CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

220358Orig1s000

PRODUCT QUALITY REVIEW(S)

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Title:	NDA IQA Template Title Page- EXEC SUMMARY
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Office of Pharmaceutical Quality

New Drug Application (NDA)
Integrated Quality Assessment Template

NDA Executive Summary

1. Application/Product Information

NDA Number	220358		
Applicant Name	Vanda Pharmaceuticals Inc.		
Drug Product Name	milsaperidone		
Dosage Form	Tablet		
Proposed Strength(s)	1, 2, 4, 6, 8, 10, 12 mg		
NDA Classification	Type 1 - NME		
Route of Administration	Oral		
Maximum Daily Dose	24 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of schizophrenia in adults		
Drug Product Description	Film coated tablets		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	(b) (4)		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Zhixing Shan	Sam (Sukhamaya) Bain
	Drug Product/ Labeling	Eric Bow	Valerie Amspacher/ Julia Pinto
	Manufacturing	Jinal Dadhania	Jingbo Xiao
	Biopharmaceutics	Jia Leo	Ta-Chen Wu

	Microbiology	N/A	N/A
	Other (specify)	N/A	N/A
	RBPM	Stephanie Ngan	
	ATL	Valerie Amspacher	
Consults			

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

Strength	50 cc HDPE bottle	23 cc HDPE bottle	Blister pack
1 mg	36 months	3 months	24 months
2 mg	24 months	Not applicable	24 months
4 mg	24 months	Not applicable	24 months
6 mg	24 months	24 months	24 months
8 mg	24 months	24 months	24 months
10 mg	24 months	Not applicable	Not applicable
12 mg	24 months	Not applicable	Not applicable

b. Additional Comments for Action

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The CMC recommendation is approval for this application. This is based on reviews by drug substance, drug product, process facilities and biopharmaceutics.

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:

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 1 (eCTD 0001)	21 Feb 2025	All, original submission
Supporting document 5 (eCTD 0005)	13 May 2025	Drug product
Supporting document 9 (eCTD 0009)	31 Jul 2025	Drug substance
Supporting document 10 (eCTD 0010)	15 Aug 2025	Process, Biopharmaceutics
Supporting document 12 (eCTD 0012)	27 Aug 2025	Drug product
Supporting document 13 (eCTD 0013)	12 Sep 2025	Process
Supporting document 15 (eCTD 0015)	17 Sep 2025	Drug product
Supporting document 16 (eCTD 0016)	19 Sep 2025	Drug product
Supporting document 17 (eCTD 0017)	26 Sep 2025	Drug product
Supporting document 18 (eCTD 0018)	2 Oct 2025	Biopharmaceutics
Supporting document 19 (eCTD 0019)	21 Oct 2025	Drug product
Supporting document 20 (eCTD 0020)	3 Nov 2025	Biopharmaceutics
Supporting document 23 (eCTD 0023)	4 Dec 2025	Drug product
Supporting document 24 (eCTD 0024)	5 Dec 2025	Biopharmaceutics
Supporting document 25 (eCTD 0025)	16 Dec 25	Process
Supporting document 27 (eCTD 0027)	8 Jan 2026	Drug product

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Important: Do Not Change the Header or Footer

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	220358
Assessment Cycle Number	1
Drug Product Name	BYSANTI (milsaperidone)

Assessment Recommendation: Choose an item.

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	**7**
Patient Information	N/A	**n/a**
Instruction for Use (IFU)	N/A	**n/a**
Container Labels	Adequate	**7**
Carton Labeling	Adequate	**7**

Brief Description of Outstanding Issues:

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
0001, SD# 1	2/21/2025	Package Insert, container labels
0007, SD# 7	6/18/2025	Package Insert, container Labels

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

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

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

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	**BYSANTI® (milsaperidone) tablets, for oral use**
Route(s) of administration	Adequate	**oral use**
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	n/a – will be updated to 2026 if approved
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s)[4] and strength(s) in metric system[5]	Adequate	1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg tablets.
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]

(b) (4)

[redacted]

[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)

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

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	
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*	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)
applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."		

Assessment: *Adequate*

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

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Tablet
Strength(s) in metric system	Adequate	1, 2, 4, 6, 8, 10, 12 mg
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on	N/A	

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
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.		
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	Multiple – see above
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*

1.2.3 Section 11 (DESCRIPTION)[14]

(b) (4)

[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	BYSANTI, milsaperidone
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	BYSANTI tablets are intended for oral administration only
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	Adequate	Inactive ingredients are: colloidal silicon dioxide, crospovidone, hydroxypropylmethylcellulose, lactose

[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,

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)
brand names. [§ 201.57(c)(12)(i)(C)].		monohydrate, magnesium stearate, microcrystalline cellulose, and water (removed during processing).
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	an atypical antipsychotic belonging to the chemical class of piperidinyl-benzisoxazole derivatives
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	benzenemethanol, 4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxy-α- methyl-, (αS)- molecular formula is $C_{24}H_{29}FN_2O_4$ and its molecular weight is 428.50.
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	

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)
For oral prescription drug products, include gluten statement[19] (if applicable).	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

Assessment: *Adequate*

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

(b) (4)

[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	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	1, 2, 4, 6, 8, 10, 12 mg
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	See above table. *Note:14 count bottles are only for physician samples. The 14 count bottles are available for the 1, 6, and 8 mg strengths.*
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	See table above:

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)
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	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Inadequate	Store BYSANTI tablets at controlled room temperature, (b) (4) excursions permitted to 15° to 30 °C (59° to 86°F) *[See USP Controlled Room Temperature]*. Protect BYSANTI tablets from exposure to light and moisture. Comment in the OND labeling document sent to the applicant to align with USP room temperature 20–25°C (68–77°F), with excursions between 15–30°C (59–86°F)
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber	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)
latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*[21]		
Include information about child-resistant packaging[22] (if chosen by manufacturer).	N/A	

Assessment: *Adequate*

Adequate pending minor revision to state the storage condition as a range from 20–25°C (68–77°F).

