

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206192Orig1s000

CHEMISTRY REVIEW(S)

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

METHODS VALIDATION REPORT SUMMARY

TO: Gaetan Ladoucer (Drug Substance) and Donghao Lu (Drug Product), CMC Reviewers

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FROM: FDA

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SUBJECT: Methods Validation Report Summary

Application Number: 206192

Name of Product: Cobimetinib, 20 mg tablet

Applicant: Genentech

Applicant's Contact Person: Lal Ninan, Ph.D.

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Telephone: (650) 467-8564 Email: ninan.lal@gene.com

Date Methods Validation Consult Request Form Received by DPA: 02/19/2015

Date Methods Validation Package Received by DPA: 02/19/2015

Date Samples Received by DPA: 03/24/2015

Date Analytical Completed by DPA: 05/21/2015

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes.
2. Methods are acceptable with modifications (as stated in accompanying report).
3. Methods are unacceptable for regulatory purposes.

Comments: See attached summary for analyst comments and results.



Date: May 20, 2015

To: Gaetan Ladoucer, Ph.D., Drug Substance, CMC Reviewer
Donghao Lu, Drug Product, CMC Reviewer

Through: David Keire, Ph.D., CDER/OPQ/OTR/DPA, Lab Chief, Branch I

From: Cindy Diem Ngo, Chemist, CDER/OPQ/OTR/DPA
Nicholas Batz, Ph.D., Chemist, CDER/OPQ/OTR/DPA

Subject: Method Evaluation of NDA 206192: Cobimetinib, 20 mg Tablet

The following methods were evaluated and found acceptable for quality control and regulatory purposes.

- 1) 3.2.S.4.2.3: Identity, Assay, and Organic Impurities of Cobimetinib Drug Substance by HPLC
- 2) 3.2.S.4.2.8: Determination of [REDACTED] (b) (4) by Gas Chromatography
- 3) 3.2.P.5.2.4: Identity, Assay, and Degradation Product by HPLC
- 4) 3.2.P.5.2.5: Uniformity of Dosage units by Content Uniformity
- 5) 3.2.P.5.2.6: Dissolution for Cobimetinib Film-Coated Tablets 20mg

Analyst worksheets can be viewed here: <http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f880a3c1f3>

Summary of Results:

1) **3.2. S.4.2.3 Identity, Assay, and Organic Impurities of Cobimetinib Drug Substance by HPLC**

- Identification: The Cobimetinib drug substance peak had the same retention time as the Cobimetinib reference standard ((b) (4)).
- Assay: The assay value for Cobimetinib drug substance ((b) (4) % w/w) was (b) (4) % and met specification ((b) (4) %).
- Organic impurities assay: Two impurities were detected in the drug substance. Both (b) (4) and (b) (4) were below the limit of quantitative (0.05%). Therefore, no impurity was detected at a level greater than 0.05% (w/w) in the drug substance Cobimetinib.

2) **3.2.S.4.2.8 Determination of (b) (4) by Gas Chromatography**

- Both prepared samples **PASSED** the limit test. Peak areas for each sample were below the peak area for the reference standards. The (b) (4) reference standard was a concentration of (b) (4) ppm and the (b) (4) standard was prepared at (b) (4) ppm.

	(b) (4) Peak Area (TIC)	(b) (4) Peak Area (TIC)
Reference Standard	(b) (4)	(b) (4)
Sample 1	(b) (4)	Not detected
Sample 2	(b) (4)	Not detected

3) **3.2. P.5.2.4 Identity, Assay, and Degradation Product by HPLC**

- Identification: The Cobimetinib peak associated with the drug product sample had the same retention time as the Cobimetinib reference standard (b) (4).
- Assay: Specifications for percent content and mg/tablet were met. See table below.

	Average of sample 1 & 2	Specifications
% Content	(b) (4)	(b) (4)
mg/tablet	(b) (4)	(b) (4)

- Degradation: There were no impurity or degradation peaks above the 0.05% threshold for the drug product.

4) **3.2. P.5.2.5 Uniformity of Dosage units by Content Uniformity**

- The sample met the Acceptance Criteria of UPS <905> Uniformity of Dosage Units.

Tablet #	Injection 1	Injection 2	Average	Content in mg/tablet	% Content
Tablet 1	(b) (4)				
Tablet 2					
Tablet 3					
Tablet 4					
Tablet 5					
Tablet 6					
Tablet 7					
Tablet 8					
Tablet 9					
Tablet 10					
Attachment CDN D25-D64			Average	(b) (4)	
SD					
%RSD					
Minimum					
Maximum					

Calculation of Acceptance Value: determined by the formula in which the terms are defined in Table 2 of UPS <905> Uniformity of Dosage Units.

- AV = (b) (4), PASS.

5) **3.2. P.5.2.6 Dissolution for Cobimetinib, Film-Coated Tablets 20mg**

- Q value for each vessel after 20 minutes was greater than (b) (4)% of declared content. The drug product met specification.

Time point	5 min	10 min	15 min	20 min	30 min	45 min	60 min
Average % Dissolution	(b) (4)						
SD							
%RSD							
Minimum							
Maximum							

All listed methods evaluated are acceptable for quality control and regulatory purposes.

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/s/

LAURA POGUE
05/21/2015

DAVID A KEIRE
05/21/2015



Recommendation:
NDA: Approval

NDA 206192
Review #1
Review Date: 11-May-15

Drug Name/Dosage Form	cobimetinib
Strength	20 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Genentech, Inc.
US agent, if applicable	Sarah Wayson, Ph.D., Regulatory Program Management

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0000 (Original Submission)	December 19, 2014
0005 (Quality Amendment)	January 8, 2015
0016 (Quality Amendment)	March 16, 2015
0019 (Labeling and Packaging)	March 23, 2015
0023 (Labeling and Packaging)	April 6, 2015
0026 (Quality Amendment)	April 30, 2015

Quality Review Team

DISCIPLINE	REVIEWER
Drug Substance	Gaetan Ladouceur
Drug Product	Donghao Lu
Process	Zhengfang Ge
Microbiology	Zhengfang Ge
Facility	Sunita Iyer
Biopharmaceutics	Maziar Kakhi
Business Process Manager	Rabiya Laiq
Application Technical Lead	Olen Stephens
Laboratory (OTR)	N/A
ORA Lead	Peter Perdue Jr
Environmental Assessment (EA)	Donghao Lu

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Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS ¹	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type III	(b) (4)	(b) (4)	Adequate		Based on information provided in the NDA
	Type III			Adequate		Based on information provided in the NDA
	Type IV			Adequate		Based on information provided in the NDA

¹ Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

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

APPLICATION NUMBER	DESCRIPTION
(b) (4)	IND
109,307	IND
(b) (4)	IND
	IND
	IND

3. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Pharmacology/Toxicology				
Other				

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 206192 is recommended for approval from a CMC perspective. There are no outstanding deficiencies and the manufacturing facilities have an approval recommendation. Labeling comments will be negotiated through the clinical project manager. A 30-month shelf-life will be granted through the approval letter based on stability data (b) (4). The product should be stored below 30°C (86°F).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

Cobimetinib fumarate ((S)-[3,4-difluoro-2-(2-fluoro-4-iodophenylamino) phenyl] [3-hydroxy-3-(piperidin-2-yl) azetididin-1-yl]methanone hemifumarate) is a (b) (4) white to off-white solid with (b) (4)

The drug substance is soluble under physiologically relevant conditions. The single stereogenic center does not racemize under drug substance storage conditions or drug product manufacture. The (b) (4) starting materials and their suppliers are designated as (b) (4)

Description of these starting materials is described in the review below under section 2.3.S.2.2. The synthesis of cobimetinib fumarate is a (b) (4). The drug substance is not manufactured under (b) (4).

B. Drug Product [Established Name] Quality Summary

Cobimetinib white, film-coated tablets are debossed with “COB” on one side and contain 20 mg of the free base. These non-sterile, immediate release tablets are formulated with USP/NF compendial excipients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, (b) (4)/PEG 3350, talc, (b) (4). The (b) (4) tablets are manufactured by (b) (4)

. The tablets are

stored in 70 mL white, opaque, square, high-density polyethylene bottles (b) (4)

Sufficient stability data was submitted at 30°C/75% RH to support a (b) (4) month shelf life with labeling to store the product below 30°C (86 °C). Note that these storage conditions and stability data were established to enable marketing in climate zones warmer and more humid than the US market. This approach is consistent with labeling for other clinical divisions, such as antiviral products.

1. Summary of Product Design
 - a. Critical equipment

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Cotellic
Non Proprietary Name of the Drug Product	Cobimetinib Tablets
Non Proprietary Name of the Drug Substance	Cobimetinib
Proposed Indication(s) including Intended Patient Population	Indicated for use in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutation
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	60 mg (three tablets)
Alternative Methods of Administration	None

D. Biopharmaceutics Considerations

1. BCS Classification: The applicant did not request BCS Class 1 designation.
2. Biowaivers/Biostudies
 - Biowaiver Requests: None
 - PK studies: None
 - IVIVC: None

E. Novel Approaches: None

F. Any Special Product Quality Labeling Recommendations: None

G. Process/Facility Quality Summary (see Attachment A)

H. Life Cycle Knowledge Information (see Attachment B)

Olen Stephens, Ph.D.
Acting Branch Chief
OPQ/ONDP/DP/Branch 2

Olen
Stephens -S

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Primary Quality Review

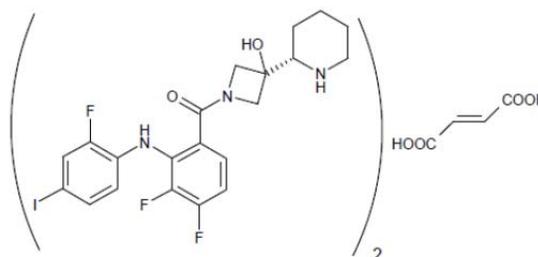
ASSESSMENT OF THE DRUG SUBSTANCE

2.3.S DRUG SUBSTANCE

2.3.S.1 General Information

Applicant's Response:

- U.S. Adopted Name (USAN): Cobimetinib Fumarate, or Cobimetinib (free base)
- CAS Registry number: 1369665-02-0, or 934660-93-2 (free base)
- Chemical name (IUPAC): (S)-[3,4-difluoro-2-(2-fluoro-4-iodophenylamino) phenyl] [3-hydroxy-3-(piperidin-2-yl) azetidin-1-yl]methanone hemifumarate
- Company or Laboratory Codes: RO5515041-001, RO5514041-000 (free base)
- Molecular formula: C₄₆H₄₆F₆I₂N₆O₈ (2 C₂₁H₂₁F₃IN₃O₂ • C₄H₄O₄)
- Molecular weight: 1178.71 g/mol (salt), 531.32 g/mol (free base)
- Chirality: Cobimetinib has one chiral center of (S)-configuration.
- Molecular Structure:



- Appearance: White to off-white solid.
- Melting Point: 233-241°C by differential scanning calorimetry.
- Optical Rotation: +5.989° (in DMSO)
- pKa: 8.86 (piperidine)
- log D: 2.42 (at pH 7.4)
- Polymorphism: (b) (4)
- Hygroscopicity:
- Solubility: Solubility in aqueous media is pH dependent. In water (37°C), cobimetinib shows a solubility of 0.72 mg/mL, while in 0.1 M HCl (37°C), its solubility is 48.21 mg/mL. In nonpolar organic solvents, such as toluene the solubility is low (< 0.05% w/w). Slightly higher solubility can be reached in polar organic solvents, such as ethanol (0.18% w/w), and methanol (0.82% w/w).

Reviewer's Assessment:

Adequate. Only (b) (4) has been observed in an extensive polymorph screen. Noteworthy, in an intrinsic dissolution experiment, it was found that (b) (4)

2.3.S.2 Manufacture***S.2.2 Description of the Manufacturing Process and Controls***

(b) (4)

0 Page(s) has been withheld in full as b4 (CC1/15) immediately following this page

2.3.S.4 Control of Drug Substance

9. Is the proposed specification adequate to assure the identity, strength, purity, and quality of the drug substance?
10. Are all the analytical procedures appropriately described and validated for their intended use?

