

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**212725Orig1s000**

**212726Orig1s000**

**PRODUCT QUALITY REVIEW(S)**

**Recommendation: Approval for Both NDAs**

**NDAs 212725 and 212726**

**Review 1**

Drug Name/Dosage Form	Tradename (entrectinib) capsules
Strength	100 and 200 mg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Genentech
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
<i>0001 (1), Original Submission</i>	<i>12/18/2018</i>	<i>Drug Substance (DS), Drug Product (DP), Manufacturing, Biopharmaceutics, and Microbiology</i>
<i>0009 (9), Response to CMC IR</i>	<i>02/06/2019</i>	<i>DP, Manufacturing, Biopharmaceutics</i>
<i>0015 (15), Response to CMC IR</i>	<i>02/27/2019</i>	<i>DP</i>
<i>0021 (22), General Correspondence</i>	<i>03/06/2019</i>	<i>Manufacturing</i>
<i>0024 (24), Response to CMC IR</i>	<i>03/29/2019</i>	<i>DS, DP, and Manufacturing</i>

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	<i>Gaetan Ladouceur</i>	<i>Su (Suong) Tran</i>
Drug Product	<i>Olen Stephens</i>	<i>Anamitro Banerjee</i>
Manufacturing	<i>David Anderson</i>	<i>Rakhi Shah</i>
Microbiology	<i>David Anderson</i>	<i>Rakhi Shah</i>
Biopharmaceutics	<i>Parnali Chatterjee</i>	<i>Banu Zolnik</i>
Regulatory Business Process Manager	<i>Rabiya Haider</i>	<i>NA</i>
Application Technical Lead	<i>Nina Ni</i>	<i>NA</i>
Laboratory (OTR)	<i>NA</i>	<i>NA</i>
ORA Lead	<i>NA</i>	<i>NA</i>
Environmental	<i>Olen Stephens</i>	<i>Anamitro Banerjee</i>

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## Quality Review Data Sheet

### 1. RELATED/SUPPORTING DOCUMENTS

#### A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	Adequate	Information provided in NDA	
	Type III		Adequate	Information provided in NDA		
	Type III		Adequate	Information provided in NDA		
	Type III		Adequate	Information provided in NDA		
	Type III		Adequate	Information provided in NDA		
	Type III		Adequate	Information provided in NDA		
	Type IV		Adequate	Information provided in NDA		

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	120500 (for NDA 212726) and 135124 (for NDA 212725)	Initial INDs

### 2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			



# QUALITY ASSESSMENT



CDRH	NA			
Clinical	NA			
Other	NA			

**Note:** Per agreement reached with the FDA, NDA 212726 is being submitted in parallel to NDA 212725. CMC information (Module 2.3 and Module 3) is provided in the NDA 212726 only. In the NDA 212725, reference is made to the NDA 212726 Module 3 for CMC information for entrectinib. Thus, this CMC review covers CMC review for both NDAs 212725 and 212726.

## Executive Summary

### I. Recommendations and Conclusion on Approvability

From the chemistry, manufacturing, and controls standpoint, Both NDAs are recommended for approval. There are no outstanding CMC issues that impact approvability of both NDAs 212725 and 212726.

Based on the provided stability data, a 24-month expiration dating period is granted for Tradename (entrectinib) capsules, 100 and 200 mg when stored below 30°C (86°F).

### II. Summary of Quality Assessments

#### A. Product Overview

Pursuant to 21 CFR 314.50 and section 505(b)(1) of the Federal Food, Drug and Cosmetic Act, on 12/18/2018, Genentech, Inc. submitted NDAs 212725 and 212726 to support marketing approval of entrectinib capsules, 100 and 200 mg for the treatment of

- Adult and pediatric patients with neurotrophic tyrosine receptor kinase (NTRK) Fusion-positive, (b) (4) metastatic solid tumors under NDA 212726
- Patients with metastatic non-small cell lung cancer (NSCLC) that is ROS1-positive under NDA 212725

Per agreement reached with the FDA, NDA 212726 is being submitted in parallel to NDA 212725. CMC information (Module 2.3 and Module 3) is provided in the NDA 212726 only. In the NDA 212725, reference is made to the NDA 212726 Module 3 for CMC information for entrectinib. Thus, this CMC review covers CMC review for both NDAs.

NDA 212725 has been granted for orphan drug designation (ODD) for the treatment of patients with ROS1-positive, (b) (4) metastatic NSCLC. Entrectinib is administered to adults at a dose of 600 mg orally, once daily, until disease progression or unacceptable toxicity. The development on entrectinib presented in the NDA 212725 has been conducted under Investigation New Drug Application (IND) 135124.

NDA 212726 was granted for orphan drug designation (ODD) and breakthrough therapy designation (BTD) for the treatment of adult and pediatric patients with NTRK fusion-positive (b) (4) metastatic solid tumors, who have progressed (b) (4) (b) (4). Entrectinib is administered to adults at a dose of 600 mg orally, once daily, until disease progression or unacceptable toxicity. Entrectinib is administered to pediatric patients who can swallow capsules at a dose of 300 mg/m<sup>2</sup> orally, once daily, until disease progression or unacceptable toxicity. The development on entrectinib presented in the NDA 212726 has been conducted under Investigation New Drug Application (IND) 120500.

Genentech requested priority review for both NDAs which was granted for NDA 212726 only.

Entrectinib, a kinase inhibitor is a small molecule new molecular entity with the molecular formula of C<sub>31</sub>H<sub>34</sub>F<sub>2</sub>N<sub>6</sub>O<sub>2</sub> and the molecular weight of 560.64 Daltons. Entrectinib is white to (b) (4) pale pink (b) (4) powder (b) (4). Entrectinib, an achiral molecule is a free base with the melting point between 198.2 to 200.7°C. Entrectinib is non-hygroscopic and shows an exponential increase in aqueous solubility in acidic media compared to neutral conditions: solubility is higher than 40 mg/mL in 0.07 M HCl (at pH 1.2), 0.03 mg/mL at pH 5.3, and 0.002 mg/mL at pH 6.4. Solubility of entrectinib in FeSSIF is substantially higher than in FaSSIF (approx. 40 times higher after 1 hour and over 30 times higher after 24 hours), which is indicative of a potential food effect. However, the pivotal clinical formulation (F2A) and the proposed to-be-marketed commercial formulation (F06) include an (b) (4) (b) (4). The clinical study, RXDX-101-15 not only established BA/BE between F2A and F06 formulations but also established the absence of food effect on in vivo exposure with F06 formulation, which is reviewed by clinical pharmacology review team.

Entrectinib is considered as a Biopharmaceutics Classification System (BCS) Class 2 compound with low solubility and low-moderate permeability. Entrectinib exhibits polymorphisms with (b) (4) being selected for development and for use in the commercial drug product.

The proposed commercial drug product is an immediate-release hard Hypromellose (HPMC) capsule containing 100 mg and 200 mg of entrectinib for oral administration.

- Entrectinib capsule, 100 mg, is a size 2, (b) (4) capsule with yellow opaque body and cap with ENT 100 imprinted in blue on the body and is packaged in 70 cc HDPE bottle with 30 capsule counts.
- Entrectinib capsule, 200 mg, is a size 0, (b) (4) capsule with orange opaque body and cap with ENT 200 imprinted in blue on the body and is packaged in 200 cc HDPE bottle with 90 capsule counts.

The 100 mg dosage form was designed using a size 2 capsule (b) (4)  
 (b) (4)  
 (b) (4).

The drug products are packaged in HDPE bottle with (b) (4)  
 (b) (4) caps.

