CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208692Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approval
NDA 505b(2): 208692

NDA 208692
Review # 1

Drug Name/Dosage Form	Cabozantinib/tablet
Strength	20mg, 40mg and 60mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Exelixis, Inc.
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
NDA 208692	December 22, 2015	

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Xing Wang	OPQ/ONDP/DIVISION I/Branch 2
Drug Product	Xing Wang	OPQ/ONDP/DIVISION I/Branch 2
Process	Ying Zhang	OPQ/OPF/DPA1
Microbiology	Ying Zhang	OPQ/OPF/DPA1
Facility	Laura Fontan	OPQ/OPF
Biopharmaceutics	Fang Wu	OPQ/ONDP/DB
Regulatory Business Process Manager	Kristine Leahy	OPQ/OPRO/DRBPMI/RBPMBI
Application Technical Lead	Xiao Hong Chen	ONDP/DIVISION I/Branch 2
Laboratory (OTR)	N/A	
ORA Lead	Paul Perdue	ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Assessment (EA)	Raanan Bloom	ONDP/IO

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	Code[1]	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type III		(b) (4)	4	Adequate		
	Type III			3&4	Adequate	25-Oct-2012	
	Type III			3&4	Adequate	24-Apr-2012	
	Type III			4	Adequate		
	Type IV			4	Adequate		
	Other						

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	72596	XL-184 Powder, for oral solution. Initial IND
NDA	203756	Cabozantinib (S)-Malate capsules (20mg & 80mg)

2. CONSULTS:

3.

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			

Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other				

Executive Summary

I. Recommendations

The NDA is recommended for approval from the CMC standpoint.

A. Recommendation and Conclusion on Approvability

Sufficient CMC information is provided in this NDA to assure the identity, strength, purity, and quality of the drug product. The Office of Compliance has provided an overall "Acceptable" recommendation for the facilities involved in this application (refer to Panorama 6-Nov-2015).

The labels/labeling issues have been resolved as of this review through meetings with the clinical division. Therefore, from the OPQ perspective, this NDA is recommended for approval.

A 36 month shelf life is granted for the drug product stored at 25°C (77°F), excursions permitted to 15° to 30 °C (59° to 86°F).

The following comment should be included in the action letter:

> "Continue monitoring the trends of XL184 freebase Assay range (as is) and Assay of the Cabozantinib (S)-malate (b) (4) (b) (4) and (b) (4) those Assay ranges as more batches are manufactured and experience is gained."

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

N/A.

II. Summary of Quality Assessments

NDA 203,756 for Cometriq® (cabozantinib) capsules for the treatment of progressive, metastatic medullary thyroid carcinoma was approved by FDA 29 November 2012. This present NDA (assigned 208,692) is submitted for the cabozantinib tablet formulation, which will be commercialized under a different trade name and with a different indication (for the ttreatment of advanced renal cell carcinoma (RCC) in patients who have received (b) (4) prior therapy). Most of the drug substance information remains unchanged except the following changes:

1. (b) (4)
2.

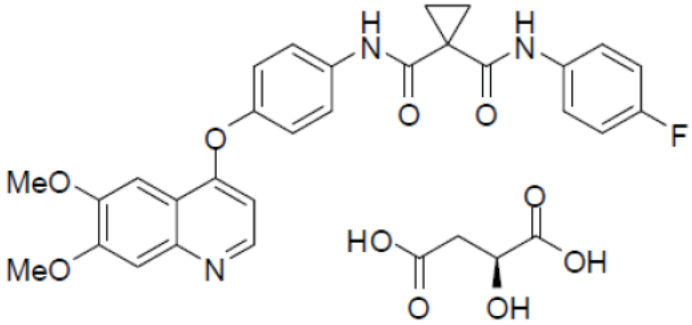
3. (b) (4)
4.
5.

The drug product is a tablet formulation with 3 strengths, 20, 40 and 60 mg.

A. Drug Substance [USAN Name] Quality Summary

Cabozantinib (S)-malate is an (b) (4). The commercial polymorphic form (b) (4). Bulk material is (b) (4) and has very low (b) (4). The drug substance name and structure for are shown below:

INN: Cabozantinib
USAN: Cabozantinib (S)-malate
CAS #: 1140909-48-3
Chemical Name: N-{4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-N′-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate
Molecular Formula:
Molecular Weight: 635.6 Daltons (L-malate salt); 501.5 Daltons (freebase)



(b) (4)

The proposed commercial manufacturing process is a (b) (4)

(b) (4)

The drug substance specification includes testing for appearance, identity, assay/ordinary impurities, counter ion content, four GTIs, water content, residual solvents, inorganic impurities, crystal form, heavy metals and particle size distribution.

Updated long term stability data was submitted that includes (b) (4) data stored at (b) (4) The applicant retested a (b) (4) retest date for cabozantinib (*S*)-malate at the recommended storage conditions of (b) (4), which is deemed acceptable.

B. Drug Product [Established Name] Quality Summary

The drug product is provided as immediate release tablets with three strengths contain a (b) (4) with each tablet consisting of (b) (4) Drug Substance with microcrystalline cellulose, lactose anhydrous, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The tablets are coated with an (b) (4) Yellow film coating (b) (4)

- Cabozantinib 20-mg tablets are yellow film-coated round tablets, debossed with "XL" on one side and "20" on the other side of the tablet.
- Cabozantinib 40-mg tablets are yellow film-coated triangle-shaped tablets, debossed with "XL" on one side and "40"on the other side of the tablet.
- Cabozantinib 60-mg tablets are yellow film-coated oval-shaped tablets, debossed with "XL" on one side and "60" on the other side of the tablet.

