# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 218879Orig1s000

# PRODUCT QUALITY REVIEWS

# Office of Pharmaceutical Quality

## New Drug Application (NDA)
## Integrated Quality Assessment

NDA 218879
Subvenite (lamotrigine) Oral Suspension

# NDA Executive Summary

## 1. Application/Product Information

| | | | |
|---|---|---|---|
| **NDA Number** | 218879 | | |
| **Applicant Name** | OWP Pharmaceuticals, Inc. | | |
| **Drug Product Name** | Subvenite | | |
| **Dosage Form** | Suspension | | |
| **Proposed Strength(s)** | 10 mg/mL | | |
| **NDA Classification** | Type 3 - New Dosage Form | | |
| **Route of Administration** | Oral | | |
| **Maximum Daily Dose** | 500 mg | | |
| **Rx/OTC Dispensed** | Rx | | |
| **Proposed Indication** | *Epilepsy* – Adjunctive therapy for treatment of partial-onset seizures, primary generalized tonic-clonic seizures, and generalized seizures of Lennox-Gastaut syndrome in patients aged 2 years and older and monotherapy for treatment of partial-onset seizures in patients aged 16 years and older.<br>*Bipolar Disorder* – Maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy. | | |
| **Drug Product Description** | Pink, cherry-flavored suspension in HDPE bottles with child-resistant closures. | | |
| **Co-packaged product information** | N/A | | |
| **Device information** | N/A | | |
| **Storage Temperature/ Conditions** | 20°C to 25°C | | |
| **Review Team** | **Discipline** | **Primary** | **Secondary** |
| | *Drug Substance* | N/A* | N/A* |
| | *Drug Product/ Labeling* | Grace Chiou | Martha Heimann/ Julia Pinto |
| | *Manufacturing* | Khalid Khan | Tianhong Tim Zhou |
| | *Biopharmaceutics* | Swapna Pamu | Ta-Chen Wu |

| | | | |
|---|---|---|---|
| | *Microbiology* | N/A* | N/A* |
| | *Other (specify)* | N/A | N/A |
| | *RBPM* | Erica Keafer | |
| | *ATL* | Martha Heimann | |
| **Consults** | N/A | | |

* Adequate first review cycle and no new information submitted.

**2. Final Overall Recommendation - Approval**

**3. Action Letter Information**

**a. Expiration Dating:**

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

**b. Additional Comments for Action**

There are no additional comments for the action letter.

**4. Basis for Recommendation:**

**a. Summary of Rationale for Recommendation:**

OPQ recommends **APPROVAL** for NDA 218879, SUBVENITE (lamotrigine) oral suspension 10 mg/mL. The applicant has provided adequate information to ensure the identity, strength, quality, and purity and performance for this drug/device combination product. The overall manufacturing inspection recommendation is approval for all facilities associated with this application. The proposed labeling is acceptable from a product quality perspective.

During the review of the original NDA submission, the OPQ review team identified deficiencies related to potential drug impurities, the proposed dissolution test method, in-use stability studies, and facilities that were communicated in the January 3, 2025, Complete Response (CR) letter. As summarized below, the applicant has adequately addressed the outstanding deficiencies from the previous review cycle. Refer to the individual discipline reviews for additional details.

1. *Inadequate control of extractable/leachable impurities* – The applicant provided validation data for all extractables/leachables test methods and full analytical data from extraction studies. Leachables data obtained during stability studies support the proposed expiry. Based on the provided data, the controls are deemed adequate to support product quality.

2. *Inadequate control of lamotrigine related substances* – The limit of not more than (NMT) (b) (4) % for lamotrigine-related compound D proposed in the original submission exceeds the ICH Q3B qualification threshold (0.2%) and was not supported by nonclinical data. The applicant reduced the limit to NMT 0.2% in the response to the CR letter.

3. *Lack of in-use stability data* – The original NDA submission did not include data from in-use studies to support product quality once the bottle is unsealed. Although the applicant submitted a study protocol in response to an information request (IR) during the previous review cycle, the data were not received prior to the action date. In-use stability data were provided in the resubmission and are deemed adequate.

4. *Dissolution method* – The dissolution medium proposed in the original NDA submission (b) (4) was deemed inadequate. During the previous review cycle, the applicant proposed an alternate method (b) (4) as the dissolution medium; the was also deemed inadequate. The dissolution medium proposed in the resubmission, 0.05 M monobasic potassium phosphate, pH 6.8 and the dissolution test parameters were deemed adequate. Module 3 was updated in the August 8, 2025, amendment to reflect the agreed upon dissolution method.

5. *Facilities* – Three drug substance manufacturing sites, (b) (4) (b) (4) (b) (4), were proposed in the original submission. However, during the facility evaluation it was determined that the (b) (4) (b) (4) . The applicant has withdrawn both (b) (4) sites. All remaining facilities are acceptable.

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

**Recommendation by Subdiscipline:**

**Drug Substance - N/A**
Drug substance recommendation was adequate first cycle and no new information was submitted.

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

Microbiology recommendation was adequate first cycle and no new information was submitted.

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

**5. Life-Cycle Considerations**

There are no outstanding issues or lifecycle considerations.

**Established Conditions per ICH Q12: No**
**Comments**: N/A

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

**Additional Lifecycle Comments: N/A**
There are no outstanding issues or lifecycle considerations.

***Application Technical Lead Name and Date:***

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

*August 19, 2025*

Martha Heimann

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# CHAPTER IV: LABELING

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

| | |
|---|---|
| **NDA Number** | 218879 |
| **Assessment Cycle Number** | 2 |
| **Drug Product Name** | Lamotrigine oral suspension |

**Assessment Recommendation:** Choose an item.

| Item | Assessment Conclusion | SDN # where labeling is adequate ("N/A" otherwise) |
|---|---|---|
| Prescribing Information Labeling | Choose an item. | **eCTD 0008** |
| Patient Information | N/A | **NA** |
| Instruction for Use (IFU) | Choose an item. | **NA** |
| Container Labels | Choose an item. | **eCTD 0027** |
| Carton Labeling | Choose an item. | **eCTD 0027** |

**Brief Description of Outstanding Issues:**

**Submissions being reviewed:**

| Document Reviewed (eCTD #, SDN #) | Date Received | Information Provided |
|---|---|---|
| eCTD 0027, SDN 28 | July 21, 2025 | Carton/Container labels |
| eCTD 0024, SDN 25 | March 17, 2025 | Carton/Container labels |
| eCTD 0008, SDN 9 | June 7, 2025 | PI |

## 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 | Not applicable |

[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 | |
| **Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]** | | |
| Dosage form(s)[4] and strength(s) in metric system[5] | Inadequate | Revise to "10 mg/mL" |
| 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 | Not applicable |
| 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*

[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>

Adequate, pending revisions in red.

## 1.2 FULL PRESCRIBING INFORMATION

### 1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

Due to the length of this section, refer to eCTD 0008.

| 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 | No food studies were performed and as there is no labeling remarks proposing it, no additional comments at this time.<br><br>Revise to include, "Discard any unused SUBVENITE (lamotrigine) oral suspension remaining 90 days after first opening the bottle." Additionally, include "Shake well before use." |
| 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 | Not applicable |
| If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is | N/A | There is a USP monograph for compounded oral suspension, but there is not one for oral suspension that is not compounded. |

[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
[11] §201.57(c)(3)(iv)

| 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) |
|---|---|---|
| fulfilled.[12] Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11). | | |
| 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*

Adequate pending revisions in red.

### 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 | Not applicable |
| Strength(s) in metric system | Adequate | |
| If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state | N/A | |

[12] USP General Notices 2.30 Legal Recognition
[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) |
|---|---|---|
| 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. | | |
| 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 | Not applicable |
| 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]


| 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 | Not applicable |
| Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)]. | Inadequate | Revise so "Oral Suspension" is not capitalized. |
| 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 | N/A | Not applicable |

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)
[15] Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| 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 | Revise so AED is written as "an antiepileptic drug" as it is unclear to the average person. |
| 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)]. | Inadequate | |
| 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 | Not applicable |
| 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*

Adequate pending revisions in red.

