CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215602Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION: Approval

NDA 215602
Review #1

Drug Product Name	Fleqsuvy (baclofen)
Dosage Form	Suspension
Strength	5 mg/mL
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Azurity Pharmaceuticals
US agent, if applicable	N/A

QUALITY TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Friedrich Burnett	Donna Christner
Drug Product	Mariappan Chelliah	Julia Pinto
Manufacturing	Ramesh Dandu	Chengjiu Hu
Microbiology	Aditi Das	Yuansha Chen
Biopharmaceutics	Kaushalkumar Dave	Okpo Eradiri
Regulatory Business Process Manager	Erica Keafer	
Application Technical Lead	Martha Heimann	
Laboratory (OTR)	---	---
Environmental	---	---

Submission(s)	Document Date	Discipline(s) Affected
SD-01, Original NDA	4/5/2021	All

SD-02, Response to IR	5/28/2021	Microbiology
SD-03, Response to IR	6/3/2021	Drug product, Manufacturing
SD-04, Response to IR	6/28/2021	Drug product, Biopharmaceutics
SD-05, Response to IR	7/26/2021	Drug product
SD-06, Container Carton Labeling and Response to IR	8/25/2021	Drug product
SD-07, Response to IR	10/5/2021	Biopharmaceutics, Manufacturing
SD-08, Response to IR	11/4/2021	Drug product
SD-09, Container Carton Labeling	11/23/2021	Biopharmaceutics, Drug product
SD-10, Response to IR	12/6/2021	Drug product, Biopharmaceutics
SD-11, Response to IR	12/17/2021	Drug product
SD-12, Container Carton Labeling	12/21/2021	Drug product

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		
	III			--	N/A [1]	
	III			--	N/A [1]	
	IV			Adequate	1/3/2022	M. Chelliah

[1] Adequate information was provided in NDA. Therefore, the DMF was not reviewed.

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

Document	Application Number	Description
IND	133462	Development of oral suspension formulation.
NDA	17851	Novartis NDA for Lioresal (baclofen tablets) is referenced under 505(b)(2) to support safety and efficacy of baclofen.

2. CONSULTS

N/A

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The OPQ review team recommends **APPROVAL** of NDA 215602 for Fleqsuvy (baclofen) oral suspension.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Baclofen is a structural analog of γ-aminobutyric acid (GABA) that was initially approved in 1971 (as Lioresal® tablets) for treatment of spasticity resulting from multiple sclerosis. Per labeling, baclofen may also be of some value in patients with spinal cord injuries and other spinal cord diseases. Other approved dosage forms include a parenteral formulation for IT infusion, ODT, oral solution (1 mg/mL), and oral granules.

The proposed product is a 5 mg/mL, grape flavored, oral suspension to be marketed in a single strength, 5 mg/mL.

Proposed indication(s) including intended patient population	Treatment of spasticity resulting from multiple sclerosis. Patients 12 years and older.
Duration of treatment	Chronic
Maximum daily dose	80 mg
Alternative methods of administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

The synthetic scheme, control of materials, control of critical steps and intermediates, process validation studies, manufacturing process and development, characterization, impurities/degradant characterization, specifications, the analytical procedures, reference standards, container closure system have all been cross-

referenced to DMF (b) (4) and determined to be adequate as per the last review dated 02-FEB-2021 by F. Sequeira.

The Applicant has provided the following information in the NDA for ease of review:

(b) (4)

Information in the DMF supports a retest period of (b) (4)-months while being stored (b) (4)

Drug Product: Adequate

Baclofen Oral Suspension, 5 mg/mL, is an orange to yellow suspension that will be marketed in HDPE bottles containing 120 mL or 300 mL of the suspension, packaged in HDPE bottles. Inactive ingredients include compendial excipients commonly used in the formulation of oral suspension, color additives that meet appropriate regulatory (21 CFR) requirements, and artificial grape flavor. Compendial excipients and color additives are qualified base on prior use at similar or higher levels in FDA-approved oral products. Artificial grape flavor is acceptable based on information the manufacturer's DMF (b) (4) Although the drug product is formulated as a suspension, (b) (4)% of the drug substance is fully dissolved solubilized and only (b) (4)% of the drug is remains as a suspended solid.