Information Request:

1.Modify the storage conditions to align with USP controlled room temperature, 20°C to 25°C (68–77°F), with excursions permitted between 15–30°C (59–86°F)

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] 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	Distributed by: Vanda Pharmaceuticals Inc. Washington, D.C. 20037 USA

Assessment: *Adequate*

2.0 PATIENT LABELING – n/a

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]	n/a	
Special preparation instructions (if applicable).	n/a	
Storage and handling information (if applicable).	n/a	
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).	n/a	
Alphabetical listing of inactive ingredients (if applicable).	n/a	
Name and location of business (street address, city, state, and	n/a	

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

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
zip code) of manufacturer, distributor, and/or packer.		

Assessment: Choose an item. *n/a – Patient labeling* (*Labeling (e.g., Medication Guides, Instructions for Use, Patient Information) not submitted*

3.0 CONTAINER AND CARTON LABELING[25]

3.1 Container Labels[26]

(b) (4)

[redacted]

[25] Carton and Container Labeling Resources

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

5 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

3.2 Carton Labeling

(Copy/paste or refer to a representative example of a proposed carton labeling)

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name[27], (font size and prominence) [§ 201.10(g)(2)].	Adequate	Choose an item.	Bysanti (milsaperidone)
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[28]	Adequate	Choose an item.	1, 2, 4, 6, 8, 10 , 12 mg
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	N/A	Choose an item.	
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	Choose an item.	60 count for bottles For blisters: • Titration pack A: two each of 1, 2, 4, and 6 mg tablets (8 total), • Titration pack B: (b) (4) 1 mg tablets, two 2 mg tablets, and two 6 mg tablets (b) (4)

[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)
			• Titration pack C: (b) (4) 1 mg tablets, two 2 mg tablets, two 6 mg tablets, (b) (4)
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Choose an item.	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Choose an item.	
Lot number and expiration date [§ 201.18 & 201.17].	Inadequate	Choose an item.	IR sent by DMEPA
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Inadequate	Choose an item.	Store at (b) (4) IR below to align with USP controlled room temp 20-25°C…
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	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)
ingredients. For ingredients added to adjust the pH or make isotonic, include the name and 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	Choose an item.	
Linear Bar code [§ 201.25(c)(2)].[30]	Adequate	Choose an item.	
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Inadequate	Choose an item.	(b) (4) IR sent by DMEPA
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Choose an item.	Distributed by Vanda Pharmaceuticals Inc, Washington, DC 20037
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Adequate	Choose an item.	Keep out of reach of children
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	Choose an item.	
If there is a USP monograph for the drug product and it contains a labeling	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)
requirement, ensure the labeling requirement is fulfilled.			
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*

Adequate pending minor revisions

1. *Information Requests addressing issues with the container/carton labels were sent in conjunction with DMEPA.*

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

Primary Labeling Assessor Name and Date: Eric Bow Ph.D. 10/1/2025

Secondary Assessor Name and Date (and Secondary Summary, as needed): Valerie Amspacher Pharm.D.. 10/1/2025

[31] USP General Notices 3.20 Indicating Conformance

Eric Bow

Digitally signed by Eric Bow
Date: 1/06/2026 01:21:52PM
GUID: 5df160d800320e19970e198e30e1cc2e

Valerie Amspacher

Digitally signed by Valerie Amspacher
Date: 1/08/2026 03:48:13PM
GUID: 5714dbd10078d2d3d9b60a0ceb819fc3

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CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

NDA Number	NDA-220358-ORIG-1
Assessment Cycle Number	01
Drug Product Name/ Strength	Milsaperidone Tablet/ 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg
Route of Administration	Oral
Applicant Name	Vanda Pharmaceuticals Inc.
Therapeutic Classification/ OND Division	Neurologic Disorders /Division of Psychiatry (DP)
RLD/RS Number	N/A
Proposed Indication	• Treatment of schizophrenia in adults • Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults
Primary Reviewer	Jia Leo, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.

Assessment Recommendation: **Adequate**

Assessment Summary:

The Applicant is seeking approval of milsaperidone immediate-release (IR) tablets, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg via 505(b)(1) pathway. Milsaperidone is a major metabolite of iloperidone, the active pharmaceutical ingredient (API) of Fanapt® tablets (under NDA 022192, available in the same dosage strengths), owned by the Applicant. The composition of milsaperidone core tablets is essentially identical to that of commercially available Fanapt® (iloperidone) tablets, except for the substitution of milsaperidone in place of iloperidone. (b) (4) The Applicant conducted three pivotal clinical studies (single-dose study, multiple-dose study, and food effect study) comparing milsaperidone tablets and iloperidone tablets.

Biopharmaceutics review is focused on the proposed dissolution method, acceptance criterion, and the formulation bridging in support of the application. The key Biopharmaceutics findings are summarized below:

1. Dissolution Method and Acceptance Criterion:

The drug substance, milsaperidone, is highly soluble, per BCS criteria. The Applicant initially proposed an in-house dissolution method (b) (4) The data provided to support the selection of

dissolution parameters and discriminating ability were deemed inadequate and the deficiencies were conveyed to the Applicant in the information request (IR) dated 7/29/2025. In response, the Applicant decided to adopt the standard paddle method (i.e., USP Apparatus 2 (Paddle), 0.1N HCl, 500 mL, 50 rpm, at 37°C) (b) (4) The newly proposed method is deemed acceptable.

