CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217700Orig1s000
218033Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	217700		
Applicant Name	Day One Biopharmaceuticals, Inc.		
Drug Product Name	Tovorafenib		
Dosage Form.	Tablet		
Proposed Strength(s)	100 mg		
Route of Administration	Oral		
Maximum Daily Dose	600 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of pediatric patients 6 months of age and older with relapsed or refractory pediatric low-grade glioma (LGG) harboring a BRAF fusion or rearrangement, or BRAF V600 mutation.		
Drug Product Description	The tovorafenib drug product is an immediate release film coated tablet for oral administration in a 100 mg dosage strength. The orange film coating is (b) (4). The tables are debossed with “D101” and “100” on opposite sides of the tablet.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20 - 25°C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Kabir Shahjahan	Haripada Sarker
	Drug Product/ Labeling	Xiao Hong Chen	Xing Wang

	Manufacturing	Xiumei Ruan	Christine Falabella
	Biopharmaceutics	Hardikkumar Patel	Anitha Govada
	Microbiology	N/A	N/A
	Other (specify):		
	RBPM	Janell Artis	
	ATL	Xiao Hong Chen	
Consults	N/A		

2. Final Overall Recommendation - *Approval*

3. PMC

The final dissolution method (USP apparatus II, 65 rpm, 900 mL 0.1 N HCl with 0.25% SDS) is optimal and discriminating for the proposed drug product. However, Biopharmaceutics acknowledges the Applicant's concerns regarding the lack of sufficient dissolution profile data generated with the final method and the recommended dissolution acceptance criterion of Q=(b) (4)% in (b) (4) minutes. Therefore, Biopharmaceutics is willing to accept the Applicant's proposal to implement a dissolution acceptance criterion of Q=(b) (4)% in 45 minutes (SN 0038, SDN 38), but on an interim basis only.

Therefore, a Post-Marketing Commitment (PMC) has been proposed and accepted by the applicant to submit additional dissolution profile (multi time-point) data generated from commercial batches using the final dissolution method (USP apparatus II, 65 rpm, 900 mL 0.1 N HCl with 0.25% SDS at 37°C) and the interim acceptance criterion of Q=(b) (4)% in 45 minutes until the appropriate acceptance criterion for the dissolution test of the drug product is finalized.

PMC #4608-xx

PMC Description

(b) (4)

Note that until a new revised dissolution acceptance criterion is found acceptable by FDA, the currently recommended dissolution method (USP apparatus II, 65 rpm, 900 mL 0.1 N HCl with 0.25% SDS at 37°C) and the interim acceptance criterion of Q=(b) (4)% in 45 minutes will be used for batch release and stability testing on an interim basis

***** At the time of finalizing this review the last 2 digit numbers for the PMC #4608-xx have not been assigned. Refer to the NDA approval letter for the final PMC number.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The applicant provided adequate CMC information for Tovorafenib Tablets, and all drug substance and drug product manufacturing and testing facilities are found acceptable.

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	**-**	**Adequate**

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: N/A

Xiao Chen

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	Tablet/Immediate Release
NDA Number	217700
Assessment Cycle Number	1, ORIG-1 [505(b)(1)]
Drug Product Name/ Strength	Ojemda (tovorafenib) Tablets, 100 mg
Route of Administration	Oral
Applicant Name	Day One Biopharmaceuticals Inc.
Therapeutic Classification/ OND Division	Oncology/OND/OOD/Division of Oncology 2
RLD/RS Number	Not Applicable
Proposed Indication	Treatment of pediatric patients 6 months of age and older with relapsed or refractory pediatric low-grade glioma (LGG) harboring a BRAF fusion or rearrangement, or BRAF V600 mutation

Assessment Recommendation: **Adequate**

A. Assessment Summary:

The Applicant, Day One Biopharmaceuticals, is seeking approval of NDA 217700 for Ojemda (tovorafenib) Immediate Release (IR) Tablets, 100 mg. The drug substance, tovorafenib is characterized as a new molecular entity (NME) and exhibits low solubility in its crystalline form. (b) (4) has also been proposed for a different dosage form, Ojemda (tovorafenib) powder for oral suspension (PfOS) in a separate application (NDA 218033).

Dissolution Method and Acceptance Criterion: The Applicant's originally proposed QC dissolution method (0.25% SDS in 900 mL 0.1 N HCl, USP apparatus II, (b) (4) rpm) and acceptance criterion (Q=(b) (4)% in 45 minutes) was found inadequate. Therefore, the Applicant was advised to develop a suitable dissolution method with adequate discriminating ability towards Critical Bioavailability Attributes (CBAs). The Applicant developed the following dissolution method: USP Apparatus II, 65 rpm, 900 mL 0.1 N HCl with 0.25% SDS, which demonstrated appropriate discriminating ability against CBAs ((b) (4)). Therefore, the dissolution method was deemed adequate by Biopharmaceutics. Based on the overall dissolution method development data, clinical data, and registration

batch dissolution profile data generated with the final method, a dissolution acceptance criterion of Q=(b) (4)% in (b) (4) minutes was recommended. However, because the Applicant is unable to provide additional stability data using the final dissolution method prior to the NDA's action date, the drug product Quality Review Team expressed concerns regarding the lack of sufficient dissolution data to support the proposed shelf-life of 24 months. Additionally, it is noted that out of the nine batches (three registration, three clinical, and three process validation) tested using the final method, one batch required testing at Stage 2, and another batch required testing at Stage 3 to comply with the recommended acceptance criterion of Q=(b) (4)% at (b) (4) minutes. Therefore, the Applicant was requested to provide additional dissolution profile data from commercial batches and process validation batches at release and on stability through Post-Marketing Commitment (PMC) and an interim dissolution acceptance criterion of Q=(b) (4)% in 45 minutes using the final dissolution method, was recommended on an interim basis. The Applicant submitted the PMC (#4608-XX) as requested on 4/10/2024.

Final Dissolution Method and Interim Acceptance Criterion:

Apparatus Type	Rotation Speed	Medium/ Volume	Temperature	Interim Acceptance Criterion
USP apparatus II (Paddle)	65 rpm	0.1 N HCl with 0.25% SDS/ 900 mL	37.0 ± 0.5 °C	Q=(b) (4)% in 45 minutes

The Applicant has provided adequate dissolution data to support the bridging of the pivotal clinical batches to the registration/commercial batches (debossed) using the final quality control (QC) method and dissolution specifications.

Overall recommendation: From a Biopharmaceutics perspective, NDA 217700 for Ojemda (tovorafenib) Tablets, 100 mg is recommended for APPROVAL.

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking	Comments
(b) (4)				

(b) (4) content of API	Medium	(b) (4) content of API is CQA (b) (4)	Low	(b) (4) content of API (LOQ: NMT (b) (4) %) is controlled in drug product specifications
(b) (4)	Medium	(b) (4) can impact drug release and drug absorption	Low	The proposed dissolution method shows sensitivity to the (b) (4)

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
New NDA (SN#0001/SDN#1)	6/21/2023
Biopharm IR response (SN#0015/SDN#15)	12/1/2023
Biopharm IR response (SN#0023/SDN#23)	12/22/2023
Biopharm IR response (SN#0033/SDN#33)	2/16/2024
CMC IR response (SN#0038/SDN#38)	3/8/2024
Biopharm IR response (SN#0039/SDN#39)	3/13/2024
Biopharm IR response (SN#0049/SDN#51)	4/4/2024
PMC#4608-XX (SN#0050/SDN#53)	4/10/2024

Highlight Key Issues from Last Cycle and Their Resolution: Not Applicable

Concise Description of Outstanding Issues *(list bullet points with key information and update as needed)*: Refer to Post-Approval Commitments

B. 1. BCS DESIGNATION

Assessment: There is no official BCS designation request for the proposed drug product.

