CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213973Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA OPQ Review and Evaluation

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

All FDA assessment is indicated in blue colored fonts

Drug Substance Retest Period: Applicant to insert proposed retest period and storage conditions

A retest period of (b) (4) months is supported for ripretinib drug substance (b) (4) (b) (4).

FDA Assessment: **The proposed retest period for ripretinib drug substance (b) (4) (b) (4) is supported by the stability data provided in sec. 3.2.S.7.1 of the NDA (Drug Substance – Stability Summary and Conclusions).**

Drug Product Expiration Dating Period: Applicant to insert proposed shelf life and storage conditions

An initial shelf life of 18 months will be applied to the drug product packaged in either package configuration (b) (4) when stored under the following conditions:

Store in the original container at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F) (see USP controlled room temperature). Reference is made to the pre-NDA official meeting minutes dated October 31, 2019 (reference ID: 4513802) where the Agency agreed with Deciphera's proposal to submit the initial application with 9-months long-term stability data followed by a stability update within 90-days of the original application. The shelf-life proposal may be revised (e.g. to (b) (4) months) based on the updated data through 12 months of testing.

FDA Assessment:
A shelf life of 18 months may be granted when the drug product is stored in the recommended storage conditions. See stability section below for details.

NDA 213973

Review # 1

[Applicant will complete this section.]

Drug Name/Dosage Form	Ripretinib/Tablets
Strength	50 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Indication	Treatment of patients with advanced gastrointestinal stromal tumors who have received prior treatment with imatinib, sunitinib, and regorafenib.
Applicant	Deciphera Pharmaceuticals, LLC
US agent, if applicable	N/A

[FDA will complete these sections.]

Submit Date(s)	12/13/2019
Received Date(s)	12/13/2019
PDUFA Goal Date	08/13/2020
Division/Office	OPQ
Review Completion Date	
Established Name	Ripretinib
(Proposed) Trade Name	Refer to the finalized labeling
Pharmacologic Class	Kinase inhibitor
Recommendation on Regulatory Action	Approval

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission (SD # 1)	10/15/2019	Facilities and Biopharmaceutics
Original Submission (SD # 6)	12/13/2019	Process and Facilities, Drug Product
Original Submission (SD # 9)	01/20/2020	Process
Response to Information request (SD #15)	02/12/2020	Process

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Response to Information request (SD #19)	2/21/2020	Drug substance
Updated stability data (SD # 18)	02/24/2020	Biopharmaceutics
Response to Information request (SD #19)	02/25/2020	Drug Product
Response to Information request (SD #21)	03/03/2020	Process
Response to Information request (SD #24)	03/11/2020	Process
Response to Information request (SD #26)	03/16/2020	Drug Substance
Response to Information request (SD #27)	03/19/2020	Process
Response to Information request (SD #28)	03/20/2020	Drug Substance

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Raymond Frankewich	Ali Al Hakim
Drug Product	Tefsit Bekele	Anamitro Banerjee
Process and Facility	Sridhar Thumma	Rakhi Shah
Microbiology	Sridhar Thumma	Rakhi Shah
Biopharmaceutics	Mei Ou	Banu Zolnik
Regulatory Business Process Manager	Shamika Brooks	
Application Technical Lead	Xing Wang	NA
ORA Lead	Caryn McNab	NA
Environmental	Raanan Bloom	NA

ORBIS Partner Agency Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Health Canada (Quality)		
Health Canada (Biopharmaceuics)		
TGA		

RELATED/SUPPORTING DOCUMENTS

DMFs:

[Applicant will complete]				[FDA will complete]	
DMF #	**Type**	**Holder**	**Item Referenced**	**Status**	**Comments**
(b) (4)	III		(b) (4)	Adequate	Per MAPP 5015.5 (Rev. 1).
	III			Adequate	
	III			Adequate	
	III			Adequate	
	III			Adequate	
	III			Adequate	
	III			Adequate	

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

[Applicant will complete this section.]

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	125279	Ripretinib IND

CONSULTS

[FDA will complete this section.]

None

Evaluation of the Quality Information

[Applicant to provide link to the data in m3 sections as appropriate]

1 EXECUTIVE SUMMARY

[FDA will complete this section.]

Complete CMC information has been submitted to NDA 213973 and found to be adequate upon completion of the review. All the facilities are approvable based on acceptable compliance history and pre-approval inspections. OPQ recommends **APPROVAL** of NDA 213973 for Ripretinib 50 mg tablet. OPQ grants an **18-month expiration period** to the drug product when stored in the original container at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F) (see USP controlled room temperature). In addition, OPQ grants a (b) (4) month re-test period for the drug substance when stored (b) (4) in the described packaging.

