

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210861Orig1s000

211710Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 211710

Review # 1

Drug Name/Dosage Form	Larotrectinib solution
Strength	20 mg/mL solution (100 mL)
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Loxo Oncology, Inc.
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0002	March 26, 2018	All CMC
0009	May 23, 2018	Drug Product
0010	May 25, 2018	Drug Substance, Drug Product
0012	June 01, 2018	Drug Product
0013	June 15, 2018	Drug Product, Microbiology
0014	June 21, 2018	Drug Product
0015	June 22, 2018	Process
0016	June 28, 2018	Drug Product
0019	July 09, 2018	Drug Product, Microbiology
0020	July 10, 2018	Drug Product, Microbiology
0030	August 02, 2018	Biopharmaceutics
0031	August 06, 2018	Microbiology
0042	August 24, 2018	Drug Product
0043	September 18, 2018	Drug Product, Process, Facilities
0044	September 20, 2018	Microbiology
0047	September 28, 2018	Microbiology
0048	October 05, 2018	All CMC
0050	October 30, 2018	Process, Facility
0053	November 06, 2018	Drug Product, Microbiology

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Rohit Tiwari	Charles Jewell
Drug Product	Olen Stephens	Anamitro Banerjee
Process	Christina Capacci-Daniel	Ying Zhang
Microbiology	Jonathan Burgos	Elizabeth Berr
Facility	Christina Capacci-Daniel	Ying Zhang
Biopharmaceutics	Gerlie Gieser/Banu Zolnik	Banu Zolnik
Regulatory Business Process Manager	Steven Kinsley	
Application Technical Lead	Anamitro Banerjee	
Laboratory (OTR)		
ORA Lead	Caryn McNab/Michael Tollon	
Environmental	Ron Bloom (EA)	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

. DMFs:

	Type		Status	Comments
(b) (4)	Type IV	(b) (4)	Acceptable	Currently supports approved NDAs and sufficient information in the NDA
	Type IV		Acceptable	Reviewed 07/24/2018
	Type IV		Acceptable	Reviewed 07/18/2018
	Type IV		Acceptable	Reviewed 07/18/2018
	Type IV		Acceptable	Reviewed 07/18/2018
	Type IV		Acceptable	Reviewed 07/18/2018

. Other Do

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	210861	Larotrectinib Capsules
IND	121211	Larotrectinib
IND	(b) (4)	Larotrectinib

2. CONSULTS

None

Executive Summary

I. Recommendations and Conclusion on Approvability

The NDA 211710 is recommended for APPROVAL from the CMC point of view. The quality information provided in this NDA is acceptable.

II. Summary of Quality Assessments

A. Product Overview

This submission (NDA 211710) is a 505(b)(1) application submitted concurrently with the NDA 210861 that was granted breakthrough designation for the treatment of unresectable or metastatic solid tumors with NTRK-fusion proteins in adult and pediatric patients who require systemic therapy and who have either progressed following prior treatment or who have no acceptable alternative treatments. This NDA was also granted orphan drug designation for the treatment of solid tumors with NTRK-fusion proteins and rare pediatric disease designation for the treatment of infantile fibrosarcoma.

Several OND and CMC only meetings were held with the review team prior to the submission. The applicant also submitted the NDA 210861 for larotrectinib 25 mg and 100 mg capsules. The drug substance is an NME.

Proposed Indication(s) including Intended Patient Population	<i>Treatment of adult and pediatric patients with locally advanced or metastatic solid tumors harboring an NTRK gene fusion</i>
Duration of Treatment	<i>Until the patient is no longer benefiting from the therapy or until unacceptable toxicity occurs</i>
Maximum Daily Dose	<i>200 mg</i>
Alternative Methods of Administration	<i>None</i>

B. Quality Assessment Overview

Larotrectinib is a chiral, non-hygroscopic, off-white to yellow to pinkish yellow crystalline solid freely soluble in water at low pH, but sparingly soluble at high pH. Larotrectinib is sparingly in most organic solvents, except for methanol and ethanol. The applicant reports a melting point of ~219°C and two pK_a values of 2.0 and 6.3 (these are obviously pK_a values of the conjugate acid). The applicant indicates that only one crystalline form has been detected.

All the drug substance information is provided in the NDA 210861 and is cross-referenced in this NDA.

The drug product consists of 100 mL solution of 20 mg/mL larotrectinib oral solution filled in 100 mL (b) (4) bottle, (b) (4) and capped (b) (4) child resistant (b) (4) closure (b) (4). The oral solution contains Hydroxypropyl Betadex, (b) (4) Sodium Citrate, Purified Water, Dihydrate, (b) (4)

(b) (4) Flavor, (b) (4) as excipients. No novel excipients, or excipients of human or animal origin are used. Purified water and hydroxypropyl betadex are of compendial grade. The specifications for the (b) (4) flavors, (b) (4) (b) (4) (b) (4) are adequate. The components are compatible with the container closure system.

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The proposed specifications for the oral solution includes tests for appearance, identity, assay, purity, related substances, elemental impurities, pH, deliverable volume, microbial enumeration testing, and antimicrobial preservative effectiveness test. The proposed specifications and the associated analytical methods were found appropriate for this dosage form. The batch data for 3 batches of the oral solution (batch size (b) (4) manufactured using 3 different drug substance lots) conform to the proposed specifications. The drug product batches manufactured at the proposed commercial site (b) (4)

The applicant has modified the manufacturing (b) (4) (b) (4). The applicant will manufacture additional batches to confirm that the corrective actions address the (b) (4) concerns.

The proposed 100 mL (b) (4) Bottle, (b) (4) and capped with a (b) (4) closure (b) (4) is compatible with the proposed product based on the information provided in the submission. The applicant did not provide LOA for the DMFs for container closure components, however, provided

adequate information in the NDA to support the use of container closure. **The applicant was asked to provide the LOAs for the container closure component DMFs post action as General Information or in the Annual Reports.**

Based on the stability data provided by the applicant for three registration batches of each strength manufactured at (b) (4) the proposed commercial scale ((b) (4) commercial scale), the applicant proposed expiration dating period of (b) (4) months when stored at 2-8 °C. However, (b) (4) in some of the batches manufactured in the commercial drug product manufacturing site (b) (4), a 12 month expiration dating period may be granted for the product when stored under refrigerated conditions. The expiration dating period was conveyed to the applicant during the late cycle meeting.

The applicant was asked to address two prominent microbiological issues encountered during the review: the missing *Burkholderia cepacia* complex (BCC) monitoring program, and data supporting the minimum effective levels of (b) (4) (b) (4) two preservative components, methylparaben and potassium sorbate) in the drug product. The BCC risk assessment and validation of the proposed BCC detection methodology provided by the applicant in response to the Agency's information request was found adequate. The applicant also performed Antimicrobial Effectiveness Testing (AET), per USP <51>, on 5 non-GMP batches containing decreasing levels (b) (4) (b) (4) when compared to the proposed final drug product formulation). All the test formulations, including batch 5 (- (b) (4) met the USP <51> acceptance criteria. Additionally, AET is part of the release and stability specification for each batch, providing further assurance that the product's preservative content is adequately controlled. The application was found adequate following the resolution of these concerns.

Additionally, a late-cycle amendment, SDN 0053 (6-Nov-2018) was submitted to address in-use stability concerns for the drug product remaining in the bottle after a (b) (4) day administration period. The applicant provided AET and microbial enumeration data demonstrating that even with a reduced amount of (b) (4) in formulation variants, the drug product sufficiently limits microbial growth to be used beyond a typical (b) (4) day in-use period. Accelerated and supportive stability data demonstrate the drug product has sufficient chemical stability to be used beyond a (b) (4) day in-use period. Therefore, the current label that is being negotiated with the applicant will be modified to remove statements that remaining larotrectinib solution must be discarded after (b) (4) days of use.

The drug substance and drug product manufacturing, packaging, and testing facilities were evaluated and found to be acceptable based on inspectional history. **A post-approval inspection is recommended for the drug product manufacturing facility, (b) (4) (b) (4) to evaluate the design and results of the final PPQ study implementing the revised (b) (4) process (b) (4).**

The applicant has submitted a claim of categorical exclusion and the required statement of no extraordinary circumstances. The applicant also submitted environmental risk assessment data to support this claim. The categorical exclusion cited at 21 CFR 25.31(b)

is appropriate for the estimated amount of drug to be produced for direct use. The claim of categorical exclusion is acceptable.

C. Special Product Quality Labeling Recommendations

None

D. Final Risk Assessment (see Attachment)



E. List of Deficiencies for Complete Response

None

Application Technical Lead Name and Date:

Anamitro Banerjee, November 19, 2018



Anamitro
Banerjee

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LABELING

I. Package Insert

1. Highlights of Prescribing Information

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	VITRAKVI (larotrectinib)
Dosage form, route of administration	Solution, (b) (4)
Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Solution: 20 mg/mL

2. Section 2 Dosage and Ad

Item	Information Provided in NDA
(Refer to Labeling Review Tool)	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	(b) (4)

3. Section 3 Dosage Forms

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Oral Solution
Strengths: in metric system	20 mg/mL
Active moiety expression of strength with equivalence statement (if applicable)	Equivalence statement missing. Applicant to be instructed to add the following: "20 mg/mL larotrectinib is equivalent to 24.6 mg/mL larotrectinib sulfate"
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	(b) (4) clear yellow to orange solution

4. Section 11 Description

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	“Larotrectinib is a (b) (4) kinase inhibitor. VITRAKVI (larotrectinib) capsules and solution (b) (4) are formulated using larotrectinib sulfate.”
Dosage form and route of administration	Solution for oral (b) (4)
Active moiety expression of strength with equivalence statement (if applicable)	“20 mg/mL larotrectinib (b) (4) (b) (4) (24.6 mg/mL larotrectinib sulfate)”
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	NA
Statement of being sterile (if applicable)	NA
Pharmacological/ therapeutic class	Tyrosine kinase inhibitor
Chemical name, structural formula, molecular weight	Adequate
If radioactive, statement of important nuclear characteristics.	NA
Other important chemical or physical properties (such as pKa or pH)	“Larotrectinib sulfate is an off-white to pinkish yellow solid that is not hygroscopic. (b) (4) (b) (4) (b) (4). The aqueous solubility of larotrectinib at 37°C is pH dependent (very soluble at pH 1.0 and freely soluble at pH 6.8, according to USP descriptive terms of solubility). ”

5. Section 16 How Supplied/Storage and Handling

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(17))
Strength of dosage form	20 mg/mL solution
Available units (e.g., bottles of 100 tablets)	100 mL bottle
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Clear yellow to orange solution
Special handling (e.g., protect from light)	NA
Storage conditions	Refrigerate solution at 2° to 8°C (36° to 46°F). Do not freeze
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured for: Loxo Oncology, Inc. Stamford, CT 06901

Reviewer’s Assessment of Package Insert: *Pending*

Labeling negotiations are on-going. The current container configuration for the oral solution could potentially provide 50-60 days worth of dosing for the youngest patients, exceeding the (b) (4) day in-use testing provided in the original NDA submission. Information requests have been submitted and data is pending that may allow a longer in-use period. As such, labeling to discard the oral solution (b) (4) days after opening may be removed. The pending data will not be available until ~10 days prior to the PDUFA date, so labeling changes may occur after finalizing this review. Any label changes will be managed through the clinical division PM directly.