All excipients in the cabozantinib tablets are compendial grade and consist of non-novel excipients. The formulation components and composition have not been modified throughout the course of development. All cabozantinib tablet batches used in clinical studies have always been manufactured from Drug Substance batches containing (b) (4) (b) (4)

A manufacturing process consists of (b) (4) (b) (4), (b) (4) the tablets (20-mg, 40-mg, and 60-mg strengths) is a 60-cc HDPE bottle in a 30-count configuration.

The drug product specification consists of testing for Appearance, Identification, Potency, Impurities, Content Uniformity, water content, dissolution, Genotoxic impurities (GTIs) and Microbial limits. They are proposed per ICH Q6A. Content

uniformity, dissolution and GTIs are considered critical quality attributes. The acceptance limits for GTI have been (b) (4) comparing to those approved in NDA 203,756.

Long term stability data including up to 36 months at 25 °C/60%RH for the drug product batches manufactured with a process representative of the proposed commercial manufacturing process and at the intended commercial site (Patheon, Mississauga, Ontario, Canada) were submitted. Based on stability results from these batches, an expiry of 36 months was granted for the drug product stored in the proposed commercial packaging system at 25 °C/60% RH.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	CABOMETYX
Non Proprietary Name of the Drug Product	Cabozantinib tablets
Non Proprietary Name of the Drug Substance	cabozantinib
Proposed Indication(s) including Intended Patient Population	CABOMETYX is a kinase inhibitor indicated for the ttreatment of advanced renal cell carcinoma (RCC) in patients who have received (b) (4) prior therapy.
Duration of Treatment	Until disease progression
Maximum Daily Dose	(b) (4) mg per day
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations

Cabozantinib is classified as a BCS Class 2 (low solubility, high permeability) that demonstrates a pH-dependent solubility profile. Cabozantinib (XL184 free base) was determined to be practically insoluble in water (<0.0001 mg/mL) and polymorphic. The applicant did not request a BE waiver.

Besides the approved capsule formulation (COMETRIQ®, NDA 203756), a tablet formulation (20 mg, 40 mg and 60 mg) was later developed and has been used in the other Phase 3 efficacy and/or safety studies, including biopharmaceutic studies XL184-308. All of the drug product batches were manufactured at the intended commercial site (Patheon, Mississauga, Ontario, Canada). The tablet formulation did not change between that used in the Phase 3 study and the proposed commercial drug product. Therefore, no BE studies are necessary.

The biopharmaceutics review evaluates the data provided to support; 1) proposed in vitro dissolution testing method and 2) the release/stability in vitro dissolution acceptance criteria. Based on biopharmaceutics reviewer's assessment the proposed dissolution method and the revised acceptance criteria (b) (4) % at 15 min.) for the dissolution specification are found to be acceptable. The method and the acceptance criterion demonstrate some discriminating capacity with regard to change of the tablet quality such as hardness. The dissolution method is

predominantly used as a quality control method; no in vitro and in vivo correlation has been established.

E. Facilities
Based on the facility reviewer's assessment, the risk associated with the manufacturing of this product is low. Both drug substance and drug product manufacturers, as well as testing sites are acceptable.

F. Novel Approaches N/A

G. Any Special Product Quality Labeling Recommendations N/A

H. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:
The NDA is recommended for approval.

Xiao Hong Chen
Acting Quality Assessment Lead
/OPQ/ONDP/DNDP 1/Branch 2
April 12, 2016

Xiaohong Chen -A

Digitally signed by Xiaohong Chen -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xiaohong Chen -A, 0.9.2342.19200300.100.1.1=1300133168
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OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:
The risk associated with the manufacturing of this product is low. Both drug substance and drug product manufacturers, as well as testing sites are acceptable.
Laura Fontan, Facility Reviewer, OPF/DIA 2/29/2016

Secondary Review Comments and Concurrence:
I concur with the facility reviewer's recommendation.
Zhihao Peter Qiu, Ph.D., 2/29/2016, OPF/DIA

ASSESSMENT OF THE BIOPHARMACUETICS

Submission:

Exelixis, Inc. is submitting an initial New Drug Application (NDA) for Cabometyx™ (cabozantinib) in accordance with section 505(b) for the treatment of advanced renal cell carcinoma (RCC) in patients who have received (b) (4) prior therapy. Cabozantinib was granted fast track designation 08 April 2015 and breakthrough therapy designation 21 August 2015 for the intended RCC indication.

The Drug Product in this NDA is an immediate release film-coated tablet formulation (containing a (b) (4)). All three proposed commercial tablet strengths (60 mg, 40 mg, and 20 mg) are (b) (4).

Solubility:

Cabozantinib is considered a BCS Class II drug substance (low solubility, high permeability) that demonstrates a pH-dependent solubility profile. Cabozantinib (XL184 free base) was determined to be practically insoluble in water (<0.0001 mg/mL) and polymorphic. The pH-solubility profile of cabozantinib is shown in the figure below (Refer to Module 3.2.S.1.3)

(b) (4)

Biopharm Table 1. Solubility of Cabozantinib (S)-Malate in Various Media and Time Points

Media	Time Point (hour)	Solubility (mg/mL)
0.1 N HCl	1	0.02
	2	0.02
	4	0.02
	24	0.01
0.01 N HCl	1	0.24
	2	0.22
	4	0.20
	24	0.11
pH 4.5 acetate buffer	1	0.01
	2	0.01
	4	0.00
	24	0.00
pH 6.5 phosphate buffer	1	0.00
	2	0.00

	4	0.00
	24	0.00
pH 7.5 phosphate buffer	1	0.00
	2	0.00
	4	0.00
	24	0.00

Formulation development:

The drug product, Cabozantinib, was initially provided as a powder-in-bottle oral suspension formulation for initiation of the Phase 1 XL184-001 study. A capsule formulation was later developed and used in Phase 2 studies, a Phase 3 study in medullary thyroid cancer, and various clinical pharmacology studies. Subsequently, cabozantinib capsules (20 mg and 80 mg) (COMETRIQ®, NDA 203756) were approved (November 29, 2012) and commercialized for the treatment of advanced medullary thyroid cancer. A tablet formulation was later developed and has been used in the other Phase 3 efficacy and/or safety studies, including Study XL184-308.