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

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

(b) (4)

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| **HOW SUPPLIED/STORAGE AND HANDLING section** | | |
| Available dosage form(s) [§ 201.57(c)(17)]. | Inadequate | Revise to Subvenite is available in an 8 oz (240 mL) bottle, NDC…" and use "10 mg/mL" for consistency. |
| 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 | |

[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) |
|---|---|---|
| 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)] | Inadequate | Revise to include, "Discard any unused SUBVENITE (lamotrigine) oral suspension remaining 90 days after first opening the bottle." Additionally, include "Shake well before use."<br>In-use stability study provided in eCTD 0023. |
| Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>). | Adequate | |
| Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*[21] | N/A | |

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

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| Include information about child-resistant packaging[22] (if chosen by manufacturer). | Adequate | |

**Assessment:** *Adequate*

Adequate, pending minor revision in red.

### 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.

(b) (4)

[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 | Not applicable |

**Assessment:** *Adequate*

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

## 2.0 PATIENT LABELING

(b) (4)

**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] | Inadequate | Revise to lower case "Oral Suspension" throughout |
| Special preparation instructions (if applicable). | N/A | Not applicable. |
| 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*

Adequate, pending revision in red.

## 3.0 CONTAINER AND CARTON LABELING[25]

[24] Established name = [Drug] [Route of Administration] [Dosage Form]
[25] Carton and Container Labeling Resources

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

| 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 | Not applicable |
| 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 | Yes | |
| Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[29] | Adequate | Yes | |
| "Rx only" displayed on the principal display [§ 201.100(b)(1)]. | Adequate | Yes | |
| NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35]. | Adequate | Yes | |
| Lot number and expiration date [§ 201.18 & 201.17]. | Adequate | Yes | |
| Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD). | Adequate | Yes | There is a section available to discard after 90 days. The Applicant did provide in-use stability data to support the 90 days. |
| For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms | N/A | Yes | |

[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) |
|---|---|---|---|
| include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement. (See USP <659>). | | | |
| 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 | 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 | Yes | |
| If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)]. | N/A | Yes | |
| Linear Bar code [§ 201.25(c)(2)].[30] | Adequate | Yes | |
| Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55]. | Adequate | Yes | |
| Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)]. | Inadequate | No | Not listed on container label. Revise so clearly stated on container label. |
| "Keep out of reach of children" statement, optional for Rx, | Adequate | Yes | Not listed on container label. |

[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) |
|---|---|---|---|
| required for OTC [§ 201.66(c)(5)(x)]. | | | |
| If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient. | Adequate | Yes | Not applicable. |
| No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>). | N/A | 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 | Yes | |
| When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.[31] | N/A | Yes | |
| And others if space is available. | N/A | Yes | |

**Assessment of Carton Labels and Container Labeling:** *Adequate*

Adequate pending revisions in red.

[31] USP General Notices 3.20 Indicating Conformance

## 4. OUTSTANDING ISSUES AND RECOMMENDATIONS

***Not applicable.***

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

*Secondary Assessor Name and Date (and Secondary Summary, as needed): Julia Pinto, Ph.D.*

Grace Chiou

Digitally signed by Grace Chiou
Date: 7/25/2025 09:18:45AM
GUID: 5c5df155002b1863abe42e6c00c2780f

Julia Pinto

Digitally signed by Julia Pinto
Date: 7/25/2025 02:33:59PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

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# CHAPTER VI: BIOPHARMACEUTICS

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

| | |
|---|---|
| **NDA Number** | 218879-RESUB-25 |
| **Assessment Cycle Number** | 2 |
| **Drug Product Name/ Strength** | Subvenite™ (lamotrigine) Oral Suspension, 10 mg/mL |
| **Route of Administration** | Oral |
| **Applicant Name** | OWP Pharmaceuticals, Inc. |
| **Therapeutic Classification/ OND Division** | Division of Neurology |
| **LD Number** | NDA-020241 (LAMICTAL® (lamotrigine) tablets, 100 mg) |
| **Proposed Indication** | Epilepsy (adjunctive therapy in patients aged 2 years and older; monotherapy in patients aged 16 years and older); Bipolar Disorder. |

***Assessment Recommendation:*** **Adequate**

**Assessment Summary:**

The Applicant submitted NDA-218879-RESU-25 for the approval of the proposed Subvenite™ (lamotrigine) Oral Suspension; 10 mg/mL via 505(b)(2) pathway. The Listed Drug (LD) is LAMICTAL® (lamotrigine) tablets, 100 mg, approved under NDA 020241. The proposed product is the first product in this dosage form and has the same indication as the LD. The recommended maximum dosage is 500 mg daily, administered orally twice a day and it is supplied as 8 oz bottle.

In the original submission[1], the Applicant developed an in-house method (b) (4) and proposed an acceptance criterion of Q= (b) (4)% in (b) (4) minutes. Based on the provided data, both proposed dissolution method and acceptance criterion were deemed unacceptable because of the use (b) (4) as dissolution medium. Applicant was sent deficiencies in the CRL dated 01/03/2025[1]. Biopharmaceutics deficiencies in the CRL were regarding developing a suitable dissolution method using a dissolution medium with buffer capacity with discriminating ability (see ***Appendix*** for details of the CRL).

In the current re-submission, the Applicant responded to those CRL deficiencies and developed a new dissolution method. Applicant also provided method development and discriminating ability data. The Biopharmaceutics review is focused on evaluation of responses to the Biopharmaceutics deficiencies in the CRL. The key findings of Biopharmaceutics assessment are summarized as follows:

[1] https://panorama.fda.gov/task/view?ID=664b769b00094d121608fbf3c4992419

1. **Dissolution method and acceptance criterion:**
   In response to the CRL, Applicant developed an in-house method (USP Apparatus 2, 40 rpm, 900 mL of 0.05 M monobasic potassium phosphate, pH 6.8 Simulated Intestinal Fluid without Enzyme, 37°C) and proposed an acceptance criterion of Q= (b)(4)% in 20 minutes.

   The selection of the paddle speed, dissolution medium, volume, and paddle speed were provided and were justified. The proposed method was shown to have discriminating ability for low and high viscosity, pH, potency with low (b)(4). The proposed method is also able to demonstrate the discriminating ability for high viscosity, low pH, low & high potency with regular (b)(4). Based on the submitted data, including clinical and exhibit batches and findings of method's discriminating ability, the proposed acceptance criterion is justified and can be accepted.

2. **Formulation bridging:**
   There has been no change for formulation composition throughout the drug development. Additionally, the to-be-marketed formulation/product was used in the bioavailability (BA) study comparing to LD under fasting condition and in food-effect bioavailability studies (refer to Office of Clinical Pharmacology review). Therefore, it is determined that no additional in vitro or in vivo study is needed to bridge the formulation/product.

3. **Biopharmaceutics Risk Assessment:**
   Considering the immediate release nature of the drug product, the risk associated with dissolution and bioavailability of Lamotrigine (highly permeable, per BCS criteria) is considered "low".

**RECOMMENDATION:**

From a Biopharmaceutics perspective, NDA-218879-ORIG-1-RESUB-25 for Subvenite™ (lamotrigine) Oral Suspension 10 mg/mL is adequate.

**FDA-approved dissolution method and acceptance criterion for batch release and stability testing:**

| USP Apparatus | RPM | Medium | Temperature | Volume (mL) | Acceptance Criterion |
|---|---|---|---|---|---|
| II (paddle) | 40 | 0.05 M monobasic potassium phosphate, pH 6.8 (Simulated Intestinal Fluid without Enzyme) | 37°C | 900 | Q= (b)(4)% in 20 minutes |

**List Submissions Being Assessed:**

| Document(s) Assessed | Date Received |
|---|---|
| Original Submission | 03/04/2024 |
| IR response (Seq 0010) | 06/14/2024 |
| CR response | 03/17/2025 |

**Highlight Key Issues from Last Cycle and Their Resolution:**
Key issues communicated in CRL are presented in ***Appendix***. In response, the Applicant developed a dissolution method using a buffer medium to address the deficiencies.

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

## B.1 BCS DESIGNATION

**Assessment:**
The Applicant did not submit any request for BCS designation.

**Solubility:**
The provided aqueous solubility data across physiologic pH range tested (pH 1.2 – 7.4) indicate that Lamotrigine is a poorly soluble drug substance as the highest single dose 250 mg is not dissolved in 250 mL of all tested dissolution media except in 0.1 N HCl and pH 4.5 buffer[2], with a pH-dependent solubility profile with the lowest solubility at pH 6.8 and 7.4 (Table 1).