Applicant's Response:

Table S.4.1-1 Specifications for the Drug Substance

Test	Acceptance Criteria	Method
Description ^a		
Appearance	(b) (4)	Visual
Color	White to off-white	Visual
(b) (4)		

Reviewer's Assessment:

All related impurities have acceptance criteria below the qualification threshold according to the ICHQ3A guideline. Two (b)(4) that were identified as potential genotoxic impurities ((b)(4)) have acceptance criteria that were found to be acceptable by the pharm/tox reviewer (Dr. Anwar Goheer, email received on 02/25/2015). All other (b)(4) have acceptance criteria within the PDE limit of ICHQ3C guideline. The (b)(4) limit has been set according to the ICH Q3D guideline. The polymorphic form is controlled by a reliable structure confirmation using (b)(4) method. Therefore, the proposed specification appears adequate to assure the quality of the drug substance.

The analytical procedures were presented (see methods listed on the above specification table). Detailed validation data for the analytical methods were adequately presented in the application. The validation data are acceptable and the analytical methods appear adequate for the intended use. It should be noted that a Methods Validation request was sent to the DPA lab in St-Louis because the drug substance is a new molecular entity. The evaluation is pending.

11. Is the proposed control strategy for the drug substance manufactured at commercial stage acceptable? Is there any residual risk upon implementation of the control strategy at the commercial scale?

Applicant's Response:

The reproducibility of the commercial manufacturing process in delivering consistent quality of drug substance was demonstrated through 10 commercial-scale batches (Campaigns T3A and T3B), in which the release specifications were fully met.

Reviewer's Assessment:

The risks associated with potential toxic impurities in the drug substance, such (b)(4) and genotoxics, were well investigated and controlled appropriately in the specification of the drug substance.

There is no evidence that the chiral center could epimerize during the manufacturing process. Moreover, the enantiomeric purity is tightly controlled in the DS specification. All other related impurities have acceptance criteria below the qualification threshold.

Also, the (b)(4) form. It was also consistently produced by the commercial manufacturing process and is appropriately controlled in the DS specification.

The proposed control strategy appears adequate. No residual risks are foreseen.

2.3.S.5 Reference Standards or Materials

12. Are the drug substance reference standards satisfactory?

Applicant's Response:

Batch BS1112SA02 was used as the reference standard for the drug substance. The reference standard has been fully characterized and its Certificate of Analysis was provided.

Reviewer's Assessment:

The reference standard was adequately qualified for the intended use.

2.3.S.6 Container Closure System

13. Is the proposed container closure system(s) for commercial packaging of the drug substance adequate to protect the drug substance from the environment (oxygen, moisture, microorganism, etc.) during the storage?

Applicant's Response:

Cobimetinib drug substance is packed in a (b) (4) plastic bag. The packaged cobimetinib Drug Substance is placed in a closed (b) (4).

Reviewer's Assessment:

The proposed container closure system is adequate for the intended use.

2.3.S.7 Stability

14. What is the proposed retest period for the drug substance? Do the drug substance stability data support the proposed retest period and storage conditions in the commercial container closure system? How does statistical evaluation of the stability data, if any and any observed trends support your proposed retest period?
15. Are the post-approval stability protocols and other stability commitments for the drug substance satisfactory?



QUALITY ASSESSMENT
NDA # 206192



Applicant's Response:

The primary stability studies were conducted with batches manufactured according to the proposed commercial process at the commercial site, (b) (4)

[Redacted]

[Redacted] (b) (4)

No significant changes were observed in the long-term and accelerated stability studies.

(b) (4)
[Redacted]

Post-approval Stability Commitment: Stability studies on the first three commercial batches of cobimetinib will be performed according to the following testing schedule:

(b) (4)
[Redacted]

Reviewer's Assessment:

The primary stability data support the proposed retest period of (b) (4) as no degradation trends were observed in the long term and accelerated stability studies. In this situation, ICH Q1E guideline allows the retest period to be (b) (4) beyond the time investigated.

A retest period of (b) (4) has been granted at the recommended storage conditions, "Do not store above 30°C".



QUALITY ASSESSMENT
NDA # 206192



OVERALL ASSESSMENT AND SIGNATURES: DRUG SUBSTANCE

Reviewer's Assessment and Signature:

The drug substance review is signed by the secondary reviewer by proxy due to the primary reviewer being on leave.

Gaetan Ladecour, Ph.D.

CMC Reviewer

OPQ/ONDP/DS/Branch 1

Supervisor Comments and Concurrence:

Kasturi Srinivasachar, Ph.D.

Acting Branch Chief

OPQ/ONDP/DS/Branch 1

Kasturi
Srinivasachar
S

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ASSESSMENT OF THE DRUG PRODUCT

2.3.P DRUG PRODUCT

Cobimetinib is a potent and highly selective inhibitor of the mitogen-activated protein kinase enzymes MEK1 and MEK2. Cobimetinib is intended for use in combination with vemurafenib for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. The recommended cobimetinib dose is 60 mg orally once a day on Days 1-21 of each 28-day treatment cycle in combination with vemurafenib 960 mg orally twice a day on Days 1-28. A single 20 mg strength tablet product for oral administration for adult population is proposed for commercialization. The proposed commercial formulation is an immediate-release film-coated tablet formulated with standard excipients (b) (4)

The development of cobimetinib drug product followed a (b) (4) development approach, (b) (4)

2.3.P.1 Description and Composition of the Drug Product

16. Are there any scientific or regulatory concerns about the proposed composition of the drug product?

Applicant's Response:

The drug product is cobimetinib tablets. It is intended to be used for oral administration. They are round, white, film-coated tablets, with "COB" debossed on one side. The proposed strength is 20 mg. The 20 mg strength allows for dosing at the desired

efficacious dose (60 mg QD) and also allows the flexibility for down-titration of the dose. The tablet product is packed for commercial use in a high-density polyethylene (HDPE) bottle with a plastic (b) (4) cap. The components and compositions of the cobimetinib tablets are listed below.

Table 1 Composition of Cobimetinib Film-Coated Tablets, 20 mg

Component	Reference to Standards	Function	Quantity per Unit Dose (mg/tablet)		
Tablet Core					
Cobimetinib Hemifumarate	In-house	Active	22 (b) (4)		
Microcrystalline Cellulose ^b	NF, Ph. Eur., JP	(b) (4)			
Lactose Monohydrate	NF, Ph. Eur., JP				
Croscarmellose Sodium	NF, Ph. Eur., JP				
Magnesium Stearate	NF, Ph. Eur., JP				
Tablet Core Weight					
Film-Coating Mixture ^d					
Polyvinyl Alcohol	USP, Ph. Eur., JPE				
Titanium Dioxide	USP, Ph. Eur., JP				
(b) (4) PEG 3350	NF, Ph. Eur.				
Talc	USP, Ph. Eur., JP				
(b) (4)	USP, Ph. Eur., JP				
Film-Coating Mixture Weight					
Total Tablet Weight			124.80		

NA = not applicable.



Reviewer's Assessment:

Genentech provided the formulation composition as per unit dose for each of the components. It is noted that the composition on % w/w basis was not listed in this composition table. However, the composition on % w/w basis was listed in the batch formula (see 3.2.P.3.2).

As shown in the composition table, there are several compendial excipients (NF, Ph. Eur., JP grade) in the formulation. The function for each component was described and the compositions are adequate for the cobimetinib immediate-release tablets. The functional uses of these components in the formulation are also adequate based on the evaluations in the following sections. The film-coating formulation is also composed of several compendial excipients (NF, Ph. Eur., JP grade). The function for each coating component was described and the compositions are adequate for immediate-release film-coating. There is no excipient with a level exceeding the FDA inactive ingredient database limit for oral administration calculated based on maximum daily dose.

2.3.P.2 Pharmaceutical Development

17. Does the information described in the pharmaceutical development section support the proposed product design, commercial formulation, dosage form, compatibility, specification, and overall control strategy of the drug product?

Applicant's Response:

QTPP and CQA: Cobimetinib drug product was designed as immediate-release film-coated tablets. Each tablet contains cobimetinib hemifumarate equivalent to 20 mg cobimetinib (as free base). The 20 mg strength allows for dosing at the desired efficacious dose (60 mg QD 21/7 with or without food, as 3 × 20 mg tablets) and also allows the flexibility for down-titration of the dose. The quality target product profile (QTPP) of the drug product is shown below, which was established based on the intended mode of action and patient needs, the properties of the drug substance, and the desired characteristics of the drug product. The justifications for the QTPP elements were provided, also shown in the table.

The critical quality attributes (CQAs; *a table was provided in the submission*) include appearance, identification, content (assay), uniformity of dosage units, degradation products, dissolution performance, residual solvents and microbial purity. Subsequent formulation and process development studies were carried out to assess the potential impact on these attributes from the materials (potential critical material attributes, pCMAs), formulation and/or process (potential critical process parameters, pCPPs) variables. The pharmaceutical development utilized quality risk assessment tools (e.g., FMEA) to identify potentially high-risk formulation and process variables, and to prioritize pharmaceutical studies.

Reviewer's Assessment:

Cobimetinib drug product was designed as immediate-release film-coated tablets and the dosage form is adequate for the intended daily dose and the patient compliance. QTPP of the finished product was provided and it was adequately established based on the proposed indication and dose, patient population, and route administration. The

justifications for each of the QTPP elements were provided and they are acceptable. The formulation was adequately designed to achieve these QTPP attributes.

Table 2 Quality Target Product Profile (QTPP)

QTPP Element		Target	Justification
Route of Administration		Oral, 60 mg qd, 21 days on/7 days' drug holiday, with or without food	Compliance of patients, efficacy, and safety
Dosage Form		Immediate-release film-coated tablet	Compliance of patients: film coating ensures that tablets are tasteless and odorless and easy to swallow; film coating prevents dust formation during packaging and ensures robustness during transportation
Dosage Strength		20 mg	To achieve required efficacy (3 × 20 mg tablets daily) and allow for down-titration if necessary
Drug Substance		Cobimetinib hemifumarate, (b) (4) suitable particle size distribution	Sufficient bioavailability, efficacy, and safety
Drug Product Quality Attributes	Appearance	Tablet conforms to description (white, round, film-coated tablet with debossing for identification)	Round, film-coated tablet of (b) (4) mg is easy to swallow
	Content	95.0% – 105.0% of label claim	To meet compendial standard
	UDU	Meets pharmacopeial acceptance criteria	To meet compendial standard
	Degradation products	ICH Q3B identification threshold or qualified	ICH
	Dissolution	Consistent with immediate release; comparable dissolution profile to clinical material (Q = (b) (4) % at 20 min)	Consistent in vitro performance
	Microbial limits	Meets pharmacopeial acceptance criteria when tested	To meet compendial standard
Container Closure System		70 mL, white, opaque, square HDPE bottle (63 tablets) with (b) (4) cap	To achieve acceptable commercial shelf life; compliance of patients
Shelf Life		Minimum (b) (4) months at or below 30°C	Sufficient stability shelf life to meet shelf-life requirements

HDPE = high-density polyethylene; UDU = uniformity of dosage units.

Reviewer's Assessment:

The quality attributes of the finished product were listed in a table. Appearance, identification, content (assay), uniformity of dosage units, degradation products, dissolution performance, residual solvents and microbial purity were listed as the critical

quality attributes (CQAs). The target and the justification for each of the quality attributes were adequately provided.

It should be noted that (b) (4) was determined not to be a CQA, with the following justification: *Cobimetinib is a stable substance* (b) (4) *has not been linked to degradation of either the Drug Substance or the Drug Product.* During the review, we had a discussion with the biopharm reviewer regarding the potential formation (b) (4) (see IR comment in the DP specification section below).

Drug Substance: Cobimetinib hemifumarate was selected from an extensive screen of possible salt forms. The solubility of cobimetinib hemifumarate is high in low pH media (> 10 mg/mL in 0.1 M HCl) and it is classified (b) (4). Cobimetinib hemifumarate has (b) (4) found through the studies, which is the (b) (4) stable form. An (b) (4) was also found in certain conditions. The drug substance material attributes of particle size distribution (PSD) and mechanical properties were considered to be medium risk for formulation and process development. The lower limit for drug substance (b) (4) was established (as drug substance with (b) (4) to tablet appearance defects).

Excipients: Several excipients (USP/NF grades) are used in the drug product formulation. (b) (4)

Table P.2-7 Excipient Compatibility Results of Extension Study

Excipient	Function	(b) (4) Open Storage (% Area)	
		Apparent Purity	Degradation Products (RRT)
Microcrystalline Cellulose	(b) (4)	(b) (4)	(b) (4)
Croscarmellose Sodium	(b) (4)	(b) (4)	(b) (4)

RH=relative humidity; RRT=relative retention time.