Cabozantinib tablet strengths of 100-mg, 60-mg, and 20-mg were developed as potential clinical dosage strengths. In the Phase 3 efficacy and/or safety studies, 60-mg and 20-mg tablet strengths were provided to meet the required patient doses. Of note, in the clinic, the 40-mg dose was supplied using two 20-mg dose tablets. Whilst the 40-mg and 100-mg tablet strengths were not provided in the submitted efficacy and/or safety studies, they were used in the biopharmaceutical studies; XL184-020 and XL184-010, respectively (see Module 2.7.1).

Review:

The biopharmaceutics review will focus on the evaluation and acceptability of the data provided to support; 1) proposed in vitro dissolution testing method and 2) the release/stability in vitro dissolution acceptance criteria.

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

Reviewer's Assessment:

1. DISSOLUTION METHOD AND ACCEPTANCE CRITERION

Proposed Dissolution method:

Dissolution apparatus:	Apparatus II (paddle)
Dissolution medium:	0.01 N HCl with 0.375% Triton X-100
Dissolution medium volume:	900 mL
Temperature:	37.0 ± 0.5 °C
Speed:	75 rpm
Sampling time:	15, 30, 45, and 60 minutes, 90 minutes*
Sample volume:	2 mL

*(infinity, agitation speed at (b) (4))

Proposed Dissolution acceptance criterion:

Q = (b) (4)% (in (b) (4) minutes)

For increased understanding of the proposed dissolution method, the following IR was issued on February 9, 2016.

1. The dissolution method development summary is incomplete. In vitro dissolution profile data (individuals, mean, RSD, and plots) with sampling time points at 10 min, 15 min, 30 min, 45 min and 60 min for the 20 mg, 40 mg and 60 mg strength tablets used in pivotal clinical trials should be submitted.

2. Since the 40 mg tablet strength were not provided in the efficacy and/or safety studies, provide in vitro dissolution profile comparison between the 40 mg strength tablet and two 20 mg tablets for bridging purposes.

3. Provide the following additional information to support your position that the proposed method (USP 2, 0.375% Triton X-100 in 0.01N HCl at 75 rpm) is discriminating and the acceptance criterion (Q = (b) (4)% in (b) (4) minutes) is meaningful for product quality assurance.

   a) Rationale for using two different approaches for determining (b) (4) (b) (4)

   b) Complete dissolution profile data (individual, mean, RSD, and plots) for each surfactant type and amount tested for method development. The minimum amount of surfactant to achieve sink conditions and robust dissolution performance is recommended. Solubility is not the only determinant of performance with respect to surfactant selection; other factors such as excipient interactions should also be considered. Include the 10 minute sampling time point in your analysis for adequate profile sampling.

   c) The agency acknowledges that you provided data to assess the discriminatory capability of the dissolution method by comparing the dissolution profiles of 20-mg and 100-mg tablets (b) (4)

(b) (4) The proposed dissolution method should have the discriminating capability with regard to the Critical Material Attributes (CMAs) or Critical Process Parameters (CPPs). The testing should compare the dissolution profiles of the reference (target) product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical material or manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables). In addition, if available, submit data showing that the selected dissolution method and acceptance criterion are adequate to reject batches that are not bioequivalent.

d) A scientific and data-based justification for the proposed acceptance criterion of Q = (b) (4)% at (b) (4) minutes when your dissolution data could support a criterion of Q = (b) (4)% at 15 minutes using the proposed method. Include in your response descriptive statistics (mean, min, max, RSDs) for pooled dissolution data from the bio-batches and primary registration stability batches at 15 (b) (4) minutes by dosage strength (20 mg, 40 mg and 60 mg) at time 0, and an estimation of the dissolution pass rate for lots at stage 1, stage 2, and stage 3 applying your proposed acceptance criterion as well as a criterion of Q = (b) (4)% at 15 minutes.

Applicant's Response to IR#1:

Applicant's response to question 1.

(b) (4)

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(b) (4)

[redacted]

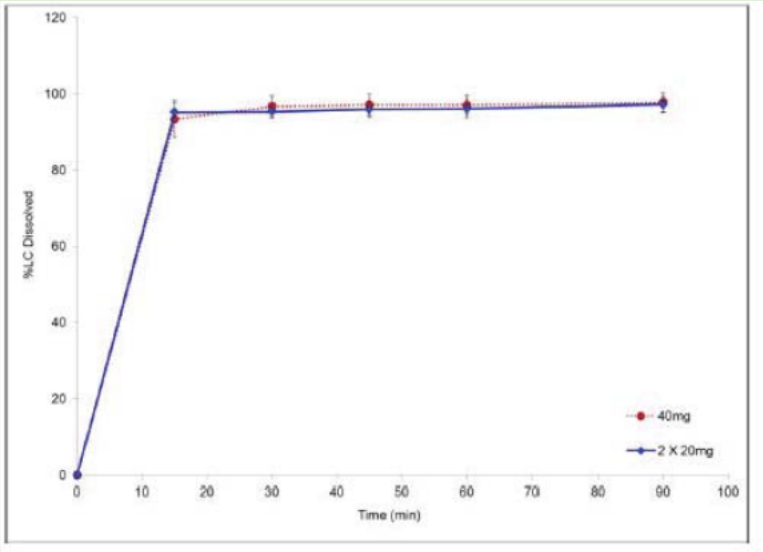
Reviewer's assessment:

