

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**216660Orig1s000**

**PRODUCT QUALITY REVIEW(S)**

**RECOMMENDATION: Approval**

**NDA 216660  
Review # 1**

|                                |                                        |
|--------------------------------|----------------------------------------|
| <b>Drug Product Name</b>       | Sodium Phenylbutyrate and Taurursodiol |
| <b>Dosage Form</b>             | for Oral Suspension                    |
| <b>Strength</b>                | 3g/1g                                  |
| <b>Route of Administration</b> | Oral                                   |
| <b>Rx/OTC Dispensed</b>        | Rx                                     |
| <b>Applicant</b>               | Amylyx Pharmaceuticals                 |
| <b>US agent, if applicable</b> | N/A                                    |

**QUALITY TEAM**

| <b>Discipline</b>                          | <b>Primary Assessment</b> | <b>Secondary Assessment</b> |
|--------------------------------------------|---------------------------|-----------------------------|
| <b>Drug Substance</b>                      | Katharine Duncan          | Gaetan Ladouceur            |
| <b>Drug Product</b>                        | Grace Chiou               | Martha Heimann              |
| <b>Manufacturing</b>                       | Miral Patel               | Ramesh Dandu                |
| <b>Microbiology</b>                        | Eric Adeeku               | Paul Dexter                 |
| <b>Biopharmaceutics</b>                    | Leah Falade               | Tapash Ghosh                |
| <b>Regulatory Business Process Manager</b> | Erica Keafer              |                             |
| <b>Application Technical Lead</b>          | Martha Heimann            |                             |
| <b>Laboratory (OTR)</b>                    | N/A                       | --                          |
| <b>Environmental</b>                       | N/A                       | --                          |

**Documents Assessed**

| <b>Submission(s)</b>     | <b>Document Date</b> | <b>Discipline(s) Affected</b>  |
|--------------------------|----------------------|--------------------------------|
| SD-1, Original NDA       | 10/29/2021           | All                            |
| SD-3, Labeling/PPI Draft | 11/10/2021           | Drug product                   |
| SD-5, Response to IR     | 11/19/2021           | Drug substance                 |
| SD-6, Response to IR     | 11/24/2021           | Drug product, biopharmaceutics |
| SD-7, Response to IR     | 11/29/2021           | Drug product                   |
| SD-10, Response to IR    | 12/14/2021           | Drug product (environmental)   |

| <b>Submission(s)</b>       | <b>Document Date</b> | <b>Discipline(s) Affected</b> |
|----------------------------|----------------------|-------------------------------|
| SD-11, Response to IR      | 12/20/2021           | Manufacturing                 |
| SD-13, Labeling/PI Draft   | 1/7/2022             | Drug product                  |
| SD-15, Quality Information | 1/12/2022            | Manufacturing                 |
| SD-19, Response to IR      | 1/28/2022            | Drug product                  |
| SD-24, Response to IR      | 2/11/2022            | Manufacturing                 |
| SD-25, Response to IR      | 2/22/2022            | Drug substance                |
| SD-26, Response to IR      | 2/23/2022            | Biopharmaceutics              |
| SD-31, Response to IR      | 3/9/2022             | Drug product                  |
| SD-32, Response to IR      | 3/10/2022            | Drug substance                |
| SD-35, Response to IR      | 3/14/2022            | Drug substance                |

# QUALITY ASSESSMENT DATA SHEET

## 1. RELATED/SUPPORTING DOCUMENTS

### A. DMFs:

| DMF #   | Type | Holder | Item Referenced | Status   | Date Assessed | Comments |
|---------|------|--------|-----------------|----------|---------------|----------|
| (b) (4) | II   |        | (b) (4)         | Adequate | 12/17/2021    | S Kelly  |
|         | II   |        |                 | Adequate | 3/7/2022      | K Duncan |
|         | III  |        |                 |          |               |          |
|         | IV   |        |                 |          |               |          |
|         | IV   |        |                 |          |               |          |

### B. Other Documents: *IND, RLD, or sister applications*

| Document | Application Number | Description                                  |
|----------|--------------------|----------------------------------------------|
| IND      | 129563             | Development of AMX-0035 for treatment of ALS |

## 2. CONSULTS

None

# EXECUTIVE SUMMARY

## I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The Office of Pharmaceutical Quality Review team has assessed NDA 216660 with respect to Chemistry, Manufacturing, and Controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such OPQ recommends approval of this NDA from a quality perspective.

## II. SUMMARY OF QUALITY ASSESSMENTS

### A. Product Overview

The applicant seeks approval for AMX0035, which is a fixed dose combination drug containing sodium phenylbutyrate and taurursodiol. The proposed indication is for use in treatment of amyotrophic lateral sclerosis (ALS).