(b) (4)

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	TRADENAME® (larotrectinib)	TRADENAME® (larotrectinib)
Dosage strength	20 mg/mL	20 mg/mL
Net contents	100 mL	100 mL
“Rx only” displayed prominently on the main panel	Increase prominence	Increase prominence
NDC number (21 CFR 207.35(b)(3)(i))	71777-392-01	71777-392-01
Lot number and expiration date (21 CFR 201.17)	Clearly denote space on carton and container label for lot number and expiration dates	
Storage conditions	Keep Refrigerated. Store at 2° to 8°C (36° to 46°F).	Keep Refrigerated. Store at 2° to 8°C (36° to 46°F).
Bar code (21CFR 201.25)	Present and adequate	Present and adequate
Name of manufacturer/distributor	Manufactured for: Loxo Oncology, Inc. Stamford, CT 06901	Manufactured for: Loxo Oncology, Inc. Stamford, CT 06901 Manufactured in United Kingdom Marketed by: Loxo Oncology, Inc. Marketed and distributed by: Bayer HealthCare Pharmaceuticals Inc.
And others, if space is available	NA	NA

Reviewer’s Assessment of Package Insert: *Pending*

➤ ***Minor edits necessary for the bottle and container label. These edits have been communicated through the clinical project manager and may be implemented prior to filing this labeling review.***

List of Deficiencies:

- 1. Increase the prominence of “Rx” on the carton and container labels.***

- 2. Clearly denote the space to be used for the lot number and expiry on the carton and container labels.*

Overall Assessment and Recommendation:

Primary Labeling Reviewer Name and Date: Olen Stephens 20-Aug-18

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



Olen
Stephens

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Banerjee

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BIOPHARMACEUTICS**Product Background:**

NDA: 211710 (NME; Priority and Rare Pediatric Disease Priority Reviews Requested; Rolling NDA; Orphan Drug Designation)

Drug Product Name / Strength: Larotrectinib Solution, 20 mg/mL

Route of Administration: Oral

Proposed Dosage: Adults - 100 mg twice daily; Pediatrics – 100 mg/m² twice daily with a maximum of 100 mg per dose

Applicant Name: Loxo Oncology, Inc.

Review Recommendation:

From the Biopharmaceutics perspective, NDA 211710 for Larotrectinib Oral Solution is recommended for **APPROVAL**.

Review Summary:

This Biopharmaceutics review focused on the evaluation of the need for bridging studies and a biowaiver request.

Dissolution testing is not applicable for the routine QC of the proposed drug product because it is a solution for oral use. The solubility of larotrectinib is pH-dependent; at 37°C, >3.63 mg/mL dissolves at pH 1.0, decreasing to about 0.779 mg/mL at pH 6.8.

The proposed to-be-marketed drug product has the same formulation and manufacturing process as the drug products used in clinical trials, and primary registration and supportive stability studies, except for a slight difference (b) (4). Such difference did not result in a significant change in the solution pH and other measured physicochemical properties of the larotrectinib oral solution. (b) (4) agents are added to the solution due to the (b) (4) of the active pharmaceutical ingredient (API).

A biowaiver request is not needed nor required because larotrectinib PK, efficacy and/or safety of the proposed to-be-marketed larotrectinib oral solution were evaluated in clinical studies involving adult patients and pediatric patients.

Bridging of Formulations**Reviewer's Assessment: ADEQUATE**

Formulation bridging data *per se* are not needed because there was essentially no change in the formulation of the proposed drug product during clinical development. The proposed commercial drug substance manufacturer (b) (4) supplied the API of the clinical trial lots and the registration stability lots. During clinical trial

use, the product was stored under refrigeration (the recommended long-term storage condition).

The proposed to-be-marketed product has the same bottle size (100 mL) and Drug Product Manufacturer (b) (4) and similar scale (b) (4) as the three primary registration stability lots.

Two supporting stability lots (i.e., 16-0035, and 17-0066) were used in Phase 1/2 clinical trials, and differ from the registration stability lots in terms of Drug Product Manufacturer (b) (4), and bottle size/calculated headspace (b) (4). [Note that an in-use stability study over 30 days was also performed using Lot 17-0066.] However, the measured physicochemical properties (such as pH, appearance, assay, impurity) of the clinical trial (supporting stability) lots and primary registration stability lots (were reported not to change during 18 months of long-term storage [2 - 8°C] and) are comparable to those in the proposed QC specifications of the final, proposed to-be-marketed drug product (b) (4). Solution color and impurities level appear to be stability indicating. Note that based on real-time stability data, the proposed product shelf-life is (b) (4) months. Note also that the density of larotrectinib oral solution is 1.2 g/mL.

Biowaiver Request

Reviewer's Assessment: NOT NEEDED

A biowaiver request is not needed nor required because larotrectinib PK, efficacy and or safety of the proposed to-be-marketed solution and the larotrectinib oral capsules [submitted as NDA 210861] were evaluated in a food-effect and relative BA study (LOXO-TRK-16007) involving healthy subjects, , QT Study (-16009), and in Phase 1 and 2 clinical trials involving adult patients (-14001) and pediatric patients (e.g., -15003). -15002, as well as several single-patient studies.

List of Deficiencies:

None

Primary Biopharmaceutics Reviewer Name and Date:

Gerlie Gieser, Ph.D. (8/10/2018)

Secondary Reviewer Name and Date):

Banu Zolnik, Ph.D. (10/15/2018)



**Gerlie
Gieser**

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Zolnik**

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MICROBIOLOGY[IQA Review Guide Reference](#)**Product Background:****NDA:** 211710**Drug Product Name/
Strength:** Larotrectinib
(20 mg/mL)**Route of Administration:** Oral**Applicant Name:** Loxo Oncology, Inc.
701 Gateway Boulevard
Suite 420
South San Francisco, CA 94080**Manufacturing Site:**

(b) (4)

Method of Sterilization:**Review Recommendation:** Adequate**Theme (ANDA only):** N/A**Justification (ANDA only):** N/A**Review Summary:****List Submissions Being Reviewed:**

Submit	Received	Review Request	Assigned to Reviewer
	03/24/2018	N/A	02/20/2018
	06/15/2018		06/19/2018
	07/09/2018		07/09/2018
	07/10/2018		07/11/2018
	08/06/2018		08/08/2018
	09/20/2018		09/20/2018

09/28/2018		10/01/2018
10/05/2018		10/05/2018
11/06/2018		11/06/2018

Highlight Key Outstanding Issues from Last Cycle: N/A
Remarks: This NDA was submitted in E-CTD format.
Concise Description Outstanding Issues Remaining:
Supporting Documents: N/A
List Number of Comparability Protocols (ANDA only): N/A

S Drug Substance

N/A

P.1 Description of the Composition of the Drug Product

(Information Located at: Sequence 0002 [03/26/2018], Section 3.2.P.1, Description and Composition of the Drug Product, Page 1; Section 3.2.P.3.2, Batch Formula, Page 1; Sequence 0013 [06/15/2018], Section 1.2, Cover Letter, Page 4/9)

Larotrectinib is a non-sterile solution for oral administration. It will be packaged in a 20 mg/mL configuration filled in 100 mL bottles (b) (4). See table below for drug product composition.

Ingredient	Quality Standard	Function	Quantity, g/Bottle
Larotrectinib Sulfate	In House Specification	Drug Substance	2.46 g
Purified Water	USP		(b) (4)
Hydroxypropyl Betadex	Parenteral Grade, Ph Eur., USP/NF		(b) (4)
Sodium Citrate Dihydrate (b) (4)	USP/NF		(b) (4)

*, Methylparaben and potassium sorbate are preservative agents included in the formulation. (b) (4)

Reviewer's Assessment: The information provided by the applicant was adequate.

Acceptable

P.2 Pharmaceutical Development

N/A

P.2.5 Microbiological Attributes

N/A

Container/Closure and Package Integrity

N/A

Antimicrobial Effectiveness Testing

(Information Located at: Sequence 0013 [06/15/2018], Section 1.2, Cover Letter, Page 3-5/9; Sequence 0019 [07/09/2018], Section 1.2, Cover Letter, Page 3-7/19; Sequence 0053 [11/06/2018], Section 1.2, Cover Letter, Page 3-14/16)

Information about the drug product antimicrobial effectiveness testing was not included in the original submission, dated 24 March 2018.