Ripretinib is a kinase inhibitor indicated for the treatment of patients with advanced gastrointestinal stromal tumor (GIST) who have received at least two prior tyrosine kinase inhibitor therapies. Ripretinib drug substance is a white to off-white crystalline solid. The drug substance is a lipophilic, weak base compound, practically insoluble in aqueous media. PSD is controlled at D90 NMT (b) (4) µm. Ripretinib drug product is an immediate release tablet for oral administration and is supplied as a 50-mg white to off-white oval shaped tablet debossed with 'DC1' on 1 side of the tablet. The composition of ripretinib tablets includes (b) (4) ripretinib drug substance and hypromellose acetate succinate (HPMCAS (b) (4)), microcrystalline cellulose, lactose monohydrate, crospovidone, silicon dioxide, and magnesium stearate. (b) (4) (b) (4) (b) (4) The specifications of the drug product are adequate to establish the drug product's identity, potency, and purity. The proposed dissolution method and acceptance criterion are acceptable. Analytical methods are appropriately validated. In vivo bridging between the clinical formulation and the commercial formulation has been established through the in vivo bioequivalence (BE) study (DCC-2618-01-002). Ripretinib tablets, 50 mg are packaged with (b) (4) desiccant (b) (4) into white HDPE bottles. Two packaging configurations are utilized, a 30-count configuration packed into a (b) (4) bottle and a 90-count packed into a (b) (4) bottle. A trend was observed for degradant (b) (4) on long-term and accelerated stability. An initial shelf life of 18 months is granted for the product when stored in the original container at USP controlled room temperature. Recommended dosage: 150 mg orally once daily.

2 APPLICATION BACKGROUND

[Applicant will complete this section.] Include information such as IND references, BTD/Fastrack/Orphan designations, etc.

Application Background and Regulatory History

Activity	Date	Summary
Orphan Drug Designation	October 2, 2014	Orphan drug designation was granted for the treatment of gastrointestinal tumors (GIST).
Type C, EOP2 – CMC	November 27, 2018	The following primary topics were addressed: 1. Justification for selection of regulatory starting materials. Information pertaining to the justification of starting materials is provided in Module 3.2.S.2.6. The commercial specifications, analytical procedures and batch analyses data for starting materials is provided in Module 3.2.S.2.3. 2. Analytical control strategies for drug substance and drug product. 3. Impurities safety qualification. Information pertaining to the qualification of drug substance impurities including results from in silico analyses is provided in Module 3.2.S.3.2. Information pertaining to the qualification of drug product degradants is provided in Module 3.2.P.5.5. 4. Registration stability protocols for drug substance and drug product. 5. Prospective post-approval change(s)
Fast Track Designation	June 21, 2019	Fast Track Designation was granted for the treatment of patients with advanced GIST who have received prior treatment with imatinib, sunitinib, and regorafenib, to demonstrate clinically meaningful and statistically robust improvement in PFS compared to placebo.
Dissolution Method Development Report (MDR) Submitted to IND 125279	August 22, 2019	The original dissolution MDR was submitted to IND 125279, Serial No: 0206 on August 22, 2019 and underwent a review by the Biopharmaceutics team. The Agency raised one question related to the dissolution method as part of preliminary comments to the pre-NDA meeting (dated October 4, 2019, reference ID: 4501746). Deciphera submitted a response to this question on November 1, 2019 and subsequently, on November 14, 2019, the Agency confirmed that there were no further questions/comments on the dissolution MDR.
Type B, Pre-NDA	October 9, 2019	The content and format of the planned submission of a New Drug Application (NDA) for ripretinib for the treatment of patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with imatinib, sunitinib, and regorafenib was discussed. CMC discussions and agreements included: • The Agency agreed with Deciphera's proposal to submit the initial application with 9-months long-

Activity	Date	Summary
		term stability data for the drug product followed by a stability update within 90-days of the original application. • Based on Deciphera's proposal to utilize concurrent validation for drug product, the Agency encouraged Deciphera to submit the process validation protocol and any available data at the time of submission. Prior to the pre-NDA meeting, Deciphera submitted a written response (via email on October 8, 2019, to Ms. Leah Her). The written response indicated that the process performance qualification (PPQ) protocol would not be available at time of submission (due to PPQ not commencing until end of January 2020), but rather, Deciphera proposed to submit the PPQ protocol within 30 days after the initial NDA submission. During the pre-NDA meeting, the Agency indicated that this proposal was acceptable (and the protocol would be considered a "minor" component). • The Agency agreed to the proposed product identifier of 'DC1'.
Breakthrough Designation	October 10, 2019	Breakthrough Therapy Designation was granted for the treatment of patients with advanced GIST who have received prior treatment with imatinib, sunitinib, and regorafenib.
Proprietary Name request	November 1, 2019	Submission of proprietary name request for ripretinib

3 SUMMARY OF CMC SPECIFIC PRESUBMISSION/SUBMISSION REGULATORY ACTIVITY

The Applicant's Position:

[To the Applicant: Insert text here.] Include CMC meeting dates and any Pre-NDA agreements

Refer to Section 2 for a comprehensive presentation of CMC-specific regulatory activity. In addition to the regulatory history presented in Section 2, Deciphera has been asked to partake in several pilot programs including "Real-Time Oncology Review" (RTOR) and Project Orbis. An informal teleconference was held on 05 September 2019 with the Agency to discuss potential participation in the on-going Oncology Center of Excellence (OCE) pilot program: RTOR. Under RTOR, pre-submission components were agreed upon during the 09 October 2019 teleconference with the Agency (Type B Pre-NDA Meeting; Ref ID 4513802). CMC-specific pre-submission content (under RTOR) is shown below.

