CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219285Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number	219285		
Applicant Name	Genentech Inc.		
Drug Product Name	Evrysdi (risdiplam)		
Dosage Form	Tablet		
Proposed Strength(s)	5 mg		
NDA Classification	Type 3 - New Dosage Form		
Route of Administration	Oral		
Maximum Daily Dose	5 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.		
Drug Product Description	Pale yellow film-coated tablet, round and curved, with EVR debossed on one side.		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	20°C to 25°C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	N/A	N/A
	Drug Product/ Labeling	Grace Chiou	Martha Heimann/ Julia Pinto
	Manufacturing	Ju Du	Shu-Wei Yang
	Biopharmaceutics	Leah Falade	Ta-Chen Wu
	Microbiology	N/A	N/A

	Other – Quality Surveillance	Jennifer Huntington and Geok Yan Loo	Mary Manibusan
	RBPM	Erica Keafer	
	ATL	Martha Heimann	
Consults	N/A		

2. Final Overall Recommendation – Approval

3. Action Letter Information

a. Expiration Dating:

36 months when stored at 20°C to 25°C.

b. Additional Comments for Action

There are no additional comments for the letter.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The Office of Pharmaceutical Quality (OPQ) recommends **APPROVAL** of NDA 219285 for EVRYSDI (risdiplam) tablets. Based on our evaluation of the available information, the applicant provided sufficient information to support an approval recommendation from the product quality perspective. The applicant provided adequate information to ensure the identity, strength, purity, and strength of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling is adequate to meet the regulatory requirements. Refer to the individual discipline primary reviews for additional information.

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

Recommendation by Subdiscipline:

Drug Substance - N/A
The applicant references their approved NDA 213535 for drug substance.

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: Yes
Comments:

The applicant proposed Established Conditions applicable to the F. Hoffman La Roche (FEI: 3003973536) and (b) (4) facilities. Both facilities have effective product quality systems and are acceptable for Established Conditions in this application.

Comparability Protocols (PACMP): No
Comments: N/A

Additional Lifecycle Comments:

There are no outstanding issues or lifecycle considerations.

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.
Senior Product Quality Assessor

December 9, 2024

Martha Heimann

Digitally signed by Martha Heimann
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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide (OPQ-ALL-WI-0006)

NDA Number	219285
Assessment Cycle Number	1
Drug Product Name	Risdiplam tablets

Assessment Recommendation: Choose an item.

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	**0001**
Patient Information	Adequate	**0001**
Instruction for Use (IFU)	Adequate	**0001**
Container Labels	Adequate	**0001**
Carton Labeling	Adequate	**0001**

Brief Description of Outstanding Issues: Adequate, pending the revisions noted below.

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
Labeling (eCTD 0001)	April 11, 2024	Prescribing Information, Instructions for Use, Carton and Container Labels, Patient Information

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

[1] Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

[redacted]

Item	Item 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[2] [21 CFR 201.57(a)(2)]		
Established name(s)[3]	Adequate	Revise to include "…tablets, for oral use"
Route(s) of administration	Inadequate	
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s)[4] and strength(s) in metric system[5]	Adequate	Adequate

[2] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018)

[3] Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).

[4] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline

[5] Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>

Item	Item 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)
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).[6]	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7]	N/A	
For injectable drug products for parenteral 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.[8]	N/A	

Assessment: *Adequate*

[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1
[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)
[8] Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>

1.2 FULL PRESCRIBING INFORMATION

(b) (4)

Item	Item 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	Adequate	Adequate

[9] See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)

Item	Item 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)
and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product).		
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	Adequate	
For parenteral products: include statement: *"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*[11]	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.[12] 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	Adequate

[10] Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments
[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition

Assessment: *Adequate*

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[13]

(b) (4)

Item	Item 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	Adequate
Strength(s) in metric system	Adequate	
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 (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	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	
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 parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and	N/A	

[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

Item	Item 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)
imaging bulk package (see USP <659>).		

Assessment: *Adequate*

1.2.3 Section 11 (DESCRIPTION)[14]

(b) (4)

Item	Item 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)[15] [§ 201.57(c)(12)(i)(A)].	Adequate	Revise to include "…tablets, for oral use". Remove reference to oral solution as it is not under this NDA.
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Inadequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency	N/A	Revise so film-coat ingredients are grouped with the other excipients and in alphabetical order.