The following deficiency was issued to the applicant in the 25 May 2018 Day 60 Letter microbiology information request:

Section 3.2.P.5.2, Analytical Procedures (Page 2/9), indicates that antimicrobial effectiveness testing according to USP <51> is performed to evaluate the drug product. More information is needed for review. Address the following:

- a. Identify the antimicrobial component(s) of the drug product formulation and their minimum content specification for release and stability.*
- b. Provide the actual results of USP <51> antimicrobial effectiveness testing performed with the drug product formulated with the antimicrobial component(s) at their minimum content specification for release or stability, whichever is lower. In your response, provide the composition of the drug product tested, a description of the test inoculum, and the acceptance criteria.*

In the 15 June 2018 response, the applicant indicated the drug product formulation contains (b) (4)

(b) (4) purified water, sucrose, glycerin, sorbitol, flavoring, citric acid, and sodium phosphate. Additionally, (b) (4) contains two preservative components, methylparaben and potassium sorbate.

However, (b) (4) the applicant indicated the amount of methylparaben and potassium sorbate cannot be quantitatively added to the drug product formulation. Consequently, the applicant was unable to demonstrate antimicrobial effectiveness of methylparaben and potassium sorbate (b) (4). As an alternative quality control approach, the applicant performed AET, per USP <51> guidelines, with drug product clinical and registration stability lots as part of its 2-year stability study and a 30 day in-use study. Data from the evaluations were not included in the 15 June 2018 submission. The applicant also indicated it planned to investigate the (b) (4) (b) (4) drug product by performing AET with drug product (b) (4)

A mid-cycle teleconference meeting was held with the applicant on 28 June 2018. During the meeting, the Agency requested AET data from the 2-year stability study as well as from the 30 day in-use study. Moreover, the applicant was informed that the Agency supported the applicant's plan to assess (b) (4) the drug product. The applicant committed to providing the stability data (see Section P.8.3 [Stability Data] below) and a proposed AET protocol (b) (4) (b) (4).

In a 09 July 2018 submission, the applicant included a proposed AET protocol (b) (4) (b) (4). For the study, the applicant plans to produce (b) (4) scale non-GMP stability batches using the proposed manufacturing processes and the same container closure system as the clinical batches ((b) (4) bottles). While the drug product stability batches will contain the same amount of the excipients and API described in the original formulation, the concentration (b) (4) will vary. (b) (4) (b) (4)

(b) (4) After formulation, the drug product lots will be stored at either 2-8°C or 25°C (60% RH). The antimicrobial effectiveness of the stored batches will be tested on 0, 4, and 8 weeks as per USP <51> guidelines, with a proposed acceptance criteria of passing for the following compendial organisms: *E. coli*, *P. aeruginosa*, *S. aureus*, *C. albicans*, and *A. brasiliensis*. The point at which one of the formulation batches fails the AET will be indicative of (b) (4) efficient drug product preservation. A proposed timeline was provided (see table below).

Stability Time Point	Schedule Pull Date	AET Results Received
T = 0	Week of Aug. 13 th	Week of Sep. 24 th
T = 4 Weeks	Week of Sep. 3 rd	Week of Oct. 15 th
T = 8 Weeks	Week of Oct. 1 st	Week of Nov. 12 th

In a 06 November 2018 submission, the applicant provided AET data from six non-GMP drug product batches evaluated by (b) (4) at release or after a four-week storage at 2-8°C or 25°C (60% RH). The container closure system (CCS) used to fill the various bulk solutions was not identical to the CCS which will be used during manufacturing. However, the utilized (b) (4) bottle/cap were the same CCS employed in the production of the

clinical trial batches. The various batch formulations and their respective AET data are shown in the tables below.

Note to Reviewer: The applicant also included Microbial Enumeration Testing data in the 06 November 2018 submission. However, these data will not be addressed in the review since only AET data was requested. Moreover, while it was not specified in the 06 November 2018 submission, the applicant indicated in the 09 July 2018 communication that the non-GMP batches would be tested as per USP <51> guidelines.

Larotrectinib (20 mg/mL) Formulation

(b) (4), *

Material	LOXO-101 Control	Batch #1 (b) (4)	Batch #2 (b) (4)	Batch #3 (b) (4)	Batch #4 (b) (4)	Batch #5 (b) (4)
LOXO-101 API	(b) (4)					
Purified Water, USP						
Hydroxypropyl Betadex, Parenteral Grade, Ph Eur., NF						
(b) (4)						
Sodium Citrate, Dihydrate, (b) (4) USP/NF (b) (4)						
Total	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

*, The LOXO-101 Control batch was manufactured with the same proposed drug product formulation. The (b) (4)

(b) (4) All drug product batches contained the same amount of API.

Antimicrobial Effectiveness Testing of LOXO-101 Control and Drug Product Batches 1-5

Microbial Purity Test	Specification	Batch Number	Time Point/Condition				
			T = 0 (Initial)	T = 4 Weeks*		T = 8 Weeks**	
				2-8°C	25°C 60%RH	2-8°C	25°C 60%RH
Antimicrobial Effectiveness Testing USP <51>	<u>Pass for Specific Organisms:</u> <i>E. coli, P. aeruginosa, S. aureus, C. albicans, and A. brasiliensis</i>	LOXO-101 Control Batch # 1 Batch # 2 Batch # 3 Batch # 4 Batch # 5	Pass		Data Not Available		

*, Samples obtained on 10 September 2018.

** , Samples obtained on 04 October 2018. According to the 09 July 2018 communication above, data will be available after 12 November 2018.

Conclusion: The AET acceptance criterion was met, at T = 0 and T = 4 weeks, when the control and test batches 1-5 were stored at 2-8°C and 25°C/60% RH.

Note to Reviewer: Of note, while the USP <51> tests were performed with drug product samples which were obtained after a 4-week storage at 2-8°C and 25°C/60% RH (10 September 2018), by the conclusion of the AET test, the samples were approximately 8 weeks old. Moreover, the fact that all the test formulations, including batch 5 (b) (4) met the acceptance criteria provides assurance that, despite the lack of a preservative content specification, the product's preservative content is adequately controlled and the product will remain adequately preserved after 4 weeks of use.

Reviewer's Assessment: The information provided by the applicant was adequate.

Acceptable

P.3 Manufacture

P.3.1 Manufacturers

(b) (4)

Reviewer's Assessment: The information provided by the applicant was adequate.

Acceptable

P. 3.3 Description of the Manufacturing Process and Process Controls

(b) (4)

P.5 Control of Drug Product

P. 5.1 Specification

(Information Located at: Sequence 002 [03/26/2018], Section 3.2.P.5.1, Specifications, Page 1/1; Sequence 0047 [09/28/2018], Section 3.2.P.5.1, Specifications [addition of BCC detection method]; Sequence 0048 [10/05/2018], Section 3.2.P.5.1, Specifications)

Microbial Purity Test	Acceptance Criterion	Method
Total aerobic microbial count (TAMC)*	(b) (4) CFU/g	USP <61>
Total combined yeast/mold count (TYMC) *	CFU/g	
Test for Specified Microorganisms*	<i>E. coli</i> : Absent**	USP <62>
	<i>Burkholderia cepacia</i> complex (BCC): Absent	METR-0744-AS (Version 3)
Antimicrobial Preservative Effectiveness	<u>Pass for Specific Organisms:</u> <i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>C. albicans</i> , and <i>A. brasiliensis</i>	USP <51>

*, Specifications are for aqueous preparations for oral use. The specifications corroborate with the recommended limits described in USP <1111>.

** ,The analytical procedure provided in Section 3.2.P.5.2 confirms 1 g of the drug product will be tested for absence of *E. coli* as per USP <1111>.

The following deficiency was issued to the applicant in the 25 September 2018 microbiology information request:

Please update Table 1 (Specifications for Larotrectinib Oral Solution) in Module 3.2.P.5.1 to include the drug product release test for absence of BCC, the test method, and the acceptance criteria.

In the 28 September 2018 response, the applicant indicated that the specifications table in Module 3.2.P.5.3 was updated. However, the sponsor did not reference the correct test method (e.g. METR-0744-AS [Version 3]). Instead, the applicant referenced USP <62>, which does not test for BCC.

The following deficiency was issued to the applicant in the 03 October 2018 microbiology information request:

The updated drug product release test for absence of BCC in Module 3.2.P.5.1 (Specifications) is acknowledged. However, please note that USP <62> does not describe a BCC test method. Please revise Table 1 (Specifications for Larotrectinib Oral Solution) in Module 3.2.P.5.1 to reference the correct BCC test method (e.g., METR-0744-AS [Version 3]).

In the 05 October 2018 response, the sponsor indicated the drug product specification was updated in Table 1 (Section 3.2.P.5.1, Specifications) to include the correct BCC test

method, METR-0744-AS (Version 3). The specifications table above was also updated above to reflect the addition of the new BCC test.

Reviewer's Assessment: The information provided by the applicant was adequate.

Acceptable

P.5.2 Analytical Procedures

N/A

P.5.3 Validation of Analytical Procedures

Endotoxins

N/A

Sterility

N/A

Microbial Limits

(Information Located at: Sequence 0013 [06/15/2018], Section 3.2.P.5.3, Validation of Analytical Procedures, Pages 31-36/36)

Data from the microbial enumeration validation analyses was not provided in the original submission, dated 24 March 2018.

The following deficiencies were issued to the applicant in the 25 May 2018 Day 60 Letter microbiology information request:

Section 3.2.P.5.2, Analytical Procedures (Page 2/9) indicates the subject drug product is tested for Total Aerobic Microbial Count (TAMC) according to USP <61>. However, USP <61> TAMC method suitability data were not provided in Section 3.2.P.5.3 (Validation of Analytical Procedures). Provide a summary of the study performed to demonstrate the suitability of the test method. In your response, include:

- 1) a description of the preparation of the drug product test and control samples;*
- 2) the amount of drug product tested;*
- 3) a description of the preparation of each inoculum;*
- 4) the enumeration method (e.g. membrane filtration, plate count);*
- 5) the acceptance criteria; and*
- 6) the actual results.*

and

Section 3.2.P.5.2, Analytical Procedures (Page 2/9) indicates the subject drug product is

tested for Total Yeasts and Molds Count (TYMC) according to USP <61>. However, USP <61> TYMC method suitability data were not provided in Section 3.2.P.5.3 (Validation of Analytical Procedures). Provide a summary of the study performed to demonstrate the suitability of the test method. In your response, include:

- 1) a description of the preparation of the drug product test and control samples;
- 2) the amount of drug product tested;
- 3) a description of the preparation of each inoculum;
- 4) the enumeration method (e.g. membrane filtration, plate count);
- 5) the acceptance criteria; and
- 6) the actual results.