CTD Section	Submission Date	Sequence
Module 1: Administrative information • Establishment Information **Module 3: Quality** • 3.2.S.2.1 (Manufacturer) • 3.2.P.3.1 (Manufacturers)	25 October 2019	0001
Module 1: Administrative information • 1.4.2 Statements of Right of Reference • 1.12.14 Environmental Assessment	08 November 2019	0002
Module 1: Administrative information • 1.14.1.1 Draft Carton and Container Labels (30 & 90 Count) • 1.14.1.2 Annotated Draft Labeling Text (Rationale in support of proposed indication) • 1.14.1.3 Draft Labeling Text (SPL, word, & PDF format)	19 November 2019	0003

Also during the 09 October 2019 teleconference with the FDA, Deciphera agreed to partake in Project Orbis with plans to submit marketing applications to Health Canada and the Australian Therapeutic Goods Administration shortly after NDA submission.

The FDA's Assessment:

[FDA will complete this section.]

Noted. No comments.

4 ENVIRONMENTAL ASSESSMENT

The Applicant's Position:

[To the Applicant: Insert text here.]

A claim for categorical exclusion from conducting an environmental impact statement or environmental assessment (EA) is made under 21 Code of Federal Regulations (CFR) Section 25.31 on the basis that the estimated introductory concentration (EIC) of the active moiety into the aquatic environment is less than 1 part per billion (ppb / µg/l). The applicant states that, to their knowledge, no extraordinary circumstances exist under 21 CFR Section 25.15(d) that would warrant preparation of an EA.

The FDA's Assessment:

[FDA will complete this section.]

The applicant provides a conservative estimate of the $EIC_{aquatic}$ (b) (4). The calculation assumes that all drug product produced in the U.S./year is expended and flows into publicly owned treatment works (POTWs) with no loss due to metabolism, degradation, or dilution and then discharged in POTW effluent. This EIC calculation meets the exclusion available at 21 CFR 25.31(b). Ripretinib toxicity studies submitted to the FDA, exhibited malformations in rats at a maternal dose of 20 mg/kg/day. This dose is significantly higher than the $EIC_{aquatic}$. A review of the literature did not indicate extraordinary circumstances; direct EAT activity is not indicated at the expected level of aquatic exposure.

The categorical exclusion cited at 21 CFR 25.31(b) is appropriate for the anticipated amount of drug to be produced and used. A statement of no extraordinary circumstances has been submitted. The claim of categorical exclusion is accepted.

5 BIOWAIVER REQUEST/BCS DESIGNATION REQUEST (if applicable/known)

The Applicant's Position:

[To the Applicant: Insert text here]

The NDA does not contain a biowaiver/BCS designation request.

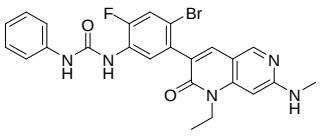
The FDA's Assessment:

Acceptable. Biowaiver request is not needed since there is only one strength drug product being proposed.

6 DRUG SUBSTANCE

a. GENERAL DESCRIPTION AND STRUCTURE

[To the Applicant: Insert text/Structure here.]

Structure	
	
USAN Name	ripretinib

IUPAC Name	1-(4-Bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl)-3-phenylurea
Molecular Weight	510.36 g/mol
Molecular Formula	$C_{24}H_{21}BrFN_5O_2$
Chirality	Ripretinib contains no stereogenic centers.
Solubility	Ripretinib is a lipophilic, weak base compound, practically insoluble in aqueous media, exhibiting solubility of only 1.6 µg/mL in simulated gastric buffer (pH 2), and solubility of < 1 µg/mL in phosphate buffered saline (pH 6.5) in the presence or absence of up to 2% bile salts. Ripretinib is sparingly soluble (≥ 30 mg/mL) in polar aprotic organic solvents including dimethylacetamide, dimethylformamide, and dimethylsulfoxide. Ripretinib is very slightly soluble (< 0.5 mg/mL) in acetone, ethyl acetate, methanol, ethanol or isopropanol. Intermediate solubilities between 1 and 13 mg/mL were obtained in 90:10 dichloromethane or 95:5 tetrahydrofuran/water, respectively.
	(b) (4)
pKa	The experimental pka value for ripretinib was assessed by a UV-metric titration between pH 1.5 and pH 12.5. Due to the exceedingly low aqueous solubility, the titration was determined under methanol-water co-solvent conditions (53.1 to 39.8 % w/w methanol). One pKa, with an aqueous value of 4.48 ± 0.01, was determined from the spectroscopic data collected by Yasuda-Shedlovsky extrapolation of the individual results obtained in various methanol-water ratios.
Appearance	White to off-white solid
	(b) (4)

[To the Applicant: Insert text here (approx. 100 words) for information not covered in the table above, as needed.]

The FDA's Assessment: **Adequate information is provided in the NDA to describe the relevant properties of ripretinib drug substance e. g. structure, formula, (b) (4) (b) (4) and solubility.**

The drug product (DP) which is called Ripretinib tablets, 50 mg is an immediate-release (IR) tablet for oral administration, 50 mg, with no coating. During the DP manufacturing process (b) (4)

(b) (4)

Recommended dose of ripretinib is 150 mg (3 50 mg tablets daily).