The provided dissolution profile data (n = 12) generated using the revised method/test condition show that dissolution of the seven pivotal clinical batches (one for each strength) in 0.1N HCl is very rapid (> 85% in 15 min). The dissolution profile data of all stability batches also confirmed very rapid dissolution (> 85% in 15 min) of the proposed drug product. The provided dissolution profile data support the proposed dissolution acceptance criterion, Q = (b) (4)% in 30 min, (b) (4)

2. Formulation bridging:

The Applicant used uncoated 1 mg milsaperidone tablet in the pivotal single dose pharmacokinetics (PK) study and the pivotal food effect study. For the pivotal multiple dose PK study, the Applicant used all strengths of the film coated milsaperidone tablet, the to-be-marketed product. The Applicant provided the requested composition data, which showed that the composition of the uncoated 1 mg milsaperidone tablet used in pivotal clinical studies is identical to that of the film-coated 1 mg milsaperidone tablet, except for the absence of film-coating. The Applicant provided comparative dissolution profiles of uncoated and the film-coated 1 mg milsaperidone tablet. Based on the dissolution profile data (n = 6), the dissolution of the uncoated and the film-coated 1 mg milsaperidone tablet is very rapid (> 85% in 15 min) and therefore is considered similar. The provided data supporting the bridging of the pivotal clinical batches and the to-be-marketed batches are adequate.

Recommendation:

From a Biopharmaceutics perspective, NDA 220358 for Milsaperidone IR tablets, 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg is Adequate and recommended for Approval.

FDA-approved dissolution method and acceptance criterion:

USP Apparatus	Speed (RPMs)	Medium /Temperature	Volume (mL)	Acceptance Criterion
II (Paddle)	50	0.1N HCl/ 37°C ± 0.5°C	500	Q = (b) (4)% in 30 min

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Sequence 0001 /Original submission	2/21/2025

Sequence 0010 / Response to Biopharmaceutics Information Request	8/15/2025
Sequence 0018 / Response to Biopharmaceutics Information Request	10/2/2025
Sequence 0020 / Response to Biopharmaceutics Information Request	11/3/2025

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

B.1 BCS DESIGNATION

Assessment:
Based on the provided aqueous solubility data, the drug substance is highly soluble per BCS criteria. However, the submitted permeability study report did not support the high permeability claim.

Solubility:
Based on the provided aqueous solubility data (**Tables 1 and 2**) and the highest single dose of 12 mg, the drug substance, milsaperidone, is soluble in less than 250 mL media across physiological pH range 1.2 – 6.8. The provided data indicate that the drug substance, milsaperidone, is highly soluble, though pH-dependent, per BCS criteria.

Table 1. Aqueous solubility of milsaperidone across pH 1.2 to 8 at 48 hours

Solvent	Solubility at RT after 48 hours (mg/mL)	Solubility at 37 °C after 48 hours (mg/mL)
Water	0.003	0.001
0.1 N HCl	11.85	18.28
0.1 N H_2SO_4	38.77	39.15
0.05 M Phosphate buffer, pH 3	2.84	2.82
0.05 M Phosphate buffer, pH 5	0.89	0.81
0.05 M Phosphate buffer, pH 6	0.38	0.31
0.05 M Phosphate buffer, pH 7	0.03	0.03
0.05 M Phosphate buffer, pH 7.4	0.01	0.01
0.05 M Phosphate buffer, pH 8	0.003	0.003
0.1 N Acetic acid	19.78	17.96

Table 2. Aqueous solubility of milsaperidone across pH 1.2 to 6.8 at 24 hours

Solvent	Initial Solubility at 37 °C (mg/mL)	Solubility at 37 °C after 24 hours (mg/mL)
0.1 N HCl, pH ~1	10.12	10.87
0.05 M Phosphate buffer, pH 4.5	0.97	1.06
0.05 M Phosphate buffer, pH 6.8	0.06	0.06
Simulated Gastric Fluid (SGF), pH ~1	3.85	2.59
Simulated Intestinal Fluid (SIF), pH ~6.8	0.05	0.05

Permeability:
The Applicant submitted a permeability study report using Caco-2 cell monolayer.[1] Based on the results, the Applicant claims that the drug substance is highly permeable. Study and results are assessed by the Office of Clinical Pharmacology.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: Adequate

Table 3. Originally proposed dissolution method

Apparatus	USP Apparatus 2 (paddles)
Speed	50 rpm
Temperature	37 ± 0.5 °C
Medium	(b) (4)
Volume	500 mL
Sampling time points	5, 10, 15, 20, 30, 45, 60 min, and infinity (b) (4)
Sample volume	5 mL

Table 4. Revised dissolution method and acceptance criterion in response to information request dated 7/29/2025

Method Source	USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Acceptance Criterion
(b) (4)	II (Paddle)	50	0.1N HCl/ 37°C ± 0.5°C	500	Q = (b) (4) % in 30 min

[1] \\CDSESUB1\EVSPROD\nda220358\0001\m3\32-body-data\32s-drug-sub\milsaperidone-formosa\32s1-gen-info\r01-1488-ilo-p88-caco-2-footer.pdf

1. Dissolution Method: Adequate

Below dissolution method development information and data are for the originally proposed dissolution condition (**Table 3**) as opposed to the revised method proposed later in the review cycle (**Table 4**).

(b) (4)

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Discriminating ability:
The Applicant evaluated discriminating ability of the dissolution method against drug substance particle size (**Table 6**) and manufacturing process parameters (**Table 7**) using 12 mg milsaperidone tablets.