In the 15 June 2018 response, the applicant provided the requested information from the Total Aerobic Microbial Count (TAMC) and Total Combined Yeast/Mold Count (TYMC) studies. Results from both evaluations are detailed below.

Counting Method Suitability

Method: The pour-plate method was utilized, as per the harmonized USP <61> and Ph.Eur.2.6.12 guidelines. Microorganisms were incubated on Tryptic Soy Agar (TSA) and Sabouraud Dextrose Agar (SCDB) plates. After incubating the inoculated media under the conditions described in the table below, counts from the control plates were compared to the counts from plates containing microorganisms exposed to drug product.

Note to Reviewer: It was not indicated whether the evaluation was performed with at least two replicates, as per USP <61> guidelines. However, clarification will not be requested since the results provided (see table below) were from average CFU counts, suggesting replicates were included in the study.

Number of Units

Tested: A total of 10 grams of drug product, from batch DEV7738, were mixed with Universal Quenching Agent (water for irrigation, peptone water, lecithin, tween80, L-Histidine, sodium thiosulphate, potassium dihydrogen phosphate, disodium hydrogen phosphate dihydrate).

Inoculum: Compendial microorganisms were used. Bacteria - *Pseudomonas aeruginosa* ATCC 9027, *Bacillus subtilis* ATCC 6633, *Staphylococcus aureus* ATCC 6538; Fungi - *Candida albicans* ATCC 10231, *Aspergillus brasiliensis* ATCC 16404. The inoculum for each of the microorganisms was not provided.

Note to Reviewer: Although the inoculum for each of the microorganisms was not described, clarification will not be requested since the applicant indicated the pour plate method performed was in accordance with USP <61>.

Acceptance

Criteria:

A mean count of any of the test organisms should not differ by a factor greater than 2 from the microorganism value observed in the plates without drug product ((b) (4) % recovery).

Test Microorganisms	Recovery of Test Microorganisms*			
	Batch DEV7738			
	Control CFU/Plate (- DP**)	Description	CFU/Plate (+ DP)	
			Dilution Ration of Test Solution	
1/10 Dilution			1/100	
Total Aerobic Microbial Count (TAMC)				
Tryptic Soy Agar				
<i>Pseudomonas aeruginosa</i> ATCC 9027	(b) (4)	Average Count	(b) (4)	(b) (4)
		% Recovery		
		Factor		
<i>Bacillus subtilis</i> ATCC 6633		Average Count		
		% Recovery		
		Factor		
<i>Staphylococcus aureus</i> ATCC 6538		Average Count		
		% Recovery		
		Factor		
<i>Candida albicans</i> ATCC 10231		Average Count		
		% Recovery		
		Factor		
<i>Aspergillus brasiliensis</i> ATCC 16404		Average Count		
		% Recovery		
		Factor		
Total Combined Yeast/Mold Count (TYMC)				
Sabouraud Dextrose Agar				
<i>Candida albicans</i> ATCC 10231		Average Count		
		% Recovery		
		Factor		

<i>Aspergillus brasiliensis</i> ATCC 16404	(b) (4)	
	Average Count	(b) (4)
	% Recovery Factor	

*, For TAMC – Bacterial Counts, TSA plates were incubated at 30-35°C for a Maximum of 3 Days; For TAMC – Fungal Counts, TSA plates were incubated at 30-35°C for a Maximum of 5 Days; For TYMC – Fungal Counts, SCDA plates were incubated at 20-25°C for a Maximum of 5 Days.

**, Microorganisms were Exposed only to UQA. Average CFU counts are from a study performed in duplicate.

Conclusion: The acceptance criterion was met.

Reviewer’s Assessment: The information provided by the applicant was adequate.

Acceptable

Test for Specified Microorganisms

(Information Located at: Sequence 0013 [06/15/2018], Section 3.2.P.5.3, Validation of Analytical Procedures, Pages 31-36/36)

Data from the tests for specified microorganisms was not provided in the original submission, dated 24 March 2018.

The following deficiency was issued to the applicant in the 25 May 2018 Day 60 Letter microbiology information request:

Section 3.2.P.5.2, Analytical Procedures (Page 2/9) indicates that the Test for E. coli is performed according to USP <62>. However, data demonstrating that the USP <62> Test for E. coli is suitable for the subject drug product were not provided in Section 3.2.P.5.3 (Validation of Analytical Procedures). Provide a summary of the study performed to demonstrate the suitability of the test method. In your response, include:

- 1) a description of the preparation of the drug product test and control samples;*
- 2) the amount of drug product tested;*
- 3) a description of the preparation of each inoculum;*
- 4) the incubation conditions (i.e. time and temperature);*
- 5) the acceptance criteria; and*
- 6) the actual results.*

In the 15 June 2018 response, the applicant provided the requested information from the test for specified microorganisms. Results from the study are detailed below.

Method: The evaluation was performed as per the harmonized USP <62> and Ph.Eur.2.6.13 guidelines. *Escherichia coli* was grown in TSB, MacConkey Broth, and MacConkey Agar. *Salmonella enterica ssp.* was grown in TSB, Rappaport Vasiliadis Broth, and XLD Agar. Incubation conditions are detailed in the table below.

Number of Units

Tested: A total of 10 grams of drug product, from batch DEV7738, were mixed with Universal Quenching Agent.

Inoculum:

Compendial microorganisms were used. *Escherichia coli* (ATCC 8739) and *Salmonella enterica ssp.* (ATCC 14028). The inoculum for each of the microorganisms was not provided.

Note to Reviewer: Although the inoculum for each of the microorganisms was not described, clarification will not be requested since the applicant indicated the study was performed in accordance with USP <62>.

Acceptance

Criteria: *Escherichia coli* (ATCC 8739) and *Salmonella enterica ssp.* (ATCC 14028) should be recovered when the microorganisms are exposed to the Larotrectinib Oral solution.

Test for Specified Microorganism	Detection	
	Media Used	Results (+ Larotrectinib Oral Solution)
<i>Escherichia coli</i> (ATCC 8739)	TSB ¹	<i>Escherichia coli</i> (ATCC 8739) Isolated
	MacConkey Broth ²	
	MacConkey Agar (90 mm Petri Dish) ³	
<i>Salmonella enterica ssp.</i> (ATCC 14028)	TSB ¹	<i>Salmonella enterica ssp.</i> (ATCC 14028) Isolated
	Rappaport Vasiliadis Broth ⁴	
	XLD Agar (90 mm Petri Dish) ⁵	

- ¹, 30-35°C for 18 Hours, 7 Minutes
- ², 42-44°C for 23 Hours, 10 Minutes
- ³, 30-35°C for 23 Hours, 11 Minutes
- ⁴, 30-35°C for 23 Hours, 09 Minutes
- ⁵, 30-35°C for 23 Hours, 11 Minutes

Conclusion: The acceptance criterion was met.

Reviewer's Assessment: The information provided by the applicant was adequate.

Acceptable

P.7 Container Closure

Summary table of the container closure system proposed

(Information Located at: Sequence 0002 [03/26/2018], Section 3.2.P.7, Container Closure System, Page 1)

Description of Container Closure System – 100 mL (b) (4) bottle, (b) (4)
 (b) (4) with a (b) (4) child resistant (b) (4)
 (b) (4) closure (b) (4)

Reviewer’s Assessment: The information provided by the applicant was adequate.
Acceptable

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(Information Located at: Sequence 0002 [03/26/2018], Section 3.2.P.8.1, Stability Summary and Conclusion, Pages 2-3/10, 5-7/10, and 10/10; Sequence 0020 [07/10/2018], Section 3.2.P.8.3, Stability Data)

Proposed Expiry: (b) (4) Months. The expiry date is based on data obtained from Long Term Storage (5°C±3°C) and Accelerated Storage (25±2°C/60±5% RH; 40±2°C/75±5% RH) condition studies. Antimicrobial Preservative Effectiveness Testing (AET) was performed on clinical stability batches at 0, 3, 6, 12, 24, 36, and 48 months (Long-Term Storage, currently on-going) and at release for batches stored under accelerated conditions. Microbial enumeration testing and AET were performed on registration stability batches at 0, 3, 6, 12, 18, and 24 months (Long-Term Storage, currently on-going) as well as at 0 months for registration batches stored under accelerated conditions. A 30 day in-use stability test was also performed. The stability antimicrobial preservative effectiveness and microbial enumeration testing specifications are the same as the proposed release specifications.

Reviewer’s Assessment: The information provided by the applicant was adequate.
Acceptable

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

(Information Located at: Sequence 0002 [03/26/2018], Section 3.2.P.8.2, Post-Approval Stability Protocol and Stability Commitment, Pages 1-2, /3)

Strength	Microbial Purity Test	Acceptance Criteria	Method
Larotrectinib (20 mg/mL)	Total aerobic microbial count (TAMC)	Max. (b) (4) CFU/Unit	USP <61>*
	Total combined yeast/mold count (TYMC)	Max. (b) (4) CFU/Unit	
	<i>E. coli</i>	Absent	USP <62>*
	Antimicrobial Preservative Effectiveness Testing	<u>Pass for Specific Organisms:</u> <i>E. coli</i> <i>P. aeruginosa</i>	USP <51>**

		<i>S. aureus</i> <i>C. albicans</i> <i>A. brasiliensis</i>	

*, Specifications are for aqueous preparations for oral use. The specifications corroborate with the recommended limits described in USP <1111>.