Solubility: Based on the solubility data provided by the Applicant, crystalline tovorafenib exhibits low solubility across physiological range.

Permeability: As per the Applicant, tovorafenib exhibits high in vitro permeability based on CaCo2 study results. However, permeability data has not been evaluated by the reviewer.

Dissolution: Not rapid across the entire physiologic pH range, refer to the assessment below.

B. 2. DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: Adequate

Crystalline tovorafenib exhibits low solubility across physiological range. Therefore, (b) (4)

Table 1: (b) (4) Solubility of tovorafenib (37 °C)

Media pH	Crystalline (mg/mL)	(b) (4)
1.2	0.003	
4.5	<0.0015	
6.5	<0.0015	
8.06	0.002	

The Applicant originally (PDR, Pg 61) proposed the following quality control dissolution method and acceptance criterion for the proposed drug product:

Apparatus	Speed	Medium	Volume/ Temperature	Acceptance Criterion
USP Apparatus II (Paddle)	(b) (4) rpm	0.1 N HCl with 0.25% SDS	900 mL/ 37 ± 0.5 °C	Q=(b) (4)% in 45 minutes

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(b) (4)

Final Dissolution Method and Interim Acceptance Criterion:

Apparatus Type	Rotation Speed	Medium/ Volume	Temperature	Interim Acceptance Criterion
USP apparatus II (Paddle)	65 rpm	0.1 N HCl with 0.25% SDS/ 900 mL	37.0 ± 0.5 °C	Q=(b) (4)% in 45 minutes

Discriminating ability: The Applicant has identified various Critical Bioavailability Attributes (CBAs: (b) (4)) to evaluate (SN#0023,

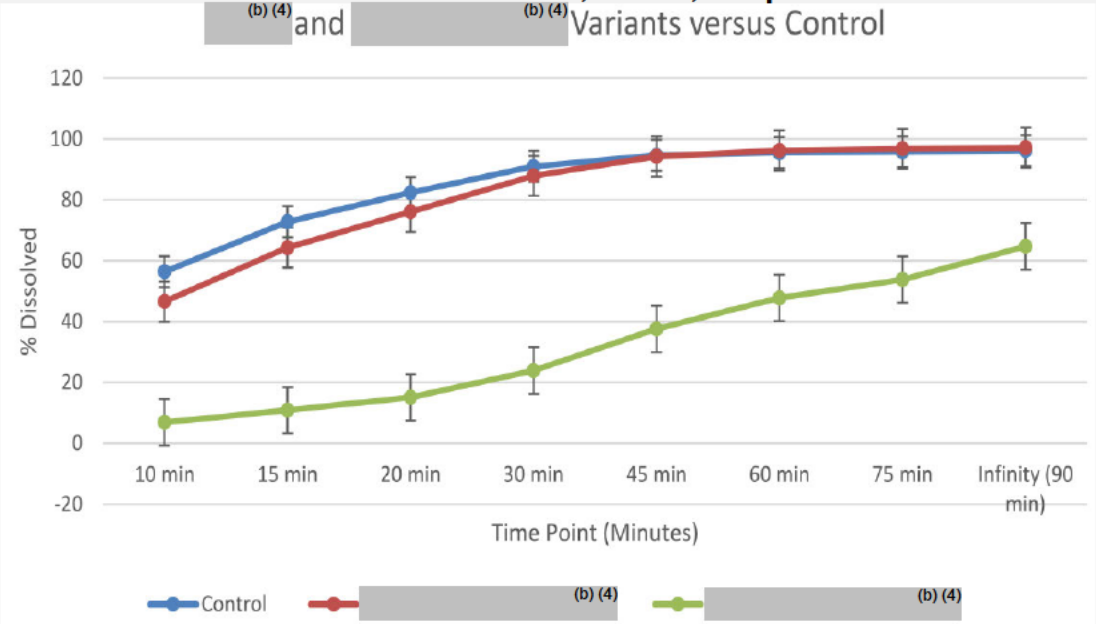
12/22/2023) the discriminating ability of the proposed dissolution method (900 mL 0.1 N HCl using 0.25% SDS, USP apparatus II, 65 rpm) against them.

(b) (4)

2) (b) (4) **content:** The dissolution profiles (Pg 16) for the drug product batches with higher ((b) (4) %) and target ((b) (4) %) (b) (4) content were similar using the proposed dissolution method.

3) (b) (4) **:** (b) (4) . The drug product batches with higher ((b) (4)) and target ((b) (4) were tested using the proposed dissolution method.

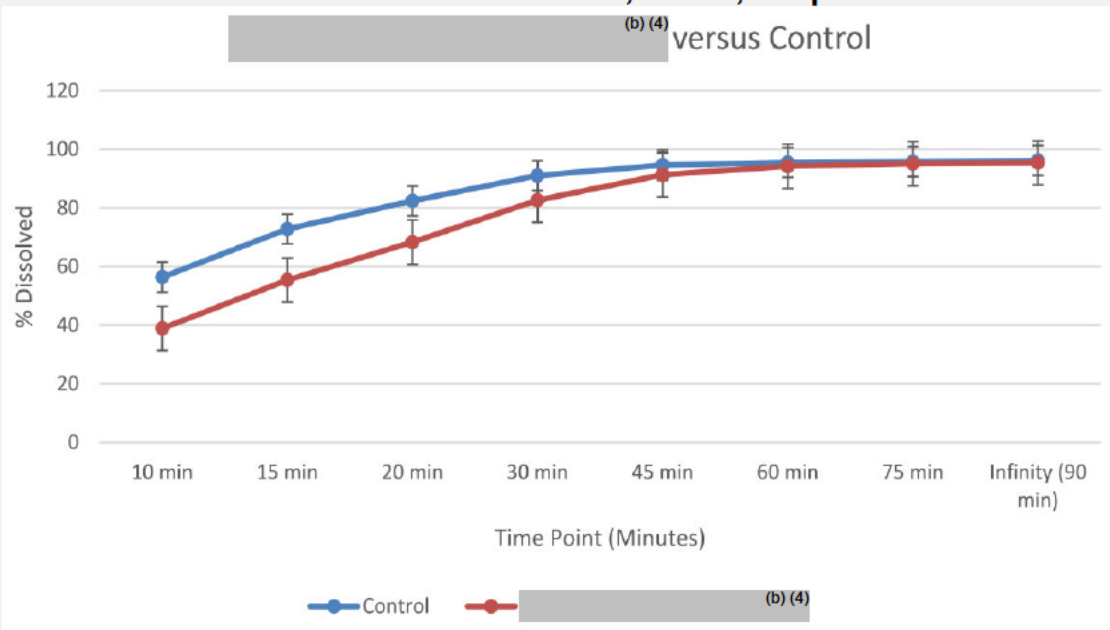
Dissolution profiles of batches with different [(b) (4)] using 0.25% SDS in 900 mL 0.1 N HCl, USP II, 65 rpm



The dissolution rate of the drug product batch with high [(b) (4)] was slower in comparison to the control drug product. This suggests that the proposed dissolution method is sensitive to variations in [(b) (4)].

4) [(b) (4)]: The drug product batches with higher ([(b) (4)]%) and target ([(b) (4)] were tested using the proposed dissolution method.