**Table 1: Lamotrigine Solubility as a Function of pH**

| Medium | pH before addition of API | pH after addition of API | Solubility (mg/ml) |
|---|---|---|---|
| Water | (b) (4) | | 0.17 |
| 0.1 N Hydrochloric acid | | | 6.52 |
| 4.5 Acetate buffer | | | 1.07 |
| 6.8 Phosphate | | | 0.17 |
| buffer | | | |
| 7.4 Phosphate buffer | | | 0.17 |

**Permeability:**
The Applicant did not provide permeability data in this submission. However, the previously available permeability data for Lamotrigine[3] suggest that the drug substance belongs to high permeability class. Therefore, lamotrigine possesses BCS Class II characteristics (i.e., poor solubility and high permeability).

**Dissolution:**
The proposed product is rapidly dissolving (more than 85% dissolved, mean values, in 15-20 minutes) (See below for more details on dissolution profile data and specifications).

## B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERION

**Assessment: Adequate**

[2] \\CDSESUB1\EVSPROD\nda218879\0003\m3\32-body-data\32s-drug-sub\lamotrigine-(b) (4)\32s1-gen-info\general-properties.pdf
[3] https://elsa.fda.gov/elsa/#/room/6b963c72-f74e-4be5-82d3-06a41eb51219

Applicant provided method development and discriminating ability data as shown below in response to the CRL[1]. The proposed product is the first product in this dosage form so there is no dissolution method listed in the FDA dissolution methods database or USP monograph.

**Dissolution method development[4]:**

(b) (4)

[redacted]

[4] \\CDSESUB1\EVSPROD\nda218879\0024\m3\32-body-data\32p-drug-prod\lamotrigine-oral-suspension-dpt-laboratories-ltd\32p2-pharm-dev\pharmaceutical-development-1.pdf

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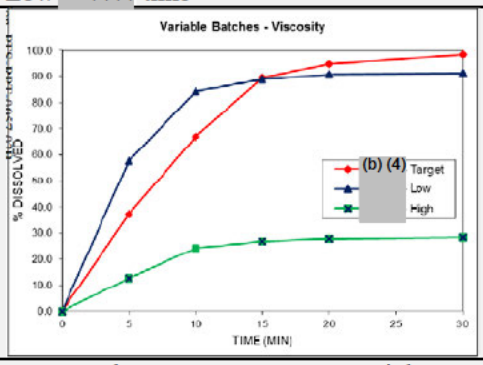
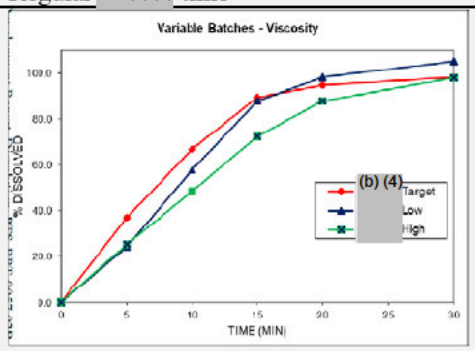
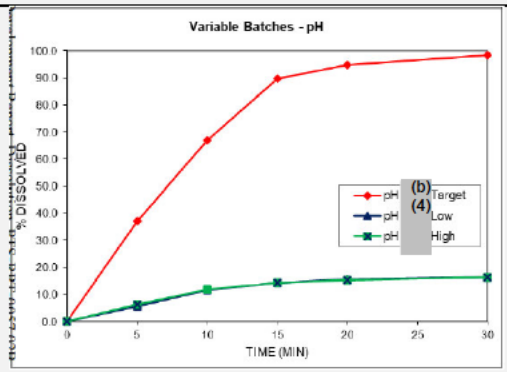
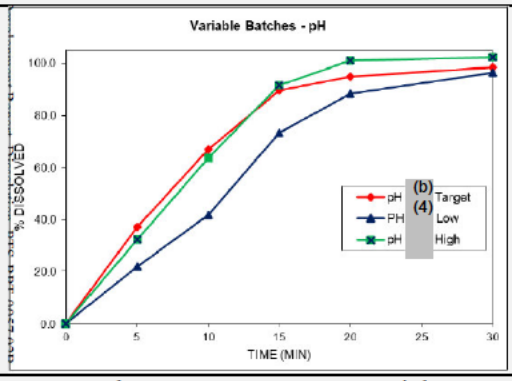
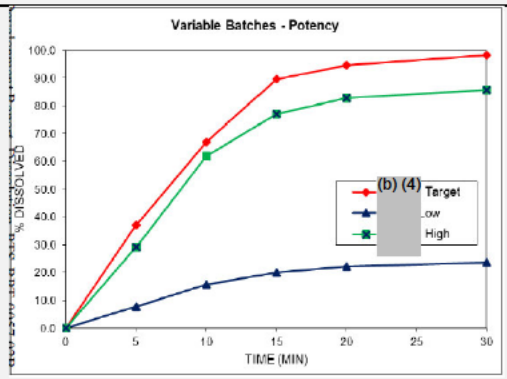
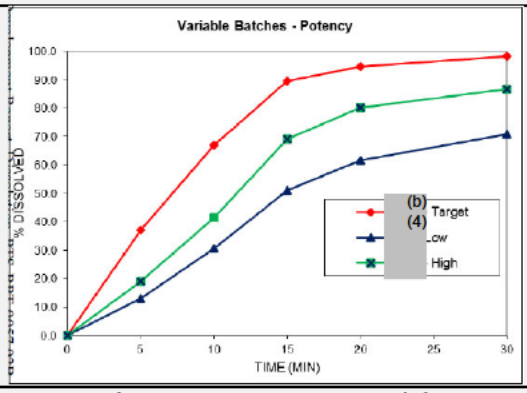
**4. Discriminating ability[5]:**

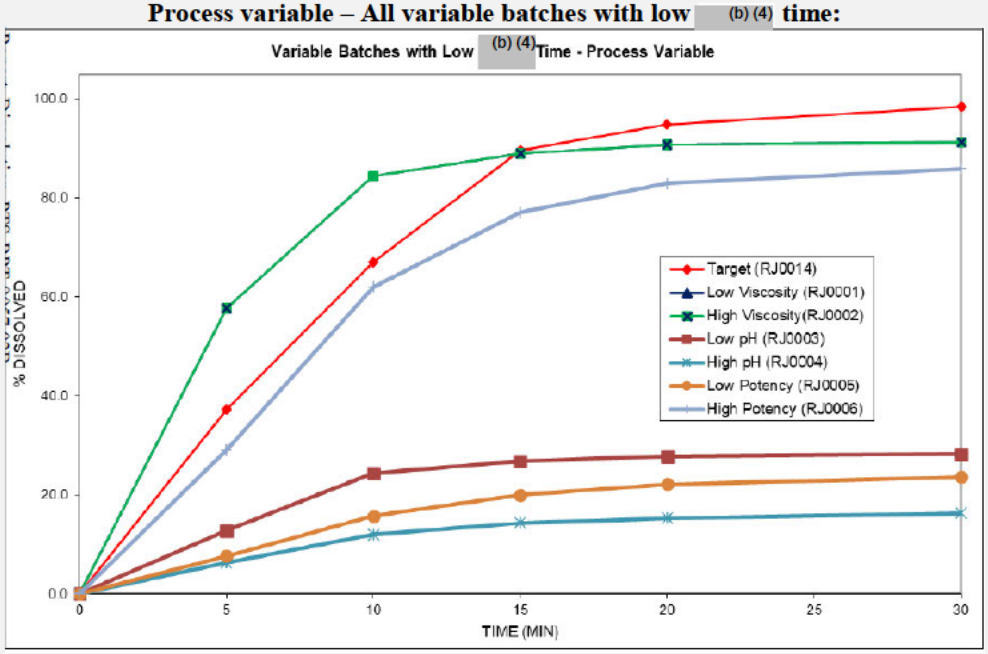
The proposed drug product is suspension with (b) (4) Lamotrigine. The rate of sedimentation is optimum and upon long-term storage the Lamotrigine re-suspends uniformly with moderate shaking. Per the Applicant, the key unit operation for the manufacturing process is (b) (4) The Applicant provided discriminating ability data towards the below parameters (Table 2).