Table P.2-6 **Excipient Compatibility Results for Drug
Substance/Excipient Binary Mixtures**

Excipient	Function	Apparent Purity	(b) (4)
			Open Storage (% Area)
			Degradation Product
Lactose Monohydrate	(b) (4)	(b) (4)	(b) (4)
(b) (4)			
Magnesium Stearate	(b) (4)	(b) (4)	(b) (4)

ND = not detected; RH = relative humidity; RRT = relative retention time.



Formulations Used in Clinical Studies: In Phase I clinical studies, the drug product was drug substance powder in bottle (PiB), (b) (4). Due to acceleration of the program, Phase I was advanced directly into Phase III. An optimized tablet formulation was used in pivotal Phase III clinical trials and proposed for commercialization. Pharmaceutical development studies showed consistent cobimetinib exposures irrespective of formulation type (solution or solid oral), addition of excipients ((b) (4))% DS in capsules or tablets), and differences in the manufacturing process. These data suggest that cobimetinib absorption is not dissolution-rate limited.

In Vitro Dissolution: In vitro dissolution performance of cobimetinib film-coated tablets, 20 mg and 60 mg (used in other clinical trials), was investigated in 900 mL of 0.1M HCl (aq) and of pH 4.5 and pH 6.8 buffers at 37°C. Agitation was carried out by rotating paddles (USP Apparatus II) at 50 rpm and 75 rpm and by rotating baskets (USP Apparatus I) at 75 rpm and 100 rpm (in pH 4.5 buffer only).

Container Closure System: 70 mL, white, opaque, square high-density polyethylene (HDPE) bottles with (b) (4) cap containing 63 film-coated tablets per bottle. The selected container closure system has been demonstrated to be suitable for use with the drug product regarding the protection, compatibility, safety, and performance. The packaging materials meet pharmacopeial requirements.

Microbiological Attributes: As the risk of microbiological contamination of the drug product is low and all tested batches were well within the requirements, routine testing of the oral-dosage form is not deemed necessary for commercial batches (b) (4). Refer to the process reviewer's evaluation of microbial limits risk.

Reviewer's Assessment:

Cobimetinib hemifumarate salt form is acceptable for use in the drug product, based on the screen studies on the possible salt forms. The (b) (4) form and the particle size are among the physicochemical properties of the drug substance that may impact drug product performance. Cobimetinib (b) (4). A comment has been sent to the sponsor (together with the biopharm comment) regarding the control on potential formation of the (b) (4) (see their IR response below). Due to the fact that drug substance with (b) (4) to tablet appearance defects, the lower limit for drug substance (b) (4) was proposed by the sponsor. It appears acceptable, (b) (4). However, it is important to assess this property from the manufacturing process point of view. The risk assessment of the drug substance potential critical material attributes can be seen below and they are acceptable, except for the concern on potential formation (b) (4).



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(b) (4)





2.3.P.4 Control of Excipients

18. Is the quality of all excipients adequately controlled with satisfactory specifications?

Applicant's Response:

Table 13 Specifications for Compendial Tested Excipients in Cobimetinib Film-Coated Tablets, 20 mg

Excipient	Specification Reference
Lactose Monohydrate	NF, Ph. Eur., JP
Microcrystalline Cellulose	NF, Ph. Eur., JP,
Croscarmellose Sodium	NF, Ph. Eur., JP
Magnesium Stearate	NF, Ph. Eur., JP,
Polyvinyl Alcohol ^a	USP, Ph. Eur., JPE
Titanium Dioxide ^a	USP, Ph. Eur., JP
(b) (4) EG 3350 ^a	NF, Ph. Eur.
Talc ^a	USP, Ph. Eur., JP
(b) (4)	Complies with USP, Ph. Eur., JP

Reviewer's Assessment:

The excipients were selected as they are commonly used tablet excipients for oral administration. All excipients are of compendial grade and are compliant with the analytical procedures described in the referenced pharmacopeias. COAs for these excipients were adequately provided.

There is no novel excipient used in the manufacture of cobimetinib film-coated tablets. The magnesium stearate (b) (4). The only excipient used in the manufacture of the finished product (b) (4). The use of lactose monohydrate in this drug product is acceptable.

2.3.P.5 Control of Drug Product

19. Is the drug product specification adequate to assure the identity, strength, quality, purity, and potency, and bioavailability of the drug product so that future commercial production batches are comparable to the pivotal clinical batches for the clinical performance in terms of the safety and efficacy

Applicant's Response:

This is the revised DP specification (March 16, 2015):

Table P.5.1-1 Specification for Cobimetinib Film-Coated Tablets, 20 mg

Test	Acceptance Criteria	Method
Description Shape ^a Debossing Color ^a	Round, film-coated tablet "COB" on one side White	Visual
Identification of Cobimetinib By IR By HPLC	Corresponds with reference spectrum Same RT as reference	FTIR HPLC
Content per Tablet of Cobimetinib ^b by HPLC ^a	(b) (4) tablet (b) (4) %	HPLC-1
Degradation Products by HPLC ^a Unspecified, Each Unspecified, Total	Max (b) (4) % Max %	HPLC-1
(b) (4)		
Uniformity of Dosage Units Ph. Eur./USP/JP, Content Uniformity	Corresponds	Content Uniformity by HPLC-2
Dissolution ^a after 20 min, Q = (b) (4) %	Corresponds to S1 or S2 or S3	UV
Microbial Limits ^c USP/Ph. Eur./JP, Nonaqueous Oral	Corresponds	USP/Ph. Eur./JP

FTIR=Fourier transform infrared; HPLC= high-performance liquid chromatography; IR=infrared; KF= Karl Fischer; RT= retention time; UV= ultraviolet.

^a Test performed also for retest/stability testing.

^b Cobimetinib free base.

^c Stability samples to be tested annually up to the end of shelf life for the long-term condition.

Reviewer's Assessment:

See reviewer's assessment on the DP specification below.

20. Are all the analytical procedures appropriately described and validated for their intended use?

Applicant's Response:

Product-Specific Analytical Procedures: A reversed-phase high-performance liquid chromatography (RP-HPLC) method is used for the determination of the identity,

content, and degradation products of cobimetinib in cobimetinib film-coated tablets. Another RP-HPLC method is used for the determination of content uniformity of cobimetinib film-coated tablets. The dissolution method employs USP II paddle apparatus rotating at 50 rpm in 900 mL of 50 mM acetate buffer at pH 4.5 held at 37°C± 0.5°C. These methods were validated for specificity, linearity/range, accuracy, precision, LOQ, LOD and solution stability and the summary for the validation results is shown below.

Table 15 Summary of Method Validation for Noncompendial Methods

Method	Validation Parameters Evaluated	Summary of Results
Identification, Assay and Degradation Products (HPLC)	Specificity, linearity, accuracy, precision, limit of quantitation, limit of detection, and robustness	The method complied with all acceptance criteria. Specificity has been demonstrated. The method is linear, accurate, and precise over the range (b)(4)% of the nominal working concentration (content and degradation products). The limit of quantitation was confirmed to be (b)(4)% for all degradation products. The limit of detection was confirmed to be below the reporting limit (b)(4)%. The method was proven to be robust and suitable for the intended use. The solutions are stable for (b)(4) days when stored at (b)(4) conditions.
Uniformity of Dosage Units by Content Uniformity (HPLC)	Specificity, linearity, accuracy, precision, and robustness	The method complied with all acceptance criteria. Specificity has been demonstrated. The method is linear, accurate, and precise over the range (b)(4)% of the nominal concentration. The method was proven to be robust and suitable for the intended use. The solutions are stable for (b)(4) days when stored at (b)(4) containers.
Dissolution	Specificity, linearity/range, accuracy, precision, and solution stability	The method complied with all acceptance criteria. Specificity has been demonstrated. The method is linear, accurate and precise over the range (b)(4)% of the working concentration. The solutions are stable for (b)(4) conditions.

HPLC = high-performance liquid chromatography.

Reviewer's Assessment:

The noncompendial analytical procedures that will be used for the analysis of commercial cobimetinib tablets were presented (see the methods listed on the above specification table). It should be noted that in addition to the validation summary table, the detailed validation data for the analytical methods were adequately presented in the submission. The validation data are acceptable and the analytical methods are adequate for the intended use. Because this is a NME, a method validation consult to DPA was sent.

No formulation-specific degradation products have been found in cobimetinib film-coated tablets. In the 3.2.S.3.2 section, three potential degradation products were described: (b)(4). The structure, chemical name, origin, and mechanism of formation of these potential degradation products were presented. They were not listed as the genotoxic impurities and thus can be adequately controlled under the unspecified impurity acceptance criteria (NMT (b)(4)%).

21. Is the proposed control strategy for the drug substance manufactured at commercial stage acceptable? Is there any residual risk upon implementation of the control strategy at the commercial scale?

Applicant's Response:

The specifications and analytical methods have been established to adequately control the identity, quality, purity, and stability of the drug product. The justifications for the specification test items were presented. The batch analyses for drug product batches manufactured during development, for stability, and/or used in clinical studies were provided.

Reviewer's Assessment:

The drug product specification includes all of the critical drug product quality attributes. The table also includes the names of the associated analytical methods. The justifications for each of the test items were adequately provided. Acceptance criteria were established based on the understanding of the drug product quality attributes and they are used to ensure that the quality of the commercial drug product is adequate for the clinical performance and patient safety. The manufacturing process and its impact on the drug product, the historical data, the stability results, and process validation data were considered when these criteria were established.

As described above, the (b) (4) of the drug product should be controlled and monitored. A comment has been sent to the sponsor to add a test and the acceptance criterion (b) (4) in drug product specification (see their IR response below).

The proposed control strategy for the drug product manufactured at commercial stage is acceptable from the specification point of view (also see process evaluation for additional information).

Among the long list of batches with analysis data, the primary stability batches are PT2338 B03 (Jan 2013), PT2338 B04 (Jan 2013), and PT2338 B05 (Jan 2013). The batch analysis data (as the representative batch analysis data) can be seen below. The test results met the DP specification.

(b) (4) (see Microbiology review comments. The sponsor omits the microbial limits in DP specification following FDA's recommendation).

Table P.5.4-6 Cobimetinib Proposed Commercial Tablet Batch Analysis: Film-Coated Tablets (cont.)

(b) (4)

**Reviewer's Assessment (IR response from the applicant):**

IR comment (sent on 3/6/2015) - QUESTION 7: (b) (4) can impact the drug product's (b) (4) dissolution. Data in Section P.8 shows that dissolution slows on stability. Add a test and the acceptance criterion for the (b) (4) drug product specification.

Response (summary, received on 3/16/2015): The Applicant agrees with the Agency's request; (b) (4) % has been proposed for release and stability testing of commercial Drug Product. This limit is supported by (b) (4) performed on up to 18 batches at release and during stability showing no significant change to critical quality attributes such as content, product degradation, dissolution, and microbial quality. A reduction in (b) (4) did not impact the overall quality of the Drug Product.

Evaluation: Acceptable.

2.3.P.7 Container Closure System

22. Is the proposed container closure system (describe it briefly with diagrams, if available) adequate to protect the product from the environment (oxygen,

moisture) to ensure the strength, purity (extractables/leachables), and performance of the drug product through the proposed expiration dating period?

Applicant's Response:

Cobimetinib film-coated tablets, 20 mg, are packaged in 70 mL nominal-volume, white, opaque, square, high-density polyethylene (HDPE) bottles. The closure is a plastic (b) (4) cap. The acceptance criteria for the bottles and for the caps were provided (below).

Table P.7.3-1 Test and Acceptance Criteria: 70 mL HDPE Bottle, Square, White, Opaque

Attribute	Analytical Procedure	Acceptance Criteria
Container Type	Visual inspection	Square bottle, unprinted
(b) (4)	Supplier certificate	Matches reference standard or reference spectrum
Color	Visual inspection	Opaque, white
Material Identification	Infrared spectroscopy	Matches reference standard or reference spectrum
Material Quality	Supplier certificate	Food grade

HDPE = high-density polyethylene.

Table P.7.3-2 Test and Acceptance Criteria: (b) (4) Screw Cap

Attribute	Analytical Procedure	Acceptance Criteria
Cap Type	Visual inspection	(b) (4)
(b) (4)	Supplier certificate	(b) (4)
Color	Visual inspection	Outer shell: opaque (white) Inner shell: opaque (white)
Material Identification	Infrared spectroscopy	Matches reference standard or reference spectrum
Material Quality	Supplier certificate	Food grade

HDPE = high-density polyethylene.