- *The proposed dissolution acceptance criterion* (b) (4) *based on the available data for 20 mg, 40 mg and 60 mg strength tablets. The dissolution data provided supports acceptance criterion of Q=* (b) (4) *% at 15 minutes for 20 mg, 40 mg and 60 mg strength tablets using the proposed dissolution method. For the 40 mg strength, the average released percentage is* (b) (4) *% at 15 minutes, however, the variability at 15 minute time point is* (b) (4) *compared with 20 mg and 60 mg strength. The Applicant will need to control the manufacturing process to decrease the variability at 15 minutes for 40 mg strength. Therefore, dissolution data (12 units, mean, SD and CV%) from additional batch for 40 mg is needed. Considering 60 mg, 40 mg, and 20 mg strengths* (b) (4) *the variability of dissolution profile for 40 mg should be similar to that*

of 20 mg and 60 mg. ***Biopharm Figure 4*** *supports the above statement and the recommended acceptance criterion. Considering the totality of the data, the acceptance criterion of Q= (b) (4)% at 15 minutes is recommended for all the three proposed strength, 20 mg, 40 mg and 60 mg cabozantinib tablets. The Applicant will need to implement and update the drug product specification table and relevant parts of the NDA submission accordingly. A IR#2 is issued based on the above assessment.*

Applicant's response to question 2. In-vitro dissolution data in 0.375% Triton X-100 in 0.01N HCl for two 20-mg tablets in comparison with single 40-mg tablet strength are presented in the following figure.

Biopharm Figure 4. Dissolution Profiles for two 20-mg tablets versus one 40-mg tablets in
0.01N HCl with USP Apparatus II (Paddle), 75 rpm, 0.375% Triton X-100 (n=6)



Reviewer's assessment:

- *As the drug is dissolved rapidly, release over (b) (4)% within 15 min for both the single 40-mg tablet and two 20-mg tablets. The dissolution profiles are comparable. Therefore, no in vivo bridging data is needed between the 40 mg strength tablet and two 20 mg tablets used in clinics.*

Applicant's response to question 3a

(b) (4)

(b) (4)

Reviewer's assessment:

Satisfactory.

Applicant's response to question 3b

(b) (4)

(b) (4)

The Applicant took into consideration surfactant solubility data, dissolution data, and previous experience with Triton X-100 (utilized for dissolution testing of commercially approved COMETRIQ), surfactant (Triton-X-100) was selected. The level of Triton X-100 was selected at 0.375%, since this concentration would achieve adequate solubility (approximately (b) (4) times the solubility for 100 mg strength tablets).

Reviewer's assessment:

- *The Applicant's response provides a rationale for selecting 0.375% Triton X-100 in 0.01 N HCl for meeting the sink condition for 100 mg strength and reaching a complete release* (b) (4)
- *The drug product with the same active ingredient, cabozantinib capsules (NDA203756), used a similar dissolution method shown as below:*

Dissolution apparatus:	Apparatus II (paddle) with sinker
Dissolution medium:	0.01 N HCl with 0.5% Triton X-100
Dissolution medium volume:	900 mL
Temperature:	37.0 ± 0.5 °C
Speed:	75 rpm
Sampling time:	15, 30, 45, and 60 minutes, 90 minutes (b) (4)
Acceptance criterion:	Q = (b) (4) % in 15 min

According to the Biopharmaceutics Assessment for NDA203756, "the drug release (b) (4) *using the selected dissolution medium (0.01 N HCl with 0.5% Triton X-100). In addition, the profile shape is not too different between using medium with surfactant of 0.5% and* (b) (4) *Triton X-100. At* (b) (4) *concentrations* (b) (4) *of surfactant Triton X-100, complete dissolution was not achieved for 80 mg strength capsule. The dissolution profile plateaus around 15 minutes for both*

conditions, which suggests that a Triton X- 100 concentration (b) (4) *0.5% will not improve the shape of the dissolution profile." Based on the above prior knowledge, the shape of the dissolution profile of the current proposed drug product will highly likely not be improved with using* (b) (4) *concentration of surfactant (Triton X-100). Therefore, taking into consideration the surfactant solubility data and sink condition for the highest strength investigated, dissolution data, and previous experience with Triton X-100 (utilized for dissolution testing of commercially approved cabozantinib capsules), selecting 0.375% surfactant (Triton-X-100) is adequate. (Refer to biopharmaceutics review for NDA203756 in DARRTS by Dr. Minerva Hughes dated 10/29/2012)*

Applicant's response to question 3c

1. To further illustrate the discriminatory capability of the dissolution method, the Applicant provided dissolution data from an earlier development batch evaluating the effect of various tablet hardness on dissolution (0.375% Triton X-100 in 0.01N HCl) presented in the following Figure. As expected, it was observed that for tablets (b) (4) a slower dissolution rate was achieved, whilst softer tablets experienced faster dissolution.

Biopharm Figure 6. Dissolution of Cabozantinib Tablets (100-mg) with Various Tablet Hardness in 0.375% Triton X-100 in 0.01N HCl, pH 2, USP Apparatus II (Paddle), 75rpm (n=3)

(b) (4)

2. The effect of critical and functional excipient concentration ranges on dissolution of the tablets was thoroughly evaluated. The studied concentration ranges were (b) (4) % from the target concentration. The **Biopharm Figure 7** shows the dissolution profile overlay plot of all the batches listed in **Biopharm Table 7**.

(b) (4)

[redacted]

3. Also, the dissolution method is predominantly used as a quality control test to ensure

batch to batch consistency; there are no data to support any in vitro/in vivo correlation.