**Table 2. Results of investigation for method's discriminating ability (n=12)**

| **Critical manufacturing process parameter:** | | |
|---|---|---|
| | Low (b) (4) time | Regular (b) (4) time |
| Viscosity variable |  |  |
| F2 | Target vs low: 40.3 Target vs High: 12.5 | Target vs low: 52 Target vs High: 40 |
| pH variable |  |  |
| F2 | Target vs low: 8.5 Target vs High: 8.5 | Target vs low: 35 Target vs High: 71 |
| Potency variable |  |  |
| F2 | Target vs low: 10.3 Target vs High: 49 | Target vs low: 23 Target vs High: 33 |

[5] \\CDSESUB1\EVSPROD\nda218879\0024\m3\32-body-data\32p-drug-prod\lamotrigine-oral-suspension-dpt-laboratories-ltd\32p2-pharm-dev\pharmaceutical-development-2.pdf

**Process variable – All variable batches with low (b) (4) time:**




Based on the above results, the proposed method is able to demonstrate discriminating ability for low and high viscosity, pH, potency with **low** (b) (4). The proposed method is also able to demonstrate the discriminating ability for high viscosity, low pH, low & high potency with **regular** (b) (4). Based on the method development and discriminating ability data, this Reviewer agrees with the Applicant's conclusion that the proposed method is able to reject aberrant batches toward the parameters tested and suitable for their test product.

**Dissolution acceptance criterion[6]:**
The Applicant provided dissolution profile data for clinical batch and target batch[7] of the proposed product using the revised method (see Table 3, 4 and Figure 4 below).

**Table 3: Dissolution data of registration batch # TDA-C (n-12)**

| Time (min) | SAMPLE | | | | | | | | | | | | SUMMARY STATISTICS | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | Mean | SD | % RSD | Min | Max |
| 0 | | | | | | | | | | | | (b) (4) | 0.0 | N/A | N/A | | (b) (4) |
| 5 | | | | | | | | | | | | | 48.0 | 17.5 | 36.4 | | |
| 10 | | | | | | | | | | | | | 76.6 | 4.5 | 5.9 | | |
| 15 | | | | | | | | | | | | | 86.1 | 0.9 | 1.0 | | |
| 20 | | | | | | | | | | | | | 89.7 | 1.2 | 1.3 | | |
| 30 | | | | | | | | | | | | | 91.0 | 1.2 | 1.3 | | |

[6] \\CDSESUB1\EVSPROD\nda218879\0024\m3\32-body-data\32p-drug-prod\lamotrigine-oral-suspension-dpt-laboratories-ltd\32p2-pharm-dev\pharmaceutical-development-1.pdf
[7] \\CDSESUB1\EVSPROD\nda218879\0024\m3\32-body-data\32p-drug-prod\lamotrigine-oral-suspension-dpt-laboratories-ltd\32p2-pharm-dev\pharmaceutical-development-2.pdf

**Table 4: Dissolution data of target batch # RJ0014 (n=12):**

| TIME (MIN) | SAMPLE | | | | | | | | | | | | SUMMARY STATISTICS | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | MEAN | SD | % RSD | MIN | MAX |
| 0 | | | | | | | | | | | | (b) (4) | 0.0 | N/A | N/A | | (b) (4) |
| 5 | | | | | | | | | | | | | 37.1 | 18.8 | 50.7 | | |
| 10 | | | | | | | | | | | | | 67.0 | 15.5 | 23.2 | | |
| 15 | | | | | | | | | | | | | 89.6 | 4.6 | 5.2 | | |
| 20 | | | | | | | | | | | | | 94.8 | 2.9 | 3.1 | | |
| 30 | | | | | | | | | | | | | 98.4 | 1.7 | 1.7 | | |

RPT-0057.02B

## B.3 BRIDGING OF FORMULATIONS:

**Assessment: Adequate**

The formulation composition is listed in Table 5 below and there has been no change for formulation composition throughout the drug development. Additionally, the to-be-marketed formulation/product was used in the bioavailability (BA) study comparing to LD under fasting condition and in food-effect BA studies (refer to Office of Clinical Pharmacology review). Therefore, it is determined that no additional in vitro or in vivo study is needed to bridge the formulation/product.

**Table 5. Formulation composition[8]:**

| Ingredients | Amount per dose (mg/mL) | % (w/v) | Amount per exhibit batch (kg) | Pharmaceutical Function | Quality Standards |
|---|---|---|---|---|---|
| **Active Ingredient** | | | | | |
| Lamotrigine | 10.0000 | 1.0000 | (b) (4) | Active | USP |
| **Inactive Ingredients** | | | | | |
| Carboxymethylcellulose Sodium | | | | (b) (4) | USP |
| Xanthan Gum | | | | | NF |
| (b) (4) | | | | | NF |
| Sodium Benzoate | | | | | NF |
| Sodium Phosphate Dibasic (b) (4) | | | | | USP |
| Saccharin Sodium (b) (4) | | | | | USP |
| Polyethylene Glycol (b) (4) | | | | | NF |
| Sorbitol Solution | | | | | USP |
| Methylparaben | | | | | NF |
| FD&C Red No. 40 (b) (4) | | | | | NA |
| FD&C Yellow No. 6 (b) (4) | | | | | NA |
| Propylene Glycol | | | | | USP |
| Glycerin | | | | | USP |
| Cherry Flavor, (b) (4) | | | | | NA |
| Sucralose | | | | | USP/NF |
| Purified Water | | | | | USP |

[8] \\CDSESUB1\EVSPROD\nda218879\0007\m3\32-body-data\32p-drug-prod\lamotrigine-oral-suspension-dpt-laboratories-ltd\32p1-desc-comp\description-and-composition.pdf

**B.4 BIOPHARMACEUTICS RISK ASSESSMENT:**

Lamotrigine is rapidly and completely absorbed after oral administration with negligible first-pass metabolism (absolute bioavailability is 98%) [9] . Considering the high absolute bioavailability, bioequivalence between proposed product and LD, as well as the immediate release nature with rapid but discriminatory dissolution of the drug product, the Biopharmaceutics risk is considered low.

***Primary Biopharmaceutics Assessor's Name:***
*Swapna Pamu, MS*

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

[9] https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/020241s066s067,020764s059s060,022251s030s031lbl.pdf

## APPENDIX

**Biopharm deficiencies communicated in Complete Response Letter (dated 01/03/2025)**[10]

We acknowledge that you have provided additional information regarding the dissolution method. However, the provided information is not satisfactory. Please see below for the additional information we recommend you provide and justify for the request.

a. We acknowledge that you have revised the dissolution method by changing the dissolution media (b) (4). Note that (b) (4) is not recommended as dissolution medium because it lacks buffering capacity. Therefore, an aqueous dissolution medium with buffering capacity within the physiologic pH range is recommended.

b. The solubility data show that lamotrigine is poorly soluble within the physiologic pH range of 1.2 to 6.8. However, the drug product seems to exhibit rapid to very rapid dissolution. Understanding this discrepancy may aid in the development of a dissolution method that is suitable for the proposed drug product. Note that for oral suspension drug products, you should include investigation of lower paddle speeds, e.g., 25, 30, 35, and 40 rpm, in your method development. Additionally, each sample tested should be taken from a different bottle and the same volume should be administered according to the labeling dosing instruction. The selection of the test conditions/parameters needs to be justified with supporting information and data.

c. We recommend you explore the discriminating ability of the proposed dissolution method/test conditions and submit that data. In general, the tests conducted to demonstrate the discriminating ability should compare the dissolution profiles of the reference (target) batch and batches that are intentionally manufactured with meaningful variations in the most relevant critical material attributes, critical formulation variables, and critical process parameters (i.e., ± 10-20% change to the specification-ranges of these variables). A discriminating method (along with the selected acceptance criterion) should be able to reject batches that fail similarity testing. In addition, if available, submit data showing that the selected dissolution method (along with the selected dissolution acceptance criterion) can reject batches that are not bioequivalent to the reference batch (i.e., the biobatch).

d. You should generate new dissolution profile data for clinical/registration batches using the revised dissolution method and propose an appropriate acceptance criterion based on the newly generated profile data and taking into consideration results of method's discriminating ability.

e. Note that comparison of the dissolution profile of the proposed product to the listed drug is not needed.

