CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219097Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	219097
Applicant Name	Shorla Pharma Ltd.
Drug Product Name	IMKELDI (imatinib) oral solution
Dosage Form.	Solution
Proposed Strength(s)	80 mg/mL
Route of Administration	Oral
Maximum Daily Dose	800 mg
Rx/OTC Dispensed	Rx
Proposed Indication	Imkeldi is a kinase inhibitor indicated for the treatment of: • Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. • Patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in blast crisis (BC), accelerated phase (AP), or in chronic phase (CP) after failure of interferon-alpha therapy. • Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL). • Pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy. • Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements. • Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown.

(b) (4)

	• Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or fluorescence in situ hybridization [FISH] demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown. • Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP). • Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). • Adjuvant treatment of adult patients following resection of Kit (CD117) positive GIST.		
Drug Product Description	The proposed drug product is provided as a clear yellow to brownish yellow colored solution, with a strawberry flavor. It contains 80 mg/mL of imatinib (equivalent to 95.57 mg/ mL of imatinib mesylate). The drug product is stored in (b) (4) -mL Polyethylene Terephthalate (PET) amber bottle capped (b) (4) tamper evident child-resistant cap (b) (4) (b) (4) foam liner.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F), USP controlled room temprature conditions.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Siva Mandadapu	Haripada Sarker
	Drug Product/ Labeling	Damien Duveau	Olen Stephens
	Manufacturing	Steve Hertz/	James Norman
	Biopharmaceutics	NA	NA

	Micro	Andrew Brown	Denise Miller
	RBPM	Dahlia Walters	
	ATL	Shalini Anand	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: An expiration dating period of **36 months** is granted for the drug product when stored at USP controlled room temprature storage conditions i.e., 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F).

b. Additional Comments for Action: n/a

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4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends ***APPROVAL*** of NDA 219097 for the commercialization of IMKELDI (imatinib) oral solution. Based on our evaluation of the available information, the Applicant provided sufficient information to support an approval recommendation from the drug product quality perspective. The Applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and quality of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

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

Recommendation by Subdiscipline:

Drug Substance - Adequate

(b) (4)

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

Additional Lifecycle Comments: N/A

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CHAPTER IV: LABELING

NDA Number	219097
Assessment Cycle Number	01
Drug Product Name	IMKELDI (Imatinib (b) (4) Oral Solution

Assessment Recommendation: Choose an item.Adequate

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Inadequate	
Patient Information	Inadequate	
Instruction for Use (IFU)	Inadequate	
Container Labels	Adequate	**01**
Carton Labeling	Adequate	**01**

Brief Description of Outstanding Issues: The edits proposed herein are being negotiated through the clinical RBPM. With these changes, the label can be considered adequate for application approval.

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
eCTD # 0001, SDN # 01	01/31/2024	Draft carton and container labels, draft labeling text, listed rug labeling.

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF 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)

Oral solution (80 mg/mL): (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)]		

[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)

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)
Established name(s)[3]	Adequate	IMKELDI (imatinib (b) (4) oral solution, for oral use. According to the guidance (b) (4) (b) (4)
Route(s) of administration	Adequate	Oral
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	Initial U.S. approval: 2001.
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s)[4] and strength(s) in metric system[5]	Adequate	Oral solution (80 mg/mL): (b) (4)

[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]	Adequate	The active ingredient is imatinib (b) (4) (D) (4)
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*

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

(*copy of proposed text*)

[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>
[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		
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).	Inadequate	Sections 2.1 (Drug Administration), 5.15 (Warmings and Precautions), and 17 (Patient Counseling Information): "It is important that Imkeldi be measured with an accurate measuring device. A household teaspoon is not an accurate measuring device. A pharmacist can provide an appropriate device and can provide instructions for measuring the correct dose." The Applicant recommends using a bottle adaptor and a syringe. This should be reflected in the labeling.
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	Adequate	Section 2.3 (Pediatric patients with Ph+ CML CP): imkeldi treatment can be given as a once daily dose or the daily dose may be split into two–one portion dosed in the morning and one portion in the evening.
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	There is no USP monograph for imatinib or imatinib (b) (4)
For radioactive products, include	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)
radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug		
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures."* with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Assessment: *Inadequate*

The Applicant recommends using a bottle adaptor and a syringe to withdraw the drug product. This should be specified in section 2.1 Drug Administration and in section 17 Patient Counseling Information. Any open bottle should be discarded after 30 days.