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)

[15] Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

Item	Item 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)
statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].		
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Inadequate	
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. [§ 201.100(b)(5)(iii)].	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Adequate	

[16] Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

[17] Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in FDA's Labeling Resources for Human Prescription Drugs for the most recent EPC list.

Item	Item 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)
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	Revise to include solubility and pKa information.
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Inadequate	
For oral prescription drug products, include gluten statement[19] (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	

Assessment: *Adequate*

This section of labeling is adequate pending the revisions noted above in red text.

[18] Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)[20]

(b) (4)

Item	Item 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) [§ 201.57(c)(17)].	Adequate	
Strength(s) in metric system. [§ 201.57(c)(17)(i)] 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. No equivalency statement.	Adequate	
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	
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 parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy	N/A	Revise to remove "tightly" from "Keep the bottle tightly closed…" and include child-resistant statement for container closure.

[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

Item	Item 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)
bulk package and imaging bulk package (see USP <659>).		
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." [§ 201.57(c)(17)(iv)]	Inadequate	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate	
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 natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*[21]	N/A	

[21] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)

Item	Item 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)
Include information about child-resistant packaging[22] (if chosen by manufacturer).	Inadequate	

Assessment: *Adequate*

Adequate, pending revisions noted above in red text.

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.

[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)

1.2.6 Manufacturing Information After Section 17 (for drug products)[23]

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	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	Adequate

Assessment: *Adequate*

2.0 PATIENT LABELING

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[24]	Adequate	Adequate
Special preparation instructions (if applicable).	Adequate	
Storage and handling information (if applicable).	Inadequate	(b) (4)
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 differ from the dosage form.	N/A	

[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)
[24] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Active ingredient(s) (if applicable).	Inadequate	Revise for inactive ingredients to be listed (b) (4) (b) (4) (b) (4) and ensure they are in alphabetical order.
Alphabetical listing of inactive ingredients (if applicable).	Inadequate	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	

Assessment: *Adequate*

Adequate, pending revisions noted above in red text.

3.0 CONTAINER AND CARTON LABELING[25]

3.1 Container Labels[26]

(b) (4)

[redacted]

[25] Carton and Container Labeling Resources

[26] Per § 201.10(h)(2)(i)(1), if the drug container is too small to bear all labeling information required by section 502(e)(1)(A)(ii) and (B) of the FD&C Act, the container label should bear: proprietary name, established name, lot number, the name of the manufacturer, packer, or distributor of the drug.

3.2 Carton Labeling

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name[27], (font size and prominence) [§ 201.10(g)(2)].	Adequate	Yes	Adequate
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[28]	Adequate	Yes	
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	

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

[28] Express as " XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	N/A	Yes	
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[29]	Adequate	Yes	
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Yes	
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	Yes	
For injectable drug products for parenteral 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. (See USP <659>).	N/A	Yes	
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5)	N/A	Yes	Adequate

[29] § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
or limited space per § 201.10(i)(2)].			
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	Yes	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	Yes	
Linear Bar code [§ 201.25(c)(2)].[30]	Adequate	Yes	
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Inadequate	Yes	Revise to "Recommended Dosage: See Prescribing Information"
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	No	"Made in Switzerland" is on the carton but not the bottle label.
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Adequate	No	Not present on bottle
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Yes	Adequate
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary	Adequate	Yes	

[30] See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
statement is required. (USP <7>).			
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	No	
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.[31]	N/A	Yes	
And others if space is available.	N/A	Yes	

Assessment of Carton Labels and Container Labeling: *Adequate*
Adequate, pending revisions noted above in red text.

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

There are no outstanding issues and recommendations other than the revisions noted above in red.

Primary Labeling Assessor Name and Date: Grace Chiou, Ph.D.

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[31] USP General Notices 3.20 Indicating Conformance

Important: Do Not Change the Header or Footer

CHAPTER VI: BIOPHARMACEUTICS

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

NDA Number	219285
Assessment Cycle Number	1
Drug Product Name/ Strength	EVRYSDI (risdiplam) Tablets/ 5 mg
Route of Administration	Oral
Applicant Name	Genetech, Inc.
Therapeutic Classification/ OND Division	Motor Neuro Disease/Division of Neurology 1
RLD/RS Number	N/A
Proposed Indication	For the treatment of spinal muscular atrophy (SMA)

Assessment Recommendation: **Adequate**

Assessment Summary:

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Dissolution	Medium	The drug substance has low solubility that is pH-dependent and high permeability.	Low	The QC dissolution method shows slight discriminating power at early time points for API PSD and (b) (4) . The solubility of the DS is highly soluble in the QC medium, and dissolution is very rapid.