[10] https://panorama.fda.gov/task/view?ID=664b769b00094dec9fb82e9c6a5bef99

Swapna Pamu

Digitally signed by Swapna Pamu
Date: 8/05/2025 08:27:12PM
GUID: 5ab948e8002c8e63080fe7187098154c

Ta-Chen Wu

Digitally signed by Ta-Chen Wu
Date: 8/06/2025 07:43:15AM
GUID: 508da6df000269e151ff37cd8f4e13a1

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**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.**

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/s/

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MARTHA R HEIMANN
08/19/2025 06:04:31 PM

# Office of Pharmaceutical Quality

## New Drug Application (NDA)
## Integrated Quality Assessment

NDA 218879
Subvenite (lamotrigine) Oral Suspension

# NDA Executive Summary

## 1. Application/Product Information

| | |
|---|---|
| **NDA Number** | 218879 |
| **Applicant Name** | OWP Pharmaceuticals, Inc. |
| **Drug Product Name** | Subvenite |
| **Dosage Form** | Suspension |
| **Proposed Strength(s)** | 10 mg/mL |
| **NDA Classification** | Type 3 - New Dosage Form |
| **Route of Administration** | Oral |
| **Maximum Daily Dose** | 500 mg |
| **Rx/OTC Dispensed** | Rx |
| **Proposed Indication** | Epilepsy:<br>Adjunctive therapy for treatment of partial-onset seizures, primary generalized tonic-clonic seizures, and generalized seizures of Lennox-Gastaut syndrome in patients aged 2 years and older.<br>Monotherapy for treatment of partial-onset seizures in patients aged 16 years and older.<br><br>Bipolar Disorder:<br>Maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy. |
| **Drug Product Description** | Oral Suspension supplied as a pink, cherry-flavored liquid in high-density polyethylene (HDPE) bottles with white, polypropylene, child-resistant closures. |
| **Co-packaged product information** | N/A |
| **Device information** | N/A |
| **Storage Temperature/ Conditions** | 20°C to 25°C |

| | | | |
|---|---|---|---|
| **Review Team** | **Discipline** | **Primary** | **Secondary** |
| | *Drug Substance* | Sophie Rubashkin | Katherine Duncan |
| | *Drug Product/ Labeling* | Grace Chiou | Martha Heimann/ Julia Pinto |
| | *Manufacturing* | Khalid Khan | Tianhong Tim Zhou |
| | *Biopharmaceutics* | Swapna Pamu | Ta-Chen Wu |
| | *Microbiology* | George Arhin | Bethanie Lee |
| | *Other (specify)* | N/A | N/A |
| | *RBPM* | Erica Keafer | |
| | *ATL* | Martha Heimann | |
| **Consults** | N/A | | |

**2. Final Overall Recommendation - Complete Response**

**3. Deficiencies**

**Drug Product**

1. We note your response in eCTD 0016 that included the method validation protocol, but not the report for the analytical method validation of the extractable/leachable studies. We are unable to assess the adequacy of the extractable/leachables studies without adequately validated analytical methods. Information Needed to Resolve the Deficiency: Provide the analytical method validation report.
2. The extractables study was repeated under 9 hours of refluxing conditions per your response in eCTD 0020. However, it was stated in the report that the GCMS analysis data was to be "provided in the next report revision." This is not acceptable as the extractables study is incomplete and does not adequately demonstrate the extractables profile for the proposed drug product.

   Information Needed to Resolve the Deficiency: Provide a complete extractables study that includes GCMS analysis data.
3. We note your response to our Information Request to provide in-use stability studies once the studies were completed. These studies are necessary to assess product quality once the proposed drug product is opened and set aside for a period of time. However, these studies were not provided.

Information Needed to Resolve the Deficiency: Provide the in-use stability studies based on the protocol provided in eCTD 0009 and the commitment to assess sedimentation as part of the in-use study in eCTD 0016.

4. The proposed stability specification of lamotrigine related compound D is listed as NMT (b) (4) %. It was justified in eCTD 0009 with reference to the USP monograph for lamotrigine tablets. This justification is not adequate as there is no specification for lamotrigine related compound D in the USP monograph for lamotrigine tablets and the proposed specification limit is above ICH qualification thresholds.

   Information Needed to Resolve the Deficiency: Revise the specification for lamotrigine related compound D to be NMT 0.2%.

**Biopharmaceutics**

5. We acknowledge that you have provided additional information regarding the dissolution method. However, the provided information is not satisfactory. Please see below for the additional information we recommend you provide and justify for the request.

   a. We acknowledge that you have revised the dissolution method by changing the dissolution media (b) (4). Note that (b) (4) is not recommended as dissolution medium because it lacks buffering capacity. Therefore, an aqueous dissolution medium with buffering capacity within the physiologic pH range is recommended.

   b. The solubility data show that lamotrigine is poorly soluble within the physiologic pH range of 1.2 to 6.8. However, the drug product seems to exhibit rapid to very rapid dissolution. Understanding this discrepancy may aid in the development of a dissolution method that is suitable for the proposed drug product. Note that for oral suspension drug products, you should include investigation of lower paddle speeds, e.g., 25, 30, 35, and 40 rpm, in your method development. Additionally, each sample tested should be taken from a different bottle and the same volume should be administered according to the labeling dosing instruction. The selection of the test conditions/parameters needs to be justified with supporting information and data.

   c. We recommend you explore the discriminating ability of the proposed dissolution method/test conditions and submit that data. In general, the tests conducted to demonstrate the discriminating ability should compare the dissolution profiles of the reference (target) batch and batches that are intentionally manufactured with meaningful variations in the most relevant critical material attributes, critical formulation variables, and critical process parameters (i.e., ± 10-20% change to the specification-ranges of these variables). A discriminating method (along with the selected acceptance criterion) should be able to reject batches that fail similarity testing. In addition, if available, submit data showing that the selected dissolution method (along with the selected dissolution acceptance

criterion) can reject batches that are not bioequivalent to the reference batch (i.e., the biobatch).

d. You should generate new dissolution profile data for clinical/registration batches using the revised dissolution method and propose an appropriate acceptance criterion based on the newly generated profile data and taking into consideration results of method's discriminating ability.

e. Note that comparison of the dissolution profile of the proposed product to the listed drug is not needed.

**Facility**

The drug substance manufacturing facility, (b) (4) , proposed to support the application is not operational. A satisfactory inspection may be required before this application may be approved. As part of your full response to this Complete Response letter, please confirm that this facility is ready for inspection. Please note that the application cannot be approved if any proposed facility for the commercial manufacturing is not acceptable for the proposed function on the action date.

**4. Basis for Recommendation:**

**a. Summary of Rationale for Recommendation:**

OPQ recommends a **COMPLETE RESPONSE** for NDA 218879, SUBVENITE (lamotrigine) oral suspension 10 mg/mL. Although the application is deemed adequate from the drug substance, microbiology and labeling perspectives, the applicant has not provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product. As summarized below, the outstanding deficiencies are related to inadequate information to support control of the drug product (b) (4) for a drug substance manufacturing facility.

The to-be-marketed product is an aqueous suspension containing lamotrigine and excipients that are commonly used in oral liquid products. Extensive deficiencies related to the proposed dissolution method, validation of analytical methods used for release and stability testing, lack of in-use stability data, and control of container closure leachables were communicated as information requests (IRs) early in the review cycle.[1] The applicant adequately addressed some of the IRs; however, the responses to the remaining IRs are either incomplete (i.e., "reports to be submitted at a later time") or inadequate.

[1] With respect to container closure leachables: Leachables would normally be considered low risk for an aqueous product. This product contains glycerin and propylene glycol (b) (4) and is intended for chronic use at doses up to 500 mg/day (50 mL suspension). Thus, the risk from leachables is potentially higher for this product.

During the review, the team was advised by ORA that one of the proposed drug substance manufacturing sites, [redacted] (b) (4) [redacted] (b) (4) As the facility is not ready for drug substance manufacture, it is deemed inadequate, [redacted] (b) (4) [redacted] The remaining facilities are currently adequate.

Refer to the Product Quality, Biopharmaceutics, and Manufacturing primary reviews for additional details regarding the deficiencies.

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

**Recommendation by Subdiscipline:**

| | | |
|---|---|---|
| **Drug Substance** | **-** | **Adequate** |
| **Drug Product** | **-** | **Inadequate** |
| **Quality Labeling** | **-** | **Adequate** |
| **Manufacturing** | **-** | **Inadequate** |
| **Biopharmaceutics** | **-** | **Inadequate** |
| **Microbiology** | **-** | **Adequate** |

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

**5. Life-Cycle Considerations**

Not applicable as the application is not recommended for approval.