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

(*copy of proposed text*)

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	Oral solution
Strength(s) in metric system	Adequate	80 mg/mL; (b) (4)
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.	Inadequate	The active ingredient is imatinib (b) (4) The strength listed in section 3 is based on the free amine, as specified in Section 11 (Description). There is no equivalency statement. Section 3 does not clearly state that the strength is based on the active moiety.

[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)
		The following equivalency statement can be included: "Each mL of Imkeldi contains 80 mg imatinib, equivalent to 95.57 mg imatinib mesylate."
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	Clear yellow to brownish yellow colored solution with a strawberry flavor.
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	

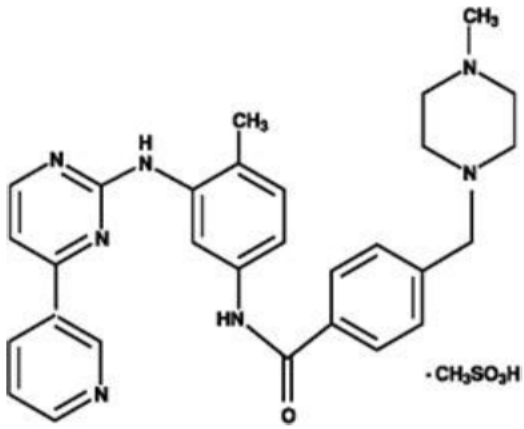
Assessment: *Inadequate*

The Applicant should clearly specify that the strength is based on the (b) (4)

1.2.3 Section 11 (DESCRIPTION)[14]

Imatinib is a (b) (4) *kinase inhibitor. Imkeldi oral solution contains imatinib mesylate equivalent to 80 mg/mL of imatinib* (b) (4) *Imatinib mesylate is designated chemically as 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2- pyrimidinyl]amino]-phenyl]benzamide methanesulfonate and its structural formula is:*

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



Imatinib oral solution is a clear, yellow to brownish yellow coloured solution. Its molecular formula is $C_{29}H_{31}N_7O \bullet CH_4SO_3$ and its molecular weight is 589.7 g/mol. Imatinib mesylate is soluble in aqueous buffers less than or equal to pH 5.5 but is very slightly soluble to insoluble in neutral/alkaline aqueous buffers. In non-aqueous solvents, the drug substance is freely soluble to very slightly soluble in dimethyl sulfoxide, methanol, and ethanol, but is insoluble in n-octanol, acetone, and acetonitrile.

Inactive Ingredients: Liquid maltitol, Glycerine, Sodium benzoate, Acesulfame potassium, Citric acid monohydrate, Strawberry flavour (Lactic Acid, Artificial Flavors, Triacetin), Purified water.

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	Imkeldi oral solution contains imatinib mesylate equivalent to 80 mg/mL of imatinib (b) (4) Imatinib mesylate is designated chemically as 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide

[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)
		methanesulfonate.
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	Oral solution.
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)].	Inadequate	The active ingredient is imatinib mesylate. The strength is based on the free amine. However, there is no equivalency provided for the mesylate salt. The following equivalency statement should be included: "Each mL of Imkeldi contains 80 mg imatinib, equivalent to 95.57 mg imatinib mesylate."
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: Liquid maltitol, Glycerin, Sodium benzoate, Acesulfame potassium, Citric acid monohydrate, Strawberry flavor (Lactic Acid, Artificial Flavors, Triacetin), Purified water. The inactive ingredients should be listed in alphabetical order.
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)	N/A	