The Applicant seeks approval for the proposed EVRYSDI (risdiplam) Tablets, 5 mg for the treatment of spinal muscular atrophy (SMA) under the 505(b)(1) pathways. Reference is made to the approved EVRYSDI (risdiplam) for oral solution, 0.75 mg/mL. In accordance with 21 CFR Part 314.50, this NDA supports the registration of a new dosage form of risdiplam as tablets. The proposed film-coated tablet can be swallowed as a whole tablet or, alternatively, be dispersed in a small amount of water prior to administration. This option is to allow for the tablets to be taken easily by children and patients with swallowing difficulties.

The clinical package in support of this NDA includes a Phase 1 open-label, crossover study assessing the bioequivalence of the proposed risdiplam dispersible tablet compared to the approved powder for oral solution. The Biopharmaceutics review focuses on the evaluation and acceptability of the proposed dissolution method and acceptance criterion. Formulation bridging is not necessary as the to-be-marketed (TBM) formulation is the same as the pivotal clinical formulation and is manufactured at the same site (F. Hoffman-La Roche AG in Kaiseraugst, Switzerland).

Reviewer's Assessment:

I. Dissolution Method and Acceptance Criterion

The Applicant proposes a dissolution method using USP Apparatus II (Paddle) at 50 rpm in 500 mL of 0.1 N HCl. Risdiplam has pH-dependent solubility with the highest solubility in 0.1 N HCl. The criterion for high solubility as per the BCS is not met only in pH 6.8. Aberrant formulations were manufactured with differing API PSD and (b) (4) to investigate the discriminating power of the proposed dissolution method. The proposed tablets have a dissolution profile that is very rapidly dissolving, and slight discrimination is seen at the early time points. The discriminating power is not expected to be clinically relevant or meaningful, considering highly soluble of the drug substance in 0.1 N HCl and very rapid dissolution for the proposed tablets. The in vivo performance is not expected to be affected by these differences. The PSD and (b) (4) are tightly controlled, and the Biopharmaceutics risk is mitigated to low.

In response to an Information Request, the Applicant proposed a dissolution acceptance criterion of "Q= (b) (4) % in 20 min". Based on the mean dissolution profile data, the proposed acceptance criterion is adequate.

The Applicant's proposed dissolution method and acceptance criterion are deemed acceptable for batch release and stability testing.

II. Formulation Bridging

A pivotal study (Study BP42066) was a randomized, open-label, multi-period crossover Phase I study evaluating the safety, food effect, bioavailability, and bioequivalence of oral doses of two different 5 mg tablet formulations of Risdiplam (including the F21 as the to-be-marketed formulation) in healthy subjects comparing it to the LD, EVRYSDI (risdiplam) for oral solution. Only one manufacturing site in Switzerland is listed for the commercial drug product. Therefore, no additional formulation bridging is not needed.

Recommendation:

From the Biopharmaceutics perspective, NDA-219285-ORIG-1 for EVRYSDI (risdiplam) Tablets, 5 mg, is recommended for **approval**.

The FDA-approved dissolution method and acceptance criteria for the proposed EVRYSDI (risdiplam) Tablets, 5 mg, for batch release and stability testing:

USP Apparatus	Speed	Medium/Temperature	Volume	Acceptance Criterion
II (Paddle)	50 rpm	0.1 N HCl/37±0.5°C	500 mL	Q= (b)(4)% in 20 min

List Submissions Being Assessed:

Document(s) Assessed	Date Received
Seq 0001-Original	04/11/2024
Seq 0010-Quality Response to IR	10/09/2024

Highlight Key Issues from Last Cycle and Their Resolution: None

Concise Description of Outstanding Issues: None

B.1 BCS DESIGNATION

Assessment:

The Applicant did not submit a claim or request for BSC Class I designation. Based on the submitted data, the drug substance can be classified as BCS Class II.