Table 6. Evaluated drug substance particle sizes

12 mg Tablet Batch	Mfg. Date	Milsaperidone Lot	D_{50} (µm)	D_{90} (µm)
SYFD240056-03	Aug 13, 2024	FA023FTR-23002	(b) (4)	
SYFD240056-05	Aug 13, 2024	FA023TRPB-23005		
SYFD240056-04	Aug 13, 2024	FA023TRPB-23006		

Table 7. Evaluated manufacturing process parameters

(b) (4)

The discriminating ability against drug substance particle size was evaluated in 500 mL 0.1N HCl, 500 mL pH (b) (4) buffer, and 500 mL pH (b) (4) buffer. The results (**Figure 3 – 5**) showed that 0.1N HCl provides no discriminating ability against drug substance particle size. Although both pH (b) (4) buffer and pH (b) (4) buffer offered discriminating ability against drug substance particle size, the dissolution of the target batch (D_{50} (b) (4) µm) showed incomplete dissolution in pH (b) (4) buffer.

Figure 3. Dissolution profiles of 12 mg milsaperidone tablets with different drug substance particle sizes (target particle size D_{50} (b) (4)µm) in 500 mL 0.1N HCl (n = 3)

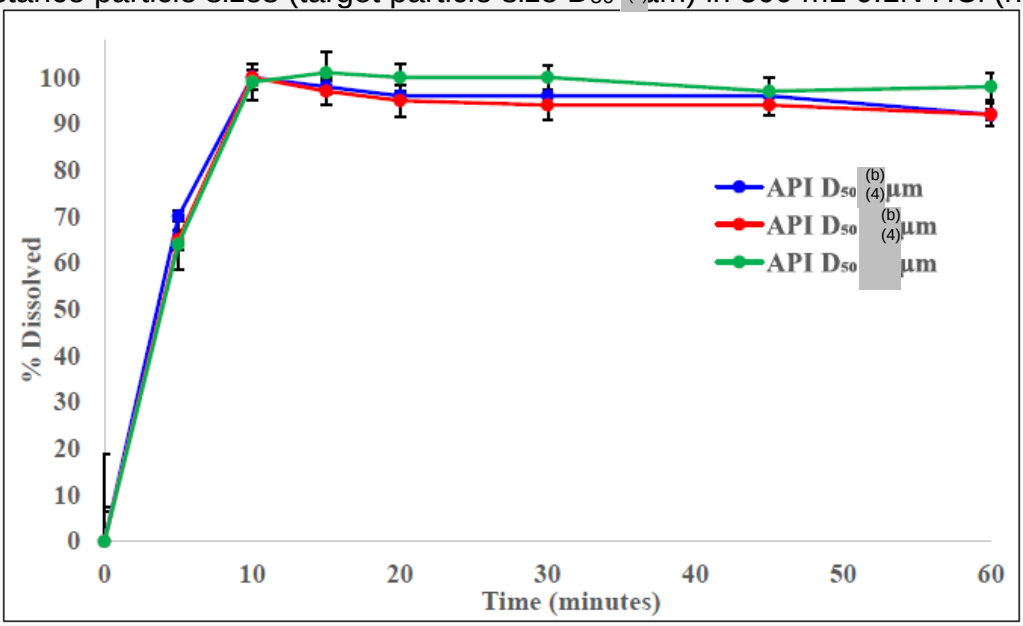


Figure 4. Dissolution profiles of 12 mg milsaperidone tablets with different drug substance particle sizes (target particle size D_{50} (b) (4)µm) in 500 mL pH (b) (4) buffer (n = 3)

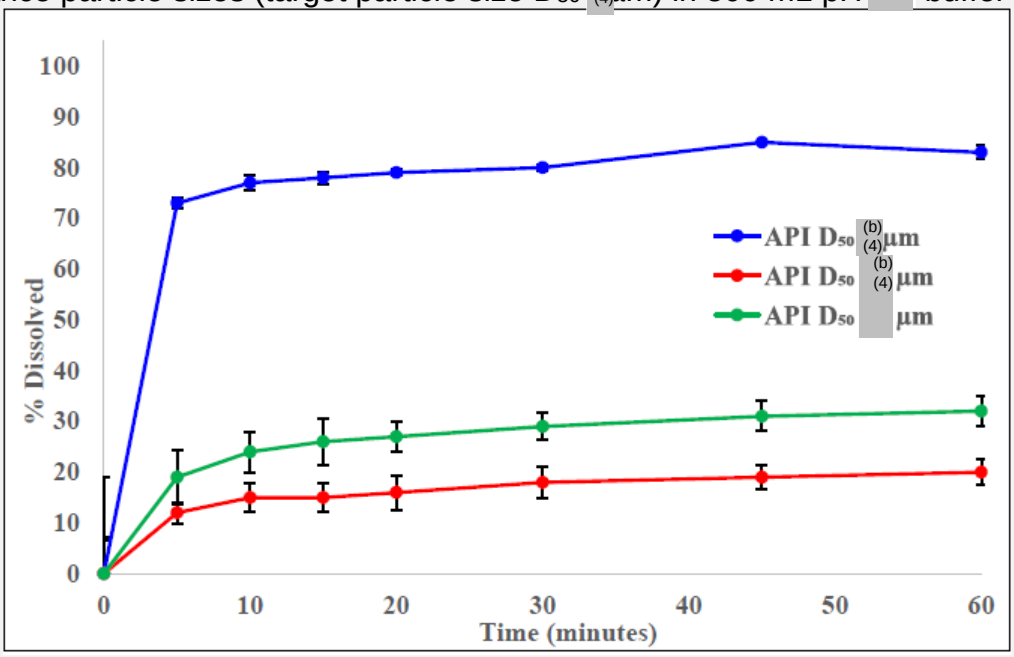
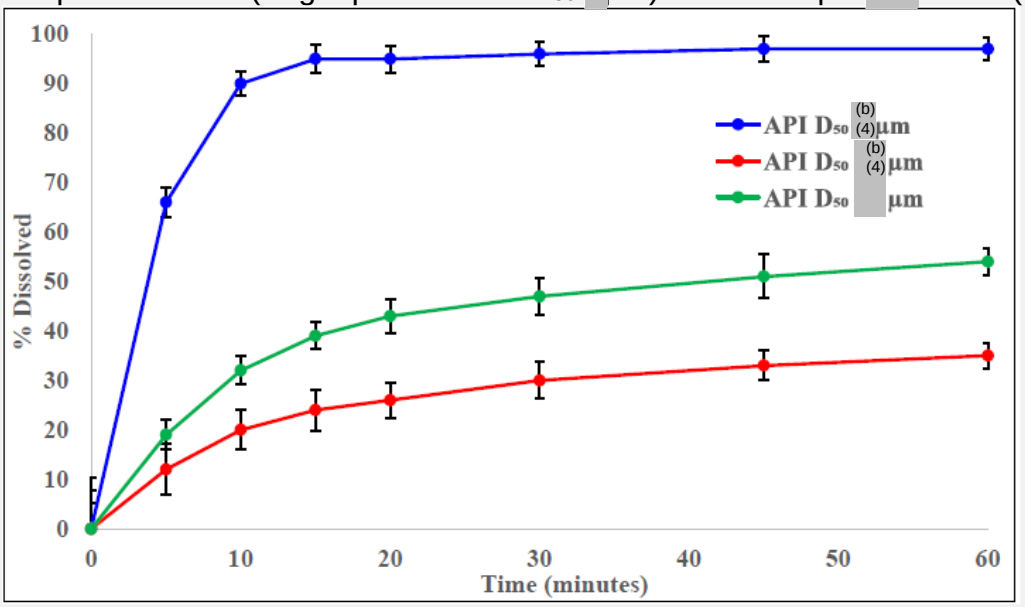