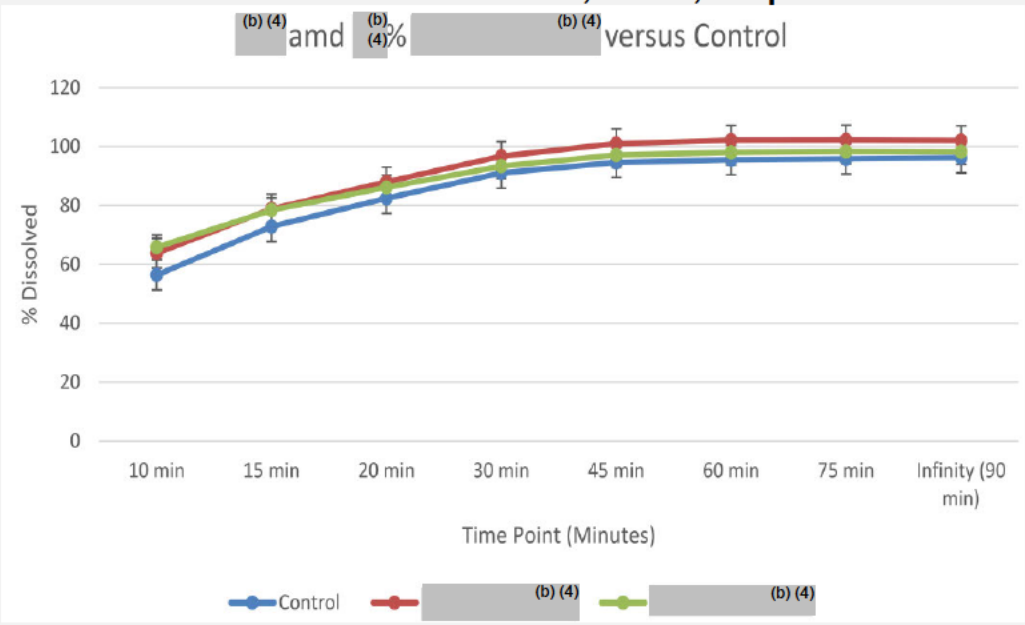
Dissolution profiles of batches with different [(b) (4)] using 0.25% SDS in 900 mL 0.1 N HCl, USP II, 65 rpm



The dissolution rate of the drug product batch with higher [redacted] is slower in comparison to the control drug product (F2=41, as calculated by the reviewer). This suggests that the proposed dissolution method is sensitive to variations in [redacted].

5) [redacted] **content:** The drug product batches with spiked [redacted]) were tested using the proposed dissolution method.

Dissolution profiles of batches with different [redacted] using 0.25% SDS in 900 mL 0.1 N HCl, USP II, 65 rpm



The dissolution profiles for the drug product batches with [redacted] and target product were similar.

6) [redacted] **content:** The dissolution profiles (Pg 20) for the drug product batches with lower ([redacted]) and target ([redacted] content were similar using the proposed dissolution method.

Overall, the proposed dissolution method was found sensitive to the drug product CBAs like [redacted].

Based on overall dissolution method development data and clinical data provided, the following dissolution method and acceptance criterion is deemed adequate for Quality Control. However, a post marketing commitment/requirement is in place to monitor the commercial batch dissolution profile during stability and release. Until the additional data is assessment, an interim acceptance criterion of Q=[redacted]% in 45 minutes will be used for batch release and stability.

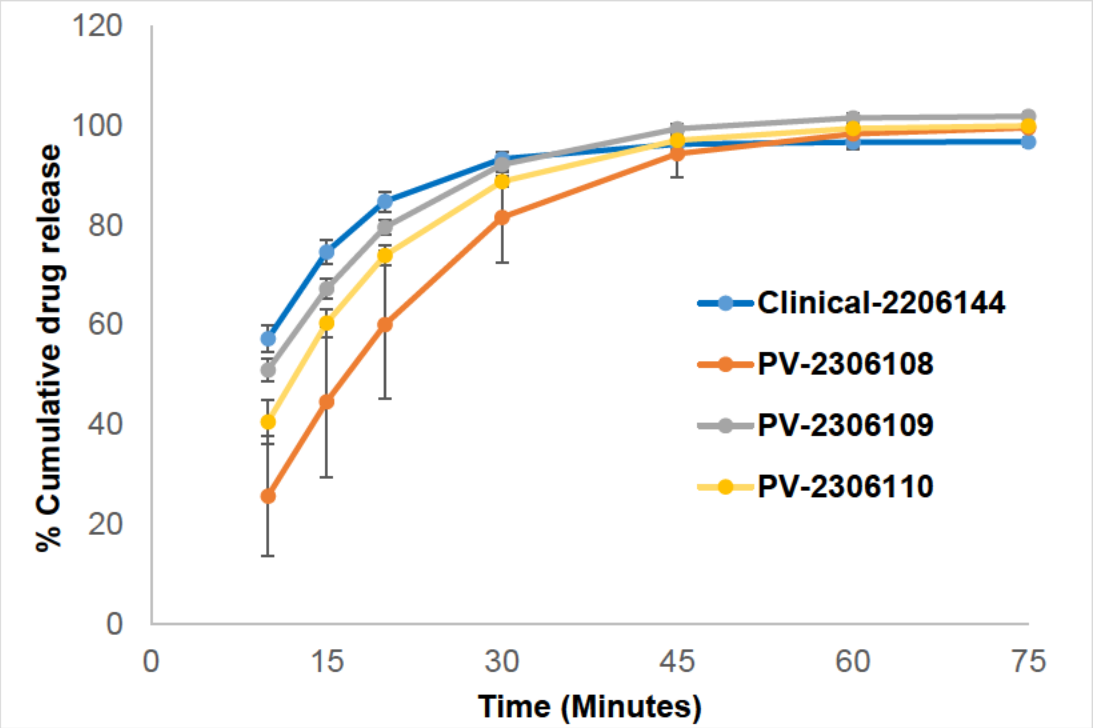
B. 3. BRIDGING OF FORMULATIONS

Assessment: Adequate

Manufacturing site: The drug product manufacturing site for clinical batches and commercial batches is the same (Quotient Sciences, PA).

Drug Product Appearance (final to-be-marketed product image): The tovorafenib film coated (T2) Tablets, 100 mg was used in the pivotal Phase 2 Clinical Study FIREFLY-1 and has the same qualitative and quantitative composition, size, and shape as the commercial Ojemda (tovorafenib) Tablets, 100 mg differing only in the use of debossing: clinical tablets are plain (unmarked) on both sides, while the commercial tablets are debossed. The Applicant has provided (SN#0038, SDN#38, 3/8/2024) dissolution data for the commercial/ process validation (PV) batches with debossing using the proposed QC method in response to IR sent on 2/16/2024.

Dissolution profiles of clinical and process validation batches (with debossing) using QC dissolution method



Two PV batches (2306108 and 2306109) exhibit drug release profiles comparable to the clinical batch (2206144). The third PV batch (2306110) demonstrates relatively slower drug release with high variability up to 30 minutes; nevertheless, it remains compliant with the proposed acceptance criterion (Q=(b)(4)% in (b)(4) minutes) during stage 3 testing. In summary, the dissolution data implies that debossing has minimal impact on the drug release from the product.

B. 4. BIOWAIVER REQUEST

Assessment: Not Applicable

There is only one strength (100 mg) proposed for marketing, and this strength was evaluated in the pivotal clinical trials. Biowaiver is neither requested nor needed.

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: None.

Post-Approval Commitments

Assessment: Adequate

The Applicant submitted following PMC (#4608-XX) on 4/10/2024 (SN#0050, SDN#53) in response to the IR sent on 4/9/2024 (Refer to B.2 review for more information):

Day One acknowledges the Agency's request and provides a formal Post-Marketing Commitment (PMC) proposal.