Solubility:

Aqueous solubility was determined in multiple media in the physiological pH range at 37°C (***Table 1***). To meet the high solubility criterion, 5 mg/250 mL (0.02 mg/mL) must be met in all conditions. The drug substance has pH-

dependent solubility with the highest solubility in 0.1 N HCl. It should be noted that the pH of the buffers was not maintained after the experiment in 0.1 N HCl. However, the solubility data can be considered supportive as a BCS designation request was not submitted. The solubility is pH-dependent, and the criterion is not met for high solubility in pH 6.8.

Table 1. Solubility of Risdiplam in Aqueous Media across the pH Range (pH 1 to 6.8) at 37°C in mg/mL

Medium/Buffer	pH	Solubility after 4 h at 37°C	pH	Solubility after 24 h at 37°C	pH
Water	8.5	0.005	8.9	0.005	8.6
Water	6.6	0.004	5.7	0.038	6.9
HCl 0.1N	1.1	43.424	5.4	40.587	5.3
SGF	1.2	36.002	5.4	35.042	5.4
Acetate Buffer 0.05M	4.5	1.989	4.6	1.610	4.6
Phosphate Buffer 0.05M	6.8	0.006	6.7	0.007	6.7
FeSSIF	5.0	0.018	5.0	0.051	5.0
FaSSIF	6.0	0.020	6.4	0.023	6.4
Tartrate Buffer 0.05M	3.0	0.826	3.9	1.305	4.0
Tartrate Buffer 0.05M	3.5	0.501	4.0	0.839	4.1
Tartrate Buffer 0.05M	4.0	0.305	4.3	0.478	4.3
Tartrate Buffer (150 mMol)[a]	3.0	4.132	3.3	2.944	NP
Tartaric Acid 0.05M	3.0	47.556	3.3	41.993	3.0

Abbreviations: NP = not performed.
[a] Degradation was observed.

Permeability:
The Applicant did not support any permeability studies for this NDA. However, the Clinical Pharmacology review of the approved solution formulation noted because the oral bioavailability of risdiplam is >80% in healthy subjects and in vitro passive permeability of risdiplam appears to be high (350 nm/s in LLC-PK1 cells and >300 nm/s in MDCKII cells), the clinical significance of efflux transporters such as P-gp and BCRP is expected to be low[1].

Dissolution:
See assessment below.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: Adequate

(b) (4)

[1] DARRTS NDA 213535 REV-CLINPHARM-21 (Primary Review) 06/05/2020

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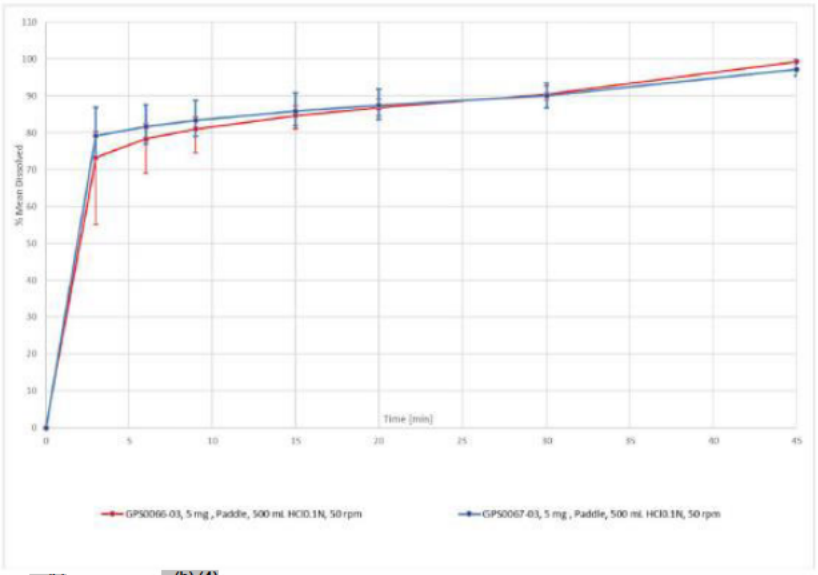
(b) (4)

The proposed dissolution method is provided below and deemed adequate:

USP Apparatus	Speed	Medium/Temperature	Volume
II (Paddle)	50 rpm	0.1 N HCl/37±0.5°C	500 mL

Discriminating Ability:
The Applicant investigated the discriminating ability of the proposed dissolution method by altering the drug substance PSD and (b) (4) (hardness) (***Figures 5 and 6***). The formulation manufactured with (b) (4) API released (b) (4) at the early time point. The dissolution method can discriminate for tablet hardness at the early time points (b) (4).