[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)
[§ 201.57(c)(12)(i)(D)].		
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Adequate	Imatinib is a (b) (4) kinase inhibitor.
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	Imatinib mesylate is designated chemically as 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2- pyrimidinyl]amino]-phenyl]benzamide methanesulfonate. Its molecular formula is $C_{29}H_{31}N_7O \cdot CH_4SO_3$ and its molecular weight is 589.7 g/mol. The chemical name, formula, and molecular weight are identical to that listed for the reference drug product Gleevec.
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	Imatinib mesylate is soluble in aqueous buffers less than or equal to pH 5.5 but is very slightly soluble to insoluble in neutral/alkaline aqueous buffers. In non-aqueous solvents, the drug substance is freely soluble to very slightly soluble in dimethyl sulfoxide, methanol, and ethanol, but is insoluble in n-octanol, acetone, and acetonitrile. Identical information to that of Gleevec.
For oral prescription drug products, include gluten statement[19] (if applicable).	N/A	No gluten listed as inactive ingredients.

[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)
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*

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

Imkeldi 80 mg/ml Oral Solution is [redacted] (b) (4) ml Amber PET bottle with a child resistant tamper-evident closure.

NDC 81927-201-01

Storage and Handling

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].

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	Imkeldi 80 mg/ml Oral Solution
Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active	Adequate	

[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)
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.		
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	(b) (4) mL bottle
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	Amber PET bottle NDC 81927-201-01
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." with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]	Inadequate	According to Section P8 Stability, any open bottle should be discarded after 30 days.

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	
Include information about child-resistant packaging[22] (if chosen by manufacturer).	Adequate	Imkeldi 80 mg/ml Oral Solution is [redacted] (b) (4) ml Amber PET bottle with a child resistant tamper-evident closure.

Assessment: *Inadequate*

A bottle should be used by 30 days after initial opening.

1.2.5 Other Sections of Labeling

NA

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

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: Shorla Oncology Inc. Cambridge, MA 02142, USA.

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	Assessor's Comments about Labeling
Established name[24]	Adequate	Imkeldi (imatinib (b) (4) oral solution. For Oral Use Only.
Special preparation instructions (if applicable).	Inadequate	"Advise patients and caregivers to measure Imkeldi with an accurate milliliter measuring device. A household teaspoon is not an accurate measuring device. Advise patients and caregivers to ask their pharmacist to recommend an appropriate measuring device and for instructions for measuring the correct dose." Specify that the pharmacist should provide a bottle adapter and a syringe.
Storage and handling information (if applicable).	Adequate	
If the product contains a desiccant, ensure the desiccant	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	Assessor's Comments about Labeling
has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differ from the dosage form.		
Active ingredient(s) (if applicable).	Choose an item.	N/A
Alphabetical listing of inactive ingredients (if applicable).	Inadequate	Inactive ingredients are listed, but not in alphabetical order.
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	Manufactured for: Shorla Oncology Inc. Cambridge, MA 02142, USA

Assessment: *Inadequate*

Specify that the pharmacist should provide a bottle adapter and a syringe.

3.0 CONTAINER AND CARTON LABELING[25]

3.1 Container Labels[26]

(Copy/paste or refer to a representative example of a proposed container label)

[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.

(b) (4)

(b) (4)

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)

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	Imkeldi (imatinib (b) (4)) oral solution.
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[28]	Adequate	Yes	(b) (4)
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	For oral use only
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>].	Adequate	Yes	Each 1 mL contains 80 mg of imatinib (equivalent to 95.57 mg of imatinib mesylate) and 0.2 mg of sodium benzoate as preservative.
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[29]	Adequate	Yes	(b) (4) mL
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Choose an item.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-	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)

[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)
date (BUD).			
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)].	Adequate	Choose an item.	Only sodium benzoate is listed. Include the following statement: "Discard after 30 days of use."
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	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)
Prescribing Information" [§ 201.5 & 201.55].			
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	Manufactured for: Shorla Oncology Inc. Cambridge, MA 02142, USA.
"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>).	Adequate	Yes	
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	N/A	Choose an	

[31] USP General Notices 3.20 Indicating Conformance

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)
available.		item.	

Assessment of Carton Labels and Container Labeling: *Adequate*

According to Section P8 Stability, any open bottle should be discarded after 30 days. Therefore, the following statement should be added: *Discard after 30 days of use*.