** , Testing will be performed at (b) (4) Specifications are for Category 3 Drug Products.

The testing schedule in the post-approval protocol is as follows:

Storage Condition	Testing Interval, Months						
	T = 0	3	6	9	12	18	24
2 - 8°C	X*	-**	-	-	X	-	X
25 ± 2°C/60 ± 5% RH	X	-	-	-	-	-	-

*, Microbial Enumeration and Antimicrobial Preservative Effectiveness will be performed.

** , Testing will not be conducted

Stability Commitment - After completing stability studies of the three registration batches and three validation batches, the applicant commits to placing one commercial batch per year on its proposed stability program.

Reviewer's Assessment: The information provided by the applicant was adequate.

Acceptable

P.8.3 Stability Data

(Information Located at: Sequence 0002 [03/26/2018], Section 3.2.P.2, Pharmaceutical Development, Pages 14, 41-42/48; Sequence 0002 [03/26/2018], Section 3.2.P.8.3, Stability Data; Sequence 0013 [06/15/2018], Section 1.2, Cover Letter, Page 5/9; Sequence 0020 [07/10/2018], Section 3.2.P.8.1, Stability Summary and Conclusion, Pages 5-7/10; Sequence 0020 [07/10/2018], Section 3.2.P.8.3, Stability Data)

Microbiologically relevant data (e.g., microbial enumeration tests and antimicrobial effectiveness testing) from on-going stability studies were included in the original submission, dated 24 March 2018. Moreover, in the 15 June 2018 submission (FDA Request 8, Page 5/9) the applicant indicated AET studies had been performed on drug product stored up to 2 years at 2-8°C and that the antimicrobial effectiveness of the drug product had also been evaluated during a 30 day in-use stability study. However, neither of the results were included in the submission. The information was requested from the applicant during the mid-cycle teleconference meeting held on 28 June 2018 (see IR below).

Following the mid-cycle teleconference, the following information request was issued to the applicant on 02 July 2018:

During the June 28, 2018 teleconference, you indicated that the results from antimicrobial effectiveness testing (AET) performed with 24 month drug product stability samples and a 30 day in-use study will be provided to the Agency for review. Please provide summaries of the AET and 30 day in-use studies and the actual results by July 13, 2018.

In the 10 July 2018 response, the applicant provided updated stability information, data from the 2 year stability study, and from the 30 day in-use study.

Batch Type	Batch Number	Stability Conditions	AET ¹	MET ²	
<u>Clinical Batch</u> ³ (60 mL Bottle with (b) (4) (b) (4) Child Resistant (b) (4) (b) (4) Closure)	16-0035	2-8°C	Pass at 0, 6, and 12 Months	Not Performed	
		25°C/60% RH	Pass at 0 Months		
		40°C/75% RH			
	Lot 17-0066	2-8°C	Pass at 0 and 6 Months (Study is On-Going)		
		25°C/60% RH	Pass at 0 Months		
		40°C/75% RH			
<u>Registration Stability Batches</u> (100 mL Bottle, (b) (4) Child Resistant (b) (4) (b) (4) Closure)	Dev 7812 (b) (4)	2-8°C	Pass at 0, 3, and 6 Months (Study is On-Going)	Pass at 0 and 6 Months (Study is On-Going)	
		25°C/60% RH	Pass at 0 Months	Pass at 0 Months	
		40°C/75% RH			
	Dev 7813 (b) (4)	2-8°C	Pass at 0, 3, and 6 Months (Study is On-Going)	Pass at 0 and 6 Months (Study is On-Going)	
		25°C/60% RH	Pass at 0 Months	Pass at 0 Months	
		40°C/75% RH			
	Dev 7814 (b) (4)	2-8°C	Pass at 0, 3, and 6 Months (Study is On-Going)	Pass at 0 and 6 Months (Study is On-Going)	
		25°C/60% RH	Pass at 0 Months	Pass at 0 Months	
		40°C/75% RH			
	30-Day In-Use Stability Study				
	<u>Clinical Batch</u> (60 mL Bottle with (b) (4) (b) (4) Child Resistant (b) (4) (b) (4) Closure)	Lot 17-0066	2-8°C	<u>Pass at 30 Days for Specific Organisms⁴:</u> <i>E. coli</i> <i>P. aeruginosa</i> <i>S. aureus</i> <i>C. albicans</i> <i>A. brasiliensis</i>	<u>Total Aerobic Microbial Count (TAMC):</u> (b) (4) CFU/g <u>Total Combined Yeast and Mold Count (TYMC):</u> (b) (4) CFU/g

¹, Antimicrobial Effectiveness Test (AET); Acceptance Criteria (for Category 3 Drug Products): Pass for Specific Organisms: *E. coli*, *P. aeruginosa*, *S. aureus*, *C. albicans*, and *A. brasiliensis*.

², Microbial Enumeration Testing (MET); Acceptance Criteria: TAMC, (b) (4) CFU/g; TYMC, (b) (4) CFU/g.

³, Although the clinical lot formulation and the proposed commercial drug product formulation are similar, they are not identical. The minor differences between the two formulations are: While the clinical lot formulation contains (b) (4) purified water and (b) (4) sodium citrate, the commercial drug product formulation contains (b) (4) purified water and sodium citrate.

⁴, T = 3-month time point results for lot 17-0066 at the 2-8°C condition was used to establish T = 0 for this study.

Note to Reviewer: Although it was indicated in Section 3.2.P.8.1 that MET was performed with the Registration Stability Batches stored at 2-8°C during the 3-month testing period, it was indicated in Section 3.2.P.8.3 (Tables 8-16) that MET was not performed at this timepoint. Clarification will not be requested from the applicant since adequate results were obtained during the study performed at 6 months.

The applicant provided results from the AET performed with Clinical Lot 16-0035 stored at 2-8°C for 24 months (see results table below). The data corroborated with the 24-month timepoint information shown in the stability table above.

AET Results (24-Month Timepoint): Clinical Lot 16-0035 (2-8°C)

Organism	Plate Count Results						Log Reduction		
	-1	-2	-3	-4	-5	CFU/mL	Specification	Result	
AET Testing Time Point: 14 days									
<i>P. aeruginosa</i>									(b) (4)
<i>E. coli</i>									
<i>S. aureus</i>									
<i>C. Albicans</i>									
<i>A. brasiliensis</i>									
AET Testing Time Point: 28 days									
<i>P. aeruginosa</i>									(b) (4)
<i>E. coli</i>									
<i>S. aureus</i>									
<i>C. Albicans</i>									
<i>A. brasiliensis</i>									(b) (4)

Similarly, the applicant provided AET and MET results from the 30 day in-use study performed with Clinical Lot 17-0066 stored at 2-8°C, which also corroborated with information shown in the stability table above. During the study, to simulate drug product administration, 0.5 mL of Larotrectinib (20 mg/mL) were removed twice daily from the 60 mL container. On day 30, the remaining drug product volume was analyzed by MET and AET.

AET Results (30 Day In-Use Test): Clinical Lot 17-0066 (2-8°C)

Organism	Plate Count Results						Log Reduction		
	-1	-2	-3	-4	-5	CFU/mL	Specification	Result	
AET Testing Time Point: 14 days									
<i>P. aeruginosa</i>									(b) (4)
<i>E. coli</i>									
<i>S. aureus</i>									
<i>C. Albicans</i>									
<i>A. brasiliensis</i>									
AET Testing Time Point: 28 days									
<i>P. aeruginosa</i>									(b) (4)
<i>E. coli</i>									
<i>S. aureus</i>									
<i>C. Albicans</i>									
<i>A. brasiliensis</i>									(b) (4)

MET Results (30 Day In-Use Test): Clinical Lot 17-0066 (2-8°C)

Attribute	Acceptance Criterion	Evaluation	Result	CFU/g
Total Aerobic Count:	(b) (4) CFU/g	Tested at a 1:10 dilution in soy broth containing 4% Tween 80 and 0.5% lecithin (TSB-M) 3-5 days, 30-35°C	Plate 1: 0 Plate 2: 0	(b) (4) CFU/g
Total Combined Yeast and Mold Count	(b) (4) CFU/g	Tested at a 1:10 dilution in soy broth containing 4% Tween 80 and 0.5% lecithin (TSB-M) 5-7 days, 20-25°C	Plate 1: 0 Plate 2: 0	(b) (4) CFU/g
<i>E. coli</i>	Absent	<i>E. coli</i> tested per 1 g (10 mL of 1:10 dilution) in 100 mL TSB-M	-	Absent

Reviewer's Assessment: The information provided by the applicant was adequate.

Acceptable**A Appendices**

N/A

A.2 Adventitious Agents Safety Evaluation

N/A

A.2.1 Materials of Biological Origin

N/A

A.2.2 Testing at Appropriate Stages of Production

N/A

A.2.3. Viral Testing of Unprocessed Bulk

N/A

A. 2.4 Viral Clearance Studies

N/A

R Regional Information***Executed Batch Records***

(Information Located at: Sequence 0002 [03/26/2018], Section 3.2.R, Regional Information, Batch Number Dev 7813-LOXO-101 20 mg/mL Oral Solution)

Executed lot #(s): Executed batch record summaries were available for exhibit batch Dev 7813. The batch was generated according to the proposed manufacturing parameters.

Reviewer's Assessment: The information provided by the applicant was adequate.

Acceptable***Comparability Protocols***

N/A

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

The recommended storage condition for the subject drug product is 2-8°C. Additional product dilution prior to administration was not indicated.

Reviewer's Assessment: The information provided by the applicant was adequate.