Reviewer's assessment:

- *In the submission, the Applicant tried to demonstrate discriminatory capability of the dissolution method by comparing the dissolution profiles of the tablets* (b) (4) *However, the dissolution method's ability to detect meaningful manufacturing changes was not illustrated by the data* (b) (4) *. The issue is that a formulation with or without any excipients,* (b) (4) *Taking the totality of the data into consideration and also a similar dissolution method has been adopted for the reference product, NDA203756, Cabozantinib capsules (20 mg and 80 mg), the proposed dissolution method is acceptable. In addition, this reviewer agrees that the dissolution method is predominantly used as a quality control method; no in vitro and in vivo correlation has been established.*

(b) (4)

Applicant's response to question 3d

The sponsor provided comparison for the proposed acceptance criterion of Q= (b) (4)% at (b) (4) minutes and 15 minutes. An acceptance criterion of Q= (b) (4)% at 15 minutes was proposed.

(b) (4)

Reviewer's assessment:

- *The failure rate for Stage II using the dissolution acceptance criteria is rather low, your proposed dissolution acceptance criterion of Q= (b) (4)% at (b) (4) minutes is not supported by the data submitted and is not acceptable. FDA recommends an acceptance criterion of Q= (b) (4)% at 15 minutes for your cabozantinib 20 mg, 40 mg and 60 mg tablet products. Provide a revised drug product regulatory specification table, revised stability protocol, and revised method protocols with the aforementioned dissolution acceptance criterion change.*

After reviewing the Applicant's response dated 2/19/2016 to IR #1, Biopharmaceutics conveyed the following comment in the FDA Information Request letter (IR#2) on 3/16/2016.

1. For 40 mg strength carbozantinib tablets, the variability (RSD%) of drug released is (b) (4) compared with those for 20 mg and 60 mg strengths. Considering 60 mg, 40 mg, and 20 mg strengths (b) (4) manufacturing process is the same, the dissolution profile and its variability for 40 mg should be similar to that of 20 mg and 60 mg. You need to investigate the root causes for this discrepancy, including but not limited to the control of the manufacturing process and analytical methodology. Submit the investigation report and additional dissolution profile data at 15, 30, 45, and 60 minutes (provide individual, mean, RSD data for 12 units) using your proposed dissolution method for three registration batches for 40 mg strength cabozantinib tablets.

2. Your proposed dissolution acceptance criterion of Q= (b) (4)% at (b) (4) minutes is not supported by the data submitted and is not acceptable. FDA recommends an acceptance criterion of Q= (b) (4)% at 15 minutes for your cabozantinib 20 mg, 40 mg and 60 mg tablet products. Provide a revised drug product regulatory specification table, revised stability protocol, and revised method protocols with the aforementioned dissolution acceptance criterion change.

Applicant's responses dated 03/22/2016 to IR #2 are summarized below:

1. The 40 mg tablet dissolution result passes FDA-recommended Q = (b) (4)% in 15 minutes acceptance criterion.

2. Additional multi-point dissolution testing on stability (T = 3, 9 and 12 months, storage condition of 25°C/60% RH and T=3 and 6 months, storage condition of 40°C/75%RH) for 40 mg tablets, bulk lot No. PCWM were performed and the data are similar to those of other dose strengths (20 mg, 60 mg, and 100 mg). Representative dissolution data at stability (T = 3 months, storage condition of 25°C/60%RH) are shown in **Biopharm Table 8** and **Biopharm Figure 9**.

(b) (4)

(b) (4)

(b) (4)

Reviewer's assessment:

The Applicant provided additional multi-point dissolution data at stability testing (T = 3, 9 and 12 months, storage condition of 25°C/60%RH and T=3 and 6 months, storage condition of 40°C/75%RH) for 40-mg tablets, bulk lot No. PCWM. Moreover, the Applicant provided multi-point dissolution testing data at release on three additional batches (bulk lot No: WGKP, WGMD, and WGMG). Based on the provided dissolution data, the 40 mg tablet dissolution results meet FDA-recommended Q = (b) (4)% in 15 minutes acceptance criterion. Additionally, based on the submitted dissolution data for 40 mg tablets in the responses dated 3/22/2016, the variability (RSD%) of drug released for 40 mg tablets at early time points (15min (b) (4)) are generally (b) (4)%, which is similar to those for 20 mg and 60 mg strength and therefore is acceptable. The (b) (4)

variability previously observed for 40 mg strength was likely due to variation in assay, not the product quality.

The Applicant accepted FDA recommended acceptance criterion of Q= (b) (4)% at 15 minutes for cabozantinib tablets (20 mg, 40 mg, and 60 mg) and updated relevant parts of the NDA.

Therefore, the Applicant's responses to IR#2 are satisfactory.

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

Four biopharmaceutics studies of cabozantinib (XL184) have been conducted: the evaluation of the effect of food intake on XL184 plasma PK (Study XL184-004); the evaluation of bioequivalence of different mixtures of crystal forms in cabozantinib drug substance (b) (4) (b) (4) (Study XL184-016); the evaluation of bioequivalence for cabozantinib capsule and tablet formulations (Study XL184-010); and the evaluation of dose proportional exposure of 20 mg, 40 mg and 60 mg cabozantinib tablet strengths (Study XL184-020).

60-mg and 20-mg tablet strengths were used in Phase 3 efficacy and/or safety studies (e.g. Study XL184-306 and study XL184-307 for the treatment of previously-treated symptomatic castration-resistant prostate Cancer for the treatment of Metastatic Castration-resistant Prostate Cancer). Of note, in the clinic, the 40-mg dose was supplied using two 20-mg strength tablets. 40-mg tablet strength was not used in the efficacy and/or safety studies and it was used in the biopharmaceutical studies, XL184-020 (Section 2.7.1). The batches used in the above clinical trials were manufactured at the intended commercial scale of (b) (4) batch size (Module 3.2.p.5.4 batch analysis).