(b) (4)

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(b) (4)

The FDA's Assessment: **Adequate**

[FDA will complete this section.]

The test attributes for the three registration batches are within the proposed acceptance criteria.

e. BIOPHARMACEUTICS

[To the Applicant: Insert text here brief summary on the data to support the adequacy of dissolution method (medium, apparatus etc.), discriminating ability of the dissolution method for critical material attributes and process parameters, justification of selection of the acceptance criterion, include multipoint dissolution profile in a graphical format from clinical/PK and primary registration batches, data to support the BCS designation request, information on the purpose and data to support the biowaiver request i.e. compositional proportionality, PK linearity, comparative dissolution profiles with f2 analysis],bridging between the formulations/process/site changes that occurred throughout development and in vitro or in vivo data to support bridging, data to support IVIVC and/or PBPK modeling, if applicable. (approx. 300 words)]

(b) (4)

BTP-516 was developed in accordance with USP <1092> and was implemented for the release and stability testing of the registration stability batches of the proposed commercial drug product. The dissolution method parameters for BTP-516, the intended commercial dissolution procedure, are presented below.

USP Apparatus	Paddle Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criterion
Apparatus 2 (Paddles)	75 ± 3 rpm	900 mL	37.0°C ± 0.5°C	0.25% (wt/v) sodium lauryl sulfate in 10 mM sodium acetate buffer at pH 4.5	Q = (b) (4) % at 30 minutes

The discriminating ability of the dissolution the commercial procedure (BTP-516) was

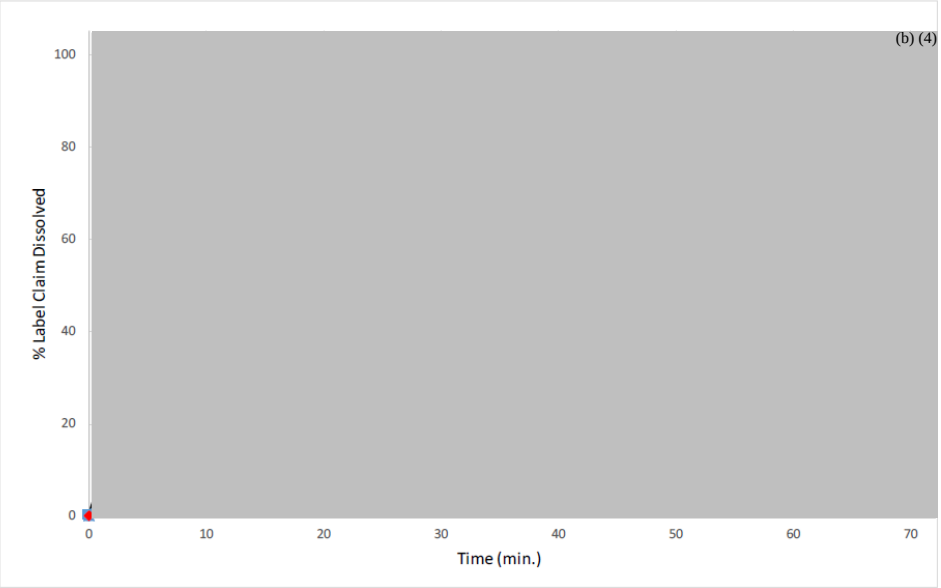
demonstrated by comparing the dissolution profiles of the reference (target) commercial drug product and test products (b) (4) (b) (4) (b) (4) A detailed discussion of these studies and the corresponding results is provided in the dissolution method development report in Module 3.2.R.2.

The justification for the selection of the dissolution acceptance criterion is based on the following factors including recommendations provided by the Agency in the EOP2 meeting minutes (dated November 28, 2018, Reference ID: 4355838):

- Multi-point dissolution data from the three primary registration batches and the five pivotal phase 3 clinical drug product batches (including clinical BE batch 18-0052).
- Single-point measurements are normally considered to be suitable for immediate-release dosage forms per ICH Q6A.
- The selection of the sampling time point should be where Q = (b) (4)% dissolution occurs.
- Establishment of the dissolution acceptance criterion is based on the individual and average in vitro dissolution data of each batch evaluated, equivalent to USP Stage S_2 testing (n = 12).
- The results of a human bioequivalence study comparing the proposed commercial drug product to the drug product used in the pivotal phase 3 study.
- Any changes to the dissolution profiles on long-term stability.

Based on the limited batch history for the intended commercial process drug product (3 registration batches), the release rate of the intended commercial drug product has been faster on average than the drug product batches used in the pivotal phase 3 clinical studies. This is demonstrated in Figure 3 which displays the mean (N=12) dissolution profile for five clinical (Phase 3) drug product batches (17-0121, 18-0052, 17-0295, 18-0447 and 18-0298) along with the composite average profile calculated for the three registration batches. Despite the observed difference(s) from in vitro results, bioequivalence was established between the intended commercial process and clinical process drug products. No significant change in dissolution data has been observed for the intended commercial ripretinib tablets when stored for up to 9-months at 25°C/60% RH and up to 6-months at 40°C/75% RH. An acceptance criterion of Q = (b) (4)% in 30-minutes is justified based on the comparison of the multi-point dissolution data from the primary registration batches and the pivotal phase 3 clinical drug product batches, the establishment of bioequivalency between the intended commercial process and clinical process drug products and the consistency of the dissolution results on stability.