Acceptable

Post-Approval Commitments:

N/A

Lifecycle Management Considerations

N/A

List of Deficiencies: N/A

Primary Microbiology Reviewer Name and Date:

Jonathan Burgos, Ph.D.
13 November, 2018

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

Elizabeth Berr, Ph.D.
13 November, 2018



**Jonathan
Burgos**

Digitally signed by Jonathan Burgos

Date: 11/15/2018 12:01:49PM

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**Elizabeth
Barr**

Digitally signed by Elizabeth Barr

Date: 11/15/2018 12:01:54PM

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay, stability	• Formulation • Container closure • Raw materials (b) (4) • Scale/equipment • Site	L		Acceptable	No change in risk assessment after review
Physical stability (phase separation)	• Formulation • Raw materials (b) (4) • Scale/equipment • Site	L		Acceptable	No change in risk assessment after review
Physical stability (solid state)	• Formulation • Raw materials (b) (4) • Scale/equipment • Site	L		Acceptable	No change in risk assessment after review
Dosing accuracy	• Dosing device • Formulation (b) (4) • Scale/equipment • Site	M		Acceptable	
Palatability	• Formulation • Excipient change (b) (4) • Scale/equipment • Site	M		Acceptable	
Microbial Limits	• Formulation • Raw materials (b) (4) • Scale/equipment • Site	L		Acceptable	No change in risk assessment after review
Leachables	• Formulation • Container closure (b) (4) • Scale/equipment • Site	M		Acceptable	



Anamitro
Banerjee

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Date: 11/19/2018 03:38:42PM

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Recommendation: APPROVAL

NDA 210861

Review # 1

Drug Name/Dosage Form	Larotrectinib capsule
Strength	25 mg and 100 capsules
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Loxo Oncology, Inc.
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0001	December 19, 2017	Drug Substance
0002	December 29, 2017	Drug Substance
0005	February 07, 2018	Drug Substance
0008	March 14, 2018	Drug Substance, Facility
0009	March 26, 2018	All CMC
0016	May 29, 2018	Drug Substance, Drug Product
0019	June 15, 2018	Drug Product
0020	June 22, 2018	Process, Facility
0033	August 02, 2018	Biopharmaceutics
0035	August 07, 2018	Biopharmaceutics
0036	August 10, 2018	Biopharmaceutics
0053	October 09, 2018	Biopharmaceutics
0059	October 25, 2018	Biopharmaceutics

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Rohit Tiwari	Charles Jewell
Drug Product	Olen Stephens	Anamitro Banerjee
Process	Christina Capacci-Daniel	Ying Zhang
Facility	Christina Capacci-Daniel	Ying Zhang
Biopharmaceutics	Gerlie Gieser	Banu Zolnik
Regulatory Business Process Manager	Steven Kinsley	
Application Technical Lead	Anamitro Banerjee	
ORA Lead	Caryn McNab	
Environmental	Ron Bloom (EA)	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

DMFs:

	Type		Status	Comments
(b) (4)	Type III	(b) (4)	Acceptable	Not reviewed for this NDA per ONDP policy
	Type III		Acceptable	
	Type III		Acceptable	
	Type III		Acceptable	
	Type III		Acceptable	
	Type III		Acceptable	
	Type III		Acceptable	

Other Doc

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	211710	Larotrectinib Oral Solution 20 mg/mL
IND	121211	Larotrectinib
IND	(b) (4)	Larotrectinib

2. CONSULTS

None

Executive Summary

I. Recommendations and Conclusion on Approvability

The NDA 210861 is recommended for APPROVAL from the CMC point of view. The quality information provided in this NDA is acceptable.

II. Summary of Quality Assessments

A. Product Overview

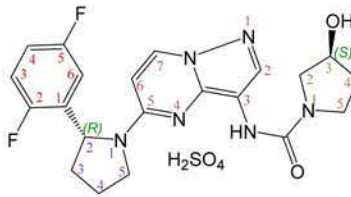
NDA 210861 is a 505(b)(1) application that was granted breakthrough designation for the treatment of unresectable or metastatic solid tumors with NTRK-fusion proteins in adult and pediatric patients who require systemic therapy and who have either progressed following prior treatment or who have no acceptable alternative treatments. This NDA was also granted orphan drug designation for the treatment of solid tumors with NTRK-fusion proteins and rare pediatric disease designation for the treatment of infantile fibrosarcoma. The applicant is requesting rare pediatric disease priority review voucher.

This NDA was submitted as a rolling submission. Several OND and CMC only meetings were held with the review team prior to the submission. The applicant also submitted the NDA 211710 for larotrectinib 20 mg/mL oral solution concurrently referencing this NDA (210861) for drug substance information. The drug substance is an NME.

Proposed Indication(s) including Intended Patient Population	<i>Treatment of adult and pediatric patients with locally advanced or metastatic solid tumors harboring an NTRK gene fusion</i>
Duration of Treatment	<i>Until the patient is no longer benefiting from the therapy or until unacceptable toxicity occurs</i>
Maximum Daily Dose	<i>150 mg</i>
Alternative Methods of Administration	<i>None</i>

B. Quality Assessment Overview

Larotrectinib is a chiral, non-hygroscopic, off-white to yellow to pinkish yellow crystalline solid freely soluble in water at low pH, but sparingly soluble at high pH. Larotrectinib is sparingly soluble in most organic solvents, except for methanol and ethanol. The applicant reports a melting point of ~219°C and two pK_a values of 2.0 and 6.3 (these are obviously pK_a values of the conjugate acid). The applicant indicates that only one crystalline form has been detected.

**Larotrectinib**

(S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate

Chemical Formula: C₂₁H₂₄F₂N₆O₆S

Molecular Weight: 526.52

The applicant provided spectroscopic evidence such as HRMS, ¹H, ¹³C, and ¹⁹F NMR, ¹H-¹³C HSQC and HMBC and IR as well as single crystal XRD with ORTEP diagram to support the proposed structure of larotrectinib. The data are consistent with the proposed structure including the stereochemistry.

The drug substance is manufactured in 4 steps:

(b) (4)

(b) (4)

(b) (4) controls and specifications for the intermediates were found adequate. The designation of the starting materials were found acceptable and consistent with ICH Q11. The applicant provided a list of impurities (related substances, residual solvents, and elemental impurities). All the related substance impurities are controlled as per ICH Q3A. The specifications and the analytical methods for the drug substance were found to be adequate to ensure adequate drug substance quality.

The drug substance is packaged

(b) (4)

(b) (4)

The batch analysis and stability data shows no OOS result or obvious trends with the exception of

(b) (4)

Based on the data presented in the application, a retest period of (b) (4) months for the drug substance when stored at (b) (4) may be granted as proposed by the applicant.

Drug Product:

The drug product consists of the larotrectinib sulfate drug substance filled into hard gelatin capsules with no excipients. The capsules are supplied in 25 mg and 100 mg strengths (expressed as free base).

Commercial scale of the drug product is (b) (4) units

(b) (4)

(b) (4)

The manufacturing process consists of

(b) (4)

(b) (4)

(b) (4) No quality critical attributes were identified that are likely to lead to a product quality failure, however, per

FDA request, the applicant established specifications for the particle size distribution of the drug substance. The analytical methods and developmental data are adequate to assure identity, strength, quality, purity, potency, bioavailability, and stability as required under 21 CFR 314.50(d)(1)(ii)(a). BSE/TSE certificates from the vendors for the hard gelatin capsule shells are provided.

In a TCON with the applicant on October 15, 2018, per FDA recommendation, the applicant agreed to use the proposed dissolution method [using 0.01N HCl; USP Apparatus 1 (basket) at 75 rpm; 900 mL] and the revised acceptance criterion ($Q = \frac{(b) (4)}{(4)}\%$ at 45 minutes) for QC testing of the drug product on **an interim basis**. **The applicant will then collect dissolution data at release and stability with the FDA recommended method using 0.1N HCl and will implement an acceptance criterion of $Q = \frac{(b) (4)}{(4)}\%$ at 15 minutes.** The applicant has agreed to submit a prior approval supplement (PAS) within a year of the NDA action date proposing the changes to the dissolution. Refer to the meeting minutes of the TCON attached to this review.

The applicant provided batch data for 3 registration batches of the capsule for each strength. No OOS data are reported.

The 25 mg capsules (60 count) are packaged in $(b) (4)$ HDPE bottles and 100 mg capsules (60 count) capsules are packed in $(b) (4)$ HDPE bottles. Both the bottles are closed with a $(b) (4)$ cap along with $(b) (4)$ seal. The applicant claims that all the components comply with FDA requirements for use as indirect food additives and provided USP<661> and USP<671> testing results.

Expiration dating period of 36 months for both the strengths as proposed by the applicant may be granted when stored under the USP controlled room temperature conditions of 20°C - 25°C with excursions allowed from 15°C - 30°C.

The applicant's request for categorical exclusion from the preparation of an environmental assessment for larotrectinib per 21 CFR 25.31(b) is acceptable as the EIC is projected to be less than 1 ppb.

The labeling for the drug product is acceptable from the CMC perspective.

The drug substance and drug product manufacturing, packaging, and testing facilities were evaluated and found to be acceptable based on inspectional history. **A post-approval inspection is recommended for the drug product manufacturing facility, $(b) (4)$ $(b) (4)$ to evaluate the continued performance of the $(b) (4)$ equipment and corrective actions from a previous inspection.**

C. Special Product Quality Labeling Recommendations

None

D. Final Risk Assessment (see Attachment)



E. List of Deficiencies for Complete Response

None

Application Technical Lead Name and Date:

Anamitro Banerjee, October 31, 2018



Anamitro
Banerjee

Digitally signed by Anamitro Banerjee

Date: 10/31/2018 08:09:09AM

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LABELING

I. Package Insert

1. Highlights of Prescribing Information

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	VITRAKVI (larotrectinib)
Dosage form, route of administration	Capsules, for oral use
Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Capsules: 25 mg and 100 mg

2. Section 2 Dosage and Administration

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	“Swallow capsules whole with water. Do not chew or crush capsules.” Note that the applicant was contacted to confirm the statement is in place due to the extremely bitter tasting drug substance. Breaking the capsule could negatively impact compliance due to taste. Also, this statement was used during the clinical study informed consent form.