All of these drug product batches were manufactured at the intended commercial site (Patheon, Mississauga, Ontario, Canada). The tablet formulation did not change between that used in the Phase 3 study and the proposed commercial drug product. Therefore, no tablet formulation changes necessitated biopharmaceutics studies.

Reviewer's Assessment:

The batches used in the biopharmaceutics clinical trials were manufactured at the intended commercial scale of (b) (4) batch size. Also, the tablet formulation did not change between that used in the Phase 3 study and the proposed commercial drug product. Therefore, no tablet formulation changes necessitated biopharmaceutics studies.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature: ADEQUATE

1. The data submitted support the proposed dissolution method, which is ADEQUATE.

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium
II	75 rpm	900 mL	37°C	0.01 N HCl with 0.375% Triton X-100

2. The originally proposed dissolution acceptance criterion of Q= (b)(4)% at (b)(4) minutes is not supported by the data submitted and is not acceptable. FDA recommends an acceptance criterion of Q= (b)(4)% at 15 minutes for cabozantinib 20 mg, 40 mg and 60 mg tablet products, shown as below. The Applicant accepted FDA recommended acceptance criterion in the responses dated 3/22/2016.

	Acceptance Range (% Cabozantinib Released)		
Time (h)	20 mg	40 mg	60 mg
15	NLT (b)(4)% (Q)	NLT (b)(4)% (Q)	NMT (b)(4)%(Q)

Therefore, from biopharmaceutics perspective, cab zantinib tablets (20 mg, 40 mg, and 60 mg) is recommended for APPROVAL.

Fang Wu
Biopharmaceutics Reviewer
CDER/OPQ/ONDP/Division of Biopharmaceutics
04/07/2016

Secondary Review Comments and Concurrence:

Concur with the recommendation for approval.

Kimberly Raines
Secondary Reviewer&Team Lead (Acting)
CDER/OPQ/ONDP/Division of Biopharmaceutics

John Z. Duan
Secondary Reviewer & Branch Chief (acting)

ASSESSMENT OF MICROBIOLOGY

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

Applicant's Response:

The USP <61> and USP <62> for microbial limit testing is conducted to assess the product microbial content. Such test is included in product release specifications.

Reviewer's Assessment:

The applicant proposed to include microbial limit test in product release specifications. They will adopt USP <61><62> test procedures for such testing. The proposed acceptance criteria comply with USP <1111>.

The applicant provided stability data from 29 batches, showing that no increase in microbial limit over storage for up to 36 months. Therefore their proposal of waiving microbial test on stability is acceptable.

2.3.P.7 Container/Closure System

41. 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:

The proposed container closure system is HDPE bottles containing (b) (4) desiccants. The amount of desiccant was optimized based on stability data.

Reviewer's Assessment:

Acceptable.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

42. 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: Not applicable.

Reviewer's Assessment:

43. 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: Not applicable.

Reviewer's Assessment:

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature:

The application is acceptable from microbiology perspective.

- Ying Zhang

Secondary Review Comments and Concurrence:

I concur with the assessment and conclusions of the primary reviewer.

Bogdan Kurtyka, QAL, OPF/Div. 1/Branch 2

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

44. Is the applicant's claim for categorical exclusion acceptable?

45. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response:

The EIC from patient use of cabozantinib, based on the 5th year production estimate of [redacted] (b) (4) As the EIC is significantly less than 1 ppb, the applicant requests a claim of categorical exclusion under 21CFR25.31(b).

Reviewer's Assessment: Adequate

In support of the claim of categorical exclusion the applicant provides supporting information in a document titled Environmental Assessment (dated, 8 December 2015; revised, 06 April 2016, to provide a complete claim for categorical exclusion). The document does not provide a full environmental assessment but rather consists of an overview of metabolism, and physical/chemical and environmental fate characterization data. No environmental effect studies are provided in the submission. A literature search did not identify any ecotoxicity findings. E, A or T activity is not noted. Based on its low water solubility and octanol/water partition, cabozantinib is likely to partition mostly into sludge or sediment, thus reducing water column exposure concentrations. Based on these findings, low production values, and the extremely low exposure concentrations (EIC value of [redacted] (b) (4) ; EEC = [redacted] (b) (4)), environmental toxicity due to approval of the application is not anticipated.

The categorical exclusion cited at 21 CFR 25.31(b) is appropriate for the anticipated amount of cabozantinib to be used, and a statement of no extraordinary circumstances has been submitted. The claim of categorical exclusion is acceptable.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:
The applicant's claim of categorical exclusion is acceptable.

Raanan Bloom
EA Reviewer/OPQ/ONDP/IO
April 5, 2016

Secondary Review Comments and Concurrence:
I concur with the review and conclusions of the primary reviewer.

Scott Furness
Deputy Director/OPQ/ONDP

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

Labeling & Package Insert

1. Package Insert

(b) (4)

[redacted]

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary name: CABOMETYX™ Established name: cabozantinib	Adequate
Dosage form, route of administration	Dosage: Tablet Route: Oral	Adequate
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	20 mg, 40 mg and 60 mg tablets	Adequate

Conclusion: Adequate

(b) "Full Prescribing Information" Section

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

3 DOSAGE FORMS AND STRENGTHS

60 mg CABOMETYX tablets are yellow film-coated, oval shaped with no score, and debossed with "XL" on one side and "60" on the other side.

40 mg CABOMETYX tablets are yellow film-coated, triangle shaped with no score, and debossed with "XL" on one side and "40" on the other side.

20 mg CABOMETYX tablets are yellow film-coated, round with no score, and debossed with "XL" on one side and "20" on the other side.

