b) (4)	(b) (4) %	NMT (b) (4) %, **PASS**
	%	NMT %, **PASS**
	%	NMT %, **PASS**
	%	NMT %, **PASS**
Sum of all Degradation products	%	NMT %, **PASS**

Reporting Limit = (b) (4) %
NMT: Not More Than

Peak Identification for Copanlisib by HPLC-UV:
The UV spectra of the copanlisib peak from the sample preparation compared well with the UV spectra of the respective standard in the resolution standard solution.

Jason Rodriguez

Digitally signed by Jason Rodriguez
Date: 7/25/2017 12:54:36PM
GUID: 508da7360002b158f072de914f432fe5

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VERIFICATION REQUEST FORM

TO: **CDER/OPQ/OTR/Division of Pharmaceutical Analysis**
Laura C. Pogue, Ph.D.
laura.pogue@fda.hhs.gov, 314-539-2155
Michael Hadwiger, Ph.D.
michael.hadwiger@hda.hhs.gov, 314-539-3811

FROM: Rajiv Agarwal, Drug Product Reviewer
Sharon Kelly, Drug Substance Reviewer
Sherita McLamore-Hines, CMC Lead
Office Name - ONDP
E-mail Address: Rajiv.Agarwal@fda.hhs.gov; Sharon.Kelly@fda.hhs.gov
Phone: 301-796-1322 301-796-1686

Through: Teshara Bouie
Teshara.Bouie@fda.hhs.gov
Phone: 301-796-1649

SUBJECT: Methods Verification Request

Application Number: NDA 209936

Name of Product: ALIQOPA (copanlisib) Injection, 60 mg

Applicant: Bayer HealthCare Pharmaceuticals Inc.

Applicant's Contact Person: Anita K Murthy, Pharm D., Deputy Director Oncology 2

Address: 100 Bayer Blvd, P.O Box 915, Whippany, NJ 07981-0915

Telephone: 862-404-5951 Email: anita.murthy@bayer.com

Date NDA Received by CDER: **3/16/2017**

Date of Amendment(s) containing the MVP:

DATE of Request:

Requested Completion Date:

User Fee Goal Date: **9/16/2017**

Submission Classification/Chemical Class: e.g. NME

Special Handling Required: No

DEA Class: N/A

Name of OTR Representative on Review Team:

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Verification Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Verification Request* as described in he A/NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the Methods Verification Requestor and the Methods Verification Project Manager of the date that the verifica ion process begins. If the requested completion date cannot be met, please promptly notify the Methods Verification Requestor and the Methods Verification Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Verification Report Summary*). The *Methods Verification Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by he director via DARRTS. The CMC Reviewer, Methods Verification Project Manager, and CMC Lead/Branch Chief should be included as cc: recipients for this document.

All information relative to this applica ion is to be held confidential as required by 21 CFR 314.430.

ATTACHMENT(S): *Methods Verification Request Sheet*, A/NDA Methods Validation Package (if not available in the EDR).

MVP Reference #	**METHODS VERIFICATION REQUEST**	NDA # 209936

⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT

ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION

⇒ ITEM 2: **Contents of Attached Methods Validation Package**	Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)	3.2.P.1
Specifications/Methods for New Drug Substance(s)	3.2.S.4.1
Specifications/Methods for Finished Dosage Form(s)	3.2.P.5.1
Supporting Data for Accuracy, Specificity, etc.	3.2.P.5.3 (DP)
Applicant's Test Results on NDS and Dosage Forms	3.2.P.5.2 (DP)
Other:	

⇒ ITEM 3: **REQUESTED DETERMINATIONS**
Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.

Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
P.5.2.01-01	Reversed-phase high performance liquid chromatography with UV-detection and external calibration.	Page 8-20	**0**	(b) (4) Any unspecified degradation product Sum of all degradation products Assay
S.4.2.01-02	High performance liquid chromatograph (HPLC) reversed phase method detection UV-range external standard method (ESTD)	Page 15-23	**0**	Impurities (4), any unspecified impurity, sum of all organic impurities, Assay

Additional Comments:

Methods Verification Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method
6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason