CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218550Orig1s000

PRODUCT QUALITY REVIEW(S)

Title:	NDA IQA Template Title Page- EXEC SUMMARY
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Template Revision: 03

Office of Pharmaceutical Quality

New Drug Application (NDA)
Integrated Quality Assessment Template

NDA Executive Summary

1. Application/Product Information

NDA Number	218550
Applicant Name	GENENTECH INC
Drug Product Name	Rozlytrek (Entrectinib)
Dosage Form	Pellets
Proposed Strength(s)	50 mg
NDA Classification	Type 3 - New Dosage Form
Route of Administration	Oral
Maximum Daily Dose	600 mg
Rx/OTC Dispensed	Rx
Proposed Indication	ROZLYTREK is a kinase inhibitor indicated for the treatment of: •Adult patients with ROS1-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test. •Adult (b) (4) with solid tumors that: ○ have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, as detected by an FDA-approved test without a known acquired resistance mutation, ○ are metastatic or where surgical resection is likely to result in severe morbidity, and ○ have progressed following treatment or have no satisfactory alternative therapy.
Drug Product Description	brownish orange or grayish orange pellets in packets
Co-packaged product information	N/A
Device information	N/A
Storage Temperature/ Conditions	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

	Discipline	Primary	Secondary
Review Team	*Drug Substance*	Kabir Shahjahan	Haripada Sarker
	Drug Product/ Labeling	Xiao Hong Chen	Xing Wang
	Manufacturing	Diane Goll	Zhaoyang Meng
	Biopharmaceutics	Gerlie Gieser	Anitha Govada
	Microbiology	N/A	
	Other (specify)	N/A	
	RBPM	Janell Artis	
	ATL	Xing Wang	
Consults	None		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

24 months.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

b. Additional Comments for Action

None

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

Entrectinib capsules were approved for the treatment of patients with metastatic non-small cell lung cancer on August 15, 2019. For the current NDA, the applicant is seeking approval of Entrectinib oral pellets for the treatment of the rare population of adult (b) (4) *with tumors that harbor NTRK or ROS1 gene fusions. The applicant has provided sufficient information to assure the identity, strength, purity, and quality of the proposed drug product. The applicant adequately justified performing most* (b) (4)*. All associated manufacturing, testing, packaging facilities were deemed acceptable. However, the applicant's prediction of fasted BE between the oral granules and oral capsules could not be verified*

via a modeling approach. Based on the OPQ review team's evaluation of the information provided in the submission, OPQ recommends APPROVAL of NDA 218550 for Rozlytrek (Entrectinib) Oral Pellets 50mg.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**N/A**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:
None

Application Technical Lead Name and Date:

Xing Wang, Ph.D.

Xing Wang

Digitally signed by Xing Wang
Date: 10/02/2023 09:56:41AM
GUID: 525daca300039122a4daaad45e49c6fb

U.S. FOOD & DRUG ADMINISTRATION

CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	(Entrectinib) oral pellets The originally proposed name, (Entrectinib) coated (b) (4), was not acceptable and has been changed to (Entrectinib) Oral Pellets (b) (4)
Route(s) of administration	Adequate	For oral use
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	• Capsules: 100 mg and 200 mg • Pellets: 50 mg per packet Note: Entrectinib capsules DP has been approved in NDA 212725. The current NDA is for the Entrectinib oral pellets.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Adequate	Special instruction for preparation and administration is provided: Sprinkle pellets on one or more spoonfuls of a soft food (e.g., applesauce, yogurt, or pudding) and take within 20 minutes of mixing. Do not crush or chew to avoid a bitter taste. The patient should drink water after taking the (b) (4) to ensure the drug has been completely swallowed. Do not divide the contents of a packet of (b) (4) to prepare a smaller dose.
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	In-use studies conducted to support the preparation and administration of the oral (b) (4)
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	N/A	

If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Capsules and oral pellets
Strength(s) in metric system	Adequate	100 mg and 200 mg capsules 50 mg oral pellets in packets
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	• 100 mg: Size 2 yellow opaque body and cap, with "ENT 100" printed in blue ink on body. • 200 mg: Size 0 orange opaque body and cap, with "ENT 200" printed in blue ink on body. • Brownish orange or grayish orange pellets
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 11 (DESCRIPTION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	ROZLYTREK® (entrectinib) capsules ROZLYTREK® (entrectinib) oral pellets
Dosage form(s) and route(s) of administration	Adequate	Capsules for oral use Oral pellets
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	All excipients listed.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	Entrectinib is a kinase inhibitor.
Chemical name, structural formula, molecular weight	Adequate	All information are provided.
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	Capsules Oral pellets
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	100 mg capsules in bottles of 30 capsules and 200 mg capsules in bottles of 90 capsules 50 mg oral pellets in each packet stored in 42-count carton
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	Oral pellets are supplied as brownish orange to grayish orange, round film-coated (b) (4), available in: 42-count carton (each packet contains 50 mg entrectinib): NDC 50242-623-42
Assess if the tablet is scored. If product meets guidelines	N/A	

and criteria for a scored tablet, state "functionally scored"		
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	The proposed storage time is (b) (4) Although it is supported by stability data, the Applicant was asked to use (b) (4) The applicant agreed.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of	N/A	

natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*		
Include information about child-resistant packaging	Adequate	IR:

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	
Special preparation instructions (if applicable)	Adequate	
Storage and handling information (if applicable)	Adequate	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	Adequate	
Alphabetical listing of inactive ingredients (if applicable)	Adequate	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	

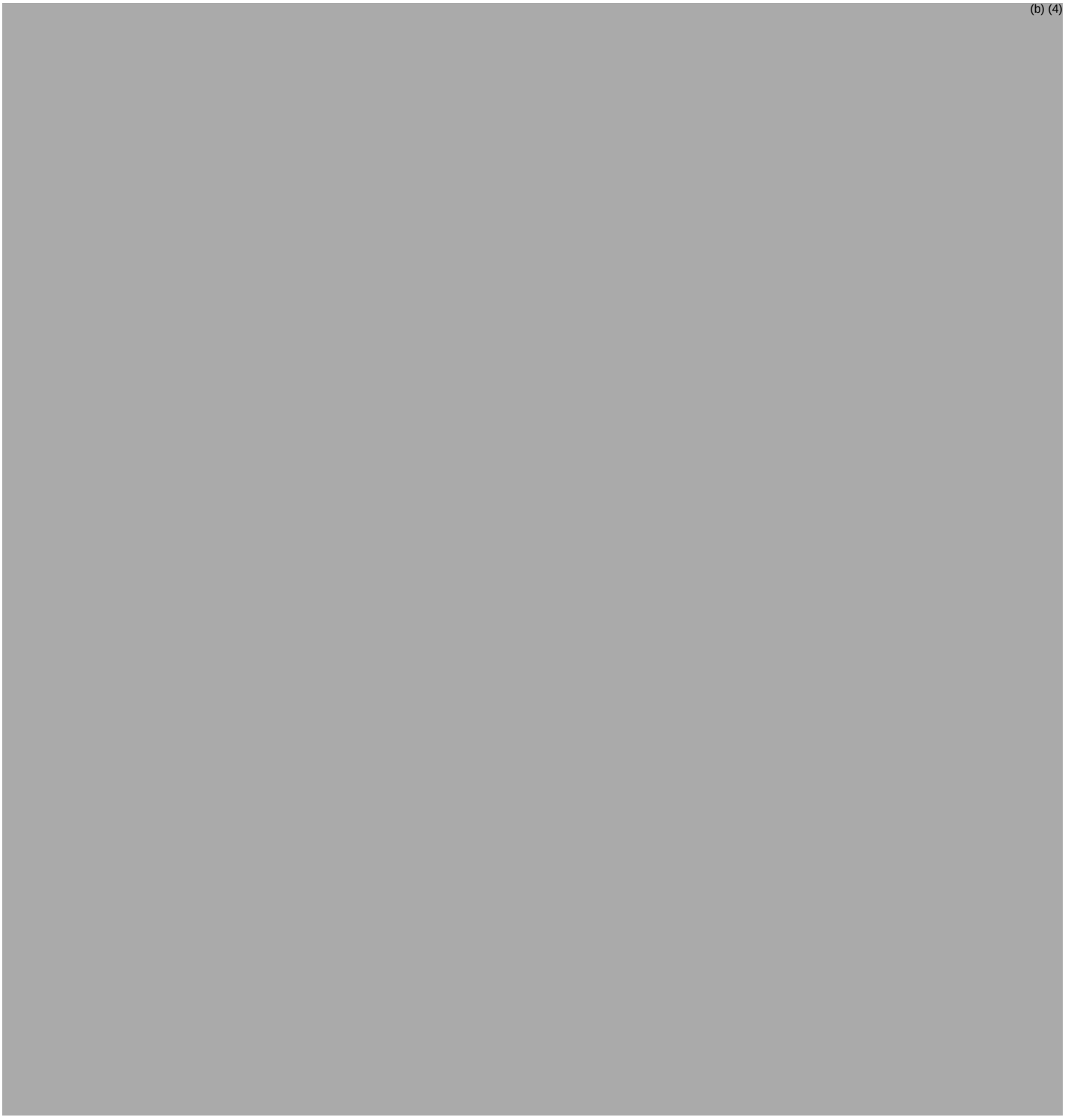
Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CONTAINER AND CARTON LABELING

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

3.1 Container Labels

(b) (4)



Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

[3] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: ***{Adequate}***

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See Carton/Container Labeling Specific Resources for a presentation about inappropriate inconsistencies of product quality information between labeling. If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these as deficiencies in this section.

Overall Assessment and Recommendation:

The applicant agreed to the FDA comments and edits for the prescribing information (PI), patient labeling, IFU and container carton labels. The updated labeling for PI and container carton labels are found acceptable.

Primary Labeling Assessor Name and Date: Xiao Hong Chen 1-Oct-2023

Secondary Assessor Name and Date: David Claffey

Xiao Chen

Digitally signed by Xiao Chen
Date: 10/02/2023 09:22:25AM
GUID: 508da7220002a138fcc70fbccbfd08bf

David Claffey

Digitally signed by David Claffey
Date: 10/02/2023 09:43:47AM
GUID: 508da71e00029e20b201195abff380c2

CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	NDA-218550-ORIG-1 [associated with NDA-212725-SUPPL-9; SN-288]
Assessment Cycle Number	1
Drug Product Name/ Strength	ROZLYTREK® (entrectinib) coated granules# 50 mg in stickpack
Route of Administration	Oral
Applicant Name	Genentech, Inc./Roche
Therapeutic Classification/ OND Division	Anticancer/Division of Oncology 2 (DO2)
RLD/RS Number	Not Applicable
Proposed Indication **Dosage and Administration**	Treatment of NTRK gene fusion-positive metastatic solid tumors Adults: 600 mg orally once daily (with or without food) (b) (4) (once daily): see labeling for the final dosage for all age and BSA subgroups Sprinkle granules on one or more spoonfuls of a soft food (e.g., applesauce, yogurt, or pudding) and take within 20 minutes of mixing. Do not crush or chew to avoid a bitter taste.

FDA recommended a dosage form designation change to "oral pellets".

Assessment Recommendation: **Adequate**

Assessment Summary:

Background:

In NDA 218550, the Applicant seeks approval of entrectinib oral granules (formerly referred to as "minitablets") as a new formulation/dosage form of Rozlytrek® developed for use in pediatric patients who cannot swallow the intact commercial oral capsules (but can swallow soft food). The contents (twenty 2.5 mg granules per stickpack) of the appropriate number of stickpacks are sprinkled over soft food vehicle and the entire mixture is administered within 20 minutes of mixing. The oral granules when sprinkled over soft food vehicles enables oral dosing (typically, 100 mg – 300 mg) to the nearest 50 mg.

As an alternative for patients who are not able to swallow the oral granules in soft-food vehicle, NDA 212725/SUPPL-9 provides for a new method of administration (i.e., *ad hoc* suspension prepared from the contents of one or more capsules) and new route of administration (via oral syringe or nasogastric/gastric tube use) for the approved Rozlytrek® Capsules 100 mg

and 200 mg. The extemporaneously prepared oral suspension enables oral or enteral dosing (typically, 20 mg – 100 mg) rounded to the nearest 10 mg.

Both NDA 218550 and NDA 212725/SUPPL-9 were submitted to seek extension of the Rozlytrek® NTRK indication from adult and pediatric patients 12 years old and above [redacted (b) (4)], based on the results of pivotal clinical trial STARTRK-NG (CO40778) and supporting clinical studies TAPISTRY (BO41932, for efficacy) and STARTRK-2 (GO40782; for safety).

Note that the new NDA 218550 for entrectinib oral granules cross-references Module 3.2.S Drug Substance and Section 3.2.P. Drug Product of the approved NDA 212725 for Rozlytrek® (entrectinib) hard capsule 100 mg and 200 mg.

Per the Biopharmaceutics Review of NDA 212725, entrectinib drug substance is a low solubility/low (to-moderate) permeability compound.

Per the Biopharmaceutics Review and the Clinical Pharmacology Review of NDA 212725/SUPPL-3, based on the *in vitro* dissolution and *in vivo* BE results of Study GP41049, entrectinib oral capsules containing Drug Substance Form A is bioequivalent to entrectinib oral capsules containing Drug Substance Form C.

Focus of Biopharmaceutics Review of NDA 218550 (Oral Granules) and NDA 212725/SUPPL-9 (Oral Capsule):
The emphasis of this Biopharmaceutics Review is the assessment of the adequacy of: (1) *[NDA 218550]* the proposed dissolution method and acceptance criterion, and comparative *in vitro* dissolution studies conducted to support the bridge to the final to-be-marketed new drug product/dosage form (the proposed entrectinib oral granules), and its administration as a dispersion in soft food vehicles, (2) *[NDA 212725/SUPPL-9]* the *in vitro* dissolution profile data submitted to support administration of the commercial oral capsules as a suspension via feeding tubes or via oral syringe, (3) as well as the Gastroplus PBPK modeling performed to support the bioequivalence of the final to-be-marketed oral granules to the commercial oral capsules under fasted conditions.

Reviewer's Assessment:

A. Oral Granules

1. Dissolution Method and Acceptance Criterion:
   The proposed dissolution method [USP Apparatus 2 (paddle) at 75 rpm, 500 mL of 50 mM potassium phosphate buffer pH 6.0 + 0.374% Tween 80; 37 °C] and the proposed dissolution acceptance criterion (Q = [redacted (b) (4)] at 30 min) are adequate for routine QC of the proposed entrectinib oral granules at batch release and during stability testing.

2. Bridging to the Final-To-Be-Marketed Entrectinib Oral Granules:
The final to-be-marketed (F17) oral granules was introduced in the pivotal and supporting clinical trials (STARTK-NG and TAPISTRY, respectively), and used in the primary stability studies.

   The provided dissolution profile data in various media support comparability of the F15 and F17 oral granules used in clinical studies; the supporting PK data will be assessed by the Clinical Pharmacology Reviewer.

3. Effect of Dispersion of Oral Granules in Soft-Food Vehicles (Applesauce, Yoghurt, Pudding) on Dissolution:
Note that in the pivotal clinical trial (STARTRK-NG) and in the supporting clinical trial (TAPISTRY), pediatric patients who cannot or have difficulty swallowing whole capsules (but are able to consume soft food or beverage) were administered the oral granules mixed with edible vehicles (e.g., applesauce, yoghurt, pudding); refer to Table 1 and Table 2 of the SN-10 IR Response).

   Based on the results of *in vitro* compatibility studies conducted by the Applicant, mixing the oral granules with applesauce or yoghurt did not significantly alter the *in vitro* dissolution profiles in various pH media (as well as dose accuracy/recovery, per the Drug Product Reviewer's assessment). In the case of pudding, the dissolution profile after a 2-hour hold time in the vehicle was observed to decrease significantly in simulated gastric fluid presumably due to this vehicle's higher pH (as compared to the two other vehicles), and high viscosity and fat content (which act as a barrier to dispersion in the dissolution medium). However, dissolution rate (as well as dose recovery) of the oral granules in pudding was enhanced significantly by decreasing the mixture's hold time to 20 minutes.

   Additionally, based on the results of these *in vitro* compatibility studies, the Applicant concluded that the administration of the oral granules as a suspension in water is not suitable due to propensity for clogging the enteral feeding tubes.

B. *Oral Capsule (Administered as Suspension)*
Effect of Alternative Mode of Administration of Oral Capsules on Dissolution:
Note that in the pivotal clinical trial (STARTRK-NG; CO40778), pediatric patients who were unable to swallow the whole capsules or the oral granules mixed with soft-food, were dosed using a suspension in water or milk prepared from the contents of the entrectinib oral capsule for administration via an oral syringe or via a nasogastric tube.

   Note also that based on the results of an *in vivo* clinical relative bioavailability study (Study GP44192/Part 1), the Applicant reported that the administration of the capsule contents as a 20 mg/mL suspension in water

or milk via oral syringe or in water via nasogastric tubes does not clinically significantly alter PK as compared to administration as the intact capsule.

As expected, the *in vitro* dissolution of entrectinib was not slower from the suspension of the capsule contents in water or milk than from the intact/whole oral capsule. Note that the 2021 FDA Guidance on *In Vitro* Testing of Oral Drug Products Administered Via Enteral Feeding does not specifically include a recommendation to perform dissolution testing to support enteral tube administration of preparations from immediate release dosage forms.

Dose accuracy/recovery, physico-chemical characterization and other compatibility tests were conducted to support the suitability of the extemporaneously prepared suspension for administration via oral syringe or via enteral feeding tubes. Per the CMC Reviewer of NDA 212725/SUPPL-9, the results and design of the conducted studies to support the alternative modes/routes of administering the commercial capsule as an ad hoc suspension are acceptable/adequate.

C. Gastroplus PBPK modeling (Virtual Fasted BE of granules and capsules)
In Fed Bioequivalence (BE) Study GP41341, the oral granules (mixed with yoghurt) and the oral capsule were shown to be bioequivalent when both treatments were given with a light meal. The submitted GastroPlus model was not deemed adequate to reliably predict the bioavailability (BA) of the oral granules in the fed state or fasted state. Thus, Applicant's prediction of fasted BE between the oral granules and oral capsules could not be verified via a modeling approach. *The Biopharmaceutics Review Team defers to the Clinical Pharmacology Review Team regarding the need to conduct a fasted BE study between the final proposed-to-be-marketed (F17) oral granules and the commercial (F06) oral capsules of entrectinib and/or a food-effect study with the oral granules.*

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Dissolution	Moderate	BCS-4	Low/Acceptable	Adequate dissolution QC specification (oral granules), and acceptable dissolution characteristics of oral granules and *ad hoc* suspension of capsule contents in administration vehicles

List of Submissions Assessed (NDA 218550):

Document(s) Assessed	Date Received
SN-1 (Original)	4/28/2023
SN-10 (Response to Early IR)	7/19/2023
SN-11 (Response to Biopharm IR – Gastroplus model)	7/21/2023
SN-15 (Response to Biopharm IR – follow-up to Early IR)	7/28/2023
SN-17 (Response to Biopharm IR – follow-up to SN-15)	8/3/2023
SN-18 (Response to CMC IR – including suspension dose accuracy)	8/7/2023
SN-19 (Response to Biopharm IR/part a – GastroPlus model)	8/8/2023
SN-21 (Response to CMC IR including (b) (4) QC testing, and Clin Pharm IR)	8/17/2023
SN-22 (Response to Biopharm IR/part b – GastroPlus model 2, and Simcyp)	8/22/2023
SN-23 (Response to CMC IR – Drug Product including (b) (4) dissolution testing)	8/28/2023
SN-24 (Response to CMC IR – change name to "oral pellets"	8/28/2023
SN-25 (Response to Biopharm IR – complete GastroPlus model 2)	8/30/2023
SN-26 (Response to CMC IR – (b) (4) QC testing including dissolution)	9/1/2023

Concise Description of Outstanding Issues:
-None

B.1 BCS DESIGNATION

Assessment:
Based on the Biopharmaceutics Review of NDA 212725 for the commercial entrectinib oral capsules, entrectinib drug substance is a low solubility/low permeability compound.

Solubility: *Low*
The solubility of entrectinib decreases as medium pH increases; entrectinib is practically insoluble at high pH conditions. The pH-solubility profile data of entrectinib drug substance (b) (4) in various aqueous media are similar, as shown in Table S.1.3-3 and Table S.1.-3-4 of NDA 212725/S-3.

Permeability: *Low*
Note that the proposed labeling states: "Following oral administration of a single oral dose of [^{14}C]-labeled entrectinib, 83% of radioactivity was excreted in feces (36% of the dose as unchanged entrectinib and 22% as M5) with minimal excretion in urine (3%)." The absolute BA of entrectinib has not been determined in humans.

Dissolution: *Not Rapid and Complete Across the Entire Physiologic pH Range*
Entrectinib oral granules (formerly referred to as "minitablets"), 50 mg (20 x 2.5 mg minitablets) are packaged in a stickpack.

The dissolution of entrectinib oral granules (50 mg) is not complete and rapid across the entire physiologic pH range (refer to Figure P.2.-17, Figure P.2.-18 and Table P.2-29). For the dissolution profiles of entrectinib oral granules in biorelevant media (with and without soft food), refer to Figure P-2-40.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA (Oral Granules)

Assessment:

DISSOLUTION METHOD - *ADEQUATE*
The final proposed commercial dissolution method parameters for the oral granules are shown in excerpted Table P.2-28 below; the only difference from those approved for the commercial oral capsule is the lower dissolution medium volume (500 mL instead of (b) (4) mL). (b) (4)

[redacted]

Table P.2-28 Summary of Dissolution Conditions for Entrectinib Coated Granules

Apparatus	USP Apparatus 2(paddle)
Agitation	75 rpm
Medium	50 mM potassium phosphate buffer pH 6.0 +0.374% (w/v) Tween 80
Volume	500 mL
Media Temperature	37°C
Quantification	HPLC with UV detection at (b) (4)

3.2.P.5.2 Dissolution

Justification for Selected Dissolution Method Parameters

(b) (4)

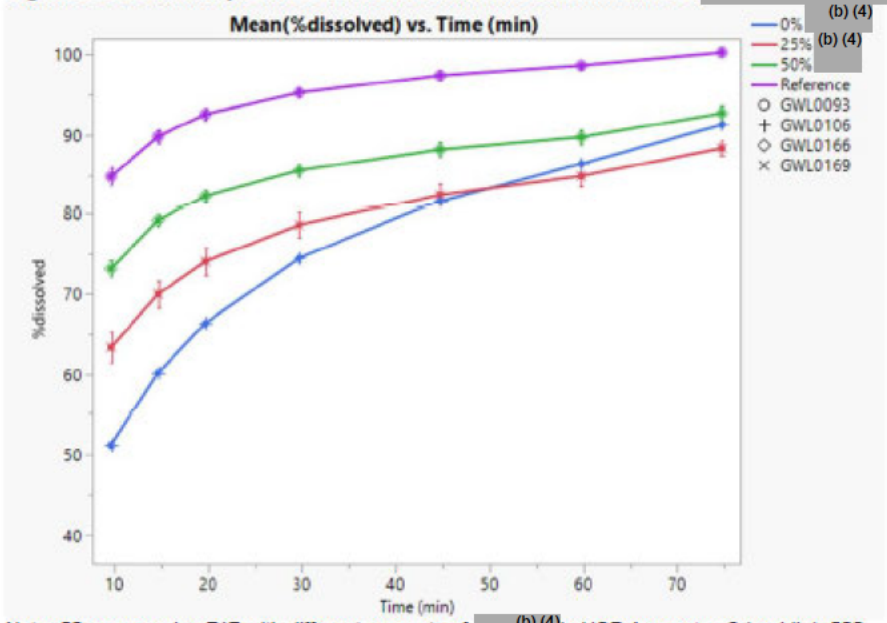
[redacted]

(b) (4)

Discriminating Power/Bio-Predictive Potential

Per the Applicant, the final proposed QC dissolution method has discriminating power for changes/differences in critical bioavailability attributes (CBAs) including the levels of the (b) (4) excipient, (b) (4). As shown in excerpted Figure 3 below, there was significant separation in the dissolution profiles of the target drug product and the product intentionally manufactured without (b) (4) is added to the oral granules formulation to provide (b) (4) In clinical studies, formulations of the oral capsule without (b) (4) exhibited significantly lower bioavailability and higher PK variability as compared to those containing (b) (4) In the SN-15 IR Response, the Applicant explained that procedural controls are already in place to ensure that the correct amount of (b) (4) and any other ingredient are present in the manufactured drug product.

Figure 3 Dissolution profiles of batches with different amounts of (b) (4)



Note: 50 mg granules F17 with different amounts of (b) (4) in USP Apparatus 2 (paddle), 500 mL 50 mM phosphate buffer, pH 6.0 + 0.374% Tween 80 at 75 rpm, n = 6. Each error bar is constructed using 1 standard deviation from the mean.

Reviewer Note: The target/reference drug product (GWL0093) is coated whereas the variant/aberrant lots are uncoated. In SN-15, the Applicant provided additional data to demonstrate that the presence/absence of coating does not significantly impact the dissolution profile data of the "minitablets" or oral granules; refer to Figure 4 of the IR Response.

Additionally, the proposed dissolution method showed discriminating power for changes/differences in the level of (b) (4) refer to Figure 5 of the SN-10 IR Response. Additionally, the dissolution method showed the anticipated rank-order relationship between minitablet (b) (4) and dissolution; refer to Figure 7 of the IR response.

Stability Indicating Potential

Per the Applicant, the proposed commercial dissolution method can detect a decrease in dissolution performance for stored drug product samples (at 40 °C for 6 months) compared to initial stability time point samples. Refer to Figure P.2-27 and Table P.2-44 of 3.2.P.2. Additionally, the proposed QC dissolution method can detect the slowdown in dissolution of stressed samples of the coated granules (stored open at 70°C/5% RH for seven days); refer to Figure 2, Figure 3 and Table 9 of the IR response in SN-15.

Analytical Method Validation

Per the Applicant, the HPLC method with UV detection (at (b) (4) used for quantification of entrectinib in the dissolution samples was successfully validated with respect to specificity, linearity, accuracy, precision (repeatability), and robustness (with respect to HPLC and dissolution parameters). The

analytical method was reported to be robust with respect to changes in paddle speed (75 (b) (4) rpm, medium volume (500 (b) (4) mL), dissolution medium buffer concentration (50 (b) (4) mM), Tween 80 concentration (0.374% (b) (4) and pH (6.0 ± 0.2), as well as age of dissolution medium (b) (4) and presence/absence of (b) (4), UV detector wavelength (b) (4) The sample solutions were reported to be stable for 7 days when kept in clear and amber glassware at ambient temperature. Per the Drug Product Reviewer, the HPLC method validation is adequate.

Sink Conditions

The solubility of entrectinib in the proposed QC dissolution medium (0.374% Tween 80 in 50 mM phosphate buffer pH 6.0) at 37 °C is (b) (4) for API (b) (4) and (b) (4) for API (b) (4) (at (b) (4)), as shown in Table P.2-32. Thus, sink conditions (~3x solubility) is anticipated to be achieved during routine QC testing of the oral granules in 500 mL of the proposed QC medium.

DISSOLUTION ACCEPTANCE CRITERIA - *ADEQUATE*

The proposed dissolution acceptance criterion is "Q = (b) (4)% at 30 min", based on the results of statistical (capability) analysis. Refer also to the additional justification for a dissolution specification time point of 30 min (b) (4) as provided by the Applicant in the SN-15 IR Response. Per the Applicant, a single-point dissolution specification is proposed based on (b) (4)

The proposed dissolution acceptance criterion (Q = (b) (4)% at 30 min) is acceptable to this Reviewer, based mainly on the dissolution profile data of the two F17 oral granules lots (i.e., GEX0299 and GEX0348) that were 13 to 36 months old at the time of use in the pivotal clinical trial (STARTRK-NG) and the supporting clinical trial (TAPISTRY); refer to IR responses in SN-15 and SN-17. Additionally, the proposed dissolution acceptance criterion is acceptable when considering capability to reject aberrant drug product lots including those intentionally manufactured with unacceptable CBA ((b) (4), as shown in excerpted Figure 3 above).

Per the proposed labeling, ROZLYTREK has QT prolongation potential. However, this Reviewer determined that it is not required to add a second/earlier dissolution value/time point as the pivotal and supporting clinical trial lots (as well as the primary stability lots) all exhibited very rapid dissolution (b) (4) at the initial time point and remained at least rapidly dissolving (b) (4) at the later stability time points; refer to Table 3 of the IR response in SN-15, and the Applicant's justification in SN-17. Note that for the determination of the adequacy of a single-point dissolution acceptance criteria, this Reviewer did not give weight to the presented 'Month 0' dissolution profile data of F17 oral granules clinical lot GEX0299 in Figure 1

of the SN-17 IR Response because per the explanatory Table 3 footnote in the same response document, the data were generated after a retest using the final QC dissolution method, i.e., using a sample that is no longer 0 month old. It was also observed from Figure 1 and Table 3 that all other clinical and primary stability lots consistently did not have as high a dissolution profile (and measured drug content/Assay) at Month 0 as reported for Lot GEX0299.

Dissolution on Stability

Based on Table P.8.3-6 ff, the primary and supportive stability batches (up to 18 months and 24 months, respectively, of long-term storage/30°C/75% RH) conformed to the proposed dissolution acceptance criterion (Q = (b) (4) % at 30 min) by USP Stage 1 (n=6) or Stage 2 (n=12) testing. The stability samples that were stored up to 6 months of accelerated storage/40°C/75% RH) are anticipated to be able to conform to "Q = (b) (4) % at 30 min" by USP Stage 3 (n = 24) testing. A trend of slower dissolution was observed at 18 months of long-term stability testing and at 6 months of accelerated stability testing. Refer to Table P.8.1-11 and Figure P.8.1-1. As described in Section B.2 above, the two F17 oral granules lots (GEX0299 and GEX03458) dosed in the STARTRK-NG and TAPISTRY Studies were up to 36 months old and 27 months old, respectively.

Based on the Applicant's regression analysis of the dissolution at 30 °C/75% RH stability data (Figure P.8.1-2), the earliest crossing time of 24.5 months was predicted with 95% confidence, thereby supporting the proposed product expiration dating period of 24 months when the product is stored below 30°C in the original container to protect from moisture. [Of note, the drug product is hygroscopic.] Per the Drug Product Reviewer, the proposed 24 months shelf-life is acceptable.

B.6 IN-VITRO SOFT-FOOD INTERACTION STUDY (Oral Granules); IN-VITRO COMPATIBILITY STUDY (Suspension from Oral Capsule)

Assessment: *ADEQUATE SUPPORTING DISSOLUTION DATA*

In the pivotal clinical trial (STARTRK-NG), pediatric patients who cannot or have difficulty swallowing whole capsules received either the oral granules mixed with soft food, or a suspension of the capsule contents in suitable liquid (administered via an oral syringe or nasogastric tube).

For the detailed instructions for preparation and administration of the oral granules in soft food vehicles, and the oral capsule (contents) as an *ad hoc* (20 mg/mL) suspension in water or milk, refer to the proposed labeling and the respective Instructions for Use.

Compatibility of Oral Granules with Various Soft Food Vehicles

Per the Applicant, not more than 5% absolute decrease in dose accuracy relative to control was observed when using applesauce and yoghurt up to a maximum hold time of 4 hours at ambient temperature. However, following 4 hours of hold time in pudding, the dose accuracy was 6.3% lower, whereas at 0 hours of hold time, a 4.1% lower dose accuracy was observed. Thus, the proposed labeling states that the oral granules in soft food vehicle (e.g., applesauce, yoghurt and pudding) be taken within 20 minutes of mixing. For details, refer to Subsection 6.1 of 3.2.P.2. Per the Drug Product Reviewer, the design and the results of the dose accuracy study for the oral granules mixed with soft-food vehicles are acceptable/adequate.

Likewise, the multi-pH **dissolution** profiles of the oral granules mixed for 2 hours with applesauce and yoghurt (but not in pudding in (b) (4) pH (b) (4) medium) were comparable to those of oral granules not mixed with soft food vehicle; refer to the excerpted Figure P.2-42 and Figure P.2-45 below. In SN-10, the Applicant provided confirmatory data to demonstrate that at the label-proposed waiting time of 20 min post-mixing with (a high proportion of) soft-food vehicle, pudding showed no significant impact on dissolution ((b) (4) (b) (4) medium) and entrectenib stability as compared to reference/control granules without pudding; refer to Figure 10 and Table 14 of the IR Response. Note that in the pivotal and supporting clinical trials, pudding was one of the soft-food vehicles used to prepare the oral granules for administration to pediatric patients.

Note also that based on studies conducted by the Applicant, it was revealed that the coated oral granules are not suitable for administration as suspension in water via the nasogastric/gastric tubes because the resulting suspension agglomerates and clogs the (b) (4) and 8 Fr enteral feeding tubes due (b) (4)

Compatibility of Suspension (Prepared from Capsule) with Feeding Tubes

Based on the results of *in vitro* studies conducted by the Applicant, the suspension of entrectinib oral capsule contents in water or formula milk is homogenous, easily redispersible and chemically stable after (b) (4) hours of hold time at room temperature, and is suitable for administration to pediatric patients via oral syringe or nasogastric tube administration [i.e., does not clog oral syringes and 8 Fr or larger diameter enteral feeding tubes, and has acceptable (90 – 100%) dose recovery] when tested over a dose range of 20 – 200 mg. Administration of a suspension volume of 30 mL (but not 10 mL) resulted in clogging when a (b) (4) enteral feeding tube was used. For additional information, refer to Section 6.1 of 3.2.P.2 of NDA212725/SUPPL-9.

Additionally, the suspensions in water and milk exhibited good **dissolution** performance (i.e., faster dissolution as compared to intact capsule, using the proposed QC dissolution method) regardless of preparation time (15 (b) (4) min)

or hold time up to (b)(4) hours. The apparent incomplete/lower *in vitro* dissolution profile of the entrectinib suspension in milk than in water (Figure P.2-8 versus Figure P.2-7) is not considered clinically meaningful because as reported by the Applicant, in Relative BA Study GP44192/Part 1, ad-hoc suspensions of the capsule contents in water (via nasogastric tube and via oral syringe) and in milk (via oral syringe) produced similar entrectinib and active metabolite (M5) AUC as compared to the intact oral capsule. In fact, following single 600 mg dose oral administrations under fasted state, the 20 mg/mL (30 mL) suspension in milk (via oral syringe) was reported to produce a 24% higher entrectinib Cmax and a 48% higher active metabolite (M5) Cmax as compared to the intact oral capsule, whereas the suspension in water (via oral syringe or nasogastric tube) resulted in a 19% lower entrectinib Cmax and a 27% lower M5 Cmax as compared to the intact oral capsule. Note that this Reviewer did not pursue additional comparative *in vitro* dissolution profile data in various pH media because the 2021 FDA Guidance does not generally recommend dissolution testing to support enteral feeding of suspensions prepared from immediate release oral dosage forms. Additionally per the Applicant, the Study GP44192 results also supported satisfactory oral palatability of the suspensions in water and milk.

B.12 BRIDGING OF FORMULATIONS

Assessment: *ADEQUATE*

Oral Granules

Bridging of the Pre-Change/Clinical/Registration to the Post-Change/Final To-Be-Marketed F17 Oral Granules

- The final proposed commercial coated granule formulation is "F17". F17 lots (produced by the proposed commercial drug product manufacturer – Almac Pharma Services Ltd/UK] was evaluated in Pivotal Phase I/II Pediatric Study CO40778/ RXDX-101-03 (STARTRK-NG), in Supportive Pediatric Study BO41932 (TAPISTRY), and in the primary/registration stability studies. (Refer to Table P.5.4-1 and Table P.5.4-2 of 3.2.P.5.4). These "F17" lots were manufactured using polymorphic (b) (4) of entrectinib drug substance/API (supplied by the proposed commercial drug substance manufacturer, Roche/Basel).

The proposed commercial batch size is (b)(4)% lower than the size of the drug product batch size used in clinical/registration studies (b)(4) kg versus (b)(4) kg).

- Per the Process Reviewer, (b) (4)

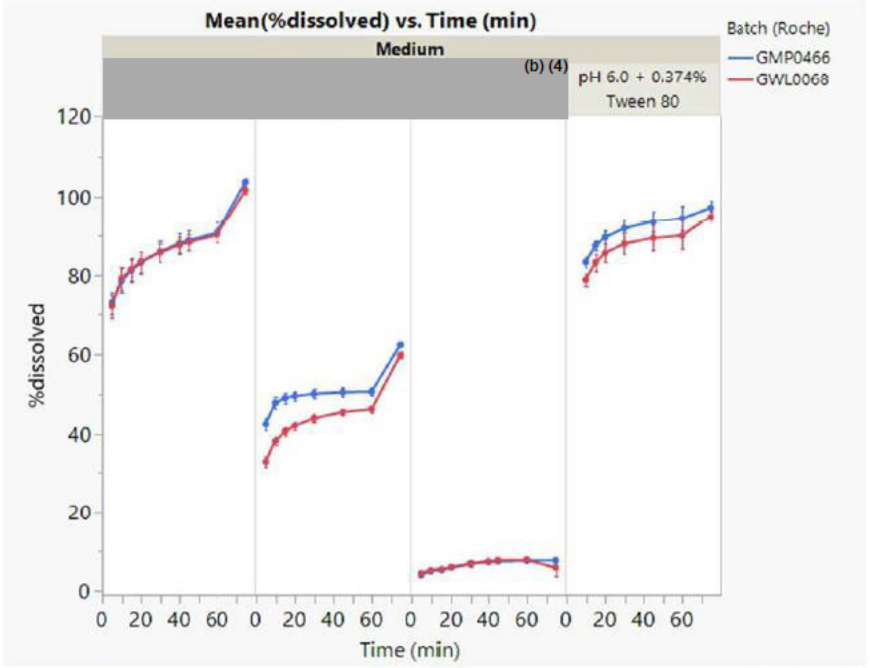
(b) (4)

Bridging of the F15 coated granules (b) (4) to the F17 coated granules (b) (4)

[*Reviewer Note*: In line with the observed changes in API polymorphic form (from (b) (4) during drug substance manufacture, i.e., post-approval of the commercial capsule formulation (F06), the patients in the pivotal clinical trial receiving the API (b) (4) formulation of the film-coated granules (i.e., F15) were eventually transitioned to its API (b) (4)' formulation variant (F17). The "F15" coated granule lots were manufactured by Roche Basel, using drug substance (b) (4) lots manufactured by (b) (4) For a full description of all developmental formulations used in STARTRK-NG, see Section 3.4 of the clinical study report.]

- The switch from F15 to F17 oral granules in the pivotal clinical trial is supported by evidence of comparable *in vitro* dissolution profiles in various pH media, as shown in excerpted Figure 3 and Table 7 below.

Figure 3 Dissolution Profiles of F15 (GMP0466 blue line) and F17 (GWL0068 red line) Formulations



QC = Quality control, (b) (4)

(b) (4)

(b) (4)

(b) (4)

Table 7 Comparison of Dissolution Profiles (f2 Test) for F15 vs F17 Coated Granules Formulations

Medium / Working Conditions	f2 Value	Profiles Comparable
(b) (4)	96	Yes
	55	Yes
	N/A[a]	Yes
QC Working Conditions	67[b]	Yes

(b) (4)

Reviewer Note: In addition to API polymorphic form (b) (4) versus (b) (4) reference (F15) and test (F17) products in excerpted Figure 3 above differ also in terms of the drug substance manufacturing site (b) (4) versus Roche/Basel) and drug product manufacturing site (Roche Basel versus Almac Pharma Services). Additionally, the proposed commercial F17 oral granules will have an approximately (b) % lower batch size.

- In SN-10, the Applicant provided additional data/information to show that the dissolution profile data of F15 and F17 oral granules lots (GMP0466 and GWL0093, respectively) are comparable (with f_2 of 69) when tested using the final proposed QC dissolution method [USP Apparatus 2 (paddle) at 75 rpm, 500 mL of 50 mM potassium phosphate buffer pH 6.0 + 0.374% Tween 80; 37°C].
- Note that excerpted Figure 3 above shows that the pre-change (F15) and the post-change (F17) drug product lots (GM00466 and GWL0068, respectively) exhibited comparable dissolution profiles in the proposed commercial QC dissolution medium, when using the penultimate apparatus type and speed (b) (4) rpm]. In SN-10, the Applicant provided additional data from dissolution methods bridging studies to demonstrate that had the comparative study been done at that time using the final proposed QC dissolution method parameters, both test and reference drug product lots would have exhibited *very rapid* dissolution (and thus, comparable dissolution profiles) because the coning produced when using the penultimate dissolution apparatus would have slowed down dissolution of both lots; refer to Figure 1 of the SN-10 IR Response.

- In SN-10, the Applicant clarified that F17 Granules Lot GWL0068 is representative of the clinical lots (including in terms of manufacturing process and batch size, (b) (4) kg), but it was not used in any clinical study.

➢ A dedicated clinical BE study is not required to bridge between the F15 and the F17 coated granules, based on the following considerations: (***1***) The compositions of these two oral granule formulations are the same. (***2***) As stated above, like the F15 granules, the final proposed commercial formulation (F17) was used in the pivotal clinical trial. (***3***) The oral capsules containing (b) (4) and (b) (4) drug substances were demonstrated to be bioequivalent. (***4***) Additionally, per the Applicant's justification in Section 3.1.1 of the Biopharmaceutics Summary (albeit, based on the limited data) pediatric patients > 1 year old receiving F15 and F17 oral granules (300 mg/m^2) in STARTRK-NG overall exhibited comparable parent drug and active metabolite exposures relative to F06 oral capsules (e.g., refer also to page 8 ff of PopPK Study Report, and Figure 7 and Figure 8 of 5.3.3.5).

Physical Appearance of the Oral Granules

Per the proposed labeling, ROZLYTREK granules are supplied as brownish orange to grayish orange, round film-coated granules, available in: 42-count carton (each packet contains 50 mg entrectinib). [Each packet contains 20 x 2.5 mg "minitablets" or pellets.] Store ROZLYTREK granules in the original container (below 30°C) in order to protect from moisture.

The labeling description of the drug product is consistent with the description of the pivotal clinical/supporting clinical/registration lots provided in 3.2.P.5.4.

Packaging

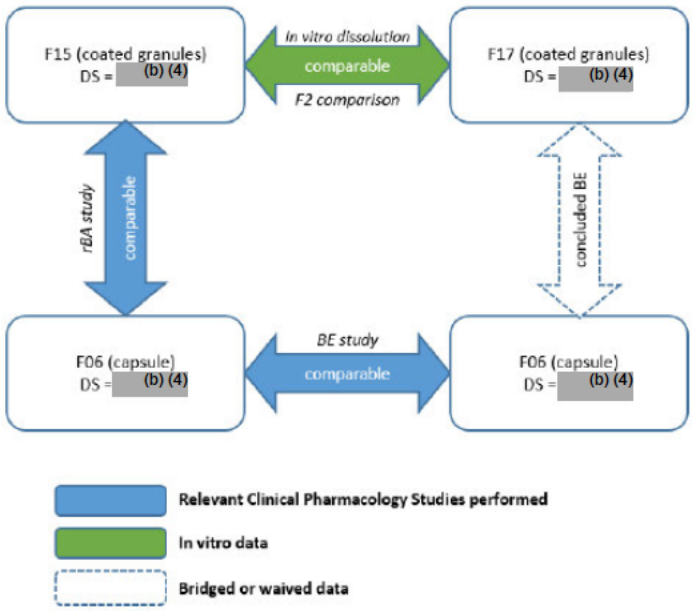
Entrectinib coated granules are packaged in a stickpack of approximately 60 x 25 mm in size, manufactured from a (b) (4) foil. The stickpacks are packaged in paper cartons. Per the Applicant, the container-closure system used in the stability studies is fully representative of the proposed commercial supply.

Oral Capsules (Administered Orally as Whole Capsule or as An Aqueous Suspension Via Oral Syringe; Alternatively, As Suspension Via Feeding Tube)

Bridging of the F17 coated granules (b) (4) to F06 Capsule (b) (4)

Per the Applicant, bridging from the commercial/approved F06 oral capsule to the proposed commercial "F17" oral granules can be accomplished *indirectly*, i.e., by using the bridging approach as depicted in excerpted Figure 2 below. [Typically, *in vivo* BA/BE data is needed to establish the link between two different formulations/dosage forms. Thus, an entirely comparative *in vitro* dissolution profile testing approach is not considered an adequate approach to bridge the F17 oral granules to the F06 oral capsules (with or without capsule shell).]

Figure 2 Scheme of bridging



Applicant's Approach to Bridge F06 Capsule (b) (4) to F17 Coated Granules (b) (4).

(b) (4) In Fasted BE Study GP41049, the (intact) oral capsules manufactured with (b) (4) drug substances were shown to be bioequivalent. Additionally, in a Fed rBA study (Study GP41341), bioequivalence was demonstrated between the approved (intact) capsule F06 and the (b) (4) coated granules (prototype – F15/F16) mixed with yoghurt, when the treatments were given with a light meal. Since the dissolution profiles of the (b) (4) (F15) and (b) (4) (F17) granules are comparable in biorelevant media and in the QC medium, BE of F17 to F06 oral capsules could also be concluded. Also, the submitted Assessment Aid states: "The available systemic exposure of entrectinib from patients receiving coated granules (F17 – (b) (4) was comparable to patients receiving coated granules (F15 – (b) (4) and capsule (F06).

Additionally, the Applicant reported that in the pivotal clinical trial (STARTRK-NG), "pediatric patients dosed orally with (b) (4) coated granules (F17) dispersed in soft food vehicle showed comparable drug exposures to pediatric patient(s) dosed orally with (b) (4) coated granules (F15) dispersed in soft food vehicle and capsule (F06) dosed via oral syringe or via nasogastric (NG) tube as an extemporaneously prepared suspension in milk or water or as a whole capsule". In STARTRK-NG, the entrectinib dose can be administered with or without a full meal. Refer to Section 2.2.5.2 of Section 2.7.2.

Note that in Study GP44192, the Applicant reported that comparable entrectinib exposures (AUC) were observed for F06 capsules administered as oral suspension and suspension via NG tube or via oral syringe versus intact F06 Capsules.

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(b) (4)

The decision to request a food-effect study for the proposed to-be-marketed entrectinib oral granules, and/or a fasted BE study between the commercial entrectinib oral capsules and the proposed commercial oral granules is deferred to the Office of Clinical Pharmacology.

B. 13 BIOWAIVER REQUEST

Assessment: *Not Applicable*

Only one strength (50 mg) of the entrectinib oral granules is proposed for marketing, and this strength was used in clinical (and stability) studies.

R. REGIONAL INFORMATION

Comparability Protocols

Not Applicable

Post-Approval Commitments

None

Lifecycle Management Considerations

Monitor commercial lots for any consistent storage-dependent trends in dissolution.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name and Date:

Gerlie Gieser, Ph.D. (9/21/2023)

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

Anitha Govada, Ph.D. (9/21/2023)

Gerlie Gieser

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Anitha Palamakula Govada

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Xing Wang

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