Reviewer's Assessment:

The proposed container closure system provides the adequate protection to ensure drug product integrity and performance through the intended shelf life. It is noted that (b) (4) the commercial container closure system. The drug substance is known (b) (4)

container closure system can be justified. Letters of Authorization for the container DMF (b) (4) and the cap DMF (b) (4) were adequately provided. The packaging components are sampled, tested, and examined for conformance with the specifications. The specifications for the packaging components were adequately provided. The proposed

container closure system is adequately qualified for suitability (protection, compatibility, safety, and performance).

2.3.P.6 Reference Standards or Materials

23. Are the proposed drug product reference standards acceptable?

Applicant's Response:

Cobimetinib Batch BS1112SA02, presented in Section S.5 Reference Standards or Materials, was qualified as a Primary Reference Standard to be used for the drug substance and the drug product. The batch analysis data for this batch were presented in Section S.4.4 - Batch Analyses.

Reviewer's Assessment:

The reference standard was adequately qualified for the intended use.

2.3.P.8 Stability

24. What is the proposed shelf-life for the drug product? Do the product stability studies and data support the proposed shelf life and storage conditions in the commercial container/closure system? Does the statistical evaluation of the stability data and observed trends support the proposed shelf-life?

25. Are the post-approval stability protocols and other stability commitments for the drug product adequate?

Applicant's Response:

There were 12 months' stability data at 30°C/75% RH and 6 months' stability data at the accelerated condition of 40°C/75% RH for three (registration) batches of cobimetinib film-coated tablets, 20 mg, manufactured at Roche, Basel, Switzerland, and packaged at Roche, Kaiseraugst, Switzerland. Primary stability samples were packaged in the proposed commercial container closure system. There were 24 months' stability data at 30°C/75% RH and 6 months' stability data at the accelerated condition of 40°C/75% RH for two supportive stability batches of cobimetinib film-coated tablets, 20 mg. In addition, there were data for several other supportive stability batches (see overall summary of the stability data available). A summary of the individual parameters analyzed and the results generated throughout the primary and supporting stability program was provided. The sponsor proposed a shelf life of (b) (4) months.

Dissolution profiles slowed down for samples stored under long-term and accelerated conditions, with the time to reach (b) (4) after storage at these conditions.

Per the agreement reached at the pre-NDA meeting, the sponsor submitted (amendment 0005, January 08, 2015) additional data including 6-month stability data under real time (30°C/75% RH) and accelerated (40°C/75% RH) conditions for 3 batches of cobimetinib film-coated tablets, 20 mg, manufactured at Roche, Basel, Switzerland, and packaged at the commercial packaging site (Roche, Segrate, Italy).

Table P.8.1-1 Summary of Stability Data Presented in Section P.8.3

Stability Study	Stability Data Presented
Primary stability	12 months' stability data at 30°C/75% RH and 6 months' stability data at the accelerated condition of 40°C/75% RH for three (registration) batches of cobimetinib film-coated tablets, 20 mg, manufactured at Roche, Basel, Switzerland, and packaged at Roche, Kaiseraugst, Switzerland, are provided and discussed in detail. Data are used, in comparison with the supportive stability data (b) (4)
Long-term stability of supportive stability batches	24 months' stability data at 30°C/75% RH and 6 months' stability data at the accelerated condition of 40°C/75% RH for two batches of cobimetinib film-coated tablets, 20 mg, manufactured at Roche, Basel, Switzerland, and packaged at Roche, Kaiseraugst, Switzerland, are provided and discussed in detail. (b) (4)
Supportive stability of a batch manufactured using (b) (4) Drug Substance	6 months' stability data at 30°C/75% RH and 6 months' stability data at the accelerated condition of 40°C/75% RH for a single batch of cobimetinib film-coated tablets, 20 mg, manufactured at Roche, Basel, Switzerland, and packaged at Roche, Kaiseraugst, Switzerland, are provided. (b) (4)
Additional supportive stability	3 months' stability data at 30°C/75% RH and 3 months' stability data at the accelerated condition of 40°C/75% RH for three batches of cobimetinib film-coated tablets, 20 mg, manufactured at Roche, Basel, Switzerland, and packaged at Roche, Kaiseraugst, Switzerland, are provided.
Additional supportive commercial packaging site stability	1 month of stability data at 30°C/75% RH and 1 month of stability data at the accelerated condition of 40°C/75% RH for three batches of cobimetinib film-coated tablets, 20 mg, manufactured at Roche, Basel, Switzerland, and packaged at the commercial packaging site (Roche, Segrate, Italy) are provided.

RH=relative humidity.

Post-approval Studies

Stability studies on the first three full-scale commercial batches packaged in 70 mL, white, opaque, square high-density polyethylene (HDPE) bottles with (b) (4) caps (63 tablets per bottle) will be performed. A minimum of one production batch will be selected at a rate of one batch per year (assuming adequate production) for stability testing.

Review of stability data

The following table summarizes the cobimetinib drug product stability studies.

(a) Description

Condition	Appearance	Trend	Evaluation
30°C/75%RH	Conforms	No significant trend observed	<i>Adequate</i>
40°C/75%RH	Conforms	No significant trend observed	<i>Adequate</i>

(b) Assay (Specification = (b)(4) %)

Condition	Range	Trend	Evaluation
30°C/75%RH	(b)(4)	No significant trend observed	<i>Adequate</i>
40°C/75%RH	(b)(4)	No significant trend observed	<i>Adequate</i>

(c) Unspecified impurity (Specification = NMT (b)(4) %)

Condition	Range	Trend	Evaluation
30°C/75%RH	(b)(4)	No significant trend observed	<i>Adequate</i>
40°C/75%RH	(b)(4)	No significant trend observed	<i>Adequate</i>

(d) Total impurity (Specification = NMT (b)(4) %)

Condition	Range	Trend	Evaluation
30°C/75%RH	(b)(4)	No significant trend observed	<i>Adequate</i>
40°C/75%RH	(b)(4)	No significant trend observed	<i>Adequate</i>

(b)(4)

(f) Dissolution (Specification: Q = (b)(4) % in 20 min)

Condition	Range (mean)	Trend	Evaluation
30°C/75%RH	(b)(4)	Decreasing over time *	*
40°C/75%RH	(b)(4)	Decreasing over time *	*

* See Biopharm review

(g) Microbial limit tests

Condition	Result	Trend	Evaluation
30°C/75%RH	Acceptable	No significant trend observed	<i>Adequate</i>
40°C/75%RH	Acceptable	No significant trend observed	<i>Adequate</i>

Reviewer's Assessment:

The proposed batch sizes for commercial manufacturing ranges between (b) (4)

The methods used were validated and are stability-indicating. The test methods are acceptable.

Dissolution profiles slowed down during the stability studies. However, all results continued to meet the specification criteria for the primary stability study. A discussion was carried out with the biopharm reviewer (see IR comment #12 regarding the justification on the proposed acceptance criterion for in vitro dissolution).

All degradation product values were (b) (4)% for samples stored under long-term (30°C/75% RH for 12 months) and accelerated (40°C/75% RH for 6 months) conditions. All samples met the specification criteria and, as there were no significant trends observed, statistical analysis was not performed. The newly-submitted stability data from the batches packaged at the commercial packaging site (Roche, Segrate, Italy) were also acceptable.

The test results for other test items were acceptable and there were no significant trends observed. Per ICH Q1E and the stability data presented, a shelf life of (b) (4) months is acceptable. There are no potential issues identified during the review for possible evaluation during inspection.

The post-approval stability protocols are acceptable. However, the sponsor needs to commit the continuing stability studies on the primary batches and the batches packaged at the commercial packaging site (Roche, Segrate, Italy) to provide the real time data for the proposed shelf life. A comment has been sent (see their IR response below).

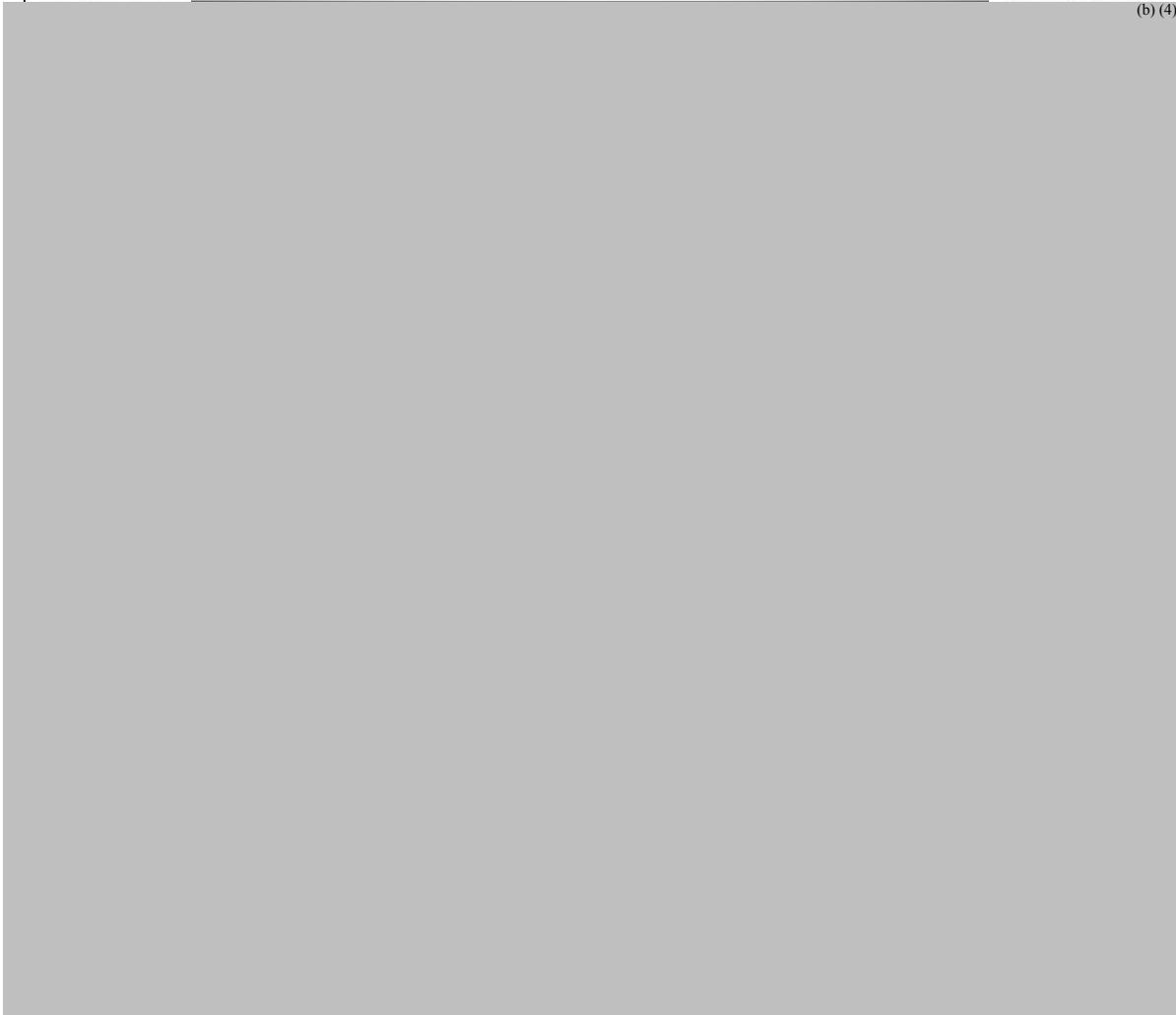
Reviewer's Assessment (IR response from the applicant):



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(b) (4)



Evaluation: Acceptable.

R.2 Comparability Protocols

26. Is a Comparability Protocol included in the application for post approval changes that might affect drug product quality including sterility assurance? If so, what post-approval changes are anticipated? How will the changes be reported and how will the validation studies be designed to support these changes?

Applicant's Response:

Reviewer's Assessment:

There are no comparability protocols submitted in this NDA.



QUALITY ASSESSMENT
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OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Reviewer's Assessment and Signature: The control strategy for the drug product is adequate to support approval of NDA 206-192.

Donghao (Robert) Lu, Ph.D.
CMC Reviewer
OPQ/ONDP/DP/Branch 2

Donghao R.
Lu -S

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ou=FDA, ou=People, cn=Donghao R. Lu
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Date: 2015.05.11 11:58:56 -04:00

Supervisor Comments and Concurrence:

Olen Stephens, Ph.D.
Acting Branch Chief
OPQ/ONDP/DP/Branch 2

Olen Stephens -S

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ASSESSMENT OF THE PROCESS

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture
Batch Formula

Batch Formula:

The applicant noted that the batch size is in the range of [REDACTED] (b) (4)

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(b) (4)

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

The facilities involved with the manufacturing, testing, packaging and labeling of the drug substance and drug product are adequate to support the approval of NDA 206192.