The proposed product is a powder for oral suspension, to be marketed in single-dose packets containing 3 g sodium phenylbutyrate and 1 g taurursodiol per packet. The proposed dose is one packet twice daily. (b) (4)

Sodium phenylbutyrate is a prodrug that is rapidly metabolized to phenylacetate in vivo. It was initially approved in 1996 for prevention and treatment of hyperammonemia in patients with urea cycle disorder. Taurursodiol is the taurine conjugate of ursodiol. Both taurursodiol and ursodiol are endogenous bile salts. Ursodiol is approved for treatment of primary biliary cholestasis. Taurursodiol is not approved as a drug in US and is considered a new molecular entity.

|                                                                     |                                              |
|---------------------------------------------------------------------|----------------------------------------------|
| <b>Proposed indication(s) including intended patient population</b> | Treatment of ALS                             |
| <b>Duration of treatment</b>                                        | Chronic                                      |
| <b>Maximum daily dose</b>                                           | 6 g sodium phenylbutyrate / 2 g taurursodiol |
| <b>Alternative methods of administration</b>                        | None                                         |

## B. Quality Assessment Overview

### **Drug Substance:** Adequate

CMC information for sodium phenylbutyrate is cross-referenced to DMF (b) (4). This DMF was last reviewed by S. Kelly on 12/17/2021 and found to be adequate. The retest period for sodium phenylbutyrate is (b) (4) months when stored at (b) (4).

CMC information of taurursodiol is cross-referenced to DMF (b) (4). DMF (b) (4) was reviewed by K. Duncan on 3/7/2022 and found to be adequate. The retest period for taurursodiol is (b) (4) months when stored at (b) (4).

Information submitted directly to the NDA for sodium phenylbutyrate and taurursodiol includes general information (nomenclature, structure, physical properties), structures of impurities, and specifications. All information submitted to the NDA is consistent with the referenced DMFs.

### **Drug Product:** Adequate

The drug product is provided in a single strength containing 3 g of sodium phenylbutyrate and 1 g of taurursodiol, respectively. The formulation contains compendial excipients, i.e., dextrates (b) (4), sorbitol, sodium phosphate dibasic (b) (4), sucralose, silicon dioxide, sodium stearyl fumarate, and maltodextrin, at levels. With the exception of sucralose and maltodextrin, which are GRAS substances, the compendial excipients are used at levels consistent with previously approved products. The formulation also contains two noncompendial ingredients, i.e., a (b) (4) and a mixed berry flavoring. The final drug product is packaged in a single dose laminate packet as the primary container closure. The drug product is to be reconstituted in 8 oz of water with vigorous stirring and taken within one hour. The Applicant provided in-use stability data to support the compatibility of the drug product with water and in-use period.

The proposed specification includes appropriate tests for an oral dosage form and justification for tests omitted from the specification. Analytical methods adequately validated.

The drug product is to be stored at 20°C - 25°C. The applicant proposed a shelf life of (b) (4) months. However, the maximum shelf life that can be granted based on the data provided is **12 months**.

**Labeling: Adequate**

Minor deficiencies identified in the proposed labeling and carton container labels were communicated to the clinical division and will be addressed during labeling negotiations.

**Manufacturing: Adequate**

The drug product - AMX0035 Powder for Oral Suspension is immediate release powder for oral suspension indicated to treat amyotrophic lateral sclerosis. The drug product is intended to be taken by emptying one packet in a cup containing 8 oz of water stirred well and taken orally within 60 minutes. It contains two active pharmaceutical ingredients (APIs) – sodium phenylbutyrate (3 g) and taurursodiol (1 g). Sodium phenylbutyrate is a highly soluble compound. Taurursodiol is a poorly soluble compound [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

The applicant has provided development studies to support the proposed parameter ranges for the commercial scale equipment, and a detailed explanation of their control strategy. The clinical/primary stability batch is manufactured at (b) (4) facility, and packaged into unit dose sachets at (b) (4), which are the commercial sites.

All the associated facilities for manufacture and testing of sodium phenylbutyrate, taurursodiol, and AMX0035 Powder for Oral Suspension are acceptable at this time. Facility status should be verified prior to final action.

**Biopharmaceutics: Adequate**

The primary study in support of this NDA is a 24-week, randomized, double-blind, placebo-controlled study and a follow-on open-label extension in patients on ALS standard of care medications. During the product development, three different formulations were manufactured, with Formulation 3 being (b) (4) as the to-be-marketed (TBM) formulation. Per Agency advice<sup>1</sup>, (b) (4)

However, dissolution testing was used to bridge the formulations throughout the product development.

The review focuses on the Biopharmaceutics evaluation and acceptability of the bridging throughout the product development as summarized below.

The first formulation (Formulation 1) was developed and manufactured at (b) (4) in (b) (4). Formulation 1 was used in the pivotal clinical study (AMX3500). Formulation 2 was further optimized by (b) (4). The optimized Formulation 2 was used in the open-label extension (Study AMX3500-OLE). Formulation 3, which is (b) (4) as the TBM formulation, was also manufactured at (b) (4).

and the release is similar between all batches. Therefore, the dissolution data support the bridging of the formulations.

**Microbiology: Adequate**

The proposed product is a nonsterile unit-dose powder that will be used to prepare the oral suspension immediately prior to dosing. The product specification includes appropriate testing and acceptance criteria that comply with USP <1111>. The

<sup>1</sup> Preliminary comments for CMC-only preNDA meeting dated 9/25/2020.  
<https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8059a778&showAsPdf=true>

sponsor has met regulatory expectations for USP <61> and <62> method suitability testing for a nonsterile drug product.