Note: red = (b) (4) µm; blue = (b) (4) µm.

Figure 5. Dissolution Profiles in 0.1N HCl at 50 rpm (N= 6) Manufactured with Drug Substance Batches with Mean Particle Sizes (d90) of (b) (4) µm and (b) (4) µm

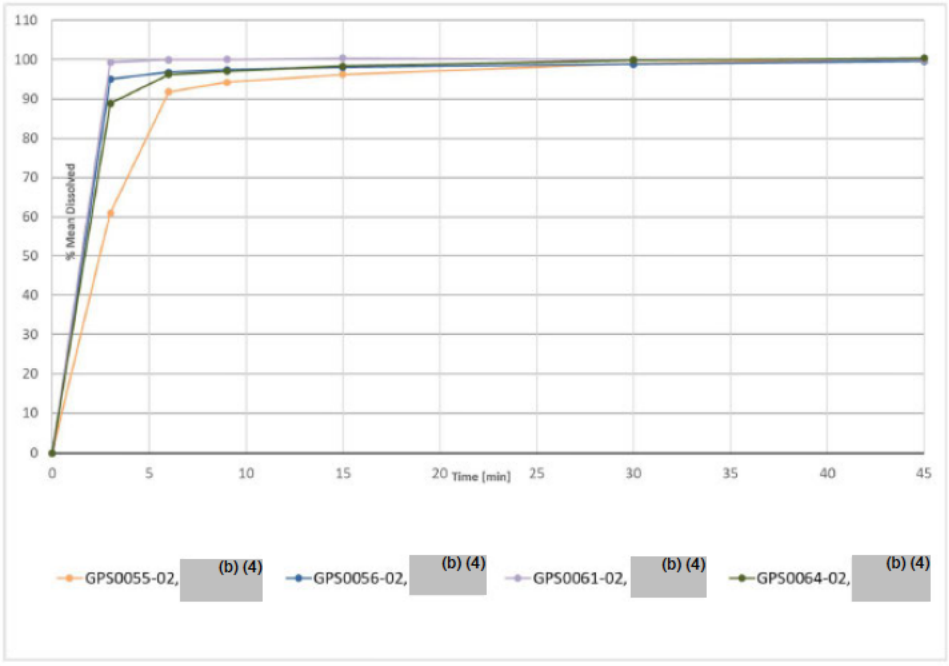


Figure 6. Dissolution Profiles at 50 rpm of Core Tablets Manufactured with Different Hardness in 0.1N HCl at 37°C (N= 6)

The drug substance has low solubility and high permeability. The dissolution is not rapid at pH 6.8 and the initial Biopharmaceutics risk is medium. The dissolution method demonstrates discrimination at early time points. The drug substance has

high solubility in 0.1 N HCl and both profiles are very rapidly dissolving (Q=(b) (4)% in 15 min). Therefore, much discrimination is not expected due to the very rapid release. The in vivo performance is not expected to be affected by these differences. The PSD and (b) (4) are tightly controlled, and the Biopharmaceutics risk is mitigated to low.

Acceptance Criterion:
The dissolution data for the pivotal clinical and registration batches is provided in the table and figure below.

Table 2. Dissolution Data for biobatch (GMP0540-04) and Registration Batches, N=12

Timepoint / Batch	3	6	9	15	20	30	45
GMP0540-04	(b) (4)						
Range	28-76	75-98	79-99	83-99	N/A	90-101	98-103
%RSD	31.9	8.2	7.1	5.8	N/A	3.8	1.4
GPS0087	(b) (4)						
Range	82-97	84-99	85-100	87-101	89-102	91-102	98-103
%RSD	6.2	5.8	5.1	4.5	3.9	3.0	1.5
GPS0088	(b) (4)						
Range	78-97	84-100	87-101	91-102	94-102	96-103	97-103
%RSD	6.8	5.4	4.7	3.5	3.0	2.2	1.7
GPS0099	(b) (4)						
Range	73-91	81-93	83-94	86-96	88-98	91-100	97-103
%RSD	7.0	5.0	4.5	3.8	3.4	2.8	1.5