**Established Conditions per ICH Q12: No**
**Comments**: N/A

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

**Additional Lifecycle Comments: N/A**

***Application Technical Lead Name and Date:***

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

*December 12, 2024*

Martha Heimann

Digitally signed by Martha Heimann
Date: 12/12/2024 02:43:40PM
GUID: 504f845f00000ed260627d268a8cdc9d

# 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** | 218879 |
| **Assessment Cycle Number** | 1 |
| **Drug Product Name** | Lamotrigine oral suspension |

**Assessment Recommendation:** Choose an item.

| Item | Assessment Conclusion | SDN # where labeling is adequate ("N/A" otherwise) |
|---|---|---|
| Prescribing Information Labeling | Adequate | 0009 |
| Patient Information | Adequate | 0009 |
| Instruction for Use (IFU) | N/A | |
| Container Labels | Adequate | 0009 |
| Carton Labeling | Adequate | 0009 |

**Brief Description of Outstanding Issues:** The labels reviewed below are adequate pending revision below.

**Submissions being reviewed:**

| Document Reviewed (eCTD #, SDN #) | Date Received | Information Provided |
|---|---|---|
| SDN 0009 | June 07, 2024 | Prescribing Information |
| SDN 0003 | October 30, 2023 | Carton and 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)

[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 | Adequate |
| Route(s) of administration | Adequate | |

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

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

| 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) |
|---|---|---|
| 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] | Inadequate | Revise to "10 mg/mL" to be consistent with Full PI (Dosage Forms and Strengths). |
| 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] | Adequate | |
| 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>

Revise dosage strength to "10 mg/mL" instead of (b) (4) to be consistent with the language used in the Full PI.

***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

## 1.2 FULL PRESCRIBING INFORMATION

### 1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

(b) (4)

[redacted]

[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)

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

(b) (4)

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| **DOSAGE AND ADMINISTRATION section** | | |
| Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product). | N/A | Container label has "Shake well before each use" and carton label has (b) (4) This should be resolved as the same language and added to here. |

[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*

Note, the images for Dosage and Administration do not capture all of the content in the draft labeling due to extent of information provided. The images captured above are those that are most relevant.

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

***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

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

(b) (4)

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| **DOSAGE FORMS AND STRENGTHS section** | | |
| Available dosage form(s) | Adequate | Adequate |
| Strength(s) in metric system | Adequate | |
| If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement. | N/A | |
| A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable. | Adequate | |
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored." | N/A | |
| For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>). | N/A | |

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

**Assessment:** *Adequate*

No proposed revision.

***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

### 1.2.3 Section 11 (DESCRIPTION)[14]

(b) (4)

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| **DESCRIPTION section** | | |
| Proprietary and established name(s)[15] [§ 201.57(c)(12)(i)(A)]. | Inadequate | Revise to SUBVENITE (lamotrigine) oral suspension instead of "SUBVENITE (lamotrigine)." Ensure "Oral Suspension" is not capitalized. |
| Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)]. | Inadequate | |
| If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency | N/A | |

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

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

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)]. | | |
| List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§ 201.57(c)(12)(i)(C)]. | 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 | |

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

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

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)]. | Adequate | |
| 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"). | 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*

Adequate, pending revision noted above.

***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

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

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

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

(b) (4)

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| **HOW SUPPLIED/STORAGE AND HANDLING section** | | |
| Available dosage form(s) [§ 201.57(c)(17)]. | Inadequate | Lower case "Oral Suspension" and remove (b) (4) as it is redundant. |
| 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 | |

[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) |
|---|---|---|
| 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 | Container label has "Shake well before each use" and carton label has (b) (4) This should be resolved as the same language and added in this section. |
| Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>). | Adequate | |
| Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*[21] | N/A | |

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

| Item | Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A") | Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate) |
|---|---|---|
| Include information about child-resistant packaging[22] (if chosen by manufacturer). | Adequate | |

**Assessment:** *Adequate*

Adequate, pending revisions noted above.

***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

### 1.2.5 Other Sections of Labeling

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

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

### 1.2.6 Manufacturing Information After Section 17 (for drug products)[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 | (b) (4) Proposed text: Adequate |

**Assessment:** *Adequate*

[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)
[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)

***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

## 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] | Inadequate | Revise so "Oral Suspension" is not capitalized. Container label has "Shake well before each use" and carton label has (b) (4) This should be the resolved as the same language and added to the medication guide. |
| Special preparation instructions (if applicable). | Adequate | |
| Storage and handling information (if applicable). | Adequate | |
| If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant 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*

Adequate, pending revisions noted above.

***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

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

## 3.0 CONTAINER AND CARTON LABELING[25]

### 3.1 Container Labels[26]

(b) (4)

[redacted]

[25] Carton and Container Labeling Resources

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

### 3.2 Carton Labeling

(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)]. | Inadequate | Yes | Revise so "Oral Suspension" is not capitalized. |

[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 | Adequate |
| 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 | Yes | |
| Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[29] | Adequate | Yes | |
| "Rx only" displayed on the principal display [§ 201.100(b)(1)]. | Inadequate | No | Rx only is missing from the container label. |
| NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35]. | Adequate | Yes | Adequate |
| Lot number and expiration date [§ 201.18 & 201.17]. | Inadequate | Yes | Revise to include lot number and expiration date. |
| Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD). | Adequate | Yes | Adequate |
| For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient- | N/A | Yes | |

[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) |
|---|---|---|---|
| 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>). | | | |
| 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 | Yes | N/A |
| For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)]. | N/A | Yes | |
| If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)]. | N/A | Yes | |
| Linear Bar code [§ 201.25(c)(2)].[30] | Adequate | Yes | Adequate |
| Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55]. | Inadequate | No | Carton says, (b) (4) [redacted] while container label says, "Shake well before each use." Revise so both statements are the same to avoid confusion. |

[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) |
|---|---|---|---|
| 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 Medication Guide to each patient. | Adequate | Yes | |
| No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>). | N/A | 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 | Yes | |
| When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.[31] | N/A | Yes | |
| And others if space is available. | N/A | Yes | |

[31] USP General Notices 3.20 Indicating Conformance

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

***Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"***

## 4. OUTSTANDING ISSUES AND RECOMMENDATIONS

See revisions noted above. Overall, there are minor revisions. However, once the revisions are addressed, the labeling will be adequate from a CMC perspective.

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

Grace Chiou

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Julia Pinto

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## CHAPTER VI: BIOPHARMACEUTICS

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

| | |
|---|---|
| **NDA Number** | 218879 |
| **Assessment Cycle Number** | 1 |
| **Drug Product Name/ Strength** | Subvenite™ (lamotrigine) Oral Suspension, 10 mg/mL |
| **Route of Administration** | Oral |
| **Applicant Name** | OWP Pharmaceuticals, Inc. |
| **Therapeutic Classification/ OND Division** | Division of Neurology |
| **LD Number** | NDA-020241 (LAMICTAL® (lamotrigine) tablets, 100 mg) |
| **Proposed Indication** | Epilepsy (adjunctive therapy in patients aged 2 years and older; monotherapy in patients aged 16 years and older); Bipolar Disorder. |

***Assessment Recommendation:*** **Inadequate**

### *A. Assessment Summary:*

The Applicant is seeking approval for the proposed Subvenite™ (lamotrigine) Oral Suspension; 10 mg/mL. The Listed Drug (LD) for this proposed product is LAMICTAL® (lamotrigine) tablets, 100 mg approved under NDA 020241. The proposed lamotrigine oral suspension has the same indications as the LD, LAMICTAL® (lamotrigine) tablets. The recommended maximum dosage is 500 mg daily, administered orally twice daily, supplied as 8 oz bottle.

The Biopharmaceutics review is focused on evaluation of (1) the adequacy of the proposed dissolution method and acceptance criterion, and (2) formulation bridging throughout product development.

***Reviewer's Assessment:***

**I. Dissolution Method and Acceptance Criterion**

This is the first product in this dosage form and there is no dissolution method listed in the FDA dissolution methods database or USP. The Applicant adopted the dissolution method listed in the FDA database for Lamotrigine Tablets.