**Environmental: Adequate**

The Applicant submitted a claim of categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR 25.31(b), which is for substances that increase in use but result in an expected introduction concentration (EIC) of < 1 ppb. In response to an IR the applicant submitted environmental toxicity and other EA data and analysis to rule out the potential for hormonal activity<sup>2</sup>. The required statement of no extraordinary circumstances was provided, in accordance with 21 CFR 25.15. Therefore, the claim of categorical exclusion from an EA is acceptable.

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<sup>2</sup> Per FDA guidance: Environmental Assessment: Questions and Answers Regarding Drugs with Estrogenic, Androgenic, or Thyroid Activity, 2016

**C. Risk Assessment**

| From Initial Risk Identification |                                                                                                     |                      | Review Assessment        |                       |          |
|----------------------------------|-----------------------------------------------------------------------------------------------------|----------------------|--------------------------|-----------------------|----------|
| Attribute/ CQA                   | Factors that can impact the CQA                                                                     | Initial Risk Ranking | Risk Mitigation Approach | Final Risk Evaluation | Comments |
| Assay, stability                 | Formulation, container closure, moisture, process parameters, raw materials, scale, equipment, site | Low                  | (b) (4)                  | Adequate              |          |
| Physical stability (solid state) |                                                                                                     | Low                  |                          | Adequate              |          |
| Content uniformity               |                                                                                                     | Low                  |                          | Adequate              |          |
| Reconstitution time              |                                                                                                     | Low                  |                          | Adequate              |          |
| Microbial limits                 |                                                                                                     | Low                  |                          | Adequate              |          |
| Palatability                     | Formulation, excipient changes, container closure, moisture, raw materials                          | Moderate             |                          | Adequate              |          |

**D. List of Deficiencies for Complete Response**

Not applicable.

*Application Technical Lead Name and Date:*

*Martha R. Heimann, Ph.D.*

Senior Product Quality Assessor for Neurology Products  
Office of New Drug Products

4/18/2022



Martha  
Heimann

Digitally signed by Martha Heimann

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# CHAPTER IV: LABELING

## [IQA NDA Assessment Guide Reference](#)

### 1.0 PRESCRIBING INFORMATION

**Assessment of Product Quality Related Aspects of the Prescribing Information:** The labeling was assessed on February 8, 2022. The labeling assessed in this review was submitted in eCTD 0001.

### 1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

| Item                                                                                                                                                                                          | Information Provided in the NDA     | Assessor's Comments                                                                                                                                |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Product Title in Highlights</b>                                                                                                                                                            |                                     |                                                                                                                                                    |
| Proprietary name                                                                                                                                                                              | (b) (4) (sodium                     | Inadequate<br>Revise to<br>(b) (4) (sodium phenylbutyrate and taurursodiol), for oral suspension. "Ursodoxicoltaurine" is used outside of the U.S. |
| Established name(s)                                                                                                                                                                           | phenylbutyrate/ursodoxicoltaurine), |                                                                                                                                                    |
| Route(s) of administration                                                                                                                                                                    | for oral (b) (4)                    |                                                                                                                                                    |
| <b>Dosage Forms and Strengths Heading in Highlights</b>                                                                                                                                       |                                     |                                                                                                                                                    |
| Summary of the dosage form(s) and strength(s) in metric system.                                                                                                                               | (b) (4)                             | Inadequate<br>Revise "sachet" to "packet" throughout.                                                                                              |
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"                                                                     | NA                                  | NA                                                                                                                                                 |
| For injectable drug products for parental 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. |  |  |
|-----------------------------------|--|--|

## 1.2 FULL PRESCRIBING INFORMATION

### 1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

| Item                                                                                                                                                                                                                        | Information Provided in the NDA                                                                                                                                                     | Assessor's Comments                                                                                                                                                                                                                                                                                                          |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>DOSAGE AND ADMINISTRATION section</b>                                                                                                                                                                                    |                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                              |
| Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product) | The contents of one sachet are to be vigorously stirred with a cup (8oz.) of room temperature water and taken orally or administered via feeding tube within 1 hour of preparation. | <p>Inadequate<br/>Revise to include length of time for stirring to avoid confusion.</p> <p>Remove "room temperature" from PI or add to Medication Guide as this is not consistent with carton and container labels.</p> <p>As the product may be administered via feeding tube, we recommend you include a rinse volume.</p> |

### 1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

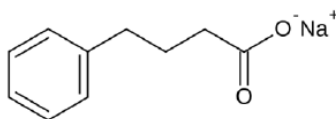
| Item                                                                                                                                                                                                                             | Information Provided in the NDA                            | Assessor's Comments                                                                                                                                                                                                                                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>DOSAGE FORMS AND STRENGTHS section</b>                                                                                                                                                                                        |                                                            |                                                                                                                                                                                                                                                                |
| Available dosage form(s)                                                                                                                                                                                                         | Powder for oral suspension.                                | <p><b>Inadequate</b><br/> <b>Revise to include color of powder and replace "sachet" with "packet."</b><br/> <b>Note, this qualifies for an exception to the USP Salt Policy as sodium phenylbutyrate is available in a tablet and powder form already.</b></p> |
| Strength(s) in metric system                                                                                                                                                                                                     |                                                            |                                                                                                                                                                                                                                                                |
| If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance                                                                                                                                                   | (b) (4) is a (b) (4) powder-filled sachet                  |                                                                                                                                                                                                                                                                |
| A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting                                                                                                   | containing 3 g sodium phenylbutyrate and 1 g taurursodiol. |                                                                                                                                                                                                                                                                |
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"                                                                                                        | NA                                                         |                                                                                                                                                                                                                                                                |
| For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package. |                                                            |                                                                                                                                                                                                                                                                |