The proposed specification is adequate to assure the identity, strength, quality, purity, or potency of the product through the proposed shelf-life. Acceptance criteria for specified, unspecified, and total impurities are consistent with the USP monograph for baclofen tablets and the applicant has justified omission of testing for elemental impurities. Non-compendial analytical methods are adequately validated and provided batch data show that the applicant can manufacture the drug product in consistent quality.

The primary container closures systems meet applicable regulatory and USP requirements. Suitability of container closures to ensure product quality is supported by extractable/leachable studies and available stability data. **Based on the**

available data, the proposed shelf-life of 24 months, when stored at controlled room temperature of 20°C to 25°C (68°F to 77° F), is acceptable.

Labeling: Adequate

The proposed labeling is acceptable from a product quality perspective.

Manufacturing: Adequate

The manufacturing process baclofen oral suspension involves (b) (4)

The applicant proposes to perform (b) (4) scale-up from exhibit/clinical/PK batches. Risk is low (b) (4). The process used to manufacture the clinical and registration batches ((b) (4) kg) is essentially equivalent to the proposed (b) (4) kg commercial manufacturing process and will be confirmed during process validation. All exhibit batches were made on similar equipment (i.e., same design and operating principles) to that proposed for the commercial scale manufacture and at the same facility.

All facilities proposed for manufacture and testing of baclofen drug substance and baclofen oral suspension were evaluated and deemed acceptable based on compliance history and/or recent 704(a)(4) assessment. The final facility recommendation (OMIR) is acceptable. Facility status should be verified prior to final action.

Biopharmaceutics: Adequate

The Biopharmaceutics review evaluated the proposed dissolution method and acceptance criterion. The applicant's originally proposed dissolution method (b) (4) were not justified. (b) (4) The applicant's originally proposed dissolution

acceptance criterion of [redacted] was not supported by the data. Considering, the high solubility of baclofen across the physiological pH, and the simplicity of the composition of the drug product, it dissolves very rapidly and hence it is not possible to develop a discriminating dissolution method. However, the biopharmaceutics risk is low for the proposed drug product owing to the characteristics of the drug substance and the drug product. Based on the provided information and data, revision of the dissolution method and acceptance criterion to 500 mL of 0.01N HCl using USP Apparatus 2 (paddle) at 25 rpm and 'NLT [redacted]% (Q) at 15 minutes', respectively was recommended. The applicant accepted the FDA recommendation and accordingly revised the dissolution method. The revised dissolution method is deemed adequate for quality control (QC) testing of the proposed drug product.

Table 1: FDA's Approved Dissolution Method and Acceptance Criterion for Baclofen Oral Suspension / 5 mg/mL

Apparatus	USP Apparatus 2 (paddle)
Paddle Speed	25 rpm
Volume	500 mL
Medium	0.01N HCl
Temperature	37.0 ± 0.5°C
Acceptance Criterion	NLT [redacted]% (Q) in 15 minutes

In-vitro and/or in-vivo bridging studies are not needed for the proposed product as there were no changes in 1) composition of the proposed product between the clinical batch, exhibit batches, and the proposed commercial batches, 2) product manufacturing site, and 3) manufacturing process in the scale-up.

Microbiology : Adequate

The formulation contains [redacted]. The proposed acceptance criterion for [redacted] assay is supported by results of antimicrobial effectiveness testing (AET) that are data that are consistent with USP <51> criteria for an aqueous oral product (category 3).

Environmental controls in the manufacturing area routine monitoring of the manufacturing and testing facility are described in sufficient detail and deemed adequate to ensure product quality from a microbiology perspective. The finished product specification includes appropriate tests and acceptance criteria for an aqueous oral product and test methods are validated.

Environmental: Adequate

The applicant provided claim for categorical exclusion from environmental assessment under 21 CFR 25.31(b). The expected introduction concentration of the active moiety into the aquatic environment resulting from approval of this product will not exceed 1 ppb.