Sunita Iyer, Ph.D.
Facilities Reviewer
OPQ/OPF/DIA/Branch 1

Sunita Iyer -S

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Supervisor Comments and Concurrence:

Zhihao (Peter) Qiu
Branch Chief
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ASSESSMENT OF THE BIOPHARMACEUTICS

33. Are the in-vitro dissolution test and acceptance criteria adequate for assuring consistent bioavailability of the drug product?

Although the dissolution method is not biorelevant, it is adequate for quality control purposes. The dissolution method is therefore acceptable. The assessment of the dissolution method and the rationale for the acceptance criterion are summarized below.

Assessment of the Proposed In Vitro Dissolution Test

In section 3.2.P.2, the Applicant describes the development of the proposed dissolution conditions for the proposed 'to-be-marketed' (TBM) formulation of cobimetinib 20 mg film-coated tablets. The dissolution method development encompassed both TBM 20 mg (b) (4) tablet strengths. (b) (4)

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Assessment of Dissolution Method Validation Report

The Applicant submitted a method validation report ([\\cdsesub1\evsprod\nda206192\0000\m3\32-body-data\32p-drug-prod\20-mg-fc-tablets\32p5-contr-drug-prod\32p53-val-analyt-proc\val-analyt-proc-dissolution.pdf](#)) to qualify the specificity, linearity, accuracy, precision, and solution stability of the analytical procedure used to quantify the level of drug release in samples taken during the dissolution of cobimetinib film-coated tablets, 20 mg.

Specificity

Specificity was established by evaluating interference from the excipients. There was no significant interference from matrix components at ^{(b) (4)} as expressed in Table 8 below.

Table 8: Dissolution Method Validation: Specificity (source: Table P.5.3.4-2 in <\\cdsesub1\evsprod\nda206192\0000\m3\32-body-data\32p-drug-prod\20-mg-fc-tablets\32p5-contr-drug-prod\32p53-val-analyt-proc\val-analyt-proc-dissolution.pdf>).

Sample	UV Absorbance at	(b) (4)
Dissolution Medium		(b) (4)
Placebo (Matrix) Components		
Reference Solution		
Sample (Test) Extract		

UV = ultraviolet.

Linearity

Test solutions were prepared at six different concentrations levels with three independent sample preparations per level ranging from (b) (4)% of the nominal cobimetinib 100% working concentration amount ((b) (4) mg/mL). Mixtures were analyzed by UV detection (b) (4). The response-concentration plot is shown in Figure 4.

Figure 4: Response-concentration plot of cobimetinib in the (b) (4)% range (source: Figure P.5.3.4-1 in <\\cdsesub1\evsprod\nda206192\0000\m3\32-body-data\32p-drug-prod\20-mg-fc-tablets\32p5-contr-drug-prod\32p53-val-analyt-proc\val-analyt-proc-dissolution.pdf>).



The correlation coefficient for the regressed line in Figure 4 is reported to be (b) (4) which satisfies the acceptance criterion of (b) (4).

Accuracy

Accuracy was determined using the test solutions prepared for the linearity investigation. The results satisfy the acceptance limits as shown in Table 9 below.

Table 9: Dissolution Method Validation: Accuracy (source: Table P.5.3.4-5 in <\\cdsesub1\evsprod\nda206192\0000\m3\32-body-data\32p-drug-prod\20-mg-fc-tablets\32p5-contr-drug-prod\32p53-val-analyt-proc\val-analyt-proc-dissolution.pdf>).

Test	Acceptance Limit(s)	Result(s)	Verdict
Overall Mean Recovery (R) with Confidence Interval (CI, 95% 2 sided)		(b) (4)	Passed
Min. Mean Recovery of the Various Levels (levels: 6)			Passed
Max. Mean Recovery of the Various Levels (levels: 6)			Passed

Precision

Instrument precision was evaluated by having an analyst make six consecutive measurements of reference solution prepared at the working concentration for the method. Expressed as a percentage of the first absorbance reading, an average of (b) (4) % was achieved with a %RSD of (b) (4) . The result meets specifications (%RSD ≤ (b) (4))

Repeatability was evaluated from the recoveries obtained from the complete set of assay determinations performed for demonstration of accuracy at six levels ((b) (4)) in triplicate. The overall and maximum RSD were (b) (4) % and (b) (4) % both of which were below the acceptance limit of (b) (4) %.

Replicate dissolution experiments with different equipment/analyst (site)/day combinations were investigated. Two analysts and two geographically distinct testing sites were employed for the study design. The overall %RSD was (b) (4) .

Robustness

Factors including paddle rotation, medium volume, pH, medium temperature and wavelength of UV response were studied as a 2⁵⁻² fractional factorial design to assess robustness testing. A statistical evaluation of the data showed that none of the factors alone influences the dissolution responses greatly ($\pm 1.5\%$ deviation from the values measured using standard working conditions).

Robustness of the UV extinction value E(1%/1cm) as well as impact of sampling working conditions (semi-automated vs. manual sampling) at the proposed single point-time specification were also studied. The results met acceptance limits.

Solution Stability

Test and reference solutions were stored at ambient conditions and their UV absorbance (b) (4) determined periodically. It was concluded that the reference and test solutions are stable for at least 7 days at ambient conditions.

Filter bias associated with the use of the proposed (b) (4) filter was investigated. A replicate study (n=6) with and without filter indicated a difference in the average recovery with and without a filter of (b) (4) %.

Assessment of Dissolution Acceptance Criterion

In Section P.5.1 (<\\cdsesub1\evsprod\nda206192\0000\m3\32-body-data\32p-drug-prod\20-mg-fc-tablets\32p5-contr-drug-prod\32p51-spec\specifications.pdf>) the Applicant proposes Q (b) (4) % at 20 min corresponding to S1, S2 or S3. The Applicant was requested to justify this criterion and submit the raw dissolution data pertaining to the stability studies described in section 3.2.P.8.3 (<\\cdsesub1\evsprod\nda206192\0000\m3\32-body-data\32p-drug-prod\20-mg-fc-tablets\32p8-stab\stability-data.pdf>).

In the March 16, 2015 response letter ([\\cdsesub1\evsprod\nda206192\0016\m1\us\cmc-resp-fda-req-info-20150316.pdf](#)) to Question 12, the Applicant stated that the acceptance criterion of $(b)_{(4)}\%$ dissolved ($Q = (b)_{(4)}\%$) at 20 minutes is based on the aforementioned release and stability data for batches, as well as the data generated through development and robustness testing. This approach is not considered adequate because at least one batch referenced in the product development report was the 20 mg prototype tablet which is compositionally very different to the proposed commercial formulation (as discussed above in the context of Figure 3).

Figure 4 is a box plot showing the % release of drug against drug product batch at release/initial analysis. The corresponding data set is located in the Applicant's (March 16, 2015) response ([\\cdsesub1\evsprod\nda206192\0016\m3\32-body-data\32p-drug-prod\cobimetinib-20-mg-f10-film-coated-tablets\32p8-stab\datasets-stability-dissolution\q13rlstb.xpt](#)).

Figure 4: Box plot for release against proposed commercial cobimetinib 20 mg drug product at release/initial analysis referenced in [\\cdsesub1\evsprod\nda206192\0016\m3\32-body-data\32p-drug-prod\cobimetinib-20-mg-f10-film-coated-tablets\32p8-stab\datasets-stability-dissolution\q13rlstb.xpt](#).

(b) (4)



The red reference line at $(b)(4)\%$ represents passing at level S1. It is evident from Figure 4 that $Q = (b)(4)$ at $(b)(4)$ min is sufficient. There is little difference between the box plot distributions at $(b)(4)$ 20 mins.

Reviewer's Assessment: Although the release data support in principle an acceptance criterion of $Q = (b)(4)$ at $(b)(4)$ min, the Applicant's proposed criterion ($Q = (b)(4)$ at 20 min) is not considered a risk to product quality and is therefore acceptable.

34. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

Assessment of Bridging of to-be-marketed (TBM) product to Prototype Formulation

Figure 5 and Table 10 present the bridging maps for the formulations used in all the reported clinical studies.

Figure 5: Overview of cobimetinib drug product bridging strategy (source: Figure P.2-5 in <\\cdsesub1\evsprod\nda206192\0000\m3\32-body-data\32p-drug-prod\20-mg-fc-tablets\32p2-pharm-dev\pharmaceutical-development.pdf>).

(b) (4)

Table 10: Formulations used in clinical, safety, and efficacy studies, and relevant bioavailability studies Table P.2-27 in <\\cdsesub1\evsprod\nda206192\0000\m3\32-body-data\32p-drug-prod\20-mg-fc-tablets\32p2-pharm-dev\pharmaceutical-development.pdf>.

(b) (4)

The Phase III clinical studies were conducted with the proposed (TBM) commercial 20 mg tablet formulation. The 20 mg prototype tablet formulation was used in studies ^{(b) (4)} in which a food effect was also investigated. A food effect study was not undertaken using the TBM 20 mg tablet formulation. The Applicant did not conduct a bioequivalence study between the TBM and prototype 20 mg formulations. Therefore, there is no adequate bridging of the 20 mg prototype formulation ^{(b) (4)} to the proposed commercial formulation. However, the Clinical Pharmacology review concludes that a postmarketing food effect study with the TBM tablet formulation is not necessary.

Reviewer's Assessment:

Proposed In Vitro Dissolution Test: The studies conducted by the Applicant to determine the choice of dissolution apparatus, dissolution medium, and method variability are found to be adequate. The data submitted to demonstrate the sensitivity of the proposed dissolution method to changes processing parameters and raw materials is inconclusive. The proposed dissolution method is acceptable for the proposed commercial formulation.

Dissolution Method Validation Report: The specificity, linearity, accuracy, precision, and solution stability of the proposed analytical procedure have been adequately demonstrated and are therefore acceptable.

Proposed Dissolution Acceptance Criterion:
The Applicant's proposed dissolution acceptance criterion, Q ^{(b) (4)} % at 20 min, is acceptable.

Bridging of the to-be-marketed product to Prototype Formulation:
The conclusion of the Clinical Pharmacology review, that a postmarketing food effect study with the TBM tablet formulation is not necessary, implies that the current lack of bridging between the 20 mg strength prototype formulation ^{(b) (4)} where a food effect was investigated) and the TBM formulation is of no concern for potential labeling purposes. Since the Phase III clinical studies were conducted with the proposed (TBM) commercial 20 mg tablet formulation, the Division of Biopharmaceutics has no further concerns with respect to the bridging of drug product formulations used in the reported clinical studies.

**OVERALL ASSESSMENT AND SIGNATURES:
BIOPHARMACUETICS**

Reviewer's Assessment and Signature:

The Division of Biopharmaceutics has reviewed the dissolution information/data provided in NDA 206192 and considers that this information supports the approval of the Application. The Division of Biopharmaceutics, therefore, recommends **APPROVAL** of NDA 206192 for Cobimetinib Tablets, 20 mg.

The dissolution method and acceptance criterion for the QC release and stability testing of Cobimetinib Tablets, 20 mg, agreed to between FDA and the Applicant are as follows :

Apparatus/RPM	Medium/Volume/Temperature	Acceptance Criterion
USP 2 50 RPM	USP acetate buffer, pH 4.5 900 mL, 37°C	Q = ^{(b) (4)} % at 20 min



QUALITY ASSESSMENT
NDA # 206192



Maziar Kakhi, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
ONDP/OPQ

Maziar Kakhi
-S

Digitally signed by Maziar Kakhi -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Maziar Kakhi -
S,
0.9.2342.19200300.100.1.1=1300377086
Date: 2015.05.11 11:24:38 -04'00'

Supervisor Comments and Concurrence:

I concur with Dr. Kakhi's assessment and recommendation of approval for NDA 206192.

Okponanabofa
Eradiri -S

Digitally signed by Okponanabofa Eradiri -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, 0.9.2342.19200300.100.1.1=2001146732,
cn=Okponanabofa Eradiri -S
Date: 2015.05.11 11:37:37 -04'00'

Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
ONDP/OPQ

ASSESSMENT OF MICROBIOLOGY

35. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response:

Periodic testing of microbial limits is proposed in the drug product specification that comply to USP/Eur/JP monograph using analytical method of USP <61>/USP <62>; Ph. Eur. 2.6.12/Ph. Eur. 2.6.13; JP 4.05 Section 1/Section 2. However it is noted in the specification that the test will be conducted for 1st and last batch of each campaign.