**1.2.3 Section 11 (DESCRIPTION)**

| Item                                                                                                                                                                                                    | Information Provided in the NDA                                                                                                                                  | Assessor's Comments                                                                                                                                                                                                                                                                                                                                                                                                              |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>DESCRIPTION section</b>                                                                                                                                                                              |                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Proprietary and established name(s)                                                                                                                                                                     | (b) (4) is a white to yellow powder for oral suspension that consists of fine to large granules.                                                                 | <p><b>Inadequate</b><br/> Revise to ensure all inactive ingredients are listed in alphabetical order. See above regarding USP Salt Policy.</p> <p>Remove "(b) (4)" from (b) (4) dextrans. Ensure inactive ingredient names are aligned with Medication Guide (e.g., silicon dioxide vs (b) (4), maltodextrin vs (b) (4) (maltodextrin). Additionally, replace (b) (4) with individual components of the flavoring excipient.</p> |
| Dosage form(s) and route(s) of administration                                                                                                                                                           |                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.                                                                                   | (b) (4) is supplied in a sachet containing 3 g sodium phenylbutyrate and 1 g taurursodiol. Each sachet also contains the following inactive ingredients: (b) (4) |                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.                                                                                                                            | dextrans, sorbitol, sodium phosphate dibasic (b) (4), silicon dioxide, sucralose, sodium stearyl fumarate, maltodextrin, (b) (4) and mixed berry flavoring.      |                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 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. | NA                                                                                                                                                               | NA                                                                                                                                                                                                                                                                                                                                                                                                                               |
| If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol                                                                                                |                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Statement of being sterile (if applicable)                                                                                                                                                              |                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Pharmacological/therapeutic class                                                                                                                                                                       |                                                                                                                                                                  | <p><b>Inadequate</b><br/> Revise to include therapeutic class.</p>                                                                                                                                                                                                                                                                                                                                                               |
| Chemical name, structural formula, molecular weight                                                                                                                                                     |                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| If radioactive, statement of important nuclear characteristics.                                                                                                                                         |                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                  |

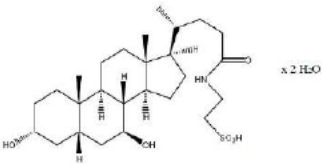
Other important chemical or physical properties (such as pKa or pH)

(b) (4) contains two active ingredients: phenylbutyrate (PB) and taurursodiol. The chemical designation for phenylbutyrate is 4-phenyl butyric acid sodium salt. Its molecular formula is  $C_{10}H_{11}NaO_2$ , and its molecular weight is 186.2 (b) (4). The phenylbutyrate chemical structure is:



Sodium phenylbutyrate is a white or yellow (b) (4) powder which decomposes at about 220°C. It is freely soluble in water and methanol, sparingly soluble in ethanol, practically insoluble in methylene chloride, acetone, diethyl ether.

Taurursodiol, also known as tauroursdeoxycholic acid, is an ambiphilic bile acid and is the taurine conjugate of ursodiol, also known as ursodeoxycholic acid. The chemical name of taurursodiol is 2-[(3 $\alpha$ , 7 $\beta$ -dihydroxy-24-oxo-5 $\beta$ -cholan-24-yl) amino] ethane sulfonic acid, dihydrate. The molecular formula is  $C_{26}H_{45}NO_6S \cdot 2H_2O$  and the molecular weight is 535.74

|  |                                                                                                                                                                                                                                                                                                                                                                                                                         |  |
|--|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
|  | <p>(dihydrate). The taurursodiol chemical structure is:</p>  <p>Taurursodiol is a white microcrystalline powder, practically odorless, with a bitter taste. It is freely soluble in ethyl alcohol, very slightly soluble in acetone and dioxane, sparingly soluble in water, and practically insoluble in ether and ethyl acetate.</p> |  |
|--|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|

#### Section 11 (DESCRIPTION) Continued

| Item                                                                                                                                                  | Information Provided in the NDA | Assessor's Comments |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|---------------------|
| For oral prescription drug products, include gluten statement if applicable                                                                           | NA                              | NA                  |
| Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity") |                                 |                     |