PMC Description:

(b) (4)

(b) (4)

Please note that, as requested by Agency's Information Request dated 03 April 2024 (SN0049), Day One has already implemented the tighter acceptance criterion (Q=(b) (4)% in (b) (4)-minutes) and completed release testing of the process validation batches. Therefore, Day One will release the process validation/commercial batches using the tighter specification and collect the data requested in this response (Q=(b) (4)% in 45-minutes, with profiles date of 15-, 20-, 30-, 45- and 60-minute) post-batch release and on stability throughout the proposed shelf life.

Lifecycle Management Considerations

None.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None.

Primary Biopharmaceutics Assessor's Name and Date: Hardikkumar H Patel, Ph.D., 4/12/2024

Secondary Assessor Name and Date (and Secondary Summary, as needed): Anitha Govada, Ph.D.,4/12/2024.

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Hardikkumar Patel

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CHAPTER IV: LABELING

NDA Number	217700
Assessment Cycle Number	1
Drug Product Name	tovorafenib

Assessment Recommendation: Adequate

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	**0014**
Patient Information	Adequate	**0014**
Instruction for Use (IFU)	N/A	**NA**
Container Labels	Adequate	**0005**
Carton Labeling	Adequate	**0005**

Brief Description of Outstanding Issues:

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
0005	08/31/2023	
0014	11/17/2023	
0024	01/08/2024	

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

[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)

(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)
Product Title in Highlights[2] [21 CFR 201.57(a)(2)]		
Established name(s)[3]	Adequate	OJEMDA (tovorafenib) tablets, for oral use
Route(s) of administration	Adequate	Oral
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	Tablets. Note: On the PI there is another dosage form, powder for oral suspension. This review pertains to the tablet. See review under NDA 218033 for assessment of the powder for oral suspension.
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	

[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>
[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)

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)
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*

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

(*copy of proposed text*) APPEARS THIS WAY ON ORIGINAL

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 and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product).	N/A	

[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>

[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)

[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

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)
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	N/A	
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	

Assessment: *Adequate*

[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition

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

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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	Tablets
Strength(s) in metric system	Adequate	100 mg
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	Tablets: 100 mg orange, film-coated, oval tablets debossed with "100" on one side and "D101" on the opposite side.
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 imaging bulk package (see USP <659>).	N/A	

Assessment: *Adequate*

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

1.2.3 Section 11 (DESCRIPTION)[14]

(*copy of proposed text*) APPEARS THIS WAY ON ORIGINAL

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	Tovorafenib tablets
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	Tablets for oral administration
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)" [§ 201.57(c)(12)(i)(C)].	N/A	
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)].	Adequate	Inactive ingredients are listed, but not in alphabetical order. The edits are made on the proposed label and the applicant accepted the edits.
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	N/A	

[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).

[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.

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 of effect. [§ 201.100(b)(5)(iii)].		
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	Tovorafenib is a kinase inhibitor.
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	It has the molecular formula $C_{17}H_{12}C_{12}F_3N_7O_2S$ and a molecular weight of 506.29. The chemical name for tovorafenib is 6-amino-5-chloro-N-[(1R)-1-[5-[[[5-chloro-4-(trifluoromethyl)-2-pyridinyl]amino]carbonyl]-2-thiazolyl]ethyl]-4-pyrimidinecarboxamide.
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)].	N/A	
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	

[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.

[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)

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 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*

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

(*copy of proposed text*) APPEARS THIS WAY ON ORIGINAL

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	Tablets
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	100 mg
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	See below.

[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)
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	Tablets: 100 mg: orange, film-coated, oval tablets debossed with "100" on one side and "D101" on the opposite side and supplied as follows: 4 blister cards (4 tablets each) per box, NDC 82950-0001-16. 5 blister cards (4 tablets each) per box, NDC 82950-0001-20. 4 blister cards (6 tablets each) per box, NDC 82950-0001-24.
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 bulk package and imaging bulk package (see USP <659>).	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." [§ 201.57(c)(17)(iv)]	N/A	

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)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].
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	
(b) (4)		

Assessment: *Adequate*

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.

[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)

[22] (b) (4)

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

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	Manufactured for: Day One Biopharmaceuticals, Inc. 2000 Sierra Point Parkway, Suite 501 Brisbane CA 94005 Manufactured by (tablets): Quotient Sciences – Philadelphia LLC 3 Chelsea Parkway, Suite 305 Boothwyn PA 19061

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	
Special preparation instructions (if applicable).	N/A	
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 differ from the dosage form.	N/A	
Active ingredient(s) (if applicable).	Adequate	

[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)
Alphabetical listing of inactive ingredients (if applicable).	Adequate	Inactive ingredients are listed, but not in alphabetical order. The edits are made on the proposed label and to be communicated to the applicant when clinical team finalized its edits on the proposed label.
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	

Assessment: *Adequate*

3.0 CONTAINER AND CARTON LABELING[25]

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

[25] Carton and Container Labeling Resources

(b) (4)

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	

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

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)
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[28]	Adequate	Yes	100 mg
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	No	Route of administration "(b) (4) " is on the carton, but not on the wallet. When communicated with DMEPA, they indicate that it is optional for oral dosage forms.
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	Choose an item.	
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[29]	Adequate	Yes	Carton contains 16 tablets 20 tablets
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	Rx
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	No	NDC is on the carton but not on the wallet. NDC is not required for all labels or labeling [§ 201.2 & 207.35].
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Yes	Lot number and expiration statement are absent on either carton or wallet. The IR was conveyed to the applicant and the correction has been made by the applicant.

[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)

[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)
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	Yes	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].
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	Choose an item.	
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	N/A	Choose an item.	
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	Choose an item.	
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	Choose an item.	

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)
Linear Bar code [§ 201.25(c)(2)].[30]	Inadequate	Yes	A linear bar code is absent on either carton or wallet. The IR will be sent by DMEPA since they have the standard language for this.
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	Yes	
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	No	
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Adequate	Yes	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Choose an item.	
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Choose an item.	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Choose an item.	
When a drug product differs from the relevant USP standard of strength, quality,	N/A	Choose an item.	

[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)
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]			
And others if space is available.	N/A	Choose an item.	

Assessment of Carton Labels and Container Labeling: *Adequate*
Two issues identified: 1). Lot number and expiration statement are absent on either carton or wallet. This has been resolved after the applicant responded adequately to our IR. 2). A linear bar code is absent on either carton or wallet. Both issue were communicated with DMEPA and they will send IRs since they have standard language for these issues.

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

The proposed USPI, PPI and container carton labeling are acceptable pending the two aforementioned container carton labeling issues to be conveyed and reviewed by DMEPA. Some minor edits have been made on the USPI and PPI, and they will be discussed in the upcoming OND labeling meeting.