The applicant justified [REDACTED] (b) (4) data were observed on drug substance [REDACTED] (b) (4). Also the manufacturing process and environment are adequately controlled and monitored, with cleaning procedures in place to prevent microbiological contamination. All clinical, primary stability batches, and additional supportive stability batches tested to date that have met microbiological quality requirements (Ph. Eur./USP/JP requirement for nonaqueous oral dosage form at release and after storage). Therefore, it can be concluded that cobimetinib is not promoting growth per the USP Chapter [REDACTED] (b) (4) pharmaceutical drug products with [REDACTED] (b) (4) are good candidates for reduced microbial limit testing for product release and stability evaluation.

Reviewer's Assessment:

See review in Assessment of the Process/Question 29

2.3.P.6 Reference Standards or Materials

36. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment:

Not applicable for solid oral dosage product

A APPENDICES**A.2 Adventitious Agents Safety Evaluation**

37. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response:

The active substance Cobimetinib and the raw materials,  (b) (4)

**Reviewer's Assessment:**

The applicant provided adequate justification and document  (b) (4) excipient.

38. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment:

See Q7, above

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY**Reviewer's Assessment and Signature:**

Refer to Manufacturing Process signature block.

Supervisor Comments and Concurrence:
Refer to Manufacturing Process signature block.

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert

(a) “Highlights” Section (21CFR 201.57(a))

-----DOSAGE FORMS AND STRENGTHS-----

(b)(4) tablet: 20 mg

Item	Information Provided in NDA	Reviewer’s Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Established Name: Cobimetinib	Adequate
Dosage form, route of administration	Dosage: (b)(4) tablet Route: Oral	Adequate
Controlled drug substance symbol (if applicable)	N/A	
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	(b)(4) tablet: 20 mg	Adequate

Conclusion: Adequate

(b) “Full Prescribing Information” Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer’s Assessment
Available dosage forms	Film-coated tablet	Adequate
Strengths: in metric system	20 mg	Adequate
A description of the identifying	White, film-coated tablets debossed	Adequate

characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.

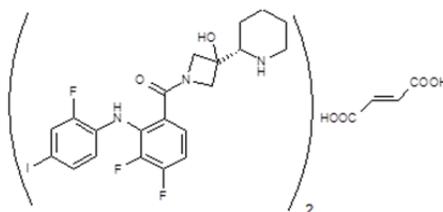
with "COB" on one side

Conclusion: Adequate

#11: Description (21CFR 201.57(c)(12))

11 DESCRIPTION

Cobimetinib (b)(4) fumarate is a kinase inhibitor. The chemical name is (S)-[3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl] [3-hydroxy-3-(piperidin-2-yl)azetidin-1-yl]methanone hemifumarate. It has a molecular formula $C_{46}H_{46}F_6I_2N_6O_8$ ($2 C_{21}H_{21}F_3IN_3O_2 \cdot C_4H_4O_4$) with a molecular mass of 1178.71 as a (b)(4) fumarate salt. Cobimetinib (b)(4) fumarate has the following chemical structure:

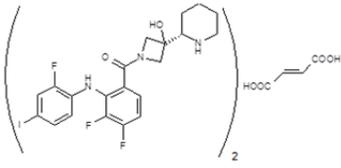


Cobimetinib is a (b)(4) fumarate salt appearing as white to off-white solid and exhibits a pH dependent solubility.

[TRADENAME] (cobimetinib) tablets are supplied as white, round, film-coated 20 mg tablets for oral administration. Each 20 mg tablet contains 22 mg of cobimetinib (b)(4) fumarate, which corresponds to 20 mg of the cobimetinib free base.

The inactive ingredients of [TRADENAME] are: **Tablet Core:** Microcrystalline Cellulose, Lactose Monohydrate, Croscarmellose Sodium, Magnesium Stearate. **Coating:** Polyvinyl Alcohol, Titanium Dioxide, Polyethylene Glycol 3350, Talc.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Cobimetinib Cobimetinib fumarate	Adequate
Dosage form and route of administration	(cobimetinib) tablets are supplied as white, round, film-coated 20 mg tablets for oral administration.	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	Each 20 mg tablet contains 22 mg of cobimetinib (b)(4) fumarate, which corresponds to 20 mg of the cobimetinib free base.	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	The inactive ingredients of [TRADENAME] are: Tablet Core: Microcrystalline Cellulose, Lactose Monohydrate, Croscarmellose Sodium, Magnesium Stearate. Coating: Polyvinyl Alcohol, Titanium Dioxide, Polyethylene Glycol 3350, Talc.	Adequate
Statement of being sterile (if applicable)	N/A	
Pharmacological/ therapeutic class	Cobimetinib (b)(4) fumarate is a	Adequate

<p>Chemical name, structural formula, molecular weight</p>	<p>kinase inhibitor (S)-[3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl] [3-hydroxy-3-(piperidin-2-yl)azetidin-1-yl]methanone hemifumarate. . It has a molecular formula C₄₆H₄₆F₆I₂N₆O₈ (2 C₂₁H₂₁F₃I₃N₃O₂ . C₄H₄O₄) with a molecular mass of 1178.71 as a (b) (4) fumarate salt. Cobimetinib (b) (4) fumarate has the following chemical structure:</p> 	<p>Adequate</p>
<p>If radioactive, statement of important nuclear characteristics.</p>	<p>N/A</p>	<p></p>
<p>Other important chemical or physical properties (such as pKa, solubility, or pH)</p>	<p>Cobimetinib is a (b) (4) fumarate salt appearing as white to off-white solid and exhibits a pH dependent solubility.</p>	<p>Adequate</p>

Conclusion: Adequate

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16 HOW SUPPLIED/STORAGE AND HANDLING

[TRADENAME] (cobimetinib) is supplied as 20 mg film-coated tablets (b) (4) debossed on one side. [TRADENAME] tablets are available in bottles of 63 tablets.

NDC 50242-717-01

Storage and Stability: [recommended edits] Store at room temperature (b) (4) below 86°F (30°C).

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	(cobimetinib) is supplied as 20 mg film-coated tablets with COB debossed on one side.	Adequate
Available units (e.g., bottles of 100 tablets)	tablets are available in bottles of 63 tablets.	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC 50242-717-01	Adequate
Special handling (e.g., protect from light, do not freeze)	(b) (4)	Adequate
Storage conditions	Store at or below 86°F (30°C).	Edits have been included to be consistent with patient labeling in other clinical divisions whose products are marketed in harsh climatic zones

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Distributed by: Genentech USA, Inc. A Member of the Roche Group 1 DNA Way South San Francisco, CA 94080-4990 [TRADENAME] is a registered trademark of Genentech, Inc. ©20XX Genentech, Inc.	Adequate

Conclusion:

2. Labels

1) Immediate Container Label



**QUALITY ASSESSMENT
NDA # 206192**



(b) (4)



Reviewer's Assessment:



QUALITY ASSESSMENT
NDA # 206192



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))		Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		Adequate
Net contents (21 CFR 201.51(a))		Adequate
Lot number per 21 CFR 201.18		Adequate
Expiration date per 21 CFR 201.17		Adequate
“Rx only” statement per 21 CFR 201.100(b)(1)		Adequate
Storage (not required)		Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		Adequate
Bar Code per 21 CFR 201.25(c)(2)**		Adequate
Name of manufacturer/distributor		Adequate
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled “sample”, “physician’s sample”, or a substantially similar statement and the contents of the package do not exceed 8 grams.

**Not required for Physician’s samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Adequate

2) Cartons



QUALITY ASSESSMENT
NDA # 206192



(b) (4)





QUALITY ASSESSMENT
NDA # 206192



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))		Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		Adequate
Net contents (21 CFR 201.51(a))		Adequate
Lot number per 21 CFR 201.18		Adequate
Expiration date per 21 CFR 201.17		Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables][201.10(a), 21CFR201.100(b)(5)(iii)]		Adequate
Sterility Information (if applicable)		N/A
“Rx only” statement per 21 CFR 201.100(b)(1)		Adequate
Storage Conditions	Note that this approach is consistent with other clinical divisions whose drugs are marketed in more harsh climatic zones	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		Adequate
Bar Code per 21 CFR 201.25(c)(2)**		Adequate
Name of manufacturer/distributor		Adequate
“See package insert for dosage information” (21 CFR 201.55)		Labeling will be negotiated through the clinical division
“Keep out of reach of children” (optional for Rx, required for OTC)		N/A
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))		N/A

Conclusion: Adequate; labeling comments will be communicated through the clinical division

Environmental Assessment Or Claim Of Categorical Exclusion

As set forth in 21 CFR Part 25.31(b), action on a New Drug Application (NDA) is categorically excluded from the requirement to prepare an Environmental Assessment or an Environmental Impact Statement if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be less than 1 part per billion (ppb). “Increased use”, as defined in 21 CFR Part 25.5(b), will occur if the drug is “administered at higher dosage levels, for longer duration or for different indications than were previously in effect, or if the drug is a new molecular entity.”

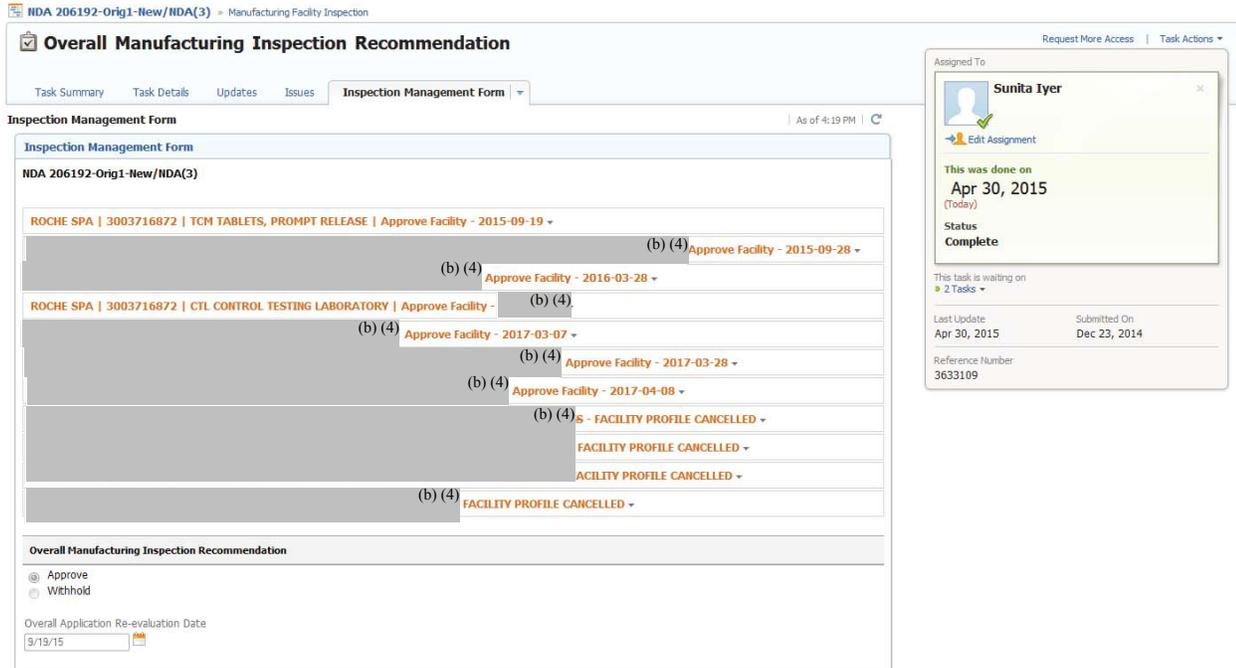
Genentech, Inc. certifies that this submission for Cobimetinib 20 mg tablets qualifies for a categorical exclusion and claims a categorical exclusion from the requirement to prepare an environmental assessment in accordance with 21 CFR Part 25.31(b) as the concentration of the active moiety, cobimetinib, will be significantly less than 1 ppb.

An exemption to perform an environmental assessment is granted as per 21 CFR Part 25.31(b).

II. Attachments

A. Facility

This information is captured above in the Facilities review section.