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

| Item                                                                                                                                                                                                                                                                                                                                                                    | Information Provided in the NDA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Assessor's Comments                                                                                                                                                                                                                                |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>HOW SUPPLIED/STORAGE AND HANDLING section</b>                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                    |
| <p>Available dosage form(s)</p> <p>Strength(s) in metric system</p> <p>Available units (e.g., bottles of 100 tablets)</p> <p>Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number</p>                                                                                                                                           | <p>Single-dose sachets of powder for oral suspension</p> <p>The primary packaging of the drug product is a laminate-pouch sachet.</p> <p>The secondary packaging configurations are:</p> <p>Seven individual sachets filled into a carton (7 sachets total)</p> <p>• (b) (4) sachets (14 sachets total) filled in a small carton; 4 small cartons are packed into a larger carton (56 sachets total).</p> <p>Store at controlled room temperature 20°C to 25°C; excursions permitted to 15°C to 30°C. Protect from moisture.</p> | <p>Inadequate</p> <p>Revise to remove (b) (4) packaging as discussed in P.7 of Drug Product review.</p> <p>Additionally, replace "sachet" with "packet."</p> <p>Include NDC numbers.</p> <p>Revise to include temperature range in Fahrenheit.</p> |
| <p>Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"</p> <p>For injectable drug products for parental 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.</p> | <p>NA</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <p>NA</p>                                                                                                                                                                                                                                          |

**Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)**

| Item | Information Provided in the NDA | Assessor's Comments |
|------|---------------------------------|---------------------|
|------|---------------------------------|---------------------|

|                                                                                                                                                                                                                                                                      |             |                                                                                                                                                                                                                                                                               |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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.)                           | See above   | Adequate                                                                                                                                                                                                                                                                      |
| If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”                                                                                                                         | NA          | NA                                                                                                                                                                                                                                                                            |
| Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.                                                                                                                                                             |             |                                                                                                                                                                                                                                                                               |
| Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.” |             |                                                                                                                                                                                                                                                                               |
| Include information about child-resistant packaging                                                                                                                                                                                                                  | Not present | Inadequate<br><div style="background-color: gray; width: 100px; height: 15px; margin-bottom: 5px;"></div> <div style="background-color: gray; width: 100px; height: 15px; margin-bottom: 5px;"></div> <div style="background-color: gray; width: 100px; height: 15px;"></div> |

### 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 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)

| Item                                                                                                                     | Information Provided in the NDA                                                                                  | Assessor's Comments                                                                                |
|--------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| <b>Manufacturing Information After Section 17</b>                                                                        |                                                                                                                  |                                                                                                    |
| Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer | Manufactured and Distributed by:<br>Amylyx Pharmaceuticals, Inc.,<br>43 Thorndike Street,<br>Cambridge, MA 02141 | Inadequate<br>Revise to either<br>"Manufactured for and Distributed by..." or<br>"Distributed by:" |

## 2.0 PATIENT LABELING

**Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):** Revise medication guide so all inactive ingredients are in alphabetical order and use same language as in PI.

**Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."**

## 3.0 CARTON AND CONTAINER LABELING

### 3.1 Container Label



| Item                                                                                                                                               | Information Provided in the NDA | Assessor's Comments about Carton Labeling                                             |
|----------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|---------------------------------------------------------------------------------------|
| Proprietary name, established name, and dosage form (font size and prominence)                                                                     | (b) (4)                         | Inadequate<br>Revise to "sodium phenylbutyrate and taurursodiol"                      |
| Dosage strength                                                                                                                                    | (b) (4)                         | Inadequate<br>“(b) (4)” should be removed                                             |
| Route of administration                                                                                                                            |                                 | Inadequate<br>Revise to include “(b) (4)”                                             |
| If the active ingredient is a salt, include the equivalency statement per FDA Guidance                                                             | See above                       | See above                                                                             |
| Net contents (e.g. tablet count)                                                                                                                   | Single-dose packet              | Adequate                                                                              |
| “Rx only” displayed on the principal display                                                                                                       | (b) (4)                         | Adequate                                                                              |
| NDC number                                                                                                                                         | (b) (4)                         | Adequate                                                                              |
| Lot number and expiration date                                                                                                                     | (b) (4)                         | Adequate                                                                              |
| Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.                                       | (b) (4)                         | Inadequate<br>Revise storage conditions on container to be aligned with carton label. |
| For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use) | NA                              | NA                                                                                    |
| Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.                      |                                 |                                                                                       |

|                                                                                                          |    |    |
|----------------------------------------------------------------------------------------------------------|----|----|
| If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol | NA | NA |
| Bar code                                                                                                 |    |    |

| Item                                                                                                                                                                                                                                                                                                                                                     | Information Provided in the NDA | Assessor's Comments about Carton Labeling               |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|---------------------------------------------------------|
| Name of manufacturer/distributor                                                                                                                                                                                                                                                                                                                         | (b) (4)                         | Adequate                                                |
| Medication Guide (if applicable)                                                                                                                                                                                                                                                                                                                         |                                 | Inadequate<br>Revise to include reference to<br>(b) (4) |
| No text on Ferrule and Cap<br>overseal<br>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.<br>And others, if space is available | NA                              | NA                                                      |

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

Adequate, pending the Applicant's acceptance of the revisions noted above in red. **Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."**

**ITEMS FOR ADDITIONAL ASSESSMENT**

**Not applicable**

***Overall Assessment and Recommendation:***

**This application is recommended for approval per labeling/labels perspective once the following changes (in red) have been made to the label.**