Primary Labeling Assessor Name and Date: Xiao Hong Chen, March 22, 2024

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

[31] USP General Notices 3.20 Indicating Conformance

Xiao Chen

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David Claffey

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/s/

XIAOHONG CHEN
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NDA Executive Summary

1. Application/Product Information

NDA Number.	218033		
Applicant Name	Day One Biopharmaceuticals, Inc.		
Drug Product Name	Tovorafenib		
Dosage Form.	Powder for oral suspension		
Proposed Strength(s)	25 mg/mL 300 mg/bottle		
Route of Administration	Oral		
Maximum Daily Dose	600 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of pediatric patients 6 months of age and older with relapsed or refractory pediatric low-grade glioma (LGG) harboring a BRAF fusion or rearrangement, or BRAF V600 mutation.		
Drug Product Description	Tovorafenib Powder for Reconstitution (PfR) is packaged as a 300-mg active strength (to deliver) in a glass bottle equipped with (b) (4) caps with a heat induction seal liner. It is reconstituted with water to a 25 mg/mL active concentration and dosed with a syringe.		
Co-packaged product information	Co-packaged with an oral syringe and bottle adaptor		
Device information:	Syringe and bottle adaptor		
Storage Temperature/ Conditions	20 - 25°C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Kabir Shahjahan	Haripada Sarker
	Drug Product/ Labeling	Jessica Zarenkiewicz	Thomas Oliver

	Manufacturing	Xiumei Ruan	Christine Falabella
	Biopharmaceutics	Hardikkumar Patel	Anitha Govada
	Microbiology	N/A	N/A
	Other (specify):		
	RBPM	Janell Artis	
	ATL	Xiao Hong Chen	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. PMC

The final dissolution method (USP apparatus II, 50 rpm, 900 mL 0.1 N HCl with 0.3% SDS) is optimal and discriminating for the proposed drug product. However, considering the lack of sufficient dissolution profile data generated with the final method with the recommended dissolution acceptance criterion of Q=(b) (4)% in (b) (4) minutes, Biopharmaceutics is proposing to implement a dissolution acceptance criterion of Q=(b) (4)% in 45 minutes, but on an interim basis only. Therefore, a Post-Marketing Commitment (PMC) has been proposed and accepted by the applicant to submit additional dissolution profile (multi time-point) data generated from commercial batches using the final dissolution method (USP apparatus II, 50 rpm, 900 mL 0.1 N HCl with 0.3% SDS at 37°C) and the interim acceptance criterion of Q=(b) (4)% in 45 minutes until the appropriate acceptance criterion for the dissolution test of the drug product is finalized.

PMC #4626-xx*

PMC Description

(b) (4)

PMC Timeline

(b) (4)

Note that until a new revised dissolution acceptance criterion is found acceptable by FDA, the currently recommended dissolution method (USP apparatus II, 50 rpm, 900 mL 0.1 N HCl with 0.3% SDS at 37ºC) and the interim acceptance criterion of Q=(b) (4)% in 45 minutes will be used for batch release and stability testing on an interim basis.

***** At the time of finalizing this review the last 2 digit numbers for the PMC #4626-xx have not been assigned. Refer to the NDA approval letter for the final PMC number.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:
The applicant provided adequate CMC information for Tovorafenib Powder for oral suspension, and all drug substance and drug product manufacturing and testing facilities are found acceptable.

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: N/A

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	Powder for Oral Suspension/Immediate Release
NDA Number	218033
Assessment Cycle Number	1, ORIG-1 [505(b)(1)]
Drug Product Name/ Strength	Ojemda (tovorafenib) Powder for Oral Suspension, 25 mg/mL
Route of Administration	Oral
Applicant Name	Day One Biopharmaceuticals, Inc.
Therapeutic Classification/ OND Division	Oncology/OND/OOD/Division of Oncology 2
RLD/RS Number	This application cross-references to (NDA# NDA 217700) for Ojemda (tovorafenib) Tablets, 100 mg)
Proposed Indication	Treatment of pediatric patients 6 months of age and older with relapsed or refractory pediatric low-grade glioma (LGG) harboring a BRAF fusion or rearrangement, or BRAF V600 mutation

Assessment Recommendation: **Adequate**

A. Assessment Summary:

The Applicant, Day One Biopharmaceuticals, is seeking approval of NDA 218033 for Ojemda (tovorafenib) Powder for Oral Suspension (PfOS), 25 mg/1 mL[1], intended for immediate release under 505 (b)(1) regulatory pathway. The drug substance, tovorafenib is characterized as a new molecular entity (NME) and exhibits low solubility in its crystalline form. (b) (4) has also been proposed for a different dosage form, Ojemda (tovorafenib) Tablets, 100 mg in a separate application (NDA 217700). Ojemda PfOS was developed as an alternate dosage form for pediatric patients or those who have trouble in swallowing a tablet.

[1] The Drug product is supplied as powder for suspension in bottle to be reconstituted with 14 mL of water to yield withdrawal of a 12 mL suspension of 25 mg/1mL.

This Biopharmaceutics review focuses on the assessment and recommendation on the adequacy of 1) the proposed dissolution method and acceptance criterion for Ojemda PfOS for quality control purposes and 2) addressing the Clinical Pharmacology's Consult on lack of food effect study using PfOS and the impact of dosage form interchangeability and re-dosing in case of emesis. 3) addressing CMC consult for change in excipient manufacturing site and drug substance (b) (4) content limits.
In vivo relative bioavailability (rBA) study and pivotal Phase 2 clinical Study FIREFLY-1 to bridge the Ojemda PfOS and Tablet dosage form submitted will be reviewed by the Office of Clinical Pharmacology.

Dissolution Method and Acceptance Criterion: The Applicant's originally proposed QC dissolution method (0.3% SDS in 900 mL 0.1 N HCl, USP apparatus II, (b) (4) rpm) and acceptance criterion (Q=(b) (4)% in 45 minutes) was found inadequate. Therefore, the Applicant was advised to develop a suitable dissolution method with adequate discriminating ability towards Critical Bioavailability Attributes (CBAs). The Applicant developed the following dissolution method: USP Apparatus II, 50 rpm, 900 mL 0.1 N HCl with 0.3% SDS, which demonstrated appropriate discriminating ability against (b) (4) . Therefore, the dissolution method was deemed adequate and acceptable by Biopharmaceutics. Based on the overall dissolution method development data, clinical data, and registration batch dissolution profile data generated with the final method, a dissolution acceptance criterion of Q=(b) (4)% in (b) (4) minutes was recommended. However, because the Applicant is unable to provide additional stability data using the final dissolution method prior to the NDA's action date, the drug product Quality Review Team expressed concerns regarding the lack of sufficient dissolution data to support the proposed shelf-life of 24 months. Additionally, it is noted that out of the seven batches (three registration and four clinical) tested using the final method, two batches required testing at Stage 2, and another batch failed Stage 2 testing (Stage 3 testing data was not provided) to comply with the recommended acceptance criterion of Q=(b) (4)% at (b) (4) minutes. Therefore, the Applicant was requested to provide additional dissolution profile data from commercial batches at release and on stability through Post-Marketing Commitment (PMC) and an interim dissolution acceptance criterion of Q=(b) (4)% in 45 minutes using the final dissolution method, was recommended on an interim basis. The Applicant submitted the PMC (#4626-XX) as requested on 4/10/2024.

Final Dissolution Method and Interim Acceptance Criterion:

Apparatus Type	Rotation Speed	Medium/ Volume	Temperature	Interim Acceptance Criterion
USP apparatus II (Paddle)	50 rpm	0.1 N HCl with 0.3% SDS/ 900 mL	37.0 ± 0.5 °C	Q=(b) (4)% in 45 minutes

Consults:

1) **Food effect:** The clinical pharmacology reviewer contacted the biopharm review team regarding the absence of food effect studies for the PfOS formulation. The Applicant claimed that PfOS isn't influenced by food, citing (1) the bioequivalence of PfOS and tablet formulations and (2) tablet's lack of food effect. The biopharm review team shared concerns about the insufficient data on PfOS' s food effect, noting that tablet exhibited a 20% reduction in Cmax due to food, and highlighting differences in dosage forms between tablet and PfOS The Office of Clinical Pharmacology (OCP) issued an IR requesting more data from the applicant on 12/6/2023. The applicant responded to the IR on 12/18/2023, which the OCP reviewed and deemed adequate. For further details, refer to the OCP's review documents ((NDA 217700 and NDA 218033). Refer to Appendix 1 for the email communication between the biopharm and the OCP reviewer.
2) **Redosing in case of emesis:** The clinical pharmacology reviewer contacted the biopharm review team to evaluate whether dissolution data for Ojemda Tablets, 100 mg (NDA 217700) and Ojemda PfOS (NDA 210833) can be used to support re-dosing if vomiting occurs after dosing. The biopharm review team notified the OCP that dissolution testing is product-specific, and different methods were used for QC for tablets and PfOS. In addition, these methods are not biorelevant. The biopharm review team expressed the view that dissolution data shouldn't be utilized to decide on re-dosing for re-dosing for PfOS or tablets due to uncertainty regarding its impact on the pharmacokinetic (PK) profile.
3) **CMC Drug Product Consult:** The drug product reviewer contacted biopharm review to team with following two questions: 1) changing manufacturer for Simethicone (b) (4) from a commercial vendor to in-house manufacturing and drug product specification limit of NMT (b) (4) . The biopharm review team informed the drug product reviewer that there are no concerns about the supplier (in-house vs. vendor) for the excipient Simethicone (b) (4) as long as its composition remains consistent. Additionally, based on dissolution data indicating no impact from (b) (4) API up to (b) (4)% and considering the XRD method's limit of quantification (LOQ) of (b) (4)%, the biopharm team has no concerns regarding the proposed specification of NMT (b) (4) content.