Figure 5. Dissolution profiles of 12 mg milsaperidone tablets with different drug substance particle sizes (target particle size D_{50} (b) (4) µm) in 500 mL pH (b) (4) buffer (n = 12)



The discriminating ability against manufacturing process parameters was evaluated in variant batches with upper range variation in 500 mL pH (b) (4) buffer and along with the twodrug substance particle size variant batches. The results (**Figure 6**) showed no discriminating ability against the tested manufacturing process parameters, which is also indicated by dissolution similarity factor f2 values > 50 (**Table 8**).

Figure 6. Dissolution profiles of 12 mg milsaperidone tablets with upper range variation of manufacturing process parameters (n = 12)

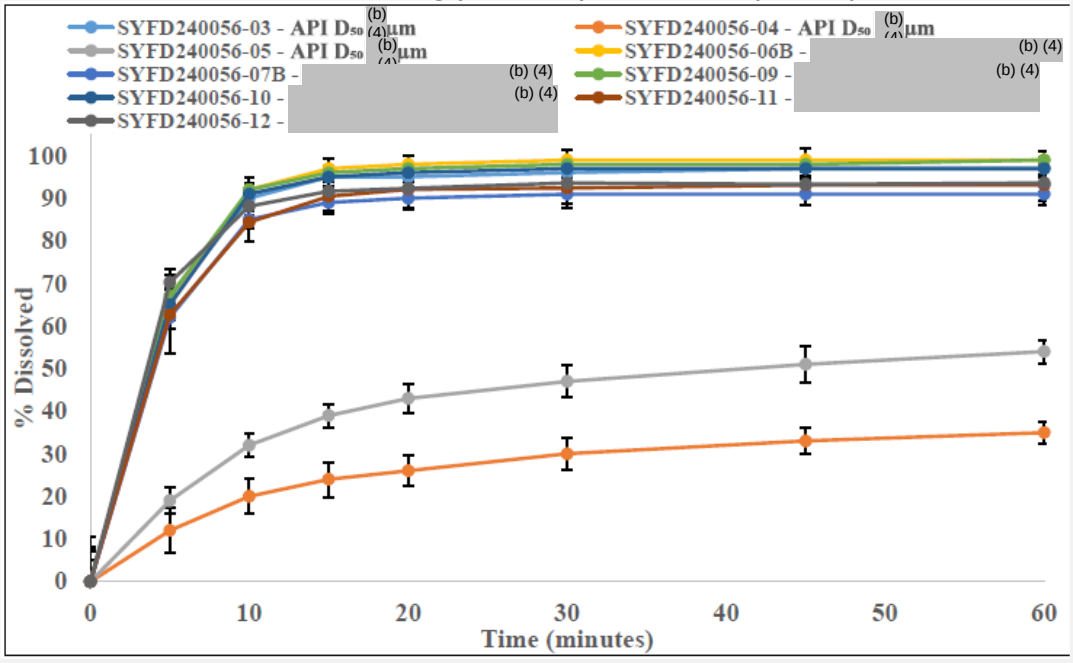


Table 8. Dissolution similarity factor f2 values for 12 mg milsaperidone variant batches with upper range variation of manufacturing process parameters

Process Parameter	Variation Studied	Batch number	f_2
(b) (4)		SYFD240056-07B	64
		SYFD240056-09	88
		SYFD240056-10	94
		SYFD240056-11	65
		SYFD240056-12	74
		SYFD240056-06B	85
(b) (4) drug substance particle size	D_{50} (b) (4) µm	SYFD240056-05	13
(b) (4) drug substance particle size	D_{50} µm	SYFD240056-04	9

Reviewer's Assessment:

The Applicant initially developed an in-house dissolution method. This Reviewer identified the following deficiencies in the dissolution method development report: 1) lack of detailed/individual dissolution data to support the evaluated dissolution parameters (b) (4) 2) no data/justification provided to support the selection of apparatus, 3) lack of information of the target batch and variant batches used in the evaluation of the discriminating ability, 4) no variant batches with variation of target parameter value (b) (4)% was evaluated, and 5) no justification for variant batches with variation much greater than target parameter value (b) (4)% was provided. These deficiencies were conveyed to the Applicant in the Information Request dated 7/29/2025 (**Appendix**).