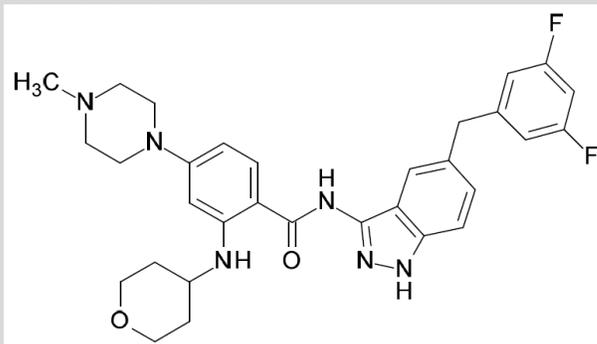
<p><b>Proposed Indication(s) including Intended Patient Population</b></p>	<ul style="list-style-type: none"> <li>• Adult and pediatric patients with neurotrophic tyrosine receptor kinase (NTRK) Fusion-positive, (b) (4) metastatic solid tumors under NDA 212726</li> <li>• Patients with metastatic non-small cell lung cancer (NSCLC) that is ROS1-positive under NDA 212725</li> </ul>
<p><b>Duration of Treatment</b></p>	<p>Continue treatment until disease progression or unacceptable toxicity</p>
<p><b>Maximum Daily Dose</b></p>	<p>Adults: 600 mg orally once daily, with or without food for both indications          (b) (4)</p>
<p><b>Alternative Methods of Administration</b></p>	<p>NA</p>

**B. Quality Assessment Overview**

**Drug Substance [Entrectinib]**

The drug substance (DS) entrectinib has the following chemical name, structural formula, molecular formula, and molecular weight.

Structure Formula:



International Non-proprietary Name (INN): Entrectinib

Chemical Name: *N*-{5-[(3,5-difluorophenyl)methyl]-1*H*-indazol-3-yl}-4-(4-methylpiperazin-1-yl)-2-[(oxan-4-yl)amino]benzamide

CAS Registry Number: 1108743-60-7

Mol. Formula: C<sub>31</sub>H<sub>34</sub>F<sub>2</sub>N<sub>6</sub>O<sub>2</sub>

Mol. Wt.: 560.64 g/mol

The characterization, nomenclature, molecular structure, CAS number, and molecular weight of the drug substance (DS) entrectinib are accurate. Entrectinib DS, a new molecular entity is a white to (b) (4) pale pink (b) (4) powder isolated as a free base. It has no chiral center and has a melting point between 198.2 to 200.7°C. It is non-hygroscopic and exhibits polymorphisms: (b) (4)

(b) (4)

(b) (4)

The drug substance is manufactured (b) (4)

(b) (4)

(b) (4)

The drug substance (DS) specification for entrectinib includes the following critical quality attributes (CQAs): appearance and color by visual inspection, identification by HPLC, IR, and XRPD (b) (4), impurities (organic impurities by HPLC and residual solvents by HS-GC), assay by HPLC, particle size by laser diffractometry, water content per USP <921>, (b) (4) by ICP-MS per USP <232>, and residue on ignition per USP <281>. Microbial test is not controlled in the DS specification with adequate justification.

Specified and unspecified impurities are controlled to the ICH Q3A qualification and identification thresholds, respectively. A total of seven compounds were identified as genotoxic or potentially genotoxic in accordance with the classification scheme outlined in ICH M7. All other compounds that underwent the assessment belong to Class 5 after being tested *in silico* negative using two orthogonal methods, or after Ames-negative testing following a positive *in silico* result in at least one of the two *in silico* methods. A thorough analysis of the clinical batches and of purging studies found only negligible amounts of the genotoxic impurities. Therefore, no specific controls are included in the drug substance specification for potential or known genotoxic impurities except for benzene.

The drug substance is (b) (4)

(b) (4)

(b) (4)

The batch analyses data of 28 DS batches are provided in the submission including the development, clinical, toxicology, stability, and commercial batches. The batch analyses data conform to the proposed DS specification for commercial, primary stability, and late clinical batches, see this review on DS section below for details. Twelve months of primary stability data are available for four DS batches. In addition, up to 24 months of supportive stability data are also provided. The container closure system used for these batches is representative of the proposed commercial packaging to support the proposed retest period of (b) (4) months while store (b) (4) in the proposed container closure system (b) (4). Forced degradation study showed that entrectinib is not sensitive to the combination of elevated temperature, thermal, light, and humidity conditions. It is however, unstable under acidic, basic, and oxidative conditions.

Twelve months stability data on four primary stability batches supports an initial retest period of (b) (4) months for entrectinib DS while (b) (4) in the proposed container closure system.

### Drug Product [Entrectinib Capsules, 100 and 200 mg]

The proposed commercial drug product (DP) is an immediate-release hard Hypromellose (HPMC) capsule containing 100 mg and 200 mg of entrectinib for oral administration. The two strengths are visually distinguishable by size, color, and script. The excipients are all compendial or composed of compendial components. Excipient of animal origin (lactose) is supported by BSE/TSE compliance statements. These excipients have all been used in approved drug products at levels greater than proposed in the current product. There are no overages in the drug product.

The F2A formulation was developed as a hard gelatin capsule product (b) (4) (b) (4). Formulation F2A was dosed in the pivotal Phase II clinical study. During the pivotal Phase II clinical study, the (b) (4) F2A drug product was changed (b) (4) (b) (4). To mitigate dissolution failures, the capsule shell was changed from hard gelatin to HPMC. The intended market formulation (F06) (b) (4) in HPMC capsule is designed to be equivalent to the clinical formulation (F2A) and enables a robust commercial-scale manufacturing process using compendial excipients. Bioequivalence between the market (F06) and pivotal (F2A) formulations was demonstrated by a comparative bioavailability/bioequivalence (BA/BE) clinical study, RXDX-101-15 (see clinical pharmacology review for details).

The drug product commercial manufacturing process involves (b) (4) (b) (4) (b) (4). The 100 mg and 200 mg capsules are dose proportional (b) (4) and use the same commercial manufacturing process. (b) (4) (b) (4). The proposed commercial batch size for the 200 mg and 100 mg capsules is (b) (4) capsules for both strengths. No scale up is proposed.

(b) (4)

The drug product specification includes the following CQAs: description of capsule and description of capsule content by visual inspection; identification by HPLC retention time and UV spectrum as reference; assay by HPLC; uniformity of dosage units by mass/weight variation; degradation products by HPLC; dissolution per USP <711> with  $Q = (b) (4)\%$  in 60 minutes;  $(b) (4)$  and microbial limits per USP <61> and <62>.

Adequate developmental data and method validation data to demonstrate control over drug substance  $(b) (4)$  is sufficient to assure the drug substance  $(b) (4)$  in the drug product. The drug product manufacturing process is

(b) (4)

$(b) (4)$  Therefore, per ICH Q6A, it is acceptable to exclude polymorphism testing. Process impurities and unspecified impurities are controlled in the drug substance at or below the ICH Q3A qualification limit; as there are no degradation products observed in the drug product, the individual impurity limit is set at the ICH Q3B qualification limit. These limits are appropriate and acceptable. The  $(b) (4)$   $(b) (4)$  further reduces the risk of abnormal assay values.

The detailed analytical method validation data are provided. Each analytical method description is also sufficiently detailed and appropriate for its intended use. The applicant did designate materials that would be available for method verification in 3.2.R. However, the drug product reviewer found the method verification is not warranted for this product. The apparent stability of the drug substance under a variety of conditions makes the assay and degradation methods lower risk relative to other drug products. Forced degradation studies showed that the entrectinib capsules were moderately susceptible to oxidative degradation (presumably forming the same degradation product seen in drug substance stress studies, RO7278383). However, this degradation only resulted in  $(b) (4)\%$  loss in assay. No other stress conditions yielded significant degradation, including photostability studies.

12 months primary stability data at 30°C/65%RH and 6 months primary stability data at 40°C/75%RH for three primary batches of each entrectinib capsules, 100 mg and 200 mg, manufactured at the intended commercial manufacturing site  $(b) (4)$  and packed at  $(b) (4)$  are provided. 6 months supportive site-specific stability data at 30°C/75%RH and 6 months stability data at 40°C/75%RH for three batches of each entrectinib capsules, 100 mg and 200 mg, manufactured at the intended commercial bulk manufacturing site  $(b) (4)$  and packed at the commercial packaging site (Roche Kaiseraugst) are also provided.

The registration and supportive (site-specific) batches are filled from the same bulk drug product batches. Also, two drug substance batches (lot #: CA17-0657 and CA17-1010)

were used to manufacture the drug product batches. (b) (4)

(b) (4)

(b) (4)

(b) (4). The registration stability batches are stored in 40 mL and 150 mL HDPE bottles for the 100 mg and 200 mg capsules, respectively. The supportive site-specific stability batches are stored in the commercial configuration of 70 mL and 200 mL HDPE bottles for the 100 mg and 200 mg capsules, respectively. Also, the commercial configuration uses a (b) (4) closure (b) (4); the registration batches have separate closures (b) (4). The supportive batches have 6 months fewer stability data than the registration batches. The drug product reviewer found the container closure configuration differences between registration stability batches and commercial batches are acceptable. See his reviewer on DP section below for a detailed evaluation.

All batches were tested for stability indicating parameters (description of capsule and capsule content, content per capsule of entrectinib, degradation products, water content, dissolution, and microbial limits). All stability data show that there is no apparent change of quality attributes on long-term (30°C/65% RH or 30°C/75% RH) or accelerated stability (40°C/75% RH). On the basis of 12 months long-term stability data for the registration stability batches, a 24-month shelf life is granted when the product is stored below 30°C (86°F).

Both photo-stability and in-use stability to simulate the actual use of the product are also provided with no significant changes/trends noted. Thus, no stated in-use period is necessary in the labeling.

The applicant's claim for categorical exclusion and request of a waiver from an environmental analysis is granted since this product is indicated for an orphan population and quantities entering the aquatic environment will be exceptionally low.

### Facility Evaluation

Office of Process and Facilities (OPF/OPQ/CDER) has recommended "Acceptable" for the following drug substance manufacturers (for manufacture, release testing, stability testing, packaging, and storage) based on Profile.

(b) (4)

Office of Process and Facilities (OPF/OPQ/CDER) has recommended "Acceptable" for the following drug product manufacturers (for manufacture, release testing, stability testing, packaging, and storage) based on Profile.

- (b) (4)
- F. Hoffmann-La Roche Ltd. (FEI #: 3002807200) in Basel, Switzerland
- F. Hoffmann-La Roche Ltd. (FEI #: 3003973536) in Kaiseraugst, Switzerland

**Biopharmaceutics Evaluation**

Biopharmaceutics review evaluated 1) the proposed dissolution method, 2) the proposed dissolution acceptance criterion, 3) the need for bridging the different formulations and packaging site throughout the product development stage, and 4) the biowaiver request for the 100 mg F06 to-be-market drug product.

The dissolution profile data for various testing parameters and discriminating ability of the proposed dissolution method below is acceptable as a quality control tool for batch release and stability testing of the 100 mg and 200 mg entrectinib capsules.

<i>Apparatus/Speed</i>	USP Apparatus 2 (paddle)/75 rpm
<i>Sinkers</i>	Helix stainless-steel sinkers
<i>Media/Volume</i>	0.374% Tween 80 in 50 mM potassium phosphate, pH 6.0/1000 mL
<i>Bath temperature</i>	37.0±0.5° C

The proposed acceptance criterion of “Q= (b) (4)% in 60 minutes” for batch release and on stability for the proposed drug product based on the bio-batch, clinical, and stability batches is also acceptable.

The comparative dissolution profiles using the proposed dissolution method and f2 similarity analysis with f2 value (50.51) > 50 indicates that three registration batches of the 100 mg and 200 mg F06 drug product manufactured at (b) (4) and packaged at (b) (4) and Roche Kaiseraugst are similar and provide a bridge between the two packaging sites.

The biowaiver request for the 100 mg F06 drug product is granted based on 1) the compositional proportionality between the 100 mg and 200 mg strength drug product with respect to entrectinib, the active pharmaceutical ingredient (API) and excipients; 2) bioequivalence between the 200 mg F06 and F2A drug products in the bioequivalence (BE) study RXDX-101-15; 3) linear pharmacokinetics of the F06 drug product between the dose ranges of 100 mg - 600 mg under fasted condition based on the bioavailability study RXDX-101-12; and 4) similarity in the dissolution profile data for the 100 mg and 200 mg F06 drug product.

**Labeling**

The container and carton labels as well as the prescribing information pertinent to the CMC sections (Highlights as well as Section 2, 3, 11, and 16) comply with all regulatory requirements from a CMC perspective after revision (see this review on labeling section below for details). The proposed proprietary name, Rozlytrek, is still under review.

**1. Special Product Quality Labeling Recommendations (NDA only)**

NA

**2. Final Risk Assessment (see Attachment below)**

**Attachment - Final Risk Assessment for Entrectinib Capsules, 100 and 200 mg**

From Initial Risk Identification			Final Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments
<b>Assay Stability</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> <li>• Container closure</li> </ul>	Low	Assessed during development and controlled via specification and container closure	Acceptable	NA
<b>Physical Stability (solid state)</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> <li>• Container closure</li> </ul>	Medium	Assessed during development and controlled via specification and container closure	Acceptable	(b) (4)
<b>Content Uniformity</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	Low	Assessed during development and controlled via DS particle size and DP specification	Acceptable	NA
<b>Dissolution</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> <li>• Container closure</li> </ul>	Medium	Assessed during development and controlled via specification	Acceptable	NA

<b>Microbial Limits</b>	<ul style="list-style-type: none"><li>• Formulation</li><li>• Raw materials</li><li>• Process parameters</li><li>• Scale/equipment</li><li>• Site</li><li>• Container closure</li></ul>	Low	Assessed during development with adequate justification provided for not controlling in DP specification	Acceptable	NA
(b) (4)					



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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	[Rozlytrek] (entrectinib) capsules
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, 100 mg and 200 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)	(b) (4)

**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	100 mg and 200 mg
Active moiety expression of strength consistent with Salt Nomenclature Guidance	Yes
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	<ul style="list-style-type: none"> <li>• 100 mg hard capsules: Size 2 yellow opaque body and cap, with “ENT 100” printed in blue ink on body.</li> <li>• 200 mg hard capsules: Size 0 orange opaque body and cap, with “ENT 200” printed in blue ink on body.</li> </ul>

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	[Rozlytrek] (entrectinib) capsules
Dosage form and route of administration	“Entrectinib is a (b) (4) kinase inhibitor (b) (4)” ... “[Rozlytrek] capsules are supplied as...”
Active moiety expression of strength with equivalence statement (if applicable)	Entrectinib is not isolated as a salt
Qualitative list of excipient list	Inactive ingredients are tartaric acid, lactose anhydrous, hypromellose, crospovidone, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate. The yellow opaque capsule shell contains hypromellose, titanium dioxide, and yellow iron oxide. The orange opaque capsule shell contains hypromellose, titanium dioxide, and FD&C yellow #6. The printing ink contains shellac, propylene glycol, strong ammonia solution, and FD&C blue #2 aluminum lake.
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	“Entrectinib is a 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)	“Entrectinib is white to pale pink powder.”

**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	100 mg and 200 mg capsules
Available units	30-count (100 mg capsules) 90-count (200 mg capsules)
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	<ul style="list-style-type: none"> <li>• 100 mg hard capsules: Size 2 yellow opaque, with “ENT 100” printed in blue ink; available in: HDPE bottles of 30 capsules: NDC 50242-091-<sup>(b) (4)</sup></li> <li>• 200 mg hard capsules: Size 0 orange opaque, with “ENT 200” printed in blue ink; available in: HDPE bottles of 90 capsules: NDC 50242-<sup>(b) (4)</sup></li> </ul>
Special handling (e.g., protect from light)	None
Storage conditions	“Storage and stability: Store <sup>(b) (4)</sup> <sup>(b) (4)</sup> below 30°C (86°F)”
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Distributed by: Genentech USA, Inc. A Member of the Roche Group 1 DNA Way South San Francisco, CA 94080-4990

**Reviewer’s Assessment of Package Insert: *Pending***

*Labeling negotiations are on-going; labeling changes will be routed through the clinical project manager. The proprietary name is still under review. The proposed proprietary name, Rozlytrek, is still under review, but no objections have been raised by the clinical division at this time.*

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))	<b>Rozlytrek™</b> (entrectinib) capsules	<b>Rozlytrek™</b> (entrectinib) capsules
Dosage strength	100 mg and 200 mg	100 mg and 200 mg
Net contents	30 capsules and 90 capsules, respectively	30 capsules and 90 capsules, respectively
“Rx only” displayed prominently on the main panel	Present	Present
NDC number (21 CFR 207.35(b)(3)(i))	50242-091-(b)(4) and 50242-(b)(4)	50242-091-(b)(4) and 50242-(b)(4)
Lot number and expiration date (21 CFR 201.17)	Present	Present
Storage conditions	Store (b)(4) below 30°C (86°F)	Store (b)(4) below 30°C (86°F)
Bar code (21CFR 201.25)	Present and adequate	Present and adequate
Name of manufacturer/distributor	Distributed by: Genentech USA, Inc. A Member of the Roche Group 1 DNA Way South San Francisco, CA 94080-4990	Distributed by: Genentech USA, Inc. A Member of the Roche Group 1 DNA Way South San Francisco, CA 94080-4990
And others, if space is available	NA	NA

**Reviewer’s Assessment of Package Insert: *Adequate pending further labelling negotiation with the applicant.***

***The proposed proprietary name, Rozlytrek, is still under review, but no objections have been raised by the clinical division at this time.***

***List of Deficiencies: None***

***Overall Assessment and Recommendation:***

**During the labeling review, the DMEPA reviewer called into question the proposed storage conditions of “Store (b)(4) below 30°C (86°F). An information request was sent to the applicant, noting that the storage conditions do not align with the USP definition (b)(4). The applicant responded by proposing to remove (b)(4)”**

(b) (4)



***Primary Labeling Reviewer Name and Date: Olen Stephens 17-Apr-19***

***Secondary Reviewer Name and Date: Anamitro Banerjee 17-Apr-19***



Olen  
Stephens

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Anamitro  
Banerjee

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Date: 4/17/2019 10:29:28AM  
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**BIOPHARMACEUTICS**

**Application No:** NDA 212726 is indicated for treatment of adult and pediatric patients with neurotrophic tyrosine receptor kinase (NTRK) fusion-positive, (b) (4) metastatic solid tumors who have either progressed (b) (4)

**Drug Product Name / Strength:** Rozlytrek® (entrectinib capsules), 100 mg and 200 mg

**Route of Administration:** Oral

**Applicant Name:** Genentech, Inc.

**Primary Reviewer:** Parnali Chatterjee, Ph.D.

**Secondary Reviewer:** Banu Zolnik, Ph.D.

***Background:***

The Applicant is seeking approval of **Rozlytrek®** (entrectinib capsules), 100 mg and 200 mg for the treatment of adult patients with tumors that express NTRK1/2/3 (NDA 212726) or ROS 1-positive, or ALK gene fusions (NDA 212725) *via* the 505 (b)(1) regulatory pathway. The recommended daily dose for entrectinib capsules (RXDX101) is 600 mg (3×200 mg) orally once daily with or without food in adults. NDA 212725 is cross referenced to this NDA 212726.

Entrectinib capsules, 100 mg and 200 mg received Orphan Drug Designation (ODD) and priority review for the treatment of patients with TRKA/B/C, ROS 1-positive, or ALK positive metastatic non-small cell lung cancer (NSCLC). A pivotal Phase II open-label, single-arm, multi-center safety and efficacy study, RXDX-101-02 (STARTRK-2) was conducted in which the F2A gelatin capsule product was dosed to the patients. The To-Be-Marketed (TBM) drug product is the F06 hypromellose (HPMC) capsule product. To establish a ‘bridge’ between the F2A formulation used in the pivotal Phase II clinical study (RXDX-101-02) and the TBM F06 drug product, a comparative bioavailability/bioequivalence (BA/BE) study, RXDX-101-15 was conducted.

**REVIEW SUMMARY:**

This Biopharmaceutics Review evaluated **1)** the proposed dissolution method, **2)** the proposed dissolution acceptance criterion, **3)** the need for bridging the different formulations and packaging site throughout the product development stage, and **4)** the biowaiver request for the 100 mg F06 TBM drug product.

➤ ***Proposed Dissolution Method:***

The dissolution profile data for various testing parameters and discriminating ability of the proposed dissolution method is **ACCEPTABLE** as a quality control tool for batch release and stability testing of the 100 mg and 200 mg proposed drug product.

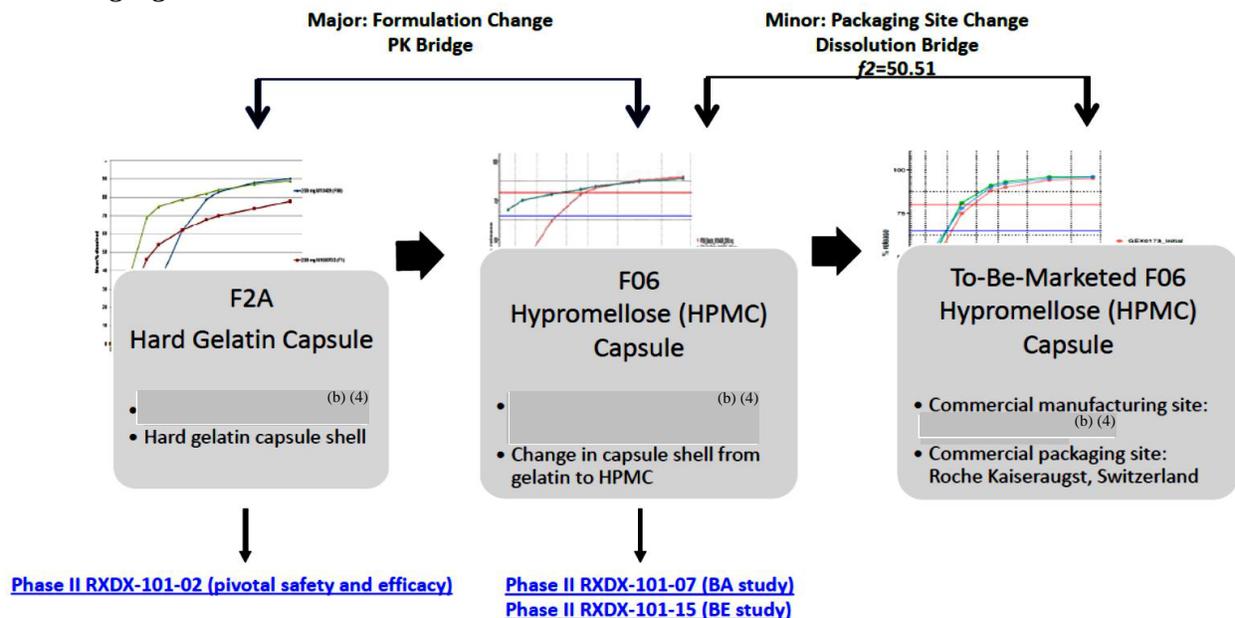
Parameters	<b>ACCEPTABLE</b> Dissolution Method
------------	--------------------------------------

<i>Apparatus/Speed</i>	USP Apparatus 2 (paddle)/75 rpm
<i>Sinkers</i>	Helix stainless-steel sinkers
<i>Media/Volume</i>	0.374% Tween 80 in 50 mM potassium phosphate, pH 6.0/1000 mL
<i>Bath temperature</i>	37.0±0.5 C

➤ **Dissolution Acceptance Criterion:**

The proposed acceptance criterion of “ $Q = \frac{(b)(4)}{(4)}\%$  in 60 minutes” for batch release and on stability for the proposed drug products based on the bio-batch, clinical, and stability batches is acceptable.

➤ **Bridging:**



▪ **Bridging of Batches due to Formulation Changes:**

The pivotal Phase II safety and efficacy study, RXDX-101-02 (STARTRK-2) was conducted with F2A gelatin capsule product. The (b) (4) F2A drug product was changed (b) (4) (b) (4). Therefore, gelatin capsule shell was replaced with hypromellose (HPMC) capsule shell in the TBM F06 drug product. A bioequivalence (BE) study RXDX-101-15 was conducted with the F2A and F06 drug product to support bridging. Refer to the OCP Review for further details. It should be noted that dissolution profile data provided for the F2A and F06 drug products using the proposed dissolution method demonstrated relatively high variability at time-points of up to 45 minutes.

▪ **Bridging of Batches due to Packaging Site Changes:**



## QUALITY ASSESSMENT Chapter VII-Biopharmaceutics



The commercial manufacturing site for the F06 drug product is (b) (4); whereas, the commercial packaging site for the TBM F06 drug product is Roche, Kaiseraugst. The comparative dissolution profiles using the proposed dissolution method and  $f_2$  similarity analysis with  $f_2$  value >50 indicates that three registration batches of the 100 mg and 200 mg F06 drug product manufactured at (b) (4) and packaged at (b) (4) and Roche Kaiseraugst are similar and provide a bridge between the two packaging sites.

➤ ***Biowaiver Request:***

The biowaiver request for the 100 mg F06 drug product is granted based on 1) the compositional proportionality between the 100 mg and 200 mg strength drug product with respect to entrectinib, the active pharmaceutical ingredient (API) and excipients; 2) bioequivalence between the 200 mg F06 and F2A drug products in the bioequivalence (BE) study RXDX-101-15; 3) linear pharmacokinetics of the F06 drug product between the dose ranges of 100 mg-600 mg under fasted condition based on the bioavailability study RXDX-101-12; and 4) similarity in the dissolution profile data for the 100 mg and 200 mg F06 drug product.

➤ ***Biopharmaceutics Risk Assessment:***

Entrectinib is a low solubility drug substance that exhibits several polymorphic forms. The F2A drug product was developed as an hard gelatin capsule product (b) (4). Formulation F2A was dosed in the pivotal Phase II clinical study. During the pivotal Phase II clinical study, (b) (4) F2A drug product was changed (b) (4). To mitigate dissolution failures, the Applicant changed the capsule shell from hard gelatin to HPMC. Further, the packaging site for the F06 commercial product was changed from (b) (4) to Roche, Kaiseraugst. Based on the overall dissolution data for changes in formulation and packaging site; from a Biopharmaceutics perspective, because the final drug product is an HPMC capsule drug product and the commercial packaging site was moved from (b) (4) to Roche, Kaiseraugst, Switzerland, the risk of dissolution failure during batch release and stability testing is relatively low.

➤ ***OVERALL REVIEW RECOMMENDATION:***

From the Biopharmaceutics perspective, NDA 212726 for Rozlytrek™ containing 100 mg and 200 mg of entrectinib is recommended for **APPROVAL**.



**BIOPHARMACEUTICS ASSESSMENT**

➤ **LIST OF SUBMISSIONS REVIEWED:**

<b>Submissions Reviewed</b>	<b>Reference ID</b>
IND 120500 Meeting Minutes	Dated 09/12/2017 ( <a href="https://darrrts.fda.gov/darrrts/ViewDocument?documentId=090140af8045aece">https://darrrts.fda.gov/darrrts/ViewDocument?documentId=090140af8045aece</a> )
	Dated 10/16/2017 ( <a href="https://darrrts.fda.gov/darrrts/ViewDocument?documentId=090140af80462e4b">https://darrrts.fda.gov/darrrts/ViewDocument?documentId=090140af80462e4b</a> )
	Dated 10/24/2017 ( <a href="https://darrrts.fda.gov/darrrts/ViewDocument?documentId=090140af80464d5d">https://darrrts.fda.gov/darrrts/ViewDocument?documentId=090140af80464d5d</a> )
	Dated 08/28/2018 ( <a href="https://darrrts.fda.gov/darrrts/ViewDocument?documentId=090140af804b1e75">https://darrrts.fda.gov/darrrts/ViewDocument?documentId=090140af804b1e75</a> )
	Dated 10/09/2018 ( <a href="https://darrrts.fda.gov/darrrts/ViewDocument?documentId=090140af804bbc27">https://darrrts.fda.gov/darrrts/ViewDocument?documentId=090140af804bbc27</a> )
	Dated 10/30/2018 ( <a href="https://darrrts.fda.gov/darrrts/ViewDocument?documentId=090140af804c14f3">https://darrrts.fda.gov/darrrts/ViewDocument?documentId=090140af804c14f3</a> )
	Original NDA Submission 212725/212726
Response to Information Request Comment #1	Dated 02/06/2109, SDN 9 ( <a href="\\cdsesub1\evsprod\nda212726\0009\m1\us\20190206-resp-fda-req.pdf">\\cdsesub1\evsprod\nda212726\0009\m1\us\20190206-resp-fda-req.pdf</a> )

➤ **DRUG SUBSTANCE**

The active ingredient in the proposed drug product is entrectinib (molecular weight 560.3 grams/mole) which is a white-to (b) (4) crystalline drug substance. The drug substance exhibits

(b) (4)

(b) (4) The Applicant notes (b) (4) to be the desired polymorphic form of drug substance in the proposed product. (b) (4) (b) (4) is controlled during the manufacturing process and during stability in the proposed product.

- **Solubility:**

The equilibrium solubility of entrectinib was conducted using shake-flask method in buffer solutions across the physiological pH range 1.2-6.8 and in simulated gastric (SGFsp) and intestinal fluids (FaSSIF and FeSSIF) at 37 C for 1 hour and 24 hours (see **Table 1**).

**Table 1.** Equilibrium solubility of entrectinib in buffer solutions across the physiological pH range 1.2-6.8 at 37 C for 1 hour and 24 hours

Aqueous Media or Buffer	pH of Medium	pH Value (Measured) 1 h/24 h	Solubility at 37°C, 1 h (mg/mL)	Solubility at 37°C, 24 h (mg/mL)
SGFsp	1.2	4.5/4.8	42.2	0.1 <sup>a</sup>
Acetate buffer (50 mM)	4.5	4.5/4.5	0.2	0.2
Potassium phosphate buffer (50 mM)	6.8	6.8/6.8	0.0	0.0
Potassium phosphate buffer (50 mM)	8.0	8.0/8.0	0.0	0.0
Deionized water	7.9	7.7/8.4	0.0	0.0
FeSSIF	5.0	5.0/5.2	4.0	3.5
FaSSIF	6.5	6.5/6.5	0.1	0.1

Abbreviations: FaSSIF = fasted-state simulated intestinal fluid; FeSSIF = fed-state simulated intestinal fluid; SGFsp = simulated gastric fluid sine pepsin.

<sup>a</sup> After 24 h equilibration, X-ray powder diffraction analysis of the residual solid revealed a solid-form change.

**Reviewer’s Assessment of Drug Substance Solubility:**

The free base exhibits high solubility (42.2 mg/mL) in SGF, pH 1.2 and low solubility in 50 mM phosphate buffer, pH 4.5-6.8 at 37 C for 1 hour (see **Table 1**). However, following 24 hour equilibration the drug substance exhibits low solubility in SGF, pH 1.2. The Applicant noted a change in the solid-state form following precipitation of the drug substance after 24 hour equilibration in SGF, pH 1.2. Consequently, the highest dose of the drug substance, i.e., 200 mg is not soluble in 250 mL buffer solutions across the physiological pH range 1.2-6.8 (**Table 1**). Therefore, entrectinib is classified as a low soluble drug substance per BCS.

- **Permeability/Absorption:**

LogD of entrectinib is 3.32 at pH 6.5 and 4.02 at pH 7.4, whereas the pKa (1) is 2.54 (base) and pKa (2) is 7.54 (base). The apparent permeability ( $P_{app}$ ) of entrectinib is  $1.07 \times 10^{-6}$  cm/s verses minoxidil (high permeability marker) that exhibits  $P_{app} = 5.25 \times 10^{-6}$  cm/s and atenolol (low permeability marker) with  $P_{app} = 0.191 \times 10^{-6}$  cm/s.

Additionally, the time to reach maximum concentration ( $T_{max}$ ) following a single 600 mg oral dose of F06 capsules in the comparative bioavailability study RXDX-101-07 is approximately 5.0 hours under fasted condition and approximately 3.0 hours under fed condition. The maximum concentration ( $C_{max}$ ) reached is 2290 nM and exposure ( $AUC_{0-\infty}$ ) is 60900 nM×hour under fasted state and 2240 nM and 54500 nM×hour under fed state.

***Reviewer’s Assessment of Permeability/Absorption:***

Based on the in vitro permeability and in vivo bioavailability studies provided by the Applicant, entrectinib can be categorized as a ‘low-moderately’ permeable drug substance.

***Particle Size:***

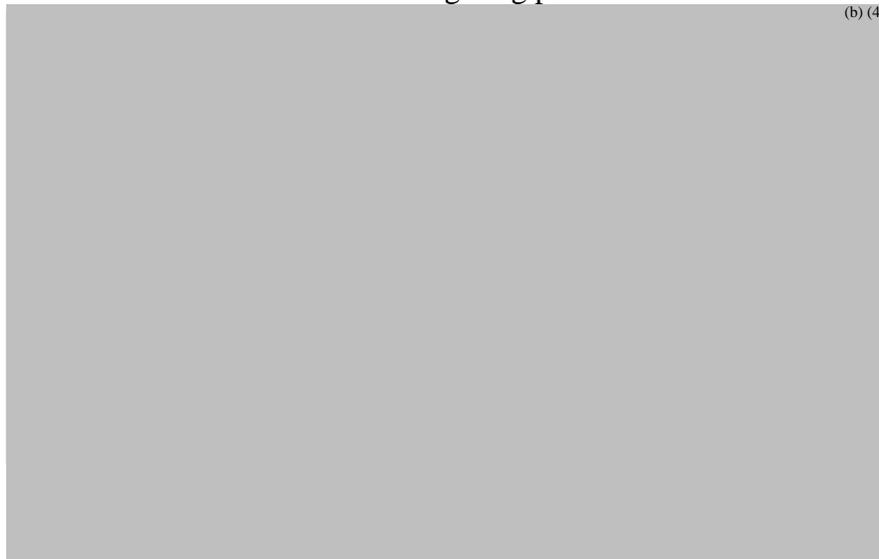
Entrectinib is a low soluble drug substance. Therefore, particle size of the drug substance can alter the dissolution profile of the drug product. Particle size of the drug substance was controlled (b) (4) and assessed as a critical material attribute (CMA) during product development. Particle size of (b) (4) (batch CA15-0919) and (b) (4) (batch CA17-0657) drug substance used during the manufacturing process of the 200 mg F06 drug product batch M10409 is provided in **Table 2**.

**Table 2.** Particle size distribution (PSD) of the drug substance in the 200 mg F06 drug product batch M10409 containing (b) (4) drug substance batch CA17-0657 and (b) (4) 200 mg F06 drug product batch AB2

Particle Size Distribution (PSD), μm	Drug substance batch CA17-0657 (b) (4) Drug product batch M10409	Drug substance batch Batch CA15-0919 (b) (4) Drug product batch AB2
D <sub>10</sub>	(b) (4)	
D <sub>50</sub>	(b) (4)	
D <sub>90</sub>	(b) (4)	

The effect of (b) (4) drug substance on the dissolution profile of the drug product batch M10409 is provided in **Figure 1**. Batch AB2 contains (b) (4) drug substance (see **Table 2**). Particle size reduction ( $D_{90} = (b) (4) \mu m$ ) did not significantly enhance the dissolution of the drug product batch M10409.

**Figure 1.** Effect of the drug substance (b) (4) on the dissolution profile of the 200 mg drug product



Therefore, the following PSD is proposed for the drug product:  $D_{10}=NLT$  (b) (4) and  $D_{90}=NMT$  (b) (4).

➤ **DRUG PRODUCT:**

The To-be-marketed (TBM) F06 drug product is an immediate-release product, with 100 mg or 200 mg entrectinib encapsulated in hypromellose (HPMC) (b) (4) capsules (see **Table 3** for composition of the F06 drug product). The TBM drug product is manufactured (b) (4).

**Table 3.** Composition of the TBM entrectinib capsules, 100 mg and 200 mg, F06 drug product

Components	Reference to Standards	Function	Quantity per Unit Dose (mg)	
			100 mg Capsule	200 mg Capsule
Capsule (b) (4)				
Entrectinib	In-house	Active	100.000 <sup>a</sup>	200.00 <sup>a</sup>
Lactose anhydrous	USP/NF, Ph. Eur., JP			(b) (4)
Microcrystalline cellulose <sup>b</sup>	USP/NF, Ph. Eur., JP			
Tartaric acid	USP/NF, Ph. Eur., JP			
Hypromellose	USP/NF, Ph. Eur., JP			
Crospovidone	USP/NF, Ph. Eur., JP			
Magnesium stearate	USP/NF, Ph. Eur., JP			
Colloidal silicon dioxide	USP/NF, Ph. Eur., JP			
Target Capsule Weight	(b) (4)			

<sup>a</sup> If necessary the amount of drug substance may be adjusted to take into account the assay of drug substance. The amount of lactose anhydrous is adjusted based on the actual amount of the drug substance.

<sup>b</sup> Microcrystalline cellulose (b) (4) is used.

Hard gelatin capsule products (F1, F2A, F2B) were dosed in the Phase I and Phase II safety and efficacy studies of the 200 mg drug product. The F2A hard gelatin capsule (b) (4) (b) (4) was dosed in the pivotal Phase II safety and efficacy study, RXDX-101-02 (STARTRK-02).

During Phase II clinical trial, formulation for the F2A hard gelatin product was further modified. The modifications included change (b) (4) (b) (4) in the capsule shell from hard gelatin to hypromellose (HPMC) to the final TBM F06 HPMC drug product.

To bridge the hard gelatin capsule F2A product used in the pivotal Phase II clinical study RXDX-101-02, to the hypromellose capsule F06 product, the Applicant provided in vitro dissolution profile data using the proposed dissolution method and conducted a relative bioavailability/bioequivalence study RXDX-101-15. The study outcomes will be discussed in latter sections under “*Bridging of Batches*”.

➤ **MANUFACTURING SITES FOR THE PROPOSED DRUG PRODUCT:**

(b) (4) is identified as the manufacturing site for the commercial F06 hypromellose capsule product. However, Roche, Kaiseraugst is identified as the commercial packaging site for the TBM F06 drug product in the submission. In vitro dissolution profile data using the proposed dissolution method are provided to bridge the two packaging sites, (b) (4) and Roche, Kaiseraugst, and will be discussed under “*Bridging of Batches*”.

➤ **DISSOLUTION INFORMATION:**

Dissolution testing was identified as a critical quality attribute (CQA) for the proposed drug product and is utilized as a quality control tool during the product development process, for the batches used in the pivotal clinical PK studies, and for batches on stability. The dissolution method was also utilized to select the final drug product F06 formulation, the final manufacturing process, to bridge the formulations, and for the ‘waiver’ of in vivo bioequivalence studies for the 100 mg strength commercial drug product.

➤ **DISSOLUTION METHOD:**

The dissolution method proposed for routine quality control testing of the proposed drug product is provided in **Table 4**. The dissolution method development was performed with the 200 mg drug product.

**Table 4.** Proposed dissolution method for quality control testing of F06 100 mg and 200 mg drug product

Parameters	Method
<i>Apparatus/Speed</i>	USP Apparatus 2 (paddle)/75 rpm
<i>Sinkers</i>	Helix, stainless-steel
<i>Media/Volume</i>	0.374% Tween 80 in 50 mM potassium phosphate, pH 6.0/1000 mL
<i>Bath temperature</i>	37.0±0.5 C

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➤ **PROPOSED DISSOLUTION ACCEPTANCE CRITERION:**

The Applicant proposed “ $Q = \text{(b) (4)}\%$  in 60 minutes” as the dissolution acceptance criterion for batch release and stability testing of the 200 mg strength proposed F06 drug product, which is acceptable based on the totality of the dissolution data as high variability in the dissolution data is observed up to 45 minutes sampling time-point.

(b) (4)

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No significant trend in the dissolution profile data is observed for the 200 mg (bio-batch M10409) F06 drug product manufactured and packaged at (b) (4) on intermediate and accelerated stability conditions.

**Reviewer’s Assessment of the Proposed Dissolution Acceptance Criterion:**

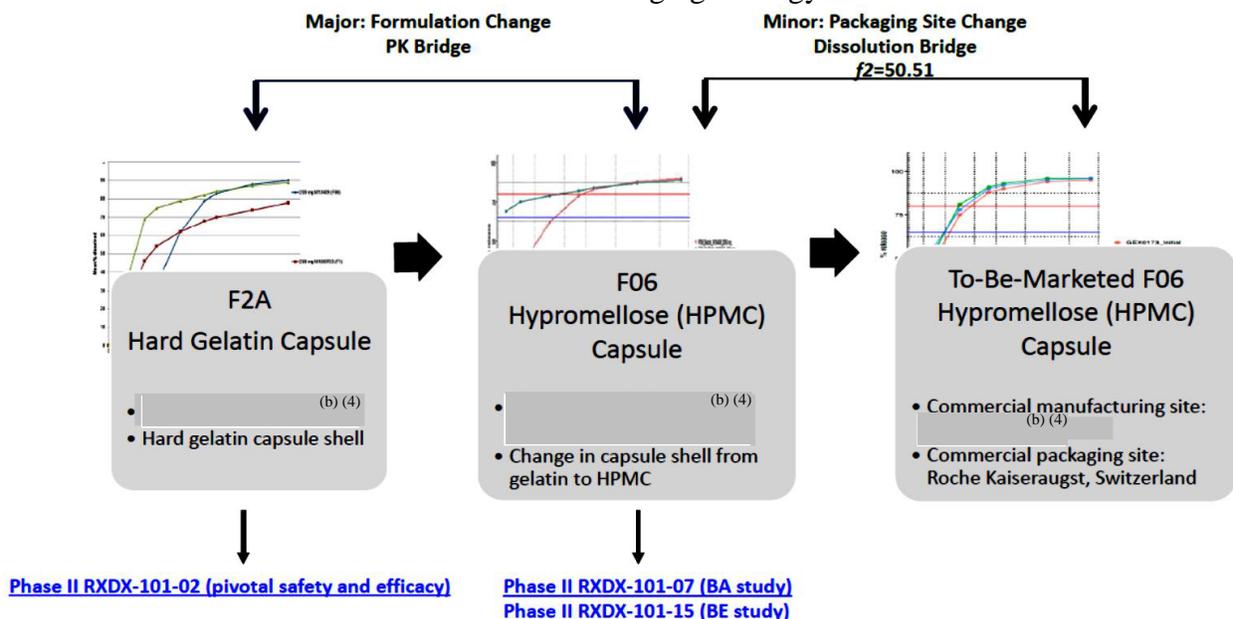
Based on the totality of the dissolution data, from a Biopharmaceutics perspective, the dissolution data support a dissolution acceptance criterion of “ $Q = \frac{(b)(4)}{(4)}\%$  in 60 minutes” for batch release and stability testing of Rozlytrek™ containing 100 mg and 200 mg of entrectinib.

➤ **Bridging of Batches due to Formulation Changes:**

Formulation F2A gelatin capsule product was dosed in the pivotal Phase II safety and efficacy study, RXDX-101-02 (STARTRK-2). Formulation F2A (b) (4) (b) (4) was changed (b) (4) (b) (4). However, downward trend in the dissolution profile data was noted for the formulation during intermediate and accelerated stability conditions (b) (4) (b) (4) (b) (4) (b) (4) (b) (4). Therefore, gelatin capsule shell was replaced with hypromellose (HPMC) capsule shell in the TBM F06 drug product.

The schematic of the drug products used in clinical development and formulation bridging strategy is provided in **Figure 8**.

**Figure 8.** Schematic Diagram of Oral Formulations Used in Clinical Development and Formulation Bridging Strategy



F2A and F06 drug products were dosed in the bioavailability study RXDX-101-07 and in the bioequivalence (BE) study RXDX-101-15 to establish a ‘bridge’ between the F2A gelatin

capsule product and TBM F06 HPMC capsule product. The dissolution profile data for the F2A and F06 drug products using the proposed dissolution method is provided in **Figure 9**.

(b) (4)

The dissolution profile data for the F2A and F06 drug products using the proposed dissolution method exhibit high variability at time-points of up to 45 minutes that precludes the ability to compute the similarity factor 'f<sub>2</sub>' value. However, the F2A and F06 drug products were dosed in the bioavailability study RXDX-101-07 and in the bioequivalence (BE) study RXDX-101-15.

The 90% confidence interval between the F06 and F2A drug products dosed in the bioavailability study RXDX-101-07 for C<sub>max</sub> (nM)=88.9-101 and for AUC<sub>0-∞</sub> (nM.h)=89.1-101 (see **Table 10**). The adequacy of the BA study is reviewed by the OCP reviewer, refer to the OCP review for further details.

**Table 10.** Statistical analysis of the pharmacokinetic parameters for the F2A and F06 drug products dosed in the bioavailability study RXDX-101-07

Test (N) vs Reference (N)	Variable	%Ratio (F0X/F2A)	CI 90% Lower	CI 90% Upper
F06 (48) vs F2A (48)	C <sub>max</sub>	94.7	88.9	101
	AUC <sub>last</sub>	94.9	89.1	101
	AUC <sub>INF</sub>	95.0	89.1	101

The 90% confidence interval for C<sub>max</sub> (nM) and AUC<sub>0-∞</sub> (nM.h) between the F06 and F2A drug products dosed in the bioequivalence (BE) study RXDX-101-15 is 88.3-98.6 and 85.4-97.9, respectively (see **Table 11**). The adequacy of the BE study is reviewed by the OCP reviewer, refer to the OCP review for further details.

**Table 11.** Statistical analysis of the pharmacokinetic parameters for the F2A and F06 drug products dosed in the bioavailability study RXDX-101-15

Test (N) vs Reference (N)	Variable	%Ratio F2A/F06	CI 90% Lower	CI 90% Upper
F06 (48) vs F2A (48)	C <sub>max</sub>	93.3	88.3	98.6
	AUC <sub>last</sub>	91.4	85.3	97.9
	AUC <sub>INF</sub>	91.4	85.4	97.9

➤ ***Bridging of Batches due to Packaging Site Changes:***

The manufacturing site for the commercial F06 drug product is (b) (4). However, the commercial packaging site for the F06 drug product is Roche Kaiseraugst, Switzerland. The Applicant provided in vitro dissolution profile data for three registration batches of the 100 mg and 200 mg drug product manufactured at (b) (4) and packaged at (b) (4) and Roche Kaiseraugst, Switzerland, using the proposed dissolution method to provide a bridge for the two packaging sites (see **Figure 10**).

(b) (4)



The similarity factor ‘ $f_2$ ’ value for the mean dissolution profile data for three registration batches of the 100 mg F06 drug product M10410, M10412, and M10413 packaged at (b) (4) and three registration batches GEX173, GEX174, and GEX175 packaged at Roche-Kaiseraugst for initial, 1 month, and 3 months at intermediate stability condition of 30 C/75% RH is >50 (calculated by this Reviewer using the Automation Tool). It should be noted that relative variability in the dissolution data is observed for the three registration batches packaged at (b) (4); however, all batches would comply at S1 and S2 with the proposed dissolution acceptance criterion of “ $Q = \frac{(b)}{(4)}\%$  in 60 minutes”.

Similar dissolution profile data is observed for the three registration batches of the 200 mg F06 drug product packaged at (b) (4) and three registration batches packaged at Roche-Kaiseraugst for initial, 1 month, and 3 months at intermediate stability condition of 30 C/75% RH, with similarity factor 'f2' value >50 (calculated by this Reviewer using the Automation Tool).

Based on the totality of the in vitro dissolution data and in vivo bioavailability study, adequate data is provided to bridge the changes in formulation and packaging site for the 100 mg and 200 mg drug product batches.

➤ **Biowaiver for the 100 mg F06 Drug Product:**

The Applicant is seeking approval of **Rozlytrek®** (entrectinib capsules), 100 mg and 200 mg for the treatment of adult patients with tumors that express NTRK1/2/3, ROS 1-positive, or ALK gene fusions. The biowaiver request for the 100 mg F06 drug product batch M10410 is granted based on the following observations:

1. The 100 mg and 200 mg strength drug product are compositionally proportional with respect to entrectinib, the active pharmaceutical ingredient (API) and excipients (see **Table 1**).
2. The 200 mg F06 drug product was dosed in the bioequivalence (BE) study RXDX-101-15, along with the F2A drug product. The 90% confidence interval (see **Table 11**) between the F06 and F2A drug products dosed in the bioequivalence (BE) study RXDX-101-15 for C<sub>max</sub> (nM) and AUC<sub>0-∞</sub> (nM.h) indicate that the two products are bioequivalent.
3. The F06 drug product exhibits linear pharmacokinetics (C<sub>max</sub>=358-1810 nM and AUC<sub>0-∞</sub>= 6190-36300 nM.h) between the dose ranges of 100 mg-600 mg under fasted condition based on the bioavailability study RXDX-101-12 (see **Table 12**).

**Table 12.** Summary of the mean pharmacokinetic parameters for the F06 drug products dosed in the bioavailability study RXDX-101-12

Analyte		Unadjusted means	
		100 mg (Part 1) (N=10)	600 mg (Part 2) (N=10)
Entrectinib	AUC <sub>inf</sub> (nM.h)	6190 (50%)	36300 (28%)
	C <sub>max</sub> (nM)	358 (35%)	1810 (25%)
	T <sub>max</sub> (h)	2.0 (1.0-3.0)	3.5 (2.0-5.0)
	t <sub>1/2</sub> (h)	20.2 (17%)	16.7 (16%)
M5	AUC <sub>inf</sub> (nM.h)	1710 (30%)	11000 (44%)
	C <sub>max</sub> (nM)	52.3 (37%)	383 (56%)
	T <sub>max</sub> (h)	5.0 (3.0-5.0)	5.0 (4.0-5.0)
	t <sub>1/2</sub> (h)	40.8 (22%)	33.8 (12%)

Source: Study RXDX-101-12 Tables 15.1 to 15.8

Geometric mean (CV%) for AUC<sub>inf</sub>, C<sub>max</sub> and t<sub>1/2</sub>. Median (range) for T<sub>max</sub>

4. The in vitro dissolution profile data for the 100 mg and 200 mg strength drug product is provided in **Figure 11**.



The similarity factor ‘f<sub>2</sub>’ value between the dissolution profile data for the 100 mg and 200 mg drug product is 50.51 (calculated by this Reviewer) suggesting that the two dissolution profiles for the 100 mg and 200 mg drug product are similar.

Based on the totality of the in vitro dissolution data and in vivo bioavailability study, an adequate data is provided to bridge the 100 mg and 200 mg bio-batch M10409. Therefore, biowaiver is granted for the 100 mg F06 drug product.

➤ **BIOPHARMACEUTICS RISK ASSESSMENT:**

Entrectinib is a low solubility drug substance. The F2A drug product was developed as an hard gelatin capsule product (b) (4). Formulation F2A was dosed in the pivotal Phase II clinical study. During the pivotal Phase II clinical study, (b) (4) F2A drug product was changed (b) (4). To mitigate dissolution failures, the Applicant changed the capsule shell from hard gelatin to HPMC. Further, the packaging site for the F06 commercial product was changed from (b) (4) to Roche, Kaiseraugst, Switzerland. Based on the overall dissolution data for changes in formulation and packaging site; from a Biopharmaceutics perspective, because the final drug product is an HPMC capsule drug product and the commercial packaging site was moved from (b) (4) to Roche Kaiseraugst, Switzerland, the risk of dissolution failure during batch release and stability testing is relatively low.

➤ **POST-APPROVAL COMMITMENTS: None**

➤ **LIST OF DEFICIENCIES: None**



➤ ***OVERALL REVIEW RECOMMENDATION:***

From the Biopharmaceutics perspective, NDA212726 for Rozlytrek™ containing 100 mg and 200 mg of entrectinib is recommended for **APPROVAL**.



Parnali  
Chatterjee

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Banu  
Zolnik

Digitally signed by Banu Zolnik  
Date: 5/09/2019 09:20:20AM  
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