Biopharmaceutics Overall Recommendation: From a Biopharmaceutics perspective, NDA 218033 for Ojemda (tovorafenib) Powder for Oral Suspension, 25 mg/mL is recommended for APPROVAL.

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking	Comments
[redacted]				(b) (4)
(b) (4) content of API	Medium	(b) (4) content of API is a CQA (b) (4) [redacted]	Low	(b) (4) content of API (LOQ: NMT (b) (4) %) is controlled in drug product specifications

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
New NDA (SN 0001/SDN 1)	06/21/2023
Biopharm IR response (SN 0011/SDN 11)	12/13/2023
Biopharm IR response (SN 0016/SDN 16)	1/31/2024
Biopharm IR response (SN 0020/SDN 20)	3/15/2024
Biopharm IR response (SN 0023/SDN 23)	3/22/2024
Biopharm IR response (SN 0027/SDN 27)	3/29/2024
Biopharm IR response (SN 00 29/SDN 31)	4/4/2024
PMC#4626-XX (SN#0030/SDN#33)	4/10/2024

Highlight Key Issues from Last Cycle and Their Resolution: Not applicable.

Concise Description of Outstanding Issues *(list bullet points with key information and update as needed)*: Refer to Post-Approval Commitments

B.1 BCS DESIGNATION

Assessment: There is no official BCS designation request for the proposed drug product.

Solubility: Based on the solubility data provided by the Applicant, crystalline tovorafenib exhibits low solubility across physiological range.

Permeability: As per the Applicant, tovorafenib exhibits high in vitro permeability based on CaCo2 study results. However, permeability data has not been evaluated by the reviewer.

Dissolution: Not rapid across the entire physiologic pH range, refer to the assessment below.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: Adequate

Crystalline tovorafenib exhibits low solubility across physiological range. (b) (4)

Table 1: (b) (4) Solubility of tovorafenib (37 °C)

Media pH	Crystalline (mg/mL)	(b) (4)
1.2	0.003	
4.5	<0.0015	
6.5	<0.0015	
8.06	0.002	

The Applicant originally (PDR, Pg 79) proposed the following quality control dissolution method and acceptance criterion for the proposed drug product:

Apparatus	Speed	Medium	Volume/ Temperature	Acceptance Criterion
USP Apparatus II (Paddle)	(b) (4) rpm	0.1 N HCl with 0.30% SDS	900 mL/ 37 ± 0.5 °C	Q=(b) (4)% in 45 minutes

The drug product is a powder for oral suspension (PfOS). The drug product is packaged as a 300-mg active strength (to deliver) in a glass bottle equipped with (b) (4) caps with a heat induction seal liner. It is reconstituted with water to a 25 mg/mL active concentration and dosed with a syringe. The bottle is overfilled to (b) (4) mg Tovorafenib active and reconstituted with 14 mL of water to allow for reproducible dosing delivery of 300 mg tovorafenib (i.e., 12 mL of 25 mg/mL tovorafenib with an oral syringe). Dissolution studies were performed using 12 mL reconstituted suspension prepared as per the drug product label.

(b) (4)

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(b) (4)

Discriminating ability: The Applicant identified various Critical Bioavailability Attributes (CBAs: (b) (4)) to evaluate (SN#0016, 1/31/2024) the discriminating ability of the proposed dissolution method (900 mL 0.1 N HCl using 0.3% SDS, USP apparatus II, 50 rpm) against them.

1) (b) (4)

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3) (b) (4): The dissolution profiles (Pg 14-16) for the drug product batches with higher (b) (4) and target (b) (4) were similar using the proposed dissolution method.
4) (b) (4) **content in the formulation:** The dissolution profiles (Pg 16-18) for the drug product batches with lower ((b) (4)%), target ((b) (4)%), and higher ((b) (4)%) (b) (4) content in the formulation were similar using the proposed dissolution method.

Overall, the proposed drug product was found sensitive to change in (b) (4). Based on the dissolution method development and clinical data provided, the Applicant was recommended (IR sent on 2/16/2024) to adopt the following dissolution method: USP apparatus II, 50 rpm, 900 mL 0.1 N HCl with 0.3% SDS and acceptance criterion of Q=(b) (4)% in (b) (4) minutes for QC of the drug product at release and stability.

The Applicant provided dissolution data (n=12) on 3/15/2024 (SN#0020, SDN#20) and 3/22/2024 (SN#0023, SDN#23) for clinical and registration batches using the finalized method as requested in the IR sent on 2/16/2024. Dissolution data suggests that all batches except one (Lot 2303072) would meet the requirements for S1/S2 dissolution testing.

Dissolution Profile of Ojemda PfOS Lot 2303072 using 0.3% SDS in 900 mL 0.1 N HCl, USP II, 50 rpm

Vessel	Time (min)							
	5	10	15	20	30	45	60	Infinity
V1	(b) (4)							
V2								
V3								
V4								
V5								
V6								
V7								
V8								
V9								
V10								
V11								
V12								
MEAN	**72.5**	**76.2**	**77.7**	**78.8**	**80.4**	**82.3**	**83.1**	**92.1**
Minimum	**70.2**	**74.0**	**75.6**	**76.5**	**78.2**	**79.8**	**80.6**	**88.4**
Maximum	**73.5**	**77.6**	**79.3**	**80.5**	**81.9**	**84.0**	**84.7**	**93.9**
Stdev	**1.0**	**1.1**	**1.1**	**1.1**	**1.0**	**1.2**	**1.1**	**1.6**
RSD	**1.4**	**1.4**	**1.4**	**1.4**	**1.3**	**1.4**	**1.4**	**1.8**

Batch 2303072 did not pass stage 2 testing with a sample size of n=12, and it remains uncertain whether it would meet the criteria for stage 3 testing with a sample size of n=24 due to the absence of additional data. The Applicant was informed (3/28/2024) that all batches are expected to meet the dissolution specification and dissolution failures should be described and any corrective actions to avert such dissolution failures should be discussed.

The Applicant accepted the acceptance criterion of Q=(b) (4)% in (b) (4) minutes on 3/29/2024 (SN#0027, SDN#27) updated analytical procedures and specifications on 4/4/2024 (SN#0029, SDN#31). However, because prior to the NDA's action date, the Applicant is unable to provide additional stability data using the final dissolution method, the drug product Quality Review Team expressed concerns regarding the lack of sufficient dissolution data to support the proposed shelf-life of 24 months (refer to Appendix 6). Additionally, it is noted that out of the seven batches (three registration and four clinical) tested using the final method, two batches required testing at Stage 2, and another batch failed Stage 2 testing (Stage 3 testing data was not provided) to comply with the recommended acceptance criterion of Q=(b) (4)% at (b) (4) minutes. Therefore, considering the absence of sufficient dissolution data, the Applicant was requested on 4/9/2024 to provide additional dissolution profile data from commercial batches and process validation batches at release and on stability through Post-Marketing Commitment (PMC) and an interim dissolution acceptance criterion of Q=(b) (4)% in 45 minutes using the final dissolution method, was recommended on an interim basis (refer to Appendix 7). The Applicant submitted the PMC (#4626-XX) as requested on 4/10/2024 (SN#0030, SDN#33).