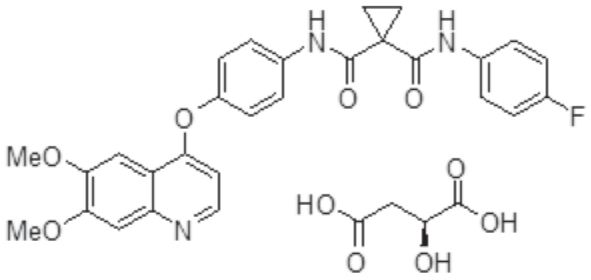
(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Tablets	Adequate
Strengths: in metric system	20 mg, 40 mg and 60 mg	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	60 mg CABOMETYX tablets are yellow film-coated, oval shaped with no score, and debossed with "XL" on one side and "60" on the other side. 40 mg CABOMETYX tablets are yellow film-coated, triangle shaped with no score, and debossed with "XL" on one side and "40" on the other side. 20 mg CABOMETYX tablets are yellow film-coated, round with no score, and debossed with "XL" on one side and "20" on the other side.	Adequate

Conclusion: Adequate

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

CABOMETYX is the (*S*)-malate salt of cabozantinib. Cabozantinib (*S*)-malate is described chemically as *N*-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2*S*)-hydroxybutanedioate. The molecular formula is $C_{28}H_{24}FN_3O_5 \cdot C_4H_6O_5$ and the molecular weight is 635.6 Daltons as malate salt. The chemical structure of cabozantinib (*S*)-malate salt is:



Cabozantinib (*S*)-malate salt is a white to off-white solid that is practically insoluble in aqueous media.

CABOMETYX (cabozantinib) tablets are supplied as film-coated tablets containing cabozantinib (*S*)-malate equivalent to 20 mg, 40 mg, or 60 mg cabozantinib and the following inactive ingredients: microcrystalline cellulose, lactose anhydrous, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate.

The film coating contains hypromellose, titanium dioxide, triacetin, and iron oxide yellow.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Provided	Adequate
Dosage form and route of administration	Provided	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	Not Provided	Inadequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Provided	Adequate
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	Not provided	Inadequate
Chemical name, structural formula, molecular weight	Provided	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	Provided	Adequate

Conclusion:
The following changes/edits are made in this section and will be conveyed to the applicant by the OND:

Include Pharmacological/therapeutic class information of cabozantinib in #11

Description of Package Insert.

Include a salt equivalency statement in Package Insert (#11 Description) per FDA guidance:http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM379753.pdf For example, CABOMETYX (cabozantinib) tablets are supplied as film-coated tablets containing 20 mg, 40 mg, or 60 mg cabozantinib, which is equivalent to X mg, Y mg, or Z mg of cabozantinib (S)-malate, respectively.

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

CABOMETYX tablets are supplied as follows:
60 mg tables are yellow film-coated, oval shaped with no score, debossed with "XL" on one side and "60" on the other side of the tablet; available in bottles of 30 tablets: NDC 42388-023-26
40 mg tablets are yellow film-coated, triangle shaped with no score, debossed with "XL" on one side and "40" on the other side of the tablet; available in bottles of 30 tablets: NDC 42388-025-26
20 mg tablets are yellow film-coated, round shaped with no score, debossed with "XL" on one side and "20" on the other side of the tablet; available in bottles of 30 tablets: NDC 42388-024-26
Store CABOMETYX at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Provided	Adequate
Available units (e.g., bottles of 100 tablets)	Bottles of 30 tablets	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided	Adequate
Special handling (e.g., protect from light, do not freeze)	N/A	N/A
Storage conditions	Provided	Adequate

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)	Manufactured for Exelixis, Inc. South San Francisco, CA 94080	Adequate

Conclusion: Adequate

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

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Cabometyx™ (cabozantinib) tablets	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strength is provided. Salt equivalency statement is provided.	Adequate
Route of administration 21.CFR 201.100(b)(3))	Oral	Adequate
Net contents* (21 CFR 201.51(a))	30 tablets	Adequate
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Not required for an oral dosage form	Adequate
Lot number per 21 CFR 201.18	Space is provided	Adequate
Expiration date per 21 CFR 201.17	Space is provide	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	Provided	Adequate
Storage (not required)	Provided	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)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Provided	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Provided	Adequate
Others	Keep out of the reach of children	Adequate

*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.

**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label

**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:
The following comment was conveyed together with DMEPA's comments to the firm on 10-Mar-2016:

Update the side panel of CABOMETYX Container Label to indicate the amount of salt according to Example 1 in Appendix 2 of the following FDA guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM379753.pdf For example, "Each tablet contains X mg of cabozantinib (equivalent to Y mg of cabozantinib (S)-malate)."

Firm has provided updated container labels on 16-Mar-2016. They are acceptable from CMC standpoint. DMEPA is sending an IR to request removing the "Store in the original package" statement. Please refer to DMEPA memo on 29-Mar-2016 for detail.

2) Carton Labeling

No carton labeling is provided.

Conclusion:
Not applicable

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:
Revisions to the proposed PI labeling (Highlight, Description and How Supplied sections) have been conveyed to the OND PM. The remaining immediate container labeling issue can refer to DMEPA's review/memo.

Xing Wang
CMC Reviewer/OPQ/ONDP/DNDP 1/Branch 2
April 4, 2016

Secondary Review Comments and Concurrence:
I concur
Anamitro Banerjee
Acting Branch Chief/OPQ/ONDP/DNDP 1/Branch 2
April 4, 2016

II. List of Deficiencies To Be Communicated

Drug Substance

Drug Product

Process

Facility

Biopharmaceutics

Microbiology

Environmental

Label/Labeling

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

OPQ Risk Mitigation Dashboard

A/NDA:	208692
Drug Product:	Cabozantinib
Dosage:	Tablet
Strength:	20 mg, 40 mg and 60 mg
Applicant:	Exelixis, Inc.