Figure 3: Dissolution Profiles (N=12) for 50 mg Ripretinib Tablets for Phase 3 Batches Compared With Mean of 3 Registration Batches and BE Batches



The FDA's Assessment: **Adequate**

[FDA will complete this section.]

In vivo bridging between the clinical formulation (BE batch 18-0052) and the commercial formulation (BE batch 18-0402) has been established through the in vivo bioequivalence (BE) study (DCC-2618-01-002). Although one of the clinical batches (18-0447) appears to exhibit slightly slower dissolution (in Figure 3 above), *f2* similarity test calculated by this Reviewer demonstrates the similarity between this batch 18-0447 and BE batch 18-0052 (*f2* = 54).

FDA considers that the proposed dissolution method BTP-516 [*USP Apparatus II Paddle, 75 rpm, 900 mL of 10 mM sodium acetate buffer, pH 4.5, containing 0.25% (w/v) sodium dodecyl sulfate (SDS)*] is acceptable as a quality control (QC) test for the proposed drug product with acceptable discriminating ability (b) (4) material attributes (b) (4) and (b) (4) parameters (b) (4) (b) (4). The overall provided data supported the proposed dissolution acceptance criterion of "*Q=* (b) (4) *% in 30 minutes*", which is also acceptable.

For detailed review, please refer to the Attachment 1 Biopharmaceutics Review.

f. CONTAINER CLOSURE SYSTEM

[To the Applicant: Insert text here (approx. 50 words + any diagrams, references to appropriate CFR and USP chapters, MVTR data etc).]

Ripretinib tablets, 50 mg are packaged with (b) (4) desiccant into white high-density polyethylene (HDPE) bottles. The bottles are closed with (b) (4) child-resistant closures with a (b) (4) seal (b) (4). An overview of the pack presentations is provided in Table 19.

Table 19: Packaging Configurations for Ripretinib Tablets, 50 mg

Fill Count[a]	HDPE Bottle	Closure Type	(b) (4) Desiccant
30	(b) (4) white	(b) (4) child resistant closure with (b) (4) seal (b) (4)	(b) (4)
90	(b) (4) white	(b) (4) child resistant closure with (b) (4) seal (b) (4)	

[a] Not all configurations may be marketed
HDPE: high-density polyethylene

The FDA's Assessment: **Adequate**

[FDA will complete this section.]

The information provided for the container closure system is sufficient and it is suitable for the intended use. Two HDPE container configurations, (b) (4) for 30 counts and (b) (4) for 90 counts are proposed for commercial use. The bottles consist of (b) (4) child resistant closure with (b) (4) seal (b) (4). The (b) (4) bottles contain the proposed tablet counts along with (b) (4). (b) (4) desiccants (b) (4). The registration batches are stored in the two proposed primary container configurations for stability studies. The summary of the proposed container closure system along with the referenced DMFs are summarized in the table below.

Table 2: Bottle and Closure Packaging Components

Packaging Component		Product Contact Surface	Manufacturer	Corporate/Manufacturer Address	DMF No.
HDPE bottle, white	HDPE bottle	(b) (4)			

Table 2: Bottle and Closure Packaging Components (Continued)

Packaging Component		Product Contact Surface	Manufacturer	Corporate/Manufacturer Address	DMF No.
Child-resistant closure	child-resistant closure	(b) (4)			
desiccant					

DMF: Drug Master File; HDPE: high-density polyethylene;

The specifications for the HDPE bottle and closure were provided. The incoming components of the container closure system are accepted based on vendor's certificate of analysis and/or a reduced set of analytical tests. The DMFs and letters of authorization to reference the respective DMFs for each component of the primary packaging were submitted. Statements for compliance to the pertinent CFR regulations for direct food contact are provided for the (b) (4) desiccant. There is no quality review for (b) (4) DMF (b) (4) however this DMF has been referenced several times by other approved drug products therefore this component of the closure is adequate for the intended use. The DMFs referenced above for the container closure system will not be reviewed as they have been previously reviewed or referenced in other NDA applications and found acceptable for use.

g. STABILITY

[Applicant to fill out]