Based on the provided solubility data, the drug substance, milsaperidone, is highly soluble. As the drug product is an immediate-release dosage form, (b) (4) This alternative option was also provided to the Applicant in the information request dated 7/29/2025 (**Appendix**).

In response, the Applicant decided to adopt the standard paddle method (i.e., USP apparatus 2, 0.1N HCl, 500 mL, 50 rpm, at 37℃) (b) (4) (**Table 4**). According to the Applicant, milsaperidone does not exhibit characteristics of narrow therapeutic index (NTI) drugs where small differences in dose or blood concentration have such significant impact on efficacy or safety related events. Additionally, the Tmax of milsaperidone is not critical for the intended use. This Reviewer agreed with the justification provided by the Applicant and accepted the employment of the standard paddle method/test condition (b) (4) Furthermore, the standard paddle method was used to test all registration stability batches at the 6-month stability timepoint and the method was fully validated.

2. Dissolution Data and Acceptance Criterion: Adequate

Proposed dissolution acceptance criterion: Q = (b) (4)% in 30 min

The proposed dissolution acceptance criterion was not assessed during the first review cycle due to the pending dissolution method. The Applicant was requested to provide detailed/individual dissolution profile data (n = 12) for pivotal clinical batches of the final dissolution method to support the proposed dissolution acceptance criterion in the IR dated 7/19/2025. In addition, the Applicant was requested to provide full dissolution profile data (n = 12) for all stability batches at current stability time point using the final proposed dissolution method (**Appendix**).

In response dated 8/15/2025, the Applicant provided the individual dissolution profile data (n = 6) for one registration batch of each tablet strength used in the pivotal pharmacokinetics (PK) study (VP-VHX-896-1103).[2] As shown, the dissolution of the seven clinical batches of milsaperidone tablets in 0.1N HCl is very rapid (> 85% in 15 min) (**Figure 7, Table 9**). Regarding the dissolution data for the stability batches, the Applicant is currently testing 18-month stability timepoint samples using 0.1 N HCl dissolution medium and expect those results to become available by 9/30/2025. Accordingly, the Applicant stated in response that they plan to submit those results to the FDA by 10/15/2025.

In response to a second IR dated 9/22/2025 (**Appendix**), the Applicant provided the requested data for clinical batches as previously requested. Similar to the dissolution profiles with 6 units, the dissolution of the seven clinical batches with 12 units in 0.1N HCl dissolution medium is very rapid (> 85% in 15 min) (**Figure 8, Table 10**). The provided dissolution data support the proposed dissolution acceptance criterion, Q = (b) (4)% in 30 min, (b) (4) No further investigation for the method's discrimination was provided or necessary, (b) (4)

In the follow up response dated 11/3/2025, the Applicant provided the stability dissolution data at 18-month time-point using 0.1N HCl dissolution medium for all registration batches. The dissolution data for the stability batches (> 85% in 15 min)[3] further confirmed the proposed dissolution acceptance criterion.

[2] \\CDSESUB1\EVSPROD\nda220358\0010\m3\32-body-data\32p-drug-prod\milsaperidone\32p2-pharm-dev\dissol-profile-develop-report.xlsx

[3] \\CDSESUB1\EVSPROD\nda220358\0020\m3\32-body-data\32p-drug-prod\vhx-896-tablet-(b) (4) (b) (4) 32p5-contr-drug-prod\32p54-batch-analys\sup-diss-data-18m.xlsx

Figure 7. Dissolution profiles of 7 clinical pharmacokinetics study batches of milsaperidone tablet in 0.1N HCl medium (n = 6)

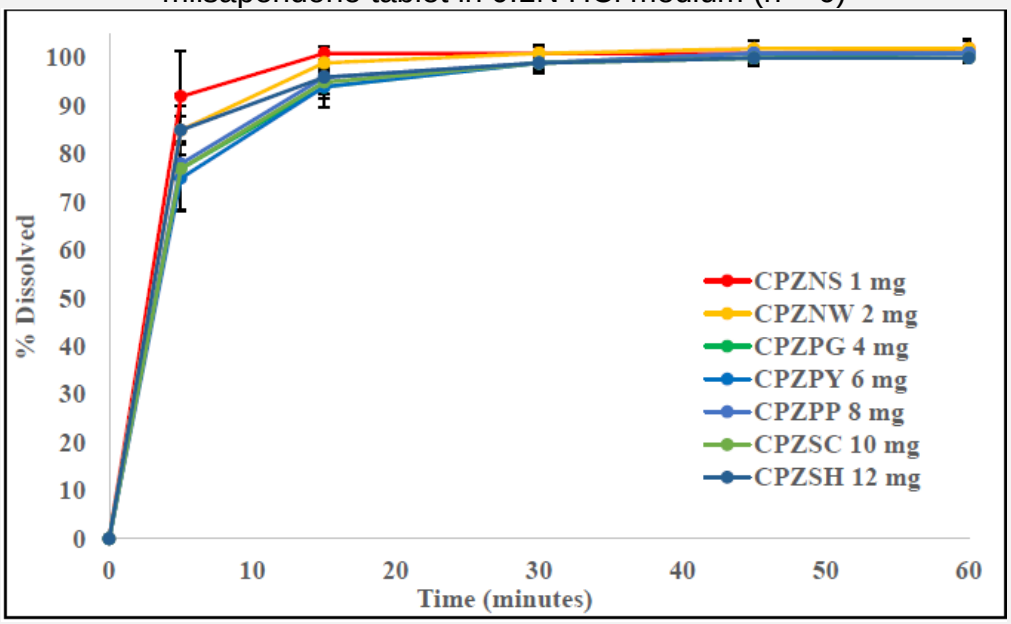


Table 9. Summary of the dissolution profiles of 7 clinical pharmacokinetics study batches of milsaperidone tablet in 0.1N HCl medium (n = 6)