Physical Stability		
Initial Risk	Medium	
Comment		
	Mitigation	**Comment**
Design	(b) (4)	

		(b) (4)
Process		(b) (4)
	Attributes of critical process intermediates are properly controlled (e.g., storage, hold time, moisture, residual solvents)	
Measurement	Method validation with customarily adequate limits of detection	(b) (4)

Chemical Stability		
Initial Risk	Low	
Comment		
	Mitigation	**Comment**
Design	Stress studies and/or literature suggest API is inherently stable and not prone to degradation	
	API and Excipient(s) compatibility properly evaluated and used to select excipients that do not show chemical incompatibilities with API	
	Differences in chemical stability of different solid forms or solvates are well-studied and well-understood if one solid form/solvate is selected above others	
	Container closure attributes are intentionally selected to improve drug product stability (b) (4)	
	Labeling specifies special storage precautions (e.g. storage temperature) that need to be taken to maintain product stability	
Process	Unit operation is intentionally selected to avoid the degradation (b) (4) (b) (4))	genotoxic impurity level was investigated during process development.
Measurement	Real time stability data demonstrates drug product is stable through granted shelf-life and well within the margin of specification limits	
	Accelerated and available long term stability data do not show significant changes	
	Adequate analytical method validation for detection of degradants, considering known degradation profile and excipient interactions	

In-Vitro Dissolution		
Initial Risk	High	
Comment		
	Mitigation	**Comment**
Design	Use of a discriminating dissolution testing method for justifying formulation design and optimization	

	Formulation design (b) (4)	
	Controlled input ingredient CMAs with no possible transformation and range justified (e.g., impact of ingredient particle size /specific surface area on rate of dissolution, input polymorph controlled)	
Process	Use of a discriminating dissolution testing method for justifying process design and optimization (b) (4)	
Measurement	Dissolution acceptance criterion/a that assures consistent bioavailability of the drug product (b) (4)	Even though dissolution acceptance criteria assure consistent bioavailability (b) (4) .
	Dissolution testing methods are well justified, characterized and understood (e.g. use of (b) (4)	

Content Uniformity		
Initial Risk	Low	
Comment		
Process/Facility	**Mitigation**	**Comment**
Unit Operation	(b) (4)	
Process Design		
Parameters	Some pertinent parameters investigated and ranges justified-Other parameters fixed w/o investigation	
Input MA	None	
Output QA	(b) (4)	
Scale-Up		
	Mitigation	**Comment**
Measurement (Routine)	BU testing (individual, average, %RSD) acceptance criteria in line with finished drug product assay release specification	

Additional CQA		
Attribute	**Rationale**	**Risk Mitigation**

NDA 208692
Review 1

Drug Name/Dosage Form	Cabozantinib (S)-maleate
Strength	20mg, 40 mg, 60 mg
Route of Administration	Oral Tablet
Rx/OTC Dispensed	
Applicant	Exelixis, Inc.
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Xiang Wang	
Drug Product	Xiang Wang	
Process	Ying Zhang	
Microbiology	N/A	
Facility	Laura Fontan	
Biopharmaceutics	Fang Wu	
Regulatory Business Process Manager	Rabiya Laiq Kristine Leahy	
Application Technical Lead	Xiao Chen	
Laboratory (OTR)	N/A	
ORA Lead	Paul Perdue	
Environmental Assessment (EA)	Raanan Bloom	

ASSESSMENT OF THE FACILITIES

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

S.2.1 Manufacturer(s)

1. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment Name	FEI Number	Responsibilities and Profile Codes	Initial Risks Identified	Current Status	Final Recommendation
		(b) (4)	Medium, Last inspection (b) (4)	PAI waived because of site history and low risk process	Acceptable based on manufacturing history
			Medium, Last inspection (b) (4)	PAI waived because of site history	Acceptable based on history
			Medium, Last inspection (b) (4)	PAI waived because of site history	Acceptable based on history

The initial facilities risk assessment for the sites associated with the manufacture of the drug substance is shown in the table.

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
	(b) (4)	CSN	(b) (4)	10	6	0	16	AC
		CTL		16	5	0	21	AC
		CTL		21	5	0	26	AC

Applicant's Response:

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2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

P.3.1 Manufacturer(s)

2. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment Name	FEI Number	Responsibilities and Profile Codes	Initial Risks Identified	Current Status	Final Recommendation
Patheon Inc., Mississauga, Ontario, Canada	3000264888	Manufacture, packaging, and testing of cabozantinib 20mg, 40 mg and 60 mg tablets	Medium, Last inspection 11/13/2015	PAI waived because of site history and low risk process	Acceptable based on profile/inspection history

The initial facilities risk assessment for the sites associated with the manufacture of the drug product is shown in the table.

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment	Recommendation
Patheon Inc	3000264888	TCM	Manufacture, packaging, and testing of cabozantinib 20mg, 40 mg and 60 mg tablets	21	6	0	27	AC

Applicant's Response:

Reviewer's Assessment:

Patheon Inc., (FEI 3000264888)

Patheon Inc (Toronto), FEI 3000264888, is a contract drug product manufacturer. The

(b) (4)

(b) (4)

Based on the firm's inspection history, the site is acceptable for the production of cabozantinib 20mg, 40 mg and 60 mg tablets. In addition, the DP manufacturing process is not complex or of high risk, according to application process reviewers.

No PAI is needed.

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

The risk associated with the manufacturing of this product is low. Both drug substance and drug product manufacturers, as well as testing sites are acceptable.

Laura Fontan, Facility Reviewer, OPF/DIA 2/29/2016

Secondary Review Comments and Concurrence:

I concur with the facility reviewer's recommendation.

Zhihao Peter Qiu, Ph.D., 2/29/2016, OPF/DIA

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

/s/

ROBYN S JORDON
05/06/2016