Performed per ICH Q1A:	Yes If no, specify		
Strength(s) and # of Batches	50 mg (3 registration batches)		
Bracketing	No **(In)Adequate** If inadequate, explain		
Matrixing	No **(In)Adequate** If inadequate, explain		
Container Closure System	**Commercial:** Yes; 30 ct / (b) (4) HDPE bottle and 90 ct / (b) (4) (b) HDPE bottle If yes, specify. If no, explain		
Storage Conditions/Storage Times			
Long-term	**25°C ± 2°C/60% RH ± 5% RH**	CCS Orientation	Upright
Min/Max storage time	**6 months**	36 months	
Intermediate	**Not Applicable**	CCS Orientation	N/A
Max storage time	Not Applicable		
Accelerated	**40°C ± 2°C/75% RH ± 5% RH**	CCS Orientation	Upright
Max storage time	**6 months**		
Specifications	Same as Release* (If not, specify and refer to 5.1) Stability tests include all relevant stability-indicating attributes from the drug product specification (i.e. description, assay, degradation products, dissolution, (b) (4)). Microbial enumeration testing is also performed at annual intervals. With the exception of specified degradation product (b) (4), the acceptance criteria for all tests included in the stability protocol are identical to the criteria utilized for release testing. As presented in Module 3.2.P.8.1, levels of specified degradant (b) (4) increase over time on storage of ripretinib tablets (at accelerated and long-term conditions). This increase is rate-limiting to the assignment of shelf life for the drug product. Based on a 13-week repeat-dose toxicity study, a stability limit of (b) (4) w/w is supported based on a safety margin of 3x and < 1x in rats and dogs, respectively. Establishing separate release and stability limits affords increased control of (b) (4) at release while maintaining a clinically relevant acceptance criteria supported by the repeat-dose toxicity studies throughout product shelf-life.		
Results			
OOS for long-term	No If yes, specify		
OOS for accelerated	No If yes, specify		
Long-term Result Range	Minimum	Maximum	Trending
Assay (b) (4)	(b) (4)		No trends observed

Degradant (b) (4) (NMT (b) (4)%)	(b) (4)		Refer to the discussion in the "Additional Information" section below
Degradant (b) (4) (NMT (b) (4)%)			No trends observed
Degradant (b) (4) (NMT (b) (4)%)			No trends observed
Individual Unspecified Degradants (NMT (b) (4)%)			No trends observed
Total Degradants (NMT (b) (4)%)			The increase in total impurities is only observed at 40°C/75%RH and (b) (4) is solely responsible.
Dissolution (Q(b) (4)% at 30 minutes)	(b) (4) (avg from n=6 vessels)	(b) (4) (avg from n=6 vessels)	No trends observed
(b) (4)	Conforms	Conforms	No trends observed
	(b) (4)		No trends observed
Additional Information	*Ensure critical quality attributes are covered and include information about any out of specifications or trending results* Although no significant change in (b) (4) levels have been observed for the registration stability samples and results remain within specification, the data demonstrate an increase in degradation over time at the 40°C/75% RH storage condition compared to that at 25°C/60% RH. Given that a trend was observed for (b) (4) on long-term and accelerated stability, a statistical analysis was performed at the long-term condition in both packaging configurations. Extrapolation of the long-term stability results was performed as outlined in ICH Q1E *Evaluation for Stability Data*. Although results from the 3 primary batches are considered poolable (based on available data through 9 months), the batches that presented the shortest estimated shelf life among all the batches/packaging configurations (Batches 18-0320 and 18-0321 in a (b) (4) bottle) were used to extrapolate shelf life for ripretinib tablets, 50 mg. Both batches exhibited the steepest slope and had the highest predicted (b) (4) levels at 18 months, which would still remain within the proposed specification limit of NMT (b) (4)% w/w (one-sided (b) (4)% confidence interval).		

	All registration batches of drug product manufactured have been placed into formal ICH stability studies and tested for TAMC and TYMC at the initial time point. The available microbial enumeration data, coupled with the (b) (4) data (see Module 3.2.P.5.6), support the removal of microbial enumeration testing from the specification, per ICH Q6A, Decision Tree 6.
Shelf Life	
Intended Storage Conditions	*Controlled room temperature: 20°–25° (68°–77° F)*
Requested / Granted	18 months | Choose an item.
Statistic Prediction Applied	Yes
Additional Information	*Include any product specific storage conditions here (e.g. discard after X weeks after opening, protect from light)* Store in the original container; the shelf life will be assigned from the date that the active ingredient is introduced into Stage 1 of the drug product manufacturing process (b) (4) (b) (4). Reference is made to the pre-NDA official meeting minutes dated October 31, 2019 (reference ID: 4513802) where the Agency agreed with Deciphera's proposal to submit the initial application with 9-months long-term stability data followed by a stability update within 90-days of the original application. The shelf-life proposal may be revised (b) (4) based on the updated data through 12 months of testing.
Post Approval Commitment	In accordance with ICH Q1A(R2), a commitment is made to place the first 3 production scale batches on long-term stability studies through the proposed shelf life and on accelerated studies for 6 months. In addition, during each year that the drug product is manufactured post-approval, 1 commercial batch will be incorporated into the ongoing stability program in each of the commercial packaging configurations. The annual batches will be tested according to the stability protocol provided in Module 3.2.P.8.2.
Per ICH Q1A	Yes; If no, explain
Additional Information	Add summary of Stress Studies

	Forced Degradation: A forced degradation study was performed to demonstrate the specificity and stability indicating nature of the analytical method used for assay and degradation product analysis of ripretinib tablets during release and stability testing. Ripretinib tablets and placebo samples were stressed under acid, base, oxidation, thermal, thermal/humidity, and light conditions. The mass balance was calculated for each condition and in all cases, the purity and homogeneity of the active peak were verified by reporting a purity angle less than the threshold angle. All chromatographic peaks were separated with no indication of interference. **Photostability:** Photostability testing was performed per ICH Q1B, Option 2. The tablets were stored in an open and closed container exposed to light and a closed container protected from light (control). The containers used in the photostability study are the same as the intended commercial primary package. All results for the open container met specification except for appearance and level of (b) (4). Test conditions evaluating the closed container (both exposed and protected) exhibit passing results for appearance, (b) (4) and all other test attributes. These results indicate that the intended commercial primary package is suitably protective from extreme photo-stress conditions. (b) (4)

The FDA's Assessment: **Adequate**

[FDA will complete this section.]