B. Lifecycle Knowledge Management

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	CHANGES & VARIATIONS	FAILURE MODE	RPN	Mitigation noted in the review	Final Risk Assessment	Lifecycle considerations
Assay, Stability	<ul style="list-style-type: none"> Formulation Container closure Raw materials Process parameters Scale/equipments Site 	<ul style="list-style-type: none"> Impurity formation due to excipient reactions or unspecified reactions 	4			
		(b) (4)	12			
Physical stability (solid state)	<ul style="list-style-type: none"> Formulation Raw materials Process parameters Scale/equipments Site 	<ul style="list-style-type: none"> (b) (4) (b) (4) 	36	See below.		The applicant performed excipient compatibility studies for MCC and (b) (4) under different conditions. The results did not reveal significant differences under the two stability conditions. If the formulation (b) (4) new compatibility studies should be requested under identical conditions to justify the use of the different (b) (4)

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	CHANGES & VARIATIONS	FAILURE MODE	RPN	Mitigation noted in the review	Final Risk Assessment	Lifecycle considerations
Content uniformity	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • Low dose • Particle size/shape • Segregation • Flow property 	32			
Microbial limits	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • (b) (4) • Equipment, process environment 	6			
Dissolution – (b) (4)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • API particle size • (b) (4) • Tab hardness • Disintegration • Size shape • Tablet scoring • Film coating • (b) (4) • (b) (4) 	24	(b) (4)		

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Reviewer Name/Date: [*Same date as draft review*]

Secondary Reviewer Name/Date:

Project Manager Name/Date:

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 206192 Submission Type: 505(b)(1)

Established/Proper Name:
Cobimetinib

Applicant: Genentech, Inc. Letter Date: 19-Dec-2014

Dosage Form: Film-coated tablets

Chemical Type: small molecule NME Stamp Date: 19-Dec-2014

Strength: 20 mg

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.			NA
3.	Are there any potential review issues to be forwarded to the Applicant, not including any filing comments stated above?		X	Not at this time.

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
Product Type				
1.	New Molecular Entity ¹	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
2.	Botanical ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
3.	Naturally-derived Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
4.	Narrow Therapeutic Index Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.	PET Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
6.	PEPFAR Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7.	Sterile Drug Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
8.	Transdermal ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.	Pediatric form/dose ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.	Locally acting drug ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
11.	Lyophilized product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
12.	First generic ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
13.	Solid dispersion product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
14.	Oral disintegrating tablet ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
15.	Modified release product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
16.	Liposome product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
17.	Biosimilar product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
18.	Combination Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
19.	Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
Regulatory Considerations				
20.	USAN Name Assigned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
21.	End of Phase II/Pre-NDA Agreements	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<p>Summary of CMC pre-NDA meeting FDA noted the following comments conveyed to Hoffman-La Roche during the pre-NDA CMC meeting held on March 5, 2014:</p> <ul style="list-style-type: none"> <input type="checkbox"/> In order to support approval of drug manufactured at an alternate drug packaging site (Segrate, Italy), FDA stated that the NDA should contain at least three batches (from the new site) with three months accelerated stability data in NDA submission and up to three batches (from the new site) on long-term stability data reported in an annual report. The Agency stated that all stability update should be submitted within the first 60 days of the NDA submission. <input type="checkbox"/> The NDA should contain acceptance criteria for (b)(4) and a periodic evaluation strategy for microbiological tests. Roche stated that they plan to submit data to support the request for omitting testing and to support the acceptance criterion (b)(4). FDA acknowledged this approach and will review the adequacy of this information during review of the NDA. <input type="checkbox"/> The NDA should contain the complete multipoint dissolution profile data for the pivotal clinical and registration stability batches both at release and on storage to support setting the final acceptance criterion. <input type="checkbox"/> NDA should provide a clear overview of any formulation changes throughout development and the effects of these changes on dissolution performance and bioavailability, where appropriate. <input type="checkbox"/> Genentech intends to ensure that all facilities are ready for FDA inspection as of December 11, 2014, the date of finalization of the NDA submission. With the initial component of the rolling submission to be submitted in October 2014, the Form 356h Box 29 will indicate that sites will be inspection ready on December 11, 2014. With the December submission, Genentech intends to provide the confirmation of inspection readiness. The FDA agreed to this plan.
22.	SPOTS (Special Products On-line Tracking System)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
24.	Comparability Protocol(s) ²	<input type="checkbox"/>	<input checked="" type="checkbox"/>	None identified in the filing review
25.	Other	<input type="checkbox"/>	<input type="checkbox"/>	
Quality Considerations				
26.	Drug Substance Coverage	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
27.	Design Space	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
28.		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
29.		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
30.		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
31.	Real Time Release Testing (RTRT)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
32.	Parametric Release in lieu of Sterility Testing	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
33.	Alternative Microbiological Test Methods	<input type="checkbox"/>	<input checked="" type="checkbox"/>	The applicant is (b) (4)
34.	Process Analytical Technology ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
35.	Non-compendial Analytical Procedures and/or specifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Description of drug product, ID by FTIR, ID, assay, and degradation products by HPLC, UoDU, dissolution.
36.		<input checked="" type="checkbox"/>	<input type="checkbox"/>	For the film-coat only
37.		<input checked="" type="checkbox"/>	<input type="checkbox"/>	Annual testing only
38.	Unique analytical methodology ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
39.	Excipients of Human or Animal Origin	<input checked="" type="checkbox"/>	<input type="checkbox"/>	(b) (4) statements provided.
40.	Novel Excipients	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
41.	Nanomaterials ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
42.	Hold Times Exceeding 30 Days	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
43.	Genotoxic Impurities or Structural Alerts	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Refer to section 3.2.S.3.2.1.2
44.	Continuous Manufacturing	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
45.	Other unique manufacturing process ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
47.	New delivery system or dosage form ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
48.	Novel BE study designs	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
49.	New product design ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
50.	Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

¹Contact Office of Testing and Research for review team considerations

²Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? <input type="checkbox"/> Drug Substance <input type="checkbox"/> Drug Product <input type="checkbox"/> Appendices ○ Facilities and Equipment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	<ul style="list-style-type: none"> ○ Adventitious Agents Safety Evaluation ○ Novel Excipients □ Regional Information <ul style="list-style-type: none"> ○ Executed Batch Records ○ Method Validation Package ○ Comparability Protocols 				
FACILITY INFORMATION					
3.	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? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: <ul style="list-style-type: none"> □ Name of facility, □ Full address of facility including street, city, state, country □ FEI number for facility (if previously registered with FDA) □ Full name and title, telephone, fax number and email for on-site contact person. □ Is the manufacturing responsibility and function identified for each facility, and □ DMF number (if applicable) 	☒	□	□	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: <ul style="list-style-type: none"> □ Is a manufacturing schedule provided? □ Is the schedule feasible to conduct an inspection within the review cycle? 	☒	□	□	
DRUG SUBSTANCE INFORMATION					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	□	□	☒	
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? <ul style="list-style-type: none"> □ general information □ manufacture <ul style="list-style-type: none"> ○ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using 	☒	□	□	The applicant is claiming reworking in cases where the PSD requirements are not met. Please refer to 3.2.S.2.2 page 15.

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	<p>the final production process(es)</p> <ul style="list-style-type: none"> ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only ○ Includes complete description of product lots and their uses during development – BLA only <ul style="list-style-type: none"> <input type="checkbox"/> characterization of drug substance <input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only <input type="checkbox"/> reference standards or materials <input type="checkbox"/> container closure system <input type="checkbox"/> stability <ul style="list-style-type: none"> ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment 				
DRUG PRODUCT INFORMATION					
7.	<p>Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> <input type="checkbox"/> Description and Composition of the Drug Product <input type="checkbox"/> Pharmaceutical Development <ul style="list-style-type: none"> ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots ○ Includes complete description of product lots and their uses during development <input type="checkbox"/> Manufacture <ul style="list-style-type: none"> ○ If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? <input type="checkbox"/> Control of Excipients <input type="checkbox"/> Control of Drug Product <ul style="list-style-type: none"> ○ Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<p>Note that the labeling current is for at or below 30 deg C; the applicant’s long-term storage condition for stability testing is set at 30 deg C.</p> <p>The applicant is proposing (b) (4)</p> <p>Note the applicant intends to (b) (4), enantiomeric purity, and disintegration time for drug product testing.</p>

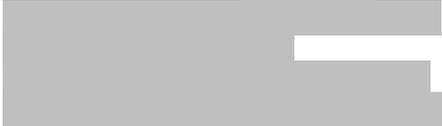
OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	<ul style="list-style-type: none"> ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Analytical validation package for release test procedures, including dissolution ☐ Reference Standards or Materials ☐ Container Closure System <ul style="list-style-type: none"> ○ Include data outlined in container closure guidance document ☐ Stability <ul style="list-style-type: none"> ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ☐ APPENDICES ☐ REGIONAL INFORMATION 				
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: <ul style="list-style-type: none"> • 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? 	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Primary biopharm reviewer (Maziar Kakhi) spoke to Clin Pharm reviewer (Ruby Leong) on 2/2/15. Clin Pharm will be reviewing BA/BE studies.
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? <i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Table P.2-25 on p.54/172 of 3.2.P.2 indicates that commercial and phase III tablets are the same. For bridging evaluation, further review required to determine if label claims are made based on results from clinical studies which made use of non-commercial tablet formulation.
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.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	3.2.P.2 (Pharm Dev), sections 2.3.1 (p.59) and 2.3.2 (p.61) indicate that sponsor considers cobimetinib ^{(b) (4)}  has not been identified by primary biopharm reviewer.
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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	There is one cited work by sucker, Fuchs, and Speiser that may require a translation depending on the drug substance reviewer.
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> <input type="checkbox"/> manufacturing flow; adjacent areas <input type="checkbox"/> other products in facility <input type="checkbox"/> equipment dedication, preparation, sterilization and storage <input type="checkbox"/> procedures and design features to prevent contamination and cross-contamination <input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> <input type="checkbox"/> avoidance and control procedures <input type="checkbox"/> cell line qualification <input type="checkbox"/> other materials of biological origin <input type="checkbox"/> viral testing of unprocessed bulk <input type="checkbox"/> viral clearance studies <input type="checkbox"/> testing at appropriate stages of production <input type="checkbox"/> novel excipients	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
17.	Are the following information available for Biotech Products: <input type="checkbox"/> Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: <ul style="list-style-type: none"> <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples			X	

**OFFICE OF PHARMACEUTICAL QUALITY
FILING REVIEW**

1A: Product Design FMEA - Solid Oral Products

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	CHANGES & VARIATIONS	FAILURE MODE	Non-High Risk Drugs				High Risk Drugs			
			PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN
Assay, Stability	<ul style="list-style-type: none"> Formulation Container closure Raw materials Process parameters Scale/equipments Site 	<ul style="list-style-type: none"> Impurity formation due to excipient reactions or unspecified reactions (b) (4) 	Highly stable drug (1)	2	Release (1)	2	Highly stable drug (1)	4	Release (1)	4
					Stability (3)	6			Stability (3)	12
Physical stability (solid state)	<ul style="list-style-type: none"> Formulation Raw materials Process parameters Scale/equipments Site 	<ul style="list-style-type: none"> (b) (4) 	(b) (4)	(b) (4)	4	8	(b) (4)	(b) (4)	4	36
Content uniformity	<ul style="list-style-type: none"> Formulation Raw materials Process parameters Scale/equipments Site 	<ul style="list-style-type: none"> Low dose Particle size/shape Segregation Flow property 	(b) (4)	3	4	24	(b) (4)	4	4	32

**OFFICE OF PHARMACEUTICAL QUALITY
FILING REVIEW**

1A: Product Design FMEA - Solid Oral Products

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	CHANGES & VARIATIONS	FAILURE MODE	Non-High Risk Drugs				High Risk Drugs			
			PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN
Microbial limits	<ul style="list-style-type: none"> Formulation Raw materials Process parameters Scale/equipments Site 	<ul style="list-style-type: none"> (b) (4) Equipment, process environment 	1	2	Release with spec (3)	6	1	2	Release with spec (3)	6
Dissolution - (b) (4)	<ul style="list-style-type: none"> Formulation Raw materials Process parameters Scale/equipments Site 	<ul style="list-style-type: none"> API particle size (b) (4) Tab hardness Disintegration Size shape Tablet scoring Film coating (b) (4) (b) (4) 	3	2	2	12	3	4	2	24

Olen Stephens -S

Digitally signed by Olen Stephens -S
 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Olen Stephens -S, 0.9.2342.19200300.100.1.1=2000558826
 Date: 2015.03.05 14:35:34 -05'00'