**Proposed dissolution method and acceptance criterion:**

(b) (4)

The Applicant did not provide adequate justification for the proposed method/parameters as part of the dissolution method development, seeing a suitable/optimal dissolution method being product-specific, or investigate discriminating ability for the proposed dissolution method. The Applicant provided dissolution profile data (n=12) for only one batch and proposed a dissolution specification of Q= (b) (4)% dissolved in (b) (4) minutes[1]. Both proposed dissolution method and acceptance criterion are not acceptable because of insufficient information submitted in the original application (***Appendix 1***). In response to request for information/data regarding method's suitability, discriminating ability, and complete dissolution profile data, the Applicant proposed a revised dissolution method by changing the dissolution medium (b) (4). The Applicant provided dissolution profile data for biobatch, registration batches, and LD generated by the revised method/test condition. However, the Applicant did not explore any other dissolution method parameters and did not provide discriminating ability data. Additionally, (b) (4) is not recommended as dissolution medium because it lacks buffering capacity. Therefore, an aqueous dissolution medium with buffering capacity within physiological pH range is recommended. Therefore, the responses are deemed inadequate and dissolution specifications for batch release and stability testing cannot be accepted.

**II. Formulation Bridging:**

There has been no change for formulation composition throughout the drug development. Additionally, the to-be-marketed formulation/product was used in the bioavailability (BA) study comparing to LD under fasting condition and in food-effect BA studies. Therefore, it is determined that no additional in vitro or in vivo study is needed to bridge the formulation/product.

**Recommendation:**

From the Biopharmaceutics perspective, NDA-218879-ORIG-1 for Subvenite™ (lamotrigine) Oral Suspension 10 mg/mL is inadequate. Biopharmaceutics deficiencies to be conveyed to the Applicant are presented in ***Appendix 2***.

**List Submissions Being Assessed:**

| Document(s) Assessed | Date Received |
|---|---|
| Original Submission | 03/04/2024 |
| IR response (Seq 0010) | 06/14/2024 |

**Highlight Key Issues from Last Cycle and Their Resolution:**
See Appendices 1 and 2 for details of the information requests/ deficiencies.

**Concise Description of Outstanding Issues:**
See Appendices 1 and 2 for details of the information requests/ deficiencies.

## B.1 BCS DESIGNATION

**Assessment:**
The Applicant did not submit a claim or request for BSC designation.

**Solubility:**
The provided aqueous solubility data across physiologic pH range tested (pH 1.2 – 7.4) indicate that Lamotrigine is a poorly soluble drug substance, per highest single dose and BCS criteria (see table 1)[2], with a pH-dependent solubility profile with the lowest solubility at pH 6.8 and 7.4.

**Table 1: Lamotrigine Solubility as a Function of pH**

| Medium | pH before addition of API | pH after addition of API | Solubility (mg/ml) |
|---|---|---|---|
| Water | (b) (4) | | 0.17 |
| 0.1 N Hydrochloric acid | | | 6.52 |
| 4.5 Acetate buffer | | | 1.07 |
| 6.8 Phosphate buffer | | | 0.17 |
| 7.4 Phosphate buffer | | | 0.17 |

**Permeability:**
The Applicant did not provide new permeability data. However, the previously available permeability data for lamotrigine suggest that lamotrigine belongs to high permeability class.

**Dissolution:**
See assessment below in B.2 section.

[1] \\CDSESUB1\EVSPROD\nda218879\0003\m3\32-body-data\32p-drug-prod\lamotrigine-oral-suspension-dpt-laboratories-ltd\32p5-contr-drug-prod\32p54-batch-analys\batch-analyses-2.pdf
[2] \\CDSESUB1\EVSPROD\nda218879\0003\m3\32-body-data\32s-drug-sub\lamotrigine- (b) (4) \32s1-gen-info\general-properties.pdf

## B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

**Assessment: Inadequate**

**Dissolution Method Development:**

(b) (4)

[redacted]

[3] \\CDSESUB1\EVSPROD\nda218879\0003\m3\32-body-data\32p-drug-prod\lamotrigine-oral-suspension-dpt-laboratories-ltd\32p2-pharm-dev\lamotrigine-ph-profiling-report.pdf

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(b) (4)

***Discriminating Ability:***
The Applicant did not investigate the discriminating ability of the originally proposed dissolution method or the revised test condition toward critical bioavailability attributes (CBA's).

In response to IR, the Applicant revised the dissolution method (replaced the media (b) (4) ) but did not provide additional information/data for selection of the method/test condition or method's discriminatory ability. Instead, the Applicant justified using the pH-profiling (Test vs LD) in Study Report (PTS-RPT.0054.01) to demonstrates that (b) (4) as dissolution medium has the discriminating ability and the acceptance criterion established to reject the batches (failed similarity testing) (see ***Appendix 1***). This Reviewer determines that the responses are inadequate and the proposed dissolution method cannot be accepted.

***Acceptance Criterion:***
The Applicant proposed a dissolution acceptance criterion as Q=(b) (4)% in (b) (4) minutes for serving as quality control for batch release and stability testing. In view of the deficiencies pertaining to the dissolution method and data (***Appendix 2***), an appropriate dissolution acceptance criterion will be assessed after the dissolution method is found acceptable.

**B.3 BRIDGING OF FORMULATIONS:**
**Assessment: Adequate**

There has been no change for formulation composition throughout the drug development. Additionally, the to-be-marketed formulation/product was used in the bioavailability (BA) study comparing to LD under fasting condition and in food-effect BA studies (refer to Office of Clinical Pharmacology review). Therefore, it is determined that no additional in vitro or in vivo study is needed to bridge the formulation/product.

**Table 4. Formulation composition[5]:**

[5] \\CDSESUB1\EVSPROD\nda218879\0007\m3\32-body-data\32p-drug-prod\lamotrigine-oral-suspension-dpt-laboratories-ltd\32p1-desc-comp\description-and-composition.pdf

| Ingredients | Amount per dose (mg/mL) | % (w/v) | Amount per exhibit batch (kg) | Pharmaceutical Function | Quality Standards |
|---|---|---|---|---|---|
| **Active Ingredient** | | | | | |
| Lamotrigine | 10.0000 | 1.0000 | (b) (4) | Active | USP |
| **Inactive Ingredients** | | | | | |
| Carboxymethylcellulose Sodium | | | | | USP |
| Xanthan Gum | | | | | NF |
| (b) (4 | | | | | NF |
| Sodium Benzoate | | | | | NF |
| Sodium Phosphate Dibasic (b) (4) | | | | | USP |
| Saccharin Sodium (b) (4) | | | | | USP |
| Polyethylene Glycol (b) (4) | | | | | NF |
| Sorbitol Solution | | | | | USP |
| Methylparaben | | | | | NF |
| FD&C Red No. 40 (b) (4) | | | | | NA |
| FD&C Yellow No. 6 (b) (4) | | | | | NA |
| Propylene Glycol | | | | | USP |
| Glycerin | | | | | USP |
| Cherry Flavor, (b) (4) | | | | | NA |
| Sucralose | | | | | USP/NF |
| Purified Water | | | | | USP |

***Primary Biopharmaceutics Assessor's Name and Date:***
*Swapna Pamu, MS; 12/12/2024*

***Secondary Assessor Name and Date:***
*Ta-Chen Wu, Ph.D., 12/12/2024*

## Appendix 1

**Information Request (dated 5/15/2024) and Applicant's Responses (dated 6/14/2024):**

1. We acknowledge that you have implemented the dissolution method listed in "FDA dissolution methods database" for lamotrigine tablets and did not conduct any method development studies nor discriminating ability studies to justify the suitability of the dissolution method for your test product. Note that every formulation is different and therefore, submission of method development and validation reports demonstrating the discriminatory ability of the proposed method is required in your submission. In general, method development should explore the suitability of each selected parameter (Apparatus, media, volume of the media, rpm etc.,).

   **Applicant's response:** Applicant stated that they have developed a discriminatory dissolution method based on the dissolution testing pH profiling studies and the FDA dissolution method database for Lamotrigine Tablets. The new dissolution method uses same parameters that are listed in FDA dissolution methods database for lamotrigine tablets with the exception of the media (b) (4)

   **Reviewer's comments:** In response to the above deficiency, the Applicant revised the proposed dissolution method by changing the media (b) (4) [6]. The Applicant provided comparative dissolution profiles of test and LD in (b) (4) media as shown below.

(b) (4)

   Based on the submitted data, dissolution profile of the proposed drug product is discriminatory compared to the profile in (b) (4) media. However, the applicant did not provide justification for the selection of (b) (4) compared to (b) (4). In general, (b) (4) is not a preferred dissolution medium because it lacks buffering capacity. It is noted that above profiles appear same as the profiles submitted in the original submission. In addition, the applicant did not provide method development data for the selected apparatus, rpm and media volume. Applicant's response is inadequate and will be asked to provide complete method development report.