The primary stability studies were performed on three registration batches packaged in each of the proposed primary packaging for ripretinib tablets ((b) (4) HDPE bottle for 30 ct and (b) (4) HDPE bottle 90 ct). The batches were within specifications at long term storage of 25 °C/60% RH through 12 months. There are no significant physical or chemical changes at long-term storage conditions. The batches were within specifications at accelerated storage of 40 °C/75% RH through 6 months, however the level of (b) (4) increased (b) (4)% (spec: NMT (b) (4)%).

Supportive stability studies included photostability study and stress stability studies at 80 °C for 3 days, acidic, basic, and oxidative conditions. Forced degradation studies were conducted to demonstrate the stability indicating nature of the proposed analytical procedures for assay and related substance analysis. The samples exposed to 80 °C heat and heat/humidity at 80 °C/75% RH for three days have the most degradants forming mostly (b) (4). The data from these two experiments suggest that (b) (4) is temperature dependent as it is formed in (b) (4)% after 3 days at 80 °C as compared to (b) (4)% (b) (4) at 80 °C/75% RH after 3 days. All degradants observed in the forced degradation studies are resolved from ripretinib using the proposed HPLC method. Thus, HPLC method is specific and stability indicating.

The drug product was evaluated for photolytic stability by comparing description, assay identification, related substances, unspecified impurities, total degradation, and dissolution of ripretinib of tablets stored in the proposed closed and opened HDPE bottles exposed to light. The results were compared to control where the tablet stored in closed HDPE bottle was protected from light. The photo-stability study was conducted per ICH Q1B guideline. All test attributes met the acceptance criteria for the sample in a closed HDPE bottle exposed to light. This result indicates that the proposed primary configuration is suitable for the intended use. The sample stored in an open container was out of specification for (b) (4). This result along with the fact that the product degrades upon humidity exposure indicate that a note to dispense the tablets to patients in the original container protected from light that contains the drug and desiccant canister must be included in the labeling.
The applicant has committed to continue the stability studies of the registration batches post approval through the proposed shelf life. They have also committed to put the first three product batches on stability through the proposed shelf life and 6 months accelerated storage conditions per the stability protocol used for the registration batches. Annual batches will also be put on stability at long term storage conditions of 25 °C/60% RH through 48 months per the stability protocol shown below. The post approval stability protocol and stability commitment are acceptable.

Table 2: Stability Test Protocol for Annual Batches of Ripretinib Tablets, 50 mg

Storage Test Type	Storage Conditions	Storage Interval (Months)						
		Initial	6	12	18	24	36	48
Long-term	25°C/ 60% RH	A, M	A	A,M	A	A,M	A,M	A,M

RH: relative humidity; (b) (4)
Key to tests:
A: description, assay, degradation products, (b) (4) dissolution, (b) (4)
M: microbial limit testing

The applicant initially requested an 18 months shelf life for ripretinib tablets based on 9 months stability data at long term storage conditions. On February 24, 2020, the applicant provided updated stability data to include 12-month test interval for all three registration batches. The applicant changed the requested shelf life (b) (4) based on the available 12-month data set. They stated that the basis for requesting (b) (4) shelf life is no significant changes of the primary batches at long term and accelerated storage conditions through 12 months and 6 months respectively were observed. However, there was a change in the level of (b) (4) impurity at 40°C/75% RH. The formation of this impurity is temperature and humidity driven and it was observed at a level of (b) (4)% after 6 months under accelerated conditions. While the acceptance criterion for (b) (4) was met when the primary batches were stored at both long term and accelerated storage conditions, significant change in the level of (b) (4) over time under elevated temperature and humidity (from (b) (4) after 6 months). The applicant performed statistical analysis at the long-term storage conditions for one primary configuration ((b) (4) HDPE bottle) using two out of the three primary batches. The analysis predict that (b) (4) will be within specifications through (b) (4) months (maximum ~(b) (4)%). The statistical analysis shows that (b) (4)% (b) (4) will form at the requested shelf life of (b) (4) months. The proposed storage conditions is 20–25 °C with temperature excursions permitted at 15–30 °C. There is a risk for an increase in (b) (4) level and failure to be within specifications at the high end of the proposed temperature (b) (4). The shelf life may be extended by 6 months beyond the period covered by the available primary stability data of 12 months. **A shelf life of 18 months may be granted**.

LABELING

[FDA will complete this section.]

Adequate

Refer to the EDR and the DMEPA reviews for the most recent USPI and Carton/Container label. The adequacy of the USPI is currently being evaluated by the clinical division. Below is a brief review of section 3, 11, 16 and highlight section of the prescribing information.

Highlights: The proprietary name, Qinlock was found not acceptable by DMEPA as it could result in medication errors due to confusion with another product that is also under review. The established name, route of administration, dosage form and strength were provided and found acceptable from the CMC perspective.