Final dissolution method and interim acceptance criterion:

Apparatus	Speed	Medium	Volume/ Temperature	Acceptance Criterion
USP Apparatus II (Paddle)	50 rpm	0.1 N HCl with 0.3% SDS	900 mL/ 37 ± 0.5 °C	Q=(b) (4)% in 45 minutes

Consults

1) **Food effect:** The clinical pharmacology reviewer contacted the biopharm review team regarding the absence of food effect studies for the PfOS formulation. The Applicant claimed that PfOS isn't influenced by food, citing (1) the bioequivalence of PfOS and tablet formulations and (2) tablet's lack of food effect.

   Assessment and recommendation: The biopharm review team shared concerns about the insufficient data on PfOS' s food effect, noting that tablet exhibited a 20% reduction in Cmax due to food, and highlighting differences in dosage forms between tablet and PfOS (PFOS does not require disintegration for the drug to be available for absorption or food interaction in contrast to Tablet formulation (b) (4)). Therefore, without supportive in-vivo/in vitro data, this reviewer could not conclude that PFOS and Tablet will exhibit similar food effect. The OCP reviewer and team lead were

informed that there is insufficient data to determine food effect on PfOS and from a biopharmaceutics perspective, an in vivo food effect study specific to PfOS should be recommended. The Office of Clinical Pharmacology (OCP) issued an IR requesting more data from the applicant on 12/6/2023. The applicant responded to the IR on 12/18/2023, which the OCP reviewed and deemed adequate. For further details, refer to the OCP's review documents ((NDA 217700 and NDA 218033). Refer to Appendix 1 for the email communication between the biopharm and the OCP reviewer.

2) **Redosing in case of emesis:** The clinical pharmacology reviewer contacted the biopharm review team to evaluate whether dissolution data for Ojemda Tablets, 100 mg (NDA 217700) and Ojemda PfOS (NDA 210833) can be used to support re-dosing if vomiting occurs after dosing.

   Assessment and recommendation: The biopharm review team notified the OCP that dissolution testing is product-specific, and different methods were used for QC for tablets and PfOS. In addition, these methods are not biorelevant. The biopharm review team expressed the view that dissolution data shouldn't be utilized to decide on re-dosing for re-dosing for PfOS or tablets due to uncertainty regarding its impact on the pharmacokinetic (PK) profile differences in dosage forms between tablet and PfOS (PFOS does not require disintegration for the drug to be available for absorption or food interaction in contrast to Tablet formulation composition (b) (4)). Refer to Appendix 2 for the email communication between the biopharm and the OCP reviewer.

3) **CMC Drug Product Consult:** The drug product reviewer contacted biopharm review to team with following two questions:
   a) Simethicone (b) (4) versus simethicone (b) (4) – this is an excipient change from a commercial vendor to in-house manufacturing for (b) (4). The DP team asked for confirmation of the applicant's statement that dissolution studies conducted to support this change had no impact on the dissolution profile of the product.
   b) (b) (4) limits – A dissolution study was conducted by spiking (b) (4) in the drug product Based on the drug product specification for limit of NMT (b) (4), the DP team asked for biopharm' s feedback on the presence of (b) (4).

   Assessment and recommendation: The biopharm review team informed the drug product reviewer that we have no concerns about the supplier (in-house vs. vendor) for the excipient Simethicone (b) (4) as long as its composition remains consistent. Additionally, based on dissolution data indicating no impact from (b) (4) API up to (b) (4)% and considering the XRD method's limit of quantification (LOQ) of (b) (4)%, the biopharm team has no concerns regarding the proposed specification of NMT (b) (4) content. Refer to Appendix 3 for the email communication between the biopharm and the drug product reviewer.

B.3 BRIDGING OF FORMULATIONS

Assessment: Not Applicable

Manufacturing site: The drug product manufacturing site for clinical batches and commercial batches is the same (Quotient Sciences, PA).

Ojemda PfOS was used in the relative bioavailability (rBA) study and pivotal Phase 2 clinical Study FIREFLY-1. The commercial formulation is identical to the clinical formulation.

B.4 BIOWAIVER REQUEST

Assessment: Not Applicable

There is only one strength (300 mg) proposed for marketing, and this strength was evaluated in the pivotal clinical trials. Biowaiver is neither requested nor needed.

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: None

Post-Approval Commitments

Assessment: Adequate

The Applicant submitted following PMC (#4626-XX) as requested on 4/10/2024 (SN#0030, SDN#33) in response to IR sent on 4/9/2024 (Refer to B.2 review for more information):

Day One acknowledges the Agency's request and provides a formal Post-Marketing Commitment (PMC) proposal.

PMC Description

- (b) (4)

- [redacted] (b) (4)

PMC Timeline

- [redacted] (b) (4)
- [redacted]

Please note that, as requested by the Agency's Information Request dated 03 April 2024 (SN0029), Day One has already implemented the tighter acceptance criterion (Q=(b) (4)% in (b) (4) minutes) and completed release testing of the process validation batches. Therefore, Day One will release the process validation/commercial using the tighter specification and collect the data requested in this response (Q=(b) (4)% in 45 minutes, with profiles date of 15-, 20-, 30-, 45- and 60- minutes) post-batch release and on stability throughout the proposed shelf life.

Lifecycle Management Considerations

Not Applicable

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None.

Primary Biopharmaceutics Assessor's Name and Date: Hardikkumar H Patel, Ph.D., 4/12/24

Secondary Assessor Name and Date (and Secondary Summary, as needed): Anitha Govada, Ph.D., 4/12/2024.

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Hardikkumar Patel

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Date: 4/12/2024 03:03:53PM
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Anitha Palamakula Govada

Digitally signed by Anitha Palamakula Govada
Date: 4/12/2024 03:39:42PM
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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	218033
Assessment Cycle Number	1
Drug Product Name	Tovorafenib, for Oral Suspension

Assessment Recommendation: Adequate following acceptance of the recommended changes detailed in this review.

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate with minor edits communicated to OND	NDA 217700 SDN 0046
Patient Information	Adequate	NDA 217700 SDN 0025
Instruction for Use (IFU)	Adequate	
Container Labels	Adequate	
Carton Labeling	Adequate	

Brief Description of Outstanding Issues:

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
NDA 217700 SDN 0005	8/31/23	Carton and Container Labels
NDA 218033 SDN 0008	11/13/23	Instructions for Use
NDA 217700 SDN 0014	11/17/23	Prescribing Information and Patient Information
NDA 217700 SDN 0035	2/26/24	Updated Patient Informaton
NDA 217700 SDN 0041	3/19/24	Updated Carton and Container Labels
NDA 217700 SDN 0046	3/29/24	Prescribing Information counterproposal

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the 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	

[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)

[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).

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)
Route(s) of administration	Adequate	
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	Present. To be updated upon approval
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s)[4] and strength(s) in metric system[5]	Adequate	
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	This review pertains to the powder for oral suspension only. See review under NDA 217700 for assessment of the tablet.
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*

[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>
[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>

The provided information pertaining to the tovorafenib powder for oral suspension formulation is adequate.