[6] \\CDSESUB1\EVSPROD\nda218879\0010\m3\32-body-data\32p-drug-prod\lamotrigine-oral-suspension-dpt-laboratories-ltd\32p2-pharm-dev\method-development-report_dissolution_pts-rpt-0057.pdf

2. We recommend that you submit data to demonstrate the discriminating ability using the proposed dissolution method/test conditions. Please be advised that in general, the tests conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations in the most relevant critical material attributes, critical formulation variables, and critical process parameters (i.e., ± 10-20% change to the specification-ranges of these variables). A discriminating method (along with the selected acceptance criterion) should be able to reject batches that failed similarity testing. In addition, if available, submit data showing that the selected dissolution method (along with the selected dissolution acceptance criterion) can reject batches that are not bioequivalent to the reference batch (e.g., biobatch).

   **Applicant's response:** pH profiling (test vs listed drug) Study Report (PTS-RPT.0054.01) demonstrates that (b) (4) has the discriminating ability. The acceptance criterion established would be able to reject the batches (failed similarity testing).

   **Reviewer's comments:** The applicant did not provide data to demonstrate discriminating ability using the proposed dissolution method/test conditions towards the critical bioavailability attributes. Applicant's response is inadequate and will be asked to provide additional data to demonstrate the discriminating ability of the proposed method.

3. For setting of dissolution acceptance criterion and in support of an NDA application and approval, we typically require dissolution profile data with n=12 for each batch of biobatch and registration batches across strengths in Excel or *.xpt* files. We request that you provide the complete dissolution profile data [individual (n=12) for each batch, mean, range, %RSD at each time point], with individual data of these batches being presented in tabular and graphical formats.

   **Applicant's response:** Dissolution profile data with n=12 has been provided for the biobatch, registration batches and one batch of the listed drug in Excel format in Section 3.2.P.2. Excel contains complete dissolution profile data [individual (n=12) for each batch, mean, range, %RSD at each time point] for the biobatch and registration batches of Lamotrigine Oral Suspension, 10 mg/mL.

   **Reviewer's comments:** In response to the above deficiency, the applicant provided dissolution profile data from 3 exhibit batches of the proposed drug product and LD using the proposed dissolution method. The applicant proposed same acceptance criterion of NLT (b) (4) % (Q) of the labeled amount of lamotrigine is dissolved in (b) (4) minutes.

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## Appendix 2

**Biopharmaceutics Deficiencies for the Applicant:**

We acknowledge that you have provided additional information regarding the dissolution method in response to the deficiencies on June 14, 2024. However, the provided information is not satisfactory based on the current practice within the agency. Please see below for the additional information we recommend you provide and justification for the request.

1. We acknowledge that you have revised the dissolution method by changing the dissolution media (b) (4). Note that (b) (4) is not recommended as dissolution medium because it lacks buffering capacity. Therefore, an aqueous dissolution medium with buffering capacity within physiological pH range is recommended.

2. The solubility data show that lamotrigine is poorly soluble within the physiologic pH range of 1.2 to 6.8. However, the drug product seems to exhibit rapid to very rapid dissolution. Understanding this discrepancy may aid in the development of a dissolution method that is suitable for the proposed drug product. Note that for oral suspension drug products, you should include investigation of lower paddle speeds, e.g., 25, 30, 35, and 40 rpm, in your method development. Additionally, each sample tested should be taken from different bottle and same volume should be administered according to the labeling dosing instruction. The selection of the test conditions/parameters needs to be justified with supporting information and data.

3. We recommend you explore the discriminating ability of the proposed dissolution method/test conditions and submit that data. In general, the tests conducted to demonstrate the discriminating ability should compare the dissolution profiles of the reference (target) batch and batches that are intentionally manufactured with meaningful variations in the most relevant critical material attributes, critical formulation variables, and critical process parameters (i.e., ± 10-20% change to the specification-ranges of these variables). A discriminating method (along with the selected acceptance criterion) should be able to reject batches that fail similarity testing. In addition, if available, submit data showing that the selected dissolution method (along with the selected dissolution acceptance criterion) can reject batches that are not bioequivalent to the reference batch (i.e., the biobatch).

4. You should generate new dissolution profile data for clinical/registration batches using the revised dissolution method and propose an appropriate acceptance criterion based on the newly generated profile data and taking into consideration results of method's discriminating ability.

5. Note that comparison of the dissolution profile of the proposed product to the listed drug is not needed.

Swapna Pamu

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Ta-Chen Wu

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U.S. FOOD & DRUG ADMINISTRATION

# MICROBIOLOGY

| | |
|---|---|
| **Product Information** | |
| **NDA Number** | 218879 |
| **Assessment Cycle Number** | 1 |
| **Drug Product Name / Strength** | Lamotrigine Oral Suspension, 10 mg/mL<br>(Proprietary name: Subvenite) |
| **Route of Administration** | Oral solution |
| **Applicant Name** | OWP Pharmaceuticals, Inc.. |
| **Manufacturing Site** | DPT Laboratories Limited<br>307 E. Josephine Street<br>San Antonio, TX, 78215<br>FEI: 1628114 DUNS: 832224526 |
| **Method of Sterilization** | N/A. Drug product is non-sterile |

***Assessment Recommendation:*** **Adequate**

***Theme: N/A***

| | |
|---|---|
| ☐ N/A | ☐ Depyrogenation Validation Data |
| ☐ Product Sterility Assurance | ☐ Product Release and/or Stability Specifications |
| ☐ Media Fill Data | ☐ Validation for Product Release and/or Stability Test Method |
| ☐ Validation of Product Test | ☐ Other (Requires Division Director Approval) |
| ☐ Due to Consult | |

***Justification:*** N/A

**Assessment Summary:** The submission **recommended** for approval on the basis of sterility assurance.

**List Submissions Being Assessed:**

| Submit | Received | Review Request | Assigned to Reviewer |
|---|---|---|---|
| March 3, 2024 | March 4, 2024 | N/A | May 20, 2024 |

| | | | |
|---|---|---|---|
| (eCTD Sequence #0003) | | | |
| June 18, 2024 (eCTD Sequence #0011) | June 18, 2024 | N/A | June 20, 2024 |

June 18, 2024 submission is response to Agency June 4, 2024 Information Request.

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

**Concise Description of Outstanding Issues:** N/A

**Select Number of Approved Comparability Protocols: 0**

## P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –**
  The drug product, Lamotrigine Oral Suspension is a non-sterile pink suspension with cherry odor for oral administration filled as 10 mg/mL in 8 oz multi-dose HDPE bottle.

- **Drug product composition** –

| Ingredient | Quantity per mL (mg/mL) | Function |
|---|---|---|
| Lamotrigine, USP | 10.00 mg | Active Pharmaceutical Ingredient |
| Carboxymethylcellulose Sodium, USP | (b) (4) | |
| Xanthan Gum, NF | | |
| (b) (4) | | |
| Sodium Benzoate, NF | | |
| Sodium Phosphate Dibasic (b) (4), USP | | |
| Saccharin Sodium (b) (4), USP | | |
| Polyethylene Glycol (b) (4), NF | | |
| Sorbitol Solution, USP | | |
| Purified water, USP | | |
| Propylene Glycol, USP | | |
| Methylparaben, NF | | |
| (b) (4) | | |
| (b) (4) | | |
| FD&C Red No. 40 (b) (4) | | |
| FD&C Yellow No. 6 (b) (4) | | |
| (b) (4) | | |

| | |
|---|---|
| (b) (4) | (b) (4) |
| Glycerin, | |
| (b) (4) | |
| (b) (4) | |
| Cherry Flavor, (b) (4) | |
| Sucralose, USP/NF | |
| (b) (4) | |

- **Description of container closure system –**

| Component | Description | Manufacturer and Distributor |
|---|---|---|
| Container | 8 oz Oblong HDPE white bottle | Manufacturer: (b) (4) |
| Closure | (b) (4), 28 mm (b) (4), Child Resistant white closure with Liner | Manufacturer: (b) (4) |

**Additional Information and Analysis**, container/closure:
The 8 oz Oblong HDPE white bottle is (b) (4) manufactured (b) (4)
(b) (4)

(b) (4)
(b) (4) Microbial specifications for the (b) (4) were not provided. Since the drug product is non-sterile and microbial limits set for the drug solution, no further comment will be made.

**Reviewer's Assessment: Adequate**

(b) (4)



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/s/

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