Batch No.	% Dissolved (n = 12)						
	Time (minutes)	5	15	30	45	60	75
CPZNS (1 mg)	Mean (%)	92	101	101	101	102	102
	Range (%)	(b) (4)					
	RSD (%)	9.4	1.4	1.5	1.5	1.9	1.8
CPZNW (2 mg)	Mean (%)	85	99	101	102	102	102
	Range (%)	(b) (4)					
	RSD (%)	7.5	1.8	1.7	1.6	1.6	1.2
CPZPG (4 mg)	Mean (%)	77	94	99	100	101	101
	Range (%)	(b) (4)					
	RSD (%)	8.8	4.1	2.3	1.5	1.4	1.5
CPZPY (6 mg)	Mean (%)	75	94	99	101	101	102
	Range (%)	(b) (4)					
	RSD (%)	6.9	2.4	1.2	1.1	1.3	1.7
CPZPP (8 mg)	Mean (%)	78	96	99	101	101	101
	Range (%)	(b) (4)					
	RSD (%)	9.9	3.6	2.0	1.5	1.3	1.0
CPZSC (10 mg)	Mean (%)	77	95	99	100	100	101
	Range (%)	(b) (4)					
	RSD (%)	8.4	2.6	1.1	0.5	0.4	0.5
CPZSH (12 mg)	Mean (%)	85	96	99	100	100	101
	Range (%)	(b) (4)					
	RSD (%)	5.1	2.0	1.2	0.9	0.9	1.1

Figure 8. Dissolution profiles of 7 clinical pharmacokinetics study batches of milsaperidone tablet in 0.1N HCl medium (n = 12)

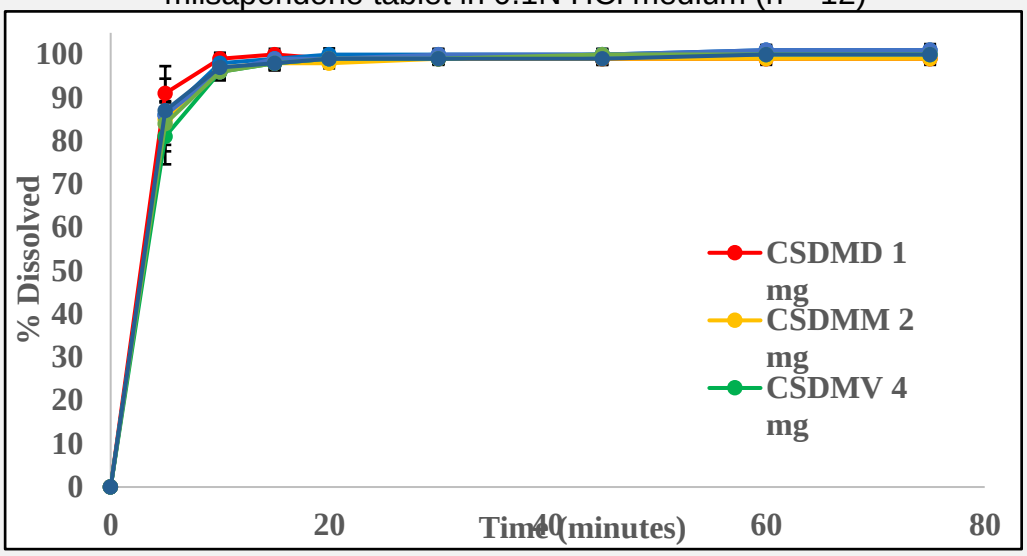


Table 10. Summary of the dissolution profiles of 7 clinical pharmacokinetics study batches of milsaperidone tablet in 0.1N HCl medium (n = 12)

Batch	% Dissolved (n = 12)									
CSDMD (1 mg)	**Time (min)**	**0**	**5**	**10**	**15**	**20**	**30**	**45**	**60**	**75**
	Mean (%)	0	91	99	100	99	99	99	99	99
	Range (%)	0	(b) (4)							
	RSD (%)	0	6.3	1.4	1.3	1.3	1.4	1.4	1.4	1.4
CSDMM (2 mg)	**Time (min)**	**0**	**5**	**10**	**15**	**20**	**30**	**45**	**60**	**75**
	Mean (%)	0	85	97	98	98	99	99	99	99
	Range (%)	0	(b) (4)							
	RSD (%)	0	4.2	2.4	1.7	1.2	1.1	1.4	1.1	1.1
CSDMV (4 mg)	**Time (min)**	**0**	**5**	**10**	**15**	**20**	**30**	**45**	**60**	**75**
	Mean (%)	0	81	96	98	99	99	100	100	100
	Range (%)	0	(b) (4)							
	RSD (%)	0	6.4	1.7	1.0	1.0	1.1	1.3	1.3	1.4
CSFWM (6 mg)	**Time (min)**	**0**	**5**	**10**	**15**	**20**	**30**	**45**	**60**	**75**
	Mean (%)	0	86	98	99	100	100	100	101	101
	Range (%)	0	(b) (4)							
	RSD (%)	0	8.4	2.2	1.2	1.4	1.3	1.2	1.2	1.4
CSFXB (8 mg)	**Time (min)**	**0**	**5**	**10**	**15**	**20**	**30**	**45**	**60**	**75**
	Mean (%)	0	86	96	99	99	100	100	101	101
	Range (%)	0	(b) (4)							
	RSD (%)	0	4.4	2.0	1.6	1.3	1.2	1.0	1.0	1.0
CSFXD (10 mg)	**Time (min)**	**0**	**5**	**10**	**15**	**20**	**30**	**45**	**60**	**75**
	Mean (%)	0	84	96	98	99	99	100	100	100
	Range (%)	0	(b) (4)							
	RSD (%)	0	4.9	1.7	1.3	1.1	1.1	0.8	0.9	0.9
CSFSS (12 mg)	**Time (min)**	**0**	**5**	**10**	**15**	**20**	**30**	**45**	**60**	**75**
	Mean (%)	0	87	97	98	99	99	99	100	100
	Range (%)	0	(b) (4)							
	RSD (%)	0	3.7	1.5	1.5	1.2	1.3	1.2	1.3	1.3