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Chiou

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Martha  
Heimann

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## CHAPTER VI: BIOPHARMACEUTICS

|                                                     |                                                                                             |
|-----------------------------------------------------|---------------------------------------------------------------------------------------------|
| <b>NDA Number</b>                                   | NDA-216660-ORIG-1                                                                           |
| <b>Drug Product Name/ Strength</b>                  | Sodium Phenylbutyrate and Taururosodiol (AMX0035)<br>Powder for Oral Suspension/3 g and 1 g |
| <b>Route of Administration</b>                      | Oral                                                                                        |
| <b>Applicant Name</b>                               | Amylyx Pharmaceuticals Inc.                                                                 |
| <b>Therapeutic Classification/<br/>OND Division</b> | Motor Neuron Disease/Division of Neurology 1 (DN1)                                          |
| <b>RLD/RS Number</b>                                | N/A                                                                                         |
| <b>Proposed Indication</b>                          | For the treatment of Amyotrophic Lateral Sclerosis (ALS)                                    |
| <b>Primary Reviewer</b>                             | Leah W. Falade, PhD.                                                                        |
| <b>Secondary Reviewer</b>                           | Tapash Ghosh, Ph.D.                                                                         |
| <b>Recommendation</b>                               | <b>ADEQUATE</b>                                                                             |

### EXECUTIVE SUMMARY

The Applicant seeks approval for its Sodium Phenylbutyrate and Taururosodiol (AMX0035) Powder for Oral Suspension, 3 g and 1 g. Reference is made to the Investigational New Drug (IND) 129563 submitted under 505(b)(1) dated 04/14/2017. The proposed drug product is a combination of two active pharmaceutical ingredients (APIs), phenylbutyrate (PB, 3 g) and ursodoxicoltaurine (taururosodiol, 1g), designed to reduce neuronal death in persons with amyotrophic lateral sclerosis (ALS) by simultaneously mitigating endoplasmic reticulum stress and mitochondrial dysfunction. The proposed drug product is a powder for oral suspension presented in sachets to be administered orally or through a feeding tube.

The primary study in support of this NDA is a 24-week, randomized, double-blind, placebo-controlled study and a follow-on open-label extension in patients on ALS standard of care medications. During the product development, three different formulations were manufactured, with Formulation 3 being (b) (4) as the to-be-marketed (TBM) formulation. In a Pre-NDA meeting for the IND held on 03/11/2020, an agreement was made with the Agency to (b) (4). However, dissolution testing was used to bridge the formulations throughout the product development.

The review focuses on the Biopharmaceutics evaluation and acceptability of the bridging throughout the product development as summarized below.

**Bridging Throughout Product Development:** The first formulation (Formulation 1) was developed and manufactured at (b) (4). Formulation 1 was used in clinical study #AMX3500. Formulation 2 was further optimized by (b) (4). The optimized Formulation 2 was used in clinical study #AMD3500-OLE. Formulation 3, which is

(b) (4) as the TBM formulation, was also manufactured at (b) (4).  
Dissolution testing was conducted (b) (4)  
(b) (4)  
(b) (4) and the release is similar  
between all batches. Therefore, the dissolution data support the bridging of the formulations.

#### **RECOMMENDATION**

From a Biopharmaceutics perspective, NDA-216660-ORIG-1 for Sodium Phenylbutyrate and Taururosodiol (AMX0035) Powder for Oral Suspension, 3 g and 1 g is **adequate** and recommended for approval.

## BIOPHARMACEUTICS ASSESSMENT

### LIST of SUBMISSIONS BEING REVIEWED

| eCTD # (SDN #) | Received date | Document    |
|----------------|---------------|-------------|
| 0001 (SDN 1)   | 10/29/2021    | Original    |
| 0006 (SDN 6)   | 11/24/2021    | IR Response |
| 0026 (SDN 26)  | 02/23/2022    | IR Response |

### BIOPHARMACEUTICS RELATED INFORMATION

|                              | Sodium Phenylbutyrate                                                                                                                                                                                                                                                                                              | Taururosodiol                                                                                                        |
|------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| <b>BCS Class Designation</b> | None claimed                                                                                                                                                                                                                                                                                                       | None claimed                                                                                                         |
| <b>Solubility</b>            | Freely soluble in water                                                                                                                                                                                                                                                                                            | Sparingly soluble in water                                                                                           |
| <b>Permeability</b>          | High in rats, no data submitted for humans                                                                                                                                                                                                                                                                         | High in rats, no data submitted for humans                                                                           |
| <b>In Vitro Drug Release</b> | (b) (4)                                                                                                                                                                                                                                                                                                            | (b) (4)                                                                                                              |
| <b>Polymorphic form</b>      | Not provided                                                                                                                                                                                                                                                                                                       | Form (b) (4)                                                                                                         |
| <b>Dosing</b>                | For the first 3 weeks of treatment, take 1 sachet daily. After 3 weeks, dosing should be increased to 1 sachet twice a day.<br>The contents of one sachet are to be vigorously stirred with a cup (8oz.) of room temperature water and taken orally or administered via feeding tube within 1 hour of preparation. |                                                                                                                      |
| <b>Absorption</b>            | Sodium phenylbutyrate is rapidly absorbed and reaches a mean C <sub>max</sub> of 188 mcg/mL by a median time of 1 hour.                                                                                                                                                                                            | Taurursodiol is slowly absorbed and reaches a mean C <sub>max</sub> of 0.871 mcg/mL with a median time of 4.5 hours. |
| <b>T<sub>max</sub></b>       | 1 hr                                                                                                                                                                                                                                                                                                               | 4 hr                                                                                                                 |
| <b>Food Effect</b>           | Significantly slower absorption (C <sub>max</sub> reduced by 75%) and lower overall exposure (AUC reduced by 55%) of sodium phenylbutyrate.                                                                                                                                                                        | A high-fat meal did not significantly affect the C <sub>max</sub> for taurursodiol, but AUC was increased by 46%.    |