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

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

The following issues are being negotiated with the Applicant through formal labeling negotiations:
Full prescribing information
Section 2: The Applicant recommends that the dispensing pharmacist should provide an appropriate dosing device and measuring instructions, such as a bottle adaptor and a syringe. The drug product is not co-packaged with an oral dosing device. The DMEPA review team was contacted to address this issue. In their review, DMEPA recommends requesting from the Applicant to draft an Instructions for Use (IFU).

Section 3:
- Clear yellow to brownish yellow colored solution *with a strawberry flavor*
- The Applicant should clearly specify that the strength is (b) (4) (b) (4)

Section 11: The active ingredient is imatinib mesylate. The strength is based on the free amine. However, there is no equivalency provided for the mesylate salt. The following equivalency statement should be included: "*Each mL of Imkeldi contains 80 mg imatinib, equivalent to 95.57 mg imatinib mesylate*."

Section 16: *A bottle should be used within 30 days after initial opening.*

Patient labeling
Specify that the pharmacist should provide a bottle adapter and a syringe.

Primary Labeling Assessor Name and Date:

Damien Y. Duveau, PhD 9/16/2024

Secondary Assessor Name and Date:

Olen M. Stephens, PhD 9/16/2024

Damien Duveau

Digitally signed by Damien Duveau
Date: 9/16/2024 09:15:41AM
GUID: 6372a17d00926df73f89d048079181fa

Olen Stephens

Digitally signed by Olen Stephens
Date: 9/16/2024 09:16:20AM
GUID: 508da71e00029e680c3cf42984dfa0ee

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VII: MICROBIOLOGY

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

Product Information	Clear yellow to brownish yellow colored solution filled in an amber color PET bottle
NDA Number	219097
Assessment Cycle Number	1
Drug Product Name/ Strength	IMKELDI (Imatinib (b) (4) / 80 mg/mL
Route of Administration	Oral
Applicant Name	Shorla Pharma Ltd
Therapeutic Classification/ OND Division	Division of Hematologic Malignancies
Manufacturing Site	(b) (4)
Method of Sterilization	Drug product is nonsterile.

Assessment Recommendation: **Adequate**

Assessment Summary: This is a multi-dose non-sterile oral drug product. The manufacturing process (b) (4) (b) (4) Supporting data meet the quality microbiology review criteria.

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
eCTD 0001	01/31/2024
eCTD 0004	06/26/2024

Highlight Key Issues from Last Cycle and Their Resolution: None.

Remarks: An Information Request (IR) was issued to the applicant by the Agency on June 12th, 2024. The applicant's responses received June 26th, 2024, are included and addressed in the appropriate sections of this review.

Concise Description of Outstanding Issues: N/A

Supporting Documents: None.

S DRUG SUBSTANCE

The drug substance is not procured sterile. The API is compounded with excipients and is [redacted] at the proposed drug product manufacturing facility. Therefore, a microbiology review will not be conducted for drug substance.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product**
  A clear yellow to brownish yellow colored solution filled in an amber color PET (polyethylene terephthalate) [redacted] ml bottle.
- **Drug product composition**

Ingredient	Function	Quantity (mg/ml)
Imatinib mesylate (eq. to Imatinib)*	Active Ingredient	95.57 (=80.00)
Liquid maltitol	[redacted]	
Glycerin		
Sodium benzoate		
Acesulfame potassium		
Citric acid monohydrate		
Strawberry flavor		
Purified water	Vehicle	QS to 1 mL
* Final quantity to be dispensed after potency correction.		

- **Description of container closure system**

Component	Description	Manufacturer
[redacted] mL bottle	PET Amber Bottle [redacted]	[redacted]
Closure (Caps)	28mm [redacted] cap with [redacted] liner	[redacted]

Assessment: *Adequate*
The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain microbiological quality.

P.2 PHARMACEUTICAL DEVELOPMENT

[redacted]

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/s/

SHALINI ANAND
10/28/2024 07:29:42 PM