3. Section 3 Dosage Forms and Strengths

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(4))
Available dosage forms	Capsules
Strengths: in metric system	25 mg and 100 mg
Active moiety expression of strength with equivalence statement (if applicable)	Equivalence statement missing. Applicant to be instructed to add the following: “25 mg larotrectinib is equivalent to 30.7 mg larotrectinib sulfate and 100 mg larotrectinib is equivalent to 123 mg larotrectinib sulfate”
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	25 mg capsule: white opaque hard gelatin capsule, size 2, with blue printing of “LOXO” and “LARO 25 mg” on body of capsule 100 mg capsule: white opaque hard gelatin capsule, size 0, with blue printing of “LOXO” and “LARO 100 mg” on body of capsule

4. Section 11 Description

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	“Larotrectinib is a (b) (4) kinase inhibitor. VITRAKVI (larotrectinib) capsules and solution (b) (4) are formulated using larotrectinib sulfate.”
Dosage form and route of administration	Capsules for oral administration
Active moiety expression of strength with equivalence statement (if applicable)	“each capsule contains 25 mg or 100 mg larotrectinib (30.7 mg and 123 mg larotrectinib sulfate, respectively)”
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	NA
Statement of being sterile (if applicable)	NA
Pharmacological/ therapeutic class	Tyrosine kinase inhibitor
Chemical name, structural formula, molecular weight	Adequate
If radioactive, statement of important nuclear characteristics.	NA
Other important chemical or physical properties (such as pKa or pH)	“Larotrectinib sulfate is an off-white to pinkish yellow solid that is not (b) (4) hygroscopic. (b) (4) (b) (4) The aqueous solubility of larotrectinib at 37°C is pH dependent (very soluble at pH 1.0 and freely soluble at pH 6.8, according to USP descriptive terms of solubility). ”

5. Section 16 How Supplied/Storage and Handling

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(17))
Strength of dosage form	25 mg capsules; 100 mg capsules
Available units (e.g., bottles of 100 tablets)	60 count bottles
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Hard gelatin opaque white capsule size #2 with blue printing of “LOXO” and “LARO 25 mg” on the body of the capsule Hard gelatin opaque white capsule size #0 with blue printing of “LOXO” and “LARO 100 mg” on the body of the capsule
Special handling (e.g., protect from light)	NA
Storage conditions	Store capsules at room temperature 20°C to 25°C (68°F to 77°F); temperature excursions between 15°C and 30°C (59°F to 86°F) are permitted
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured for: Loxo Oncology, Inc. Stamford, CT 06901

Reviewer’s Assessment of Package Insert: *Pending*

Labeling negotiations are on-going. The current container configuration for the oral solution could potentially provide 50-60 days worth of dosing for the youngest patients, exceeding the (b)(4)-day in-use testing provided in the original NDA submission. Information requests have been submitted and data is pending that may allow a longer in-use period. As such, labeling to discard the oral solution (b)(4) days after opening may be removed. The pending data will not be available until ~10 days prior to the PDUFA date, so labeling changes may occur after finalizing this review. Any label changes will be managed through the clinical division PM directly.

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

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	TRADENAME® (larotrectinib)	TRADENAME® (larotrectinib)
Dosage strength	25 mg and 100 mg	25 mg and 100 mg
Net contents	60 capsules	60 capsules
“Rx only” displayed prominently on the main panel	Increase prominence	Increase prominence
NDC number (21 CFR 207.35(b)(3)(i))	71777-390-01 – 25 mg 71777-391-01 – 100 mg	71777-390-01 – 25 mg 71777-391-01 – 100 mg
Lot number and expiration date (21 CFR 201.17)	Clearly denote space on carton and container label for lot number and expiration dates	Clearly denote space on carton and container label for lot number and expiration dates
Storage conditions	Store (b) (4) (b) (4) 20°C to 25°C (68°F to 77°F); (b) (4) excursions (b) (4) 15°C and 30°C (59°F to 86°F) (b) (4) (b) (4)	Store (b) (4) (b) (4) 20°C to 25°C (68°F to 77°F); (b) (4) excursions (b) (4) 15°C and 30°C (59°F to 86°F) (b) (4) (b) (4)
Bar code (21CFR 201.25)	Present and adequate	Present and adequate
Name of manufacturer/distributor	Manufactured for: Loxo Oncology, Inc. Stamford, CT 06901	Manufactured for: Loxo Oncology, Inc. Stamford, CT 06901 Manufactured in United Kingdom Marketed by: Loxo Oncology, Inc. Marketed and distributed by: Bayer HealthCare Pharmaceuticals Inc.
And others, if space is available	NA	NA

Reviewer’s Assessment of Package Insert: *Pending*

➤ ***Minor edits necessary for the bottle and container label. These edits have been communicated through the clinical project manager and the carton container review will be finalized through the clinical PM and after filing this review.***

List of Deficiencies:

- 1. Increase the prominence of “Rx” on the carton and container labels.***
- 2. Clearly denote the space to be used for the lot number and expiry on the carton and container labels.***

Overall Assessment and Recommendation:

Primary Labeling Reviewer Name and Date: Olen Stephens 20-Aug-18

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



Olen
Stephens

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Anamitro
Banerjee

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BIOPHARMACEUTICS**Product Background:**

NDA: 210861(NME; 505(b)(1); Priority and Rare Pediatric Disease Priority Reviews Requested; Rolling NDA)

Drug Product Name / Strength: Larotrectinib capsule, 25 mg and 100 mg

Route of Administration: Oral

Proposed Indication: Treatment of patients with unresectable or metastatic solid tumors with NTRK fusion proteins in adult and pediatric patients who require systemic therapy and who have either progressed following prior treatment or who have no acceptable alternative therapy

Proposed Dosage: Adults – 100 mg twice daily; Pediatrics – 100 mg/m² twice daily with a maximum of 100 mg per dose, with or without food; Swallow whole without chewing or crushing the capsules (due to the bitter taste of the drug).

Applicant Name: Loxo Oncology, Inc.

Review Recommendation: APPROVAL***Review Summary:***

This Biopharmaceutics Review focused on the evaluation of the data submitted to support the (1) proposed QC dissolution method and acceptance criterion, and (2) bridging studies, as well as the determination as to whether a biowaiver request is required to support the approval of the NDA.

Dissolution Method and Acceptance Criteria – ADEQUATE (on an interim basis); Future Revision Recommended

Larotrectinib is a highly soluble drug substance, and larotrectinib oral capsules (filled with the drug substance without excipients).

The currently proposed QC dissolution method [900 mL of 0.01N HCl, USP Apparatus 1 (basket) rotating at 75 rpm] and revised dissolution acceptance criterion [‘NLT ^(b)₍₄₎0% (Q) dissolved in 45 minutes] are acceptable for batch release and stability testing of both strengths of the proposed drug product on an interim basis only. The current dissolution method was deemed overly discriminating; however, the use of the current dissolution method on the interim is not anticipated to result in the release of drug products with sub-standard quality.

In a teleconference held on 10/15/2018, the FDA recommended that the Applicant conduct additional studies with the primary registration (stability) batches and future drug product batches using both the current dissolution method and the FDA recommended dissolution method (as tabulated below). A Prior-Approval Supplement (PAS) will then be submitted supported with the dissolution data collected up to 12 months of long-term storage of these batches. The Applicant agreed to submit the requested data in a PAS.

USP Apparatus	Speed	Medium	Volume	Acceptance criterion
1 (basket)	75 rpm	0.1N HCl, 37 ± 0.5°C	900 mL	NLT ^{(b) (4)} % (Q) of the label claim dissolved in 15 min

Bridging to the Proposed To-Be-Marketed Drug Product – ADEQUATE

Larotrectinib capsules contain only the drug substance (no excipients). There were no formulation and manufacturing process type changes during the development of the capsules. Thus, *in vivo* bridging data are not needed.

The change in the drug product manufacturing site, the change in the drug substance/active pharmaceutical ingredient (API) supplier, as well as the addition of the blue imprint to the capsules (for identification purposes) introduced after initiation of the clinical trials are not expected to significantly impact the *in vivo* performance of the proposed to-be-marketed drug product because the clinical trial lots and the registration stability lots with and without the blue ink text on the capsule shell all exhibited ^{(b) (4)} ^{(b) (4)} dissolution ^{(b) (4)} using the FDA recommended dissolution method. It should be noted that dissolution of the clinical trial lots was ^{(b) (4)} and incomplete, i.e., plateau reached approximately ^{(b) (4)}% in the originally proposed method due to the presence of residual ethanol in the API; however, this is no longer an issue since the Applicant changed the proposed commercial API manufacturer.

Biowaiver Request – NOT NEEDED

Note that a biowaiver was not requested nor is it required because both strengths of the larotrectinib capsules were evaluated for PK, efficacy and safety in Phase 1 and 2 clinical trials, and *in vitro* data were sufficient to qualify the relatively minor CMC changes that were introduced to the drug product after conducting the clinical trials.

List of Submissions reviewed:

- [SDN-9](#), 3/26/2018 (New NDA)
- [SDN-36](#), 6/15/2018 (Response to Quality Information Request)
- [SDN-50](#), 8/2/2018 (Response to Biopharmaceutics Information Request)
- [SDN-52](#), 8/7/2018 (Response to Biopharmaceutics Information Request)
- [SDN-53](#), 8/10/2018 (Response to Biopharmaceutics Information Request)
- [SDN-70](#), 10/9/2018 (Response to Biopharmaceutics Information Request)
- [SDN-76](#), 10/25/2018 (Response to Biopharmaceutics Information Request)

Outstanding Issues Remaining:

None that would preclude NDA approval

Prior-Approval Supplement: Submit dissolution on stability data using both current and FDA recommended dissolution methods.

BCS Designation

There is no formal BCS designation request for larotrectinib capsules, although the Applicant considers larotrectinib as a highly soluble and highly permeable (BCS Class 1) drug substance. Additionally, the Applicant believes that the drug rapidly dissolves upon administration because the plasma T_{max} is approximately 1 hour in humans.