## **BRIDGING THROUGHOUT PRODUCT DEVELOPMENT**

The first formulation (Formulation 1) was developed and manufactured at (b) (4). Formulation 1 was used in clinical study #AMX3500. Formulation 2 was further optimized by (b) (4). The optimized Formulation 2 was used in clinical study #AMD3500-OLE. Formulation 3, which is (b) (4) as the TBM formulation, was also manufactured at (b) (4). The grade of the API sodium phenylbutyrate was changed between Formulation 2 and 3. The TBM formulation is (b) (4) to Formulation 3 with the exception of the pharmacopeia status of sorbitol, sodium dibasic (b) (4), and silicon dioxide. The 3 formulations are presented in **Table 1** below.

The quantitative composition of Formulation 1 used in Phase 2 Clinical Studies did not contain (b) (4) component, while the TBM formulation contains (b) (4) mg. The addition of this excipient is considered a Level 3 change and is likely to have a significant impact on formulation quality and performance. The Office of Clinical Pharmacology (OCP) sent an Information Request (IR) via email to the Applicant on 11/19/2021 requesting a PK bridging study to bridge Formulation 1 with the TBM formulation<sup>1</sup>. The Applicant responded on 11/24/2021 (SD 6) with supporting information for the claim that changes in (b) (4) and (b) (4) will not alter the bioavailability. Based on the submitted data and internal discussion, Biopharmaceutics recommended that a PK bridging study will not be required.

---

<sup>1</sup> Panorama NDA 216660 Information Request (COR-NDAIR-01) 11/19/2021

**Table 1. Composition of AMX0035 Phase 2 Clinical Drug Product**

| Formulation                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 1                           | 2           | 3                                                                                  | Proposed Commercial |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|-------------|------------------------------------------------------------------------------------|---------------------|
| Clinical Studies                                                                                                                                                                                                                                                                                                                                                                                                                                                               | AMX3500                     | AMX3500-OLE | AMX3500<br>AMX3500-OLE,<br>AMX8000,<br>A35-002,<br>A35-003,<br>A35-005,<br>(b) (4) | -                   |
| <b>Component</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <b>Quantity/Sachet (mg)</b> |             |                                                                                    |                     |
| PB Ph. (b) (4) <sup>a</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 3000                        | 3000        | -                                                                                  | -                   |
| PB USP/Ph. Eur.                                                                                                                                                                                                                                                                                                                                                                                                                                                                | -                           | -           | 3000                                                                               | 3000                |
| Taurursodiol (Supplier Grade)                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 1000                        | 1000.0      | 1000.0                                                                             | 1000.0              |
| Dextrates, (b) (4) NF                                                                                                                                                                                                                                                                                                                                                                                                                                                          | (b) (4)                     |             |                                                                                    |                     |
| Sorbitol (b) (4)                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                             |             |                                                                                    |                     |
| Sorbitol NF/ Ph. Eur. <sup>b</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                             |                             |             |                                                                                    |                     |
| Sodium Phosphate Dibasic, (b) (4)                                                                                                                                                                                                                                                                                                                                                                                                                                              |                             |             |                                                                                    |                     |
| Sodium Phosphate Dibasic, (b) (4) USP/ Ph. Eur. <sup>b</sup>                                                                                                                                                                                                                                                                                                                                                                                                                   |                             |             |                                                                                    |                     |
| (b) (4) (Silicon Dioxide) (b) (4)                                                                                                                                                                                                                                                                                                                                                                                                                                              |                             |             |                                                                                    |                     |
| (b) (4) (Silicon Dioxide) NF/ Ph. Eur. <sup>b,c</sup>                                                                                                                                                                                                                                                                                                                                                                                                                          |                             |             |                                                                                    |                     |
| Sucralose NF/Ph. Eur.                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                             |             |                                                                                    |                     |
| Sodium Stearyl Fumarate NF/Ph. Eur./ JP <sup>d</sup>                                                                                                                                                                                                                                                                                                                                                                                                                           |                             |             |                                                                                    |                     |
| Mixed Berry Flavoring (b) (4)                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                             |             |                                                                                    |                     |
| (b) (4)                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                             |             |                                                                                    |                     |
| Mixed Berry Flavoring (b) (4)                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                             |             |                                                                                    |                     |
| (b) (4)                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                             |             |                                                                                    |                     |
| (b) (4) Maltodextrin NF/Ph. Eur.                                                                                                                                                                                                                                                                                                                                                                                                                                               |                             |             |                                                                                    |                     |
| <b>Total</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                             |             |                                                                                    |                     |
| <p>a. Ph. Eur. = European Pharmacopoeia</p> <p>b. Supplier Certificates of Analysis received at (b) (4) indicated that these ingredients were USP/NF/Ph. Eur. grade; however, the (b) (4) specifications did not require Ph. Eur. grade and Ph. Eur. testing was not performed. The supplier and grade of these materials is unchanged for the commercial formulation.</p> <p>c. Complies with the Ph. Eur. requirements for (b) (4)</p> <p>d. JP = Japanese Pharmacopoeia</p> |                             |             |                                                                                    |                     |