Section 3: The dosage form and strength were provided. Adequate description of the identifying characteristics of the dosage form, including shape, color, and imprinting were provided. A minor change was recommended.

Section 11: Description of the drug substance, molecular formula, weight, and structure were provided. A description of ripretinb tablets along with a list of all the excipients were provided. The pharmacological class, chemical/physical properties (lipophilicity, solubility), dosage form/route of administration were all provided. This section is found to be acceptable.

Section 16: The applicant provided storage conditions "Store in the original container at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F to 86°F) [see USP controlled room temperature]'. Additionally, the following statement was recommended to be added in this section "Dispense to patient in original container only. Store in the original container with the desiccant to protect from moisture and light. Replace cap securely each time after opening. Do not discard desiccant."

The container/carton label and prescribing information comply with all regulatory requirements and they are recommended for approval from a CMC perspective pending revision of the storage conditions in the prescribing information and on container/carton label.

Final Risk Assessments

[FDA will complete this section.]

Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	Medium	(b) (4)	Low	
Physical stability (b) (4)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	High		Medium	
Moisture content	• Formulation • Container closure • Process parameters • Scale/equipment • Site	Medium		Low	
Dissolution – BCS Class II & IV	• Formulation • Raw materials • Exclude major reformulations • Process parameters • Scale/equipments • Site	Low		Low	
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low		Low	

ATTACHMENT 1

BIOPHARMACEUTICS REVIEW

EXECUTIVE SUMMARY

Ripretinib is an inhibitor of tyrosine-protein kinase (KIT) or platelet-derived growth factor alpha (PDGFRA) kinase that is intended for the treatment of gastrointestinal stromal tumors (GISTs) and other KIT- and PDGFRA-driven cancers.

(b) (4)

(b) (4) The final proposed drug product (DP), Ripritinib Tablet, 50 mg, are white to off-white oval tablets debossed with 'DC1' on one side of the tablet. The final drug product is immediate release tablets for oral administration. The proposed dose is 150 mg (three 50 mg tablets) taken orally once daily.

The Biopharmaceutics Review focuses on the evaluation of (i) the in vitro dissolution method and acceptance criterion as a quality control (QC) test for the proposed drug product, Ripretinib Tablets, 50 mg; (ii) the in vitro formulation bridging between the clinical and the commercial formulations.

In Vitro Dissolution Testing of the Finished Product:
The proposed commercial dissolution method (BTP-516) has been evaluated and found acceptable. The proposed dissolution method showed discriminating ability with regards to critical material attributes (b) (4) (b) (4) parameters (b) (4) (b) (4). Therefore, the proposed dissolution method is **acceptable** as a quality control (QC) test for ripretinib tablets, 50 mg for batch release and stability testing. The overall dissolution data also support the proposed acceptance criterion of "Q (b) (4)% in 30 minutes".

The approved in vitro dissolution method and acceptance criterion for the proposed Ripretinib Tablets, 50 mg, are presented below:

USP Apparatus	II (Paddle)
Rotation Speed	75 rpm
Dissolution Medium	900 mL of 10 mM sodium acetate buffer, pH 4.5, containing 0.25% (w/v) sodium dodecyl sulfate (SDS or SLS)
Temperature	37°C±0.5°C
Sampling Time	10, 15, 20, 30, 45, 60 minutes
Acceptance Criterion	Q= (b) (4) % in 30 minutes

Formulation Bridging:

The composition and manufacture site (b) (4) of the clinical and commercial ripretinib 50 mg tablets are the same; however, the manufacturing process and the (b) (4) between the two formulations are different. Therefore, the Applicant conducted an in vivo bioequivalence (BE) study to bridge the clinical and commercial formulations. BE study will be assessed by the Office of Clinical Pharmacology (OCP). It should be noted that the clinical batch and commercial batch have comparable dissolution profiles with similarity factor (*f2*) is 53. Therefore, bridging between the clinical and commercial formulations have been established provided OCP's assessment finds the BE study adequate refer to OCP review for further details.

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 213973 for the proposed (b) (4) (ripretinib) Tablets, 50 mg, is recommended for **APPROVAL.**

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(b) (4)

Overall, this Reviewer considers the in vivo and in vitro bridging between the clinical and commercial formulation has been established. No additional studies are needed.

Recommendation Page

[FDA will complete this section.]

Drug Substance: Approval

Primary Reviewer: Raymond Frankewich Date: 04/06/2020
Secondary Reviewer: Ali Al-Hakim Date: 04/06/2020

Drug Product: Approval

Primary Reviewer: Tefsit Bekele Date: 04/01/2020
Secondary Reviewer: Anamitro Banerjee Date: 04/03/2020

Process and Facility: Approval

Primary Reviewer: Sridhar Thumma Date: 03/23/2020
Secondary Reviewer: Rakhi Shah Date: 03/23/2020

Biopharmaceutics: Approval

Primary Reviewer: Mei Ou Date: 04/03/2020
Secondary Reviewer: Banu Zolnik Date: 04/03/2020

Application Technical Lead: Approval

Xing Wang Date: 04/14/2020

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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