1.2 FULL PRESCRIBING INFORMATION

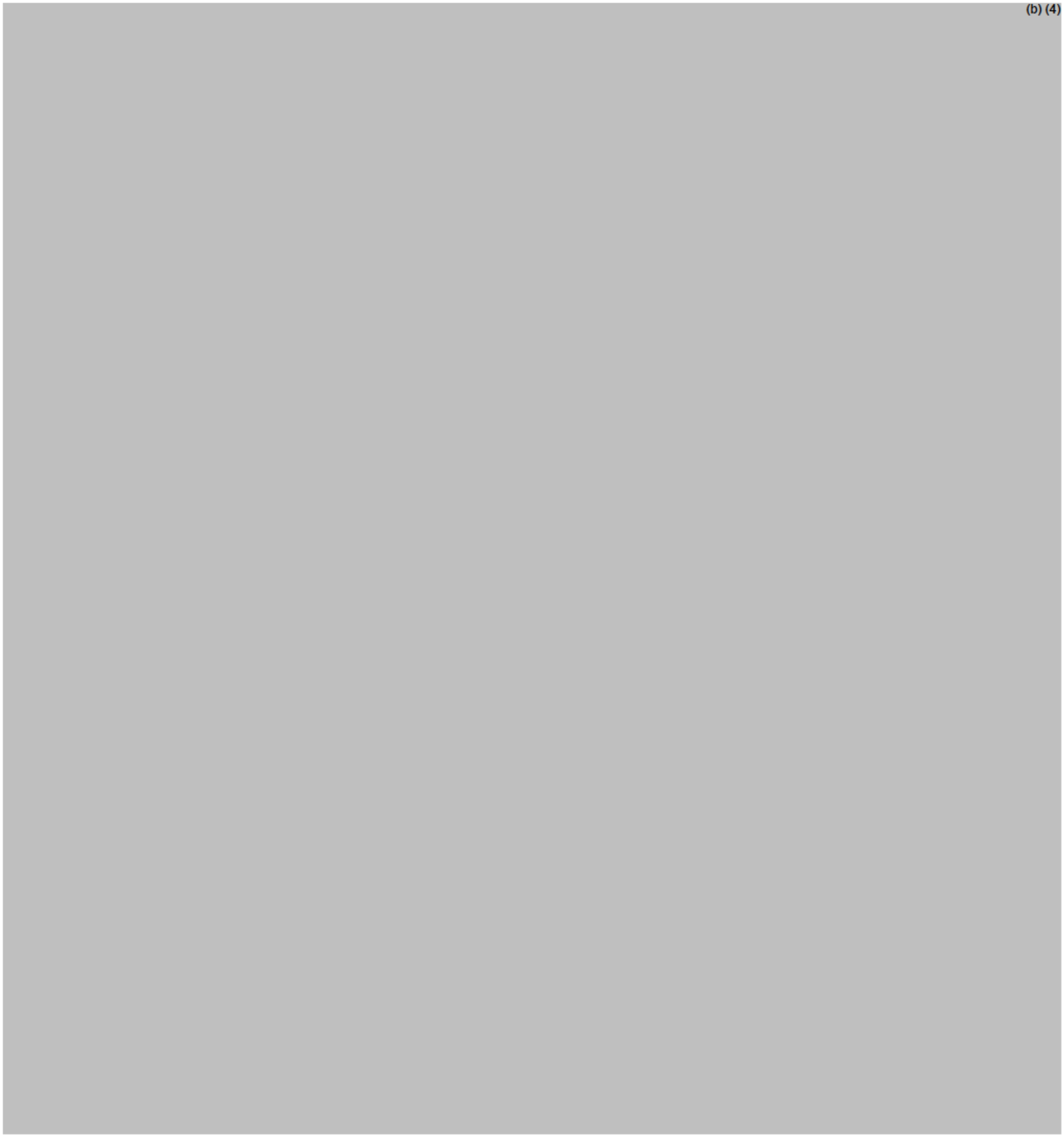
1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

(b) (4)

[redacted]

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

[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)
DOSAGE AND ADMINISTRATION section		

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)
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product).	Adequate	Detailed instructions for use are provided with the powder for oral suspension. (b) (4)
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	Adequate	See instructions for use
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*	N/A	

[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

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)
disposal procedures.x" with x numerical citation to "OSHA Hazardous Drugs."		

Assessment: *Adequate*

Dosage and administration section is adequate for the powder for oral suspension formulation. See Instructions for use of the powder for oral suspension for full dosing instructions.

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)	Inadequate	"Powder" should be removed
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	Adequate	

[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)
forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable.		
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	This review pertains to the powder for oral suspension only. See review under NDA 217700 for assessment of the tablet.
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 imaging bulk package (see USP <659>).	N/A	

Assessment: *Adequate*

The provided information pertaining to the powder for oral suspension formulation is adequate. See minor edit in red for dosage form.

1.2.3 Section 11 (DESCRIPTION)[14]

(b) (4)

[redacted]

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

(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	
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example:	N/A	

[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)
"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)].	Adequate	
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	
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	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.

[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).

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 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)].	Adequate	
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").	Adequate	
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*

Adequate. We recommend paragraphs be inserted for readability purposes.

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

(b) (4)

[redacted]

[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)
[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

(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	This review pertains to the powder for oral suspension only. See review under NDA 217700 for assessment of the tablet.

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)
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 (see USP <659>).	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." [§ 201.57(c)(17)(iv)]	Adequate	
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)
	(b) (4)	

Assessment: *Adequate*

1.2.5 Other Sections of Labeling

Not applicable for the powder for oral suspension formulation.

[22] (b) (4)

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	

Assessment: *Adequate*

2.0 PATIENT LABELING

Patient information and Instructions for use are provided for the powder for oral suspension formulation.

Link to patient information: \\CDSESUB1\EVSPROD\nda217700\0035\m1\us\draft-ppi.pdf

[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)

Link to Instructions for Use: \\CDSESUB1\EVSPROD\nda218033\0008\m1\us\ifu-pfos-pdf.pdf

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	
Special preparation instructions (if applicable).	Adequate	Instructions for use included
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 differ 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	

Assessment: *Adequate*

The patient information is adequate as it pertains to the powder for reconstitution.

A change was made to the instructions for use per DMEPA requesting removal of (b) (4) [redacted]. The updated instructions for use do not have any language pertaining to the inclusion of foam in the syringe volume but does say to remove any air bubbles out of the syringe tip. The instructions for use is adequate.

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

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

(b) (4)

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	
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[28]	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)
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	
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	Choose an item.	
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	Choose an item.	

[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)
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	Adequate	Yes	
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	Choose an item.	
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	Choose an item.	
Linear Bar code [§ 201.25(c)(2)].[30]	Adequate	Yes	
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	No	More detailed instructions present on carton label. Both versions are adequate.
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Adequate	Yes	
If there is a Medication Guide, must include a statement about dispensing a	N/A	Choose an item.	

[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)
Medication Guide to each patient.			
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Choose an item.	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Choose an item.	
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	Choose an item.	
And others if space is available.	N/A	Choose an item.	

Assessment of Carton Labels and Container Labeling: *Adequate*

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

[31] USP General Notices 3.20 Indicating Conformance

Primary Labeling Assessor Name and Date: Jessica Zarenkiewicz, PhD

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

Jessica Zarenkiewicz

Digitally signed by Jessica Zarenkiewicz
Date: 4/02/2024 10:40:55AM
GUID: 6239e6b2006583184e2eea406208dd4f

David Claffey

Digitally signed by David Claffey
Date: 4/02/2024 10:41:46AM
GUID: 508da71e00029e20b201195abff380c2

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

/s/

XIAOHONG CHEN
04/12/2024 09:23:02 PM