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 Raw materials Process parameters Scale/equipment/site	**Low**	(b) (4)	**Adequate**	
Physical stability (phase separation)	Formulation Raw materials Process parameters Scale/equipment/site	**Low**		**Adequate**	
Physical stability (solid state)	Formulation Raw materials Process parameters Scale/equipment/site	**Low**		**Adequate**	
Dosing accuracy	Dosing device Formulation Container closure Process parameters Scale/equipment/site	**Low**		**Adequate**	
Palatability	Formulation Excipient change Container closure Process parameters Scale/equipment/site	**Moderate**		**Adequate**	

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Comments**
Leachable/extractables	Formulation Container closure Raw materials Process parameters Scale/equipment/site	**Moderate**	(b) (4)	**Adequate**	
Microbial limits	Formulation Raw materials Process parameters Scale/equipment/site	**Low**		**Adequate**	
Dissolution	Formulation Raw materials Process parameters Scale/equipment/site	**Low**		**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

1/13/2022

Martha Heimann

Digitally signed by Martha Heimann
Date: 1/13/2022 02:25:14PM
GUID: 504f845f00000ed260627d268a8cdc9d

49 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

U.S. FOOD & DRUG ADMINISTRATION

CHAPTER IV: LABELING

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

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Ad

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for 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.	N/A	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active	N/A	

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

ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).		

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Adequate	Shake FLEQSUVY oral suspension well before administration. Discard unused portion 60 days after first opening.
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another	N/A	

section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 11 (DESCRIPTION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	
Dosage form(s) and route(s) of administration	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	N/A	
Chemical name, structural formula, molecular weight	Adequate	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for 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.	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	N/A	

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	Adequate	

1.2.5 Other Sections of Labeling

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

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

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	N/A	No patient labeling provided.
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	N/A	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	N/A	
Alphabetical listing of inactive ingredients (if applicable)	N/A	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	N/A	

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

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

Representative labels extracted from SN0009:

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Inadequate	The carton labels currently do not have this statement. DMEPA has already asked the Applicant to include this in the carton lable.
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, and these products require a "Not for direct infusion" statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
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.	N/A	
And others, if space is available.	N/A	

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

ITEMS FOR ADDITIONAL ASSESSMENT

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

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor: Mariappan V. Chelliah

Secondary Assessor Name: Julia Pinto

Mariappan Chelliah

Digitally signed by Mariappan Chelliah
Date: 1/03/2022 02:09:23PM
GUID: 5399cb2c00032b7c21877aa0d4d5f794

Julia Pinto

Digitally signed by Julia Pinto
Date: 1/03/2022 10:08:26PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

29 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

U.S. FOOD & DRUG ADMINISTRATION

MICROBIOLOGY

Product Information	Indicated for treatment of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity
NDA Number	215602
Assessment Cycle Number	1
Drug Product Name / Strength	Baclofen Oral Suspension (5 mg/mL)
Route of Administration	Oral
Applicant Name	Azurity Pharmaceuticals, Inc.
Manufacturing Site	(b) (4)
Method of Sterilization	Nonsterile, aqueous drug product

Assessment Recommendation: **Adequate**

Theme:

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

Justification: *view justification statements found at:* **Justification Statements**

N/A

Assessment Summary:

- The submission is **recommended** for approval.

List Submissions Being Assessed (table):

Submit	Received	Review Request	Assigned to Reviewer
04/05/2021	04/05/2021	N/A	04/12/2021
05/28/2021	05/28/2021	N/A	06/22/2021

Highlight Key Issues from Last Cycle and Their Resolution: None

Concise Description of Outstanding Issues: NA

Supporting Documents: NA

Select Number of Approved Comparability Protocols: 0

S DRUG SUBSTANCE

(b) (4)

The drug substance is not sterile; therefore, a quality microbiology review of the drug substance is not necessary.

Assessment:

Adequate

P DRUG PRODUCT

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of drug product – The drug product, Baclofen Oral Suspension is a ready-to-use aqueous formulation containing 5.0 mg/mL baclofen. It is an orange to yellow