Reviewer’s Assessment:

Solubility: *High.* The solubility of larotrectinib is pH-dependent; at 37°C, >3.63 mg/mL dissolves at pH 1.0, decreasing at higher pH to about 0.779 mg/mL at pH 6.8; refer to Table 1 and Figure 2 of the solubility report for details. Per BCS criteria, larotrectinib can be classified as a highly soluble drug substance because the amount of larotrectinib free base in the highest strength (100 mg) capsule is expected to completely dissolve in 250 mL of dissolution media across the physiologic pH range at 37°C. Per the proposed labeling, the single maximum oral larotrectinib dose is 100 mg as free base. Note that the proposed drug product (capsule) does not contain any excipients.

Permeability: *Indeterminate.* The mean absolute bioavailability of larotrectinib is ~34% following oral administration of a single 100 mg dose. In Study LOXO-TRK-16011, 86.1% of the radioactivity in the plasma samples were associated with the parent drug (33.17%), and metabolites M14 (44.23%), M28/M30 (6.01%), and M17 (2.64%).

Dissolution:

Larotrectinib oral capsules exhibit (b) (4) dissolution, i.e., at least (b) (4) % of the labelled amount of the drug dissolves in 900 mL of the FDA recommended dissolution medium (0.1N HCl), using USP Apparatus 1 (basket) rotating at 75 rpm.

Dissolution Method and Acceptance Criteria

Dissolution Method – CURRENT METHOD ACCEPTABLE ON AN INTERIM BASIS; FUTURE REVISION RECOMMENDED

The parameters of the proposed QC dissolution method are tabulated below.

Dissolution Method (VM0982.01)

Dissolution Media	900 mL of 0.01 N HCl
Temperature	37 ± 0.5°C
Apparatus	USP I (Baskets)
Speed	75 rpm
Sampling Interval	5, 10, 15, 20, 30, 45 and 60 minutes
Single Time Point Sampling	45 minutes

Filter sample aliquots through a 0.45 µm nylon syringe filter, discarding the first few mL to waste. Samples are stable for 7 days in HPLC vials at room temperature.

Per the Applicant, the basket apparatus and a low pH medium were selected to avoid the formation of a sticky mass that had a tendency to adhere to the dissolution vessel. The release of larotrectinib was found to be more complete and consistent at 75 rpm, as opposed to 100 rpm and 50 rpm.

This Reviewer agrees with the Applicant's conclusion that the proposed QC dissolution method is over-discriminating with respect to changes (b) (4) in the active pharmaceutical ingredient (API) because bioequivalent drug product batches including some clinical trial lots of the proposed drug product were shown to exhibit (b) (4) (b) (4) incomplete dissolution and thus would fail the Applicant's initially proposed QC dissolution acceptance criterion. The underlying mechanism responsible for the apparent impact of the residual alcohol in the disintegration and wetting of the capsule shell which leads to formation of a sticky mass during QC dissolution testing of capsules manufactured using the API from the original source was not revealed. However, the results of further investigation using dissolution medium with added pepsin suggest that crosslinking in the gelatin capsule shell is not the apparent cause of the slow and incomplete dissolution of the clinical trial lots in the Applicant's initially proposed QC dissolution medium (0.01N HCl). Nevertheless, it was clear from the provided data that this effect of residual alcohol on capsule dissolution rate can be solved by using 0.1N HCl as the alternative dissolution medium. Furthermore, it was clear that the relatively higher residual alcohol in the API (as well as the relatively slow *in vitro* dissolution) of the clinical trial lots did not impact *in vivo* drug product performance because the oral larotrectinib capsule was demonstrated to be bioequivalent to the oral larotrectinib solution following administration to healthy subjects in a relative BA study.

[Particle Size Distribution ($d_{10} > 0.3$ microns, $d_{50} = 1 - 10$ microns, $d_{90} < 40$ microns, by Laser Scattering Particle Size Analyzer), Residual ethanol (NMT 5000 ppm), and Water Content (NMT 2.5%, by KF) are part of the proposed API QC Specifications. Only one crystalline API form has been detected to date; however, routine XRPD testing is proposed to check for the correct API polymorph. Water content (NMT 2.5%, by KF), and dose uniformity are part of the proposed finished product QC specification.]

The quantification of the drug in the dissolution samples is accomplished using reversed phase HPLC with UV detection at 264 nm. Per the Drug Product Reviewer (Dr. Olen Stephens), the validation of the analytical method is adequate for the dissolution samples despite the change in HCl concentration in the dissolution medium.

Given that larotrectinib is a highly soluble drug substance, the proposed drug product does not contain any excipients, and considering that the proposed QC dissolution method was demonstrated to be overly sensitive to changes in non-critical quality attributes of the proposed drug product, this Reviewer determines that 0.1N HCl would be a more appropriate dissolution medium than 0.01N HCl. Note that the Office of Clinical Pharmacology confirmed that larotrectinib is not a narrow therapeutic index drug, and an early or rapid onset of action is not critical for the proposed drug product.

***Dissolution Acceptance Criteria – REVISED ACCEPTANCE CRITERION
ACCEPTABLE ON INTERIM BASIS; FUTURE REVISION RECOMMENDED***

The proposed QC dissolution acceptance criteria is ‘ $(b) (4)$ % dissolved in 45 minutes ($Q = (b) (4)$ %)’. Per the Applicant, $Q = (b) (4)$ % at 45 minutes was proposed based on the validation data. Based on the data, FDA recommended $Q = (b) (4)$ % in 45 minutes as an interim acceptance criterion until the Applicant collects dissolution data post approval as stated above. Although, the clinical batches are anticipated to only pass at USP Stage 3 dissolution testing with this FDA recommended interim acceptance criterion of $Q = (b) (4)$ % in 45 minutes, passing the clinical batches with the currently approved is no longer an issue for future drug product batches since the Applicant addressed the $(b) (4)$ dissolution issue by changing the API manufacturer.

Dissolution data for the registration stability batches are available starting at Month 3 of long-term, intermediate, and accelerated stability storage. The Applicant indicated that dissolution data are being collected for Process Validation batches starting at batch release. Note that the proposed product shelf-life is 36 months when stored at recommended storage conditions (i.e., under USP Controlled Room Temperature).

For Future Revision: Based on the available *in vitro* dissolution profile data for the clinical trial lots which exhibited $(b) (4)$ dissolution in the FDA recommended dissolution medium, this Reviewer recommends a dissolution acceptance criterion of ‘NLT $(b) (4)$ % (Q) at 15 min’ to be adopted when PAS is submitted. The Applicant agreed to revise the interim acceptance criterion to the FDA recommended dissolution acceptance criterion when additional stability data are collected post approval with the FDA recommended dissolution medium.

Bridging of Formulations

Reviewer’s Assessment: ADEQUATE

In vivo PK bridging data are not needed because there were no changes in the formulation of the proposed drug product during clinical development. Specifically, the drug product tested throughout clinical development, stability testing and proposed to be marketed is a capsule that contains only the API (no excipients).

The drug substance produced by the proposed commercial API supplier $(b) (4)$ was used in the manufacture of three registration stability lots per strength, and also two clinical trial lots. Array produced the API used to manufacture earlier clinical trial lots.

The clinical trial lots differ from the primary (registration) stability lots/proposed to-be-marketed drug product in terms of the drug product manufacturing site $(b) (4)$. $(b) (4)$ The production scales of the clinical trial lots, primary registration stability lots and the commercial product are similar $(b) (4)$ units vs. $(b) (4)$ units, respectively). Note that like one of three registration stability

lots (per strength), the final to-be-marketed drug product's capsule shell appears with a blue ink text for identification purposes.

Using the proposed QC dissolution method [900 mL of 0.01N HCl, USP Apparatus 1 (basket) at 75 rpm], the *in vitro* dissolution profiles were shown to be comparable between registration stability lots with and without blue ink on the capsule shell. Additionally, as shown by the results of FDA requested studies, the *in vitro* dissolution profiles of the registration stability lots/proposed to-be-marketed drug product and the clinical trial lots when using the FDA recommended dissolution method [900 mL of 0.1N HCl, USP Apparatus 1 (basket) at 75 rpm] were superimposable, i.e., all lots exhibited (b) (4) dissolution (approximately (b) (4)% dissolution within 10 min). For the *in vitro* dissolution profiles of the primary registration stability lots using the proposed dissolution method and the FDA recommended method, see Figures 1 and 2 below.

Figure 1
Comparative *In Vitro* Dissolution Profiles of Registration Stability Lots
With and Without Blue Ink Text On Capsule Shell
(using Applicant's currently proposed QC dissolution method)
100 mg

(b) (4)

Figure 2
In Vitro Dissolution Profiles of Primary Registration Stability Lots and Clinical Trial Lots (using FDA Recommended Dissolution Method)

(b) (4)



Primary Biopharmaceutics Reviewer: Gerlie Gieser, Ph.D. (10/26/2018)

Secondary Reviewer: Banu Zolnik, Ph.D. (10/26/2018)



**Gerlie
Gieser**

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**Banu
Zolnik**

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay, stability	• Formulation • Container closure • Raw materials (b) (4) • Scale/equipment • Site	L		Acceptable	No change in risk assessment after review
Physical stability (solid state)	• Formulation • Raw materials (b) (4) • Scale/equipment • Site	L		Acceptable	No change in risk assessment after review
Dosing accuracy	• Dosing device • Formulation (b) (4) • Scale/equipment • Site	L		Acceptable	No change in risk assessment after review
Palatability	• Formulation • Excipient change (b) (4) • Scale/equipment • Site	L		Acceptable	No change in risk assessment after review
Microbial Limits	• Formulation • Raw materials (b) (4) • Scale/equipment • Site	L		Acceptable	No change in risk assessment after review
Leachables	• Formulation • Container closure (b) (4) • Scale/equipment • Site			Acceptable	
Dissolution	• Raw Materials • Formulation • Container closure (b) (4) • Scale/equipment • Site	M	• API controls (b) (4) • Dissolution method parameter optimization	Acceptable	(b) (4)