An IR was sent to the Applicant requesting the method development report for the dissolution method used to bridge the manufacturing sites and an acceptance criterion. In the response submitted on 02/23/2022 (Seq 0026), the Applicant referenced the Pre-NDA meeting held on March 11, 2020, where the Agency recommended (b) (4). The Applicant used the following dissolution method to bridge the formulations during product development:

The Applicant provided the validation data for the dissolution method. The method meets the acceptance criteria for system suitability, accuracy, precision, repeatability, stability ( (b) (4) (b) (4) ), filter bias, and robustness. Based on the submitted data, (b) (4) (b) (4) the release is similar between all batches. Therefore, the dissolution data support the bridging of the formulations.



Leah  
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Tapash  
Ghosh

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## CHAPTER VII: MICROBIOLOGY

| Product Information                         |                                                                                               |
|---------------------------------------------|-----------------------------------------------------------------------------------------------|
| NDA Number                                  | 216660                                                                                        |
| Assessment Cycle Number                     | 01                                                                                            |
| Drug Product Name/ Strength                 | (b) (4) (AMX0035)/3 g Sodium phenylbutyrate and 1 g taurursodiol (Powder for Oral Suspension) |
| Route of Administration                     | Oral                                                                                          |
| Applicant Name                              | Amylyx Pharmaceuticals Inc.                                                                   |
| Therapeutic Classification/<br>OND Division | N/A                                                                                           |
| Manufacturing Site                          | (b) (4)                                                                                       |
| Method of Sterilization                     | Non-sterile                                                                                   |

**Assessment Recommendation: Adequate**

**Assessment Summary:** The submission is **recommended** for approval.

**Dates of Submission(s) Covered by this Review**

| Submit     | Received   | eCTD seq./Doc. # | Review Request | Assigned to Reviewer |
|------------|------------|------------------|----------------|----------------------|
| 10/29/2021 | 10/29/2021 | #0001/1          | N/A            | 11/03/2021           |

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

**Remarks:**

This is an electronic submission.  
Goal date is 04/29/2022.

**Concise Description of Outstanding Issues:** No outstanding issues.

**Supporting Documents:** None

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

Description of drug product –  
(section 3.2.P.1).

The drug product is indicated for the treatment of amyotrophic lateral sclerosis (ALS). This powder for oral suspension is a ~10-gram powder-filled sachet containing 3 g sodium phenylbutyrate and 1 g taurursodiol. It is prepared by vigorously stirring with a cup (8 oz.) of room temperature water and taken orally or administered via feeding tube within 1 h of preparation. The drug product is non-sterile and contain no preservatives.

Drug product composition –

(section 3.2.P.1).

| Ingredient                                     | Function          | Amount (mg) |
|------------------------------------------------|-------------------|-------------|
| Sodium phenylbutyrate (PB), USP/ Ph.Eur.       | Active Ingredient | 3000.0 mg   |
| Taurursodiol, Supplier                         | Active Ingredient | 1000.0 mg   |
| (b) (4) Dextrates, NF                          |                   | (b) (4)     |
| Sorbitol, NF/ Ph. Eur.                         |                   |             |
| (b) (4) Sodium Phosphate Dibasic, USP/ Ph.Eur. |                   |             |
| Sucralose, NF/ Ph. Eur.                        |                   |             |
| (b) (4) (Silicon Dioxide), NF/ Ph. Eur.        |                   |             |
| Sodium Stearyl Fumarate, NF/ Ph. Eur. / JP     |                   |             |
|                                                |                   |             |
| Mixed Berry Flavoring, Supplier                | Flavor            | (b) (4)     |

Description of container closure system –  
(section 3.2.P.7).



The primary packaging of the drug product is a laminate-pouch sachet. The secondary packaging configurations are:  
Seven individual sachets filled into a carton (7 sachets total), or  
(b) (4) sachets (fourteen sachets total) filled into a small carton  
and 4 small cartons packed into a larger carton (56 sachets total)

The cartons are not intended to (b) (4)

| Attribute               | Description |
|-------------------------|-------------|
| Description of Material | (b) (4)     |
| Web Width               |             |
| Manufacturer            |             |
| Supplier Part Number    |             |
|                         |             |

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

**Adequate**

### P.3 MANUFACTURE

#### P.3.1 MANUFACTURERS

(section 3.2.P.3.1).

The facilities involved in manufacture of AMX0035 Powder for Oral Suspension are provided below.

| Site and address | Responsibility                                      |
|------------------|-----------------------------------------------------|
| (b) (4)          | Manufacture, release, and stability of drug product |
|                  | Microbial Limits testing                            |
|                  | Packaging drug product into sachets                 |

**Adequate**

#### P.3.3 DESCRIPTION OF THE MANUFACTURING PROCESS AND PROCESS CONTROLS





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Paul  
Dexter

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MARTHA R HEIMANN  
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