B.12 BRIDGING OF FORMULATIONS

Assessment: *Adequate*

The Applicant used uncoated 1 mg milsaperidone tablet in the pivotal single dose PK study and the pivotal food effect study. For the pivotal multiple dose PK study, the Applicant used all strengths of the film-coated milsaperidone tablet (**Table 11**), the to-be-marketed product. The Applicant was requested to provide the composition of the uncoated 1 mg milsaperidone tablet used in the pivotal clinical studies and provide the dissolution profile comparison data (n = 12) for the uncoated and the film-coated 1 mg milsaperidone tablet in the IR dated 7/19/2025 (**Appendix**).

Table 11. Composition of milsaperidone tablet (film-coated)

Tablet Strength (mg)		1	2	4	6	8	10	12
Component	**Function**	**Quantity (mg/tablet)**						
Milsaperidone	Drug substance	1.00	2.00	4.00	6.00	8.00	10.00	12.00
Lactose monohydrate (b) (4)								
Crospovidone (b) (4)								
Hypromellose (b) (4)								
(b) (4) water[a]								
Microcrystalline cellulose (b) (4)								
Magnesium stearate (b) (4)								
Colloidal silicon dioxide, (b) (4)								
Core tablet weight[b] (mg)								
(b) (4) yellow	Film coating composition[c]							
pink								
blue								
(b) (4) orange								
white								
(b) (4) purple								
(b) (4) water[a]	(b) (4)	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.
Coated tablet weight (mg)								
Tablet Strength (mg)		**1**	**2**	**4**	**6**	**8**	**10**	**12**
Component	**Function**	**Quantity (mg/tablet)**						

[a] Quantity sufficient. Removed during processing.
[b] (b) (4)
[c] (b) (4)

In response, the Applicant provided the composition of the uncoated 1 mg milsaperidone tablet (batch CGYDY) that was used in in the pivotal single dose PK study and the pivotal food effect study (**Table 12 and 13**). As shown, the

composition of the uncoated 1 mg milsaperidone tablet used in pivotal clinical studies is identical to that of the film-coated 1 mg milsaperidone tablet, except for the absence of film-coating. The Applicant also provided the mean dissolution comparison data for the uncoated and the film-coated 1 mg milsaperidone tablet (**Table 14**).

Although both batches exhibit very rapid dissolution (> 85% in 15 min) based on mean dissolution data, the Applicant did not provide the requested individual dissolution data with 12 units. In the IR dated 9/22/2025, the Applicant was requested to provide the previously requested dissolution data. In response, the Applicant provided the individual dissolution data for 6 units[4] and stated that the individual dissolution data with 12 units for coated and uncoated 1 mg milsaperidone tablet will be available by 12/31/2025.

As the only difference between coated and uncoated 1 mg milsaperidone tablet is the film coating and a film coating is unlikely to affect the dissolution of a drug product, the risk of providing dissolution data for 6 units instead of 12 units is low. In addition, based on the dissolution profile data (n = 6), the dissolution of the uncoated and the film-coated 1 mg milsaperidone tablet is very rapid (> 85% in 15 min) and therefore is considered similar. The provided data supporting the bridging of the pivotal clinical batches and the to-be-marketed batches are adequate.

Table 12. Composition of uncoated milsaperidone 1 mg tablet batch CGYDY

Component	Quantity (mg/tablet)
Milsaperidone	1.00
Lactose monohydrate (b) (4)	(b) (4)
Crospovidone (b) (4)	
Hypromellose (b) (4)	
(b) (4) water[a]	
Microcrystalline cellulose (b) (4)	
Magnesium stearate (b) (4)	
Colloidal silicon dioxide, (b) (4) (b) (4)	
Core tablet weight[b] (mg)	

[a] Quantity sufficient. Removed during processing.
[b] (b) (4)

[4] \\CDSESUB1\EVSPROD\nda220358\0018\m3\32-body-data\32p-drug-prod\milsaperidone\32p5-contr-drug-prod\32p54-batch-analys\sup-diss-data.xlsx

Table 13. Batch information of uncoated milsaperidone 1 mg tablet

Uncoated bulk batch	Packaged batch	Mfg. date	Clinical study
CGWXC	CGYDY	Jan 19, 2021	VP-VHX-896-1101, VP-VHX-896-1102

Table 14. Dissolution comparison of uncoated and film-coated milsaperidone 1 mg tablet (n=6)

Batch No.	% Dissolved (n = 6)						
	Time (minutes)	5	15	30	45	60	75
CGWXC	Mean (%)	95	101	101	102	102	102
Batch No.	% Dissolved (n = 6)						
	Time (minutes)	5	15	30	45	60	75
(bulk uncoated) VAN1S1MG 0103 (film-coated)	Range (%)	(b) (4)					
	RSD (%)	3.3	2.1	2.3	2.2	2.4	2.2
	Mean (%)	95	98	99	99	98	98
	Range (%)	(b) (4)					
	RSD (%)	2.3	2.0	1.4	2.3	2.0	2.0

Appendix

Biopharmaceutics Information Requests (IRs) and Applicant's Responses

(b) (4)

2 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Ta-Chen Wu

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Date: 11/10/2025 07:29:11PM
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Jia Leo

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Valerie Amspacher

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