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

METHODS VALIDATION CONSULT REQUEST FORM

TO: FDA
Division of Pharmaceutical Analysis
Attn: Michael Trehy
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: NAME, Methods Validation Requestor, CMC Reviewers: Gaetan Ladouceur (for drug substance) and Donghao Lu (for drug product)
NAME, Methods Validation Requestor: Gaetan Ladouceur, PhD
Office of Pharmaceutical Quality (OPQ)
E-mail Address: Gaetan.Ladouceur@fda.hhs.gov, Donghao.Lu@fda.hhs.gov, Olen.Stephens@fda.hhs.gov
Phone: (301)-301-786-3878 (Gaetan Ladouceur); 301-796-1420 (Donghao Lu). 301-796-2059

Fax.: (301)- 796-9745

Through: NAME, CMC Lead or Branch Chief (as appropriate): Olen Stephens, PhD
Phone: (301)-796-3901

And Youbang Liu
ONDQA Methods Validation Project Manager
Phone: (301)-796-1926

SUBJECT: Methods Validation Request

Application Number: NDA 206192
Name of Product: Cobimetinib
Applicant: Genentech
Applicant's Contact Person: Lal Ninan, Ph.D.
Address: 1 DNA Way, MS 241A
South San Francisco, CA 94080-4990
Telephone: (650) 467-8564 email: ninan.lal@gene.com

Date NDA Received by CDER: **12/19/2014**

Submission Classification/Chemical Class: NME

Date of Amendment(s) containing the MVP:

Special Handling Required: No

DATE of Request: **02/20/2015**

DEA Class: N/A

Requested Completion Date: **06/01/2015**

Format of Methods Validation Package (MVP)

PDUFA User Fee Goal Date: **08/11/2015**

Paper Electronic Mixed

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 Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the 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 ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation 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 Validation Report Summary*). The *Methods Validation 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 the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

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

MVP Reference #	METHODS VALIDATION REQUEST			NDA #
⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT				
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION		
Not applicable.				
⇒ ITEM 2: Contents of Attached Methods Validation Package				Volume/Page Number(s)
Specifications/Methods for New Drug Substance(s)				3.2.S.4.1
Specifications/Methods for Drug Product(s)				3.2.P.5.1
Other: Note: DS means drug substance, DP means drug product				
⇒ 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
N/A	Related and Genotoxic Impurities by LC/GC	3.2.S.4.1	0	DS impurities
HPLC-1	Determination of the identity, content, and degradation	3.2.P.5.1	0	
HPLC-2	Determination of content uniformity	3.2.P.5.1	0	
N/A	Dissolution method	3.2.P.5.1	0	
Additional Comments: This NDA is assigned a priority (6 mos) review timeline. The CMC review of this NDA is not dependent on the result of the analytical method validation request.				

Methods Validation 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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GAETAN LADOUCEUR
02/19/2015

OLEN M STEPHENS
02/19/2015

YOUBANG LIU
02/19/2015

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 206192 Submission Type: 505(b)(1)

**Established/Proper Name:
Cobimetinib**

Applicant: Genentech, Inc. Letter Date: 19-Dec-2014

Dosage Form: Film-coated tablets

Chemical Type: small molecule NME Stamp Date: 19-Dec-2014

Strength: 20 mg

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.			NA
3.	Are there any potential review issues to be forwarded to the Applicant, not including any filing comments stated above?		X	Not at this time.

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
Product Type				
1.	New Molecular Entity ¹	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
2.	Botanical ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
3.	Naturally-derived Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
4.	Narrow Therapeutic Index Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.	PET Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
6.	PEPFAR Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7.	Sterile Drug Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
8.	Transdermal ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.	Pediatric form/dose ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.	Locally acting drug ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
11.	Lyophilized product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
12.	First generic ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
13.	Solid dispersion product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
14.	Oral disintegrating tablet ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
15.	Modified release product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
16.	Liposome product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
17.	Biosimilar product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
18.	Combination Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
19.	Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
Regulatory Considerations				
20.	USAN Name Assigned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
21.	End of Phase II/Pre-NDA Agreements	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<p>Summary of CMC pre-NDA meeting FDA noted the following comments conveyed to Hoffman-La Roche during the pre-NDA CMC meeting held on March 5, 2014:</p> <ul style="list-style-type: none"> <input type="checkbox"/> In order to support approval of drug manufactured at an alternate drug packaging site (Segrate, Italy), FDA stated that the NDA should contain at least three batches (from the new site) with three months accelerated stability data in NDA submission and up to three batches (from the new site) on long-term stability data reported in an annual report. The Agency stated that all stability update should be submitted within the first 60 days of the NDA submission. <input type="checkbox"/> The NDA should contain acceptance criteria for (b)(4) and a periodic evaluation strategy for microbiological tests. Roche stated that they plan to submit data to support the request for omitting testing and to support the acceptance criterion (b)(4). FDA acknowledged this approach and will review the adequacy of this information during review of the NDA. <input type="checkbox"/> The NDA should contain the complete multipoint dissolution profile data for the pivotal clinical and registration stability batches both at release and on storage to support setting the final acceptance criterion. <input type="checkbox"/> NDA should provide a clear overview of any formulation changes throughout development and the effects of these changes on dissolution performance and bioavailability, where appropriate. <input type="checkbox"/> Genentech intends to ensure that all facilities are ready for FDA inspection as of December 11, 2014, the date of finalization of the NDA submission. With the initial component of the rolling submission to be submitted in October 2014, the Form 356h Box 29 will indicate that sites will be inspection ready on December 11, 2014. With the December submission, Genentech intends to provide the confirmation of inspection readiness. The FDA agreed to this plan.
22.	SPOTS (Special Products On-line Tracking System)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
24.	Comparability Protocol(s) ²	<input type="checkbox"/>	<input checked="" type="checkbox"/>	None identified in the filing review
25.	Other	<input type="checkbox"/>	<input type="checkbox"/>	
Quality Considerations				
26.	Drug Substance Overage	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
27.	Design Space	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
28.		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
29.		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
30.		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
31.	Real Time Release Testing (RTRT)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
32.	Parametric Release in lieu of Sterility Testing	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
33.	Alternative Microbiological Test Methods	<input type="checkbox"/>	<input checked="" type="checkbox"/>	The applicant is proposing (b) (4)
34.	Process Analytical Technology ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
35.	Non-compendial Analytical Procedures and/or specifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Description of drug product, ID by FTIR, ID, assay, and degradation products by HPLC, UoDU, dissolution.
36.		<input checked="" type="checkbox"/>	<input type="checkbox"/>	For the film-coat only
37.		<input checked="" type="checkbox"/>	<input type="checkbox"/>	Annual testing only
38.	Unique analytical methodology ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
39.	Excipients of Human or Animal Origin	<input checked="" type="checkbox"/>	<input type="checkbox"/>	(b) (4) statements provided.
40.	Novel Excipients	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
41.	Nanomaterials ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
42.	Hold Times Exceeding 30 Days	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
43.	Genotoxic Impurities or Structural Alerts	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Refer to section 3.2.S.3.2.1.2
44.	Continuous Manufacturing	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
45.	Other unique manufacturing process ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
47.	New delivery system or dosage form ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
48.	Novel BE study designs	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
49.	New product design ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
50.	Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

¹Contact Office of Testing and Research for review team considerations

²Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? <input type="checkbox"/> Drug Substance <input type="checkbox"/> Drug Product <input type="checkbox"/> Appendices ○ Facilities and Equipment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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C. FILING CONSIDERATIONS					
	<ul style="list-style-type: none"> ○ Adventitious Agents Safety Evaluation ○ Novel Excipients □ Regional Information <ul style="list-style-type: none"> ○ Executed Batch Records ○ Method Validation Package ○ Comparability Protocols 				
FACILITY INFORMATION					
3.	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? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: <ul style="list-style-type: none"> □ Name of facility, □ Full address of facility including street, city, state, country □ FEI number for facility (if previously registered with FDA) □ Full name and title, telephone, fax number and email for on-site contact person. □ Is the manufacturing responsibility and function identified for each facility, and □ DMF number (if applicable) 	☒	□	□	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: <ul style="list-style-type: none"> □ Is a manufacturing schedule provided? □ Is the schedule feasible to conduct an inspection within the review cycle? 	☒	□	□	
DRUG SUBSTANCE INFORMATION					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	□	□	☒	
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? <ul style="list-style-type: none"> □ general information □ manufacture <ul style="list-style-type: none"> ○ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using 	☒	□	□	The applicant is claiming reworking in cases where the PSD requirements are not met. Please refer to 3.2.S.2.2 page 15.

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C. FILING CONSIDERATIONS					
	<p>the final production process(es)</p> <ul style="list-style-type: none"> ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only ○ Includes complete description of product lots and their uses during development – BLA only <ul style="list-style-type: none"> <input type="checkbox"/> characterization of drug substance <input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only <input type="checkbox"/> reference standards or materials <input type="checkbox"/> container closure system <input type="checkbox"/> stability <ul style="list-style-type: none"> ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment 				
DRUG PRODUCT INFORMATION					
7.	<p>Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> <input type="checkbox"/> Description and Composition of the Drug Product <input type="checkbox"/> Pharmaceutical Development <ul style="list-style-type: none"> ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots ○ Includes complete description of product lots and their uses during development <input type="checkbox"/> Manufacture <ul style="list-style-type: none"> ○ If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? <input type="checkbox"/> Control of Excipients <input type="checkbox"/> Control of Drug Product <ul style="list-style-type: none"> ○ Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<p>Note that the labeling current is for at or below 30 deg C; the applicant’s long-term storage condition for stability testing is set at 30 deg C.</p> <p>The applicant is proposing (b) (4)</p> <p>Note the applicant intends (b) (4), enantiomeric purity, and disintegration time for drug product testing.</p>

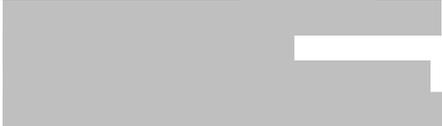
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C. FILING CONSIDERATIONS					
	<ul style="list-style-type: none"> ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Analytical validation package for release test procedures, including dissolution ☐ Reference Standards or Materials ☐ Container Closure System <ul style="list-style-type: none"> ○ Include data outlined in container closure guidance document ☐ Stability <ul style="list-style-type: none"> ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ☐ APPENDICES ☐ REGIONAL INFORMATION 				
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: <ul style="list-style-type: none"> • 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? 	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Primary biopharm reviewer (Maziar Kakhi) spoke to Clin Pharm reviewer (Ruby Leong) on 2/2/15. Clin Pharm will be reviewing BA/BE studies.
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? <i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Table P.2-25 on p.54/172 of 3.2.P.2 indicates that commercial and phase III tablets are the same. For bridging evaluation, further review required to determine if label claims are made based on results from clinical studies which made use of non-commercial tablet formulation.
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.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

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C. FILING CONSIDERATIONS					
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	3.2.P.2 (Pharm Dev), sections 2.3.1 (p.59) and 2.3.2 (p.61) indicate that sponsor considers cobimetinib ^{(b) (4)}  has not been identified by primary biopharm reviewer.
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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	There is one cited work by sucker, Fuchs, and Speiser that may require a translation depending on the drug substance reviewer.
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination <input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production <input type="checkbox"/> novel excipients	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
17.	Are the following information available for Biotech Products: <input type="checkbox"/> Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: <ul style="list-style-type: none"> o LAL instead of rabbit pyrogen o Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples			X	

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1A: Product Design FMEA - Solid Oral Products

			Non-High Risk Drugs				High Risk Drugs			
PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	CHANGES & VARIATIONS	FAILURE MODE	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN
Assay, Stability	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • Impurity formation due to excipient reactions or unspecified reactions (b) (4) 	Highly stable drug (1)	2	Release (1)	2	Highly stable drug (1)	4	Release (1)	4
					Stability (3)	6			Stability (3)	12
Physical stability (solid state)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • (b) (4) • (b) (4) 	(b) (4)	(b) (4)	4	8	(b) (4)	(b) (4)	4	36
Content uniformity	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • Low dose • Particle size/shape • Segregation • Flow property 	(b) (4)	3	4	24	(b) (4)	4	4	32

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1A: Product Design FMEA - Solid Oral Products

			Non-High Risk Drugs				High Risk Drugs			
PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	CHANGES & VARIATIONS	FAILURE MODE	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN
Microbial limits	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • (b) (4) • Equipment, process environment 	1	2	Release with spec (3)	6	1	2	Release with spec (3)	6
Dissolution – (b) (4)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipments • Site 	<ul style="list-style-type: none"> • API particle size • (b) (4) • Tab hardness • Disintegration • Size shape • Tablet scoring • Film coating • (b) (4) • (b) (4) 	3	2	2	12	3	4	2	24