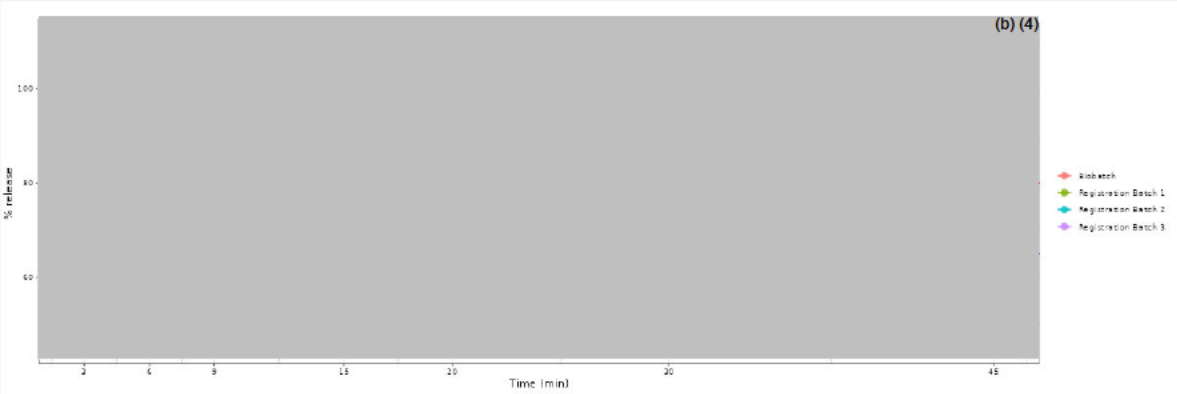


Figure 7. Dissolution Profiles for biobatch (GMP0540-04) and Registration Batches, N=12

The Applicant proposed "Q (b) (4)% in (b) (4)min" as the acceptance criterion. In an Information Request (IR), the Applicant was requested to propose an acceptance

criterion where Q [(b) (4)]% dissolution occurs. In response to the IR[2] (Seq 0010), the Applicant proposed "Q [(b) (4)]% in 20 min." The individual dissolution data[3] of the clinical and registration batches meet the acceptance criterion at Stage 2 testing. The Applicant's proposed acceptance criterion is adequate.

BB.12 BRIDGING OF FORMULATIONS

Assessment: Adequate

Study BP42066 was a randomized, open-label, multi-period crossover Phase I study evaluating the safety, food effect, bioavailability, and bioequivalence of oral doses of two different 5 mg tablet formulations of Risdiplam (F21 and F22) in healthy subjects comparing it to the LD, EVRYSDI (risdiplam) for oral solution. The two proposed formulations differed in tartaric acid [(b) (4)] and mannitol [(b) (4)] (**Table *3***). The F21 formulation was selected as the to-be-marketed (TBM) formulation. This study is the pivotal study against the LD.

One site is listed for the manufacturing site of the drug product (F. Hoffmann-La Roche AG in Kaiseraugst, Switzerland. From a Biopharmaceutics perspective, additional formulation bridging is not needed.

[2] \\CDSESUB1\EVSPROD\nda219285\0010\m1\us\quality-information-amendment.pdf
[3] \\CDSESUB1\EVSPROD\nda219285\0010\m5\53-clin-stud-rep\531-rep-biopharm-stud\5313-in-vitro-in-vivo-corr-stud-rep\5-3-1-3-study\dissolution-data.xlsx

Table 3. Description and Composition of Formulations Used in Study BP42066

Formulation		RO7034067 F22	RO7034067 F21 [a]	RO7034067 Commercial Formulation
Dosage Strength/Form		5 mg film-coated tablet	5 mg film-coated tablet	0.75 mg/mL powder for oral solution
Ingredients	Function	mg/unit dose	mg/unit dose	mg/mL
Risdiplam	Active ingredient	5	5	0.75
Tartaric Acid			(b) (4)	1.51
Microcrystalline Cellulose (b) (4)				—
Mannitol				16.81
Isomalt				2.97
Colloidal Silicon Dioxide				—
Crospovidone				—
Strawberry Flavor (b) (4)				(b) (4)
Sodium Stearyl Fumarate				—
Sodium Benzoate				0.38
PEG 6000				0.25
Sucralose				0.20
Ascorbic Acid				0.18
Disodium Edetate Dihydrate				0.09
(b) (4)				(b) (4)

PEG = polyethylene glycol.

[a] The composition of F21 is identical to the market formulation F23. They only vary in their (b) (4)

Primary Biopharmaceutics Assessor's Name and Date: Leah W. Falade, Ph.D.

Secondary Assessor Name and Date: Ta-Chen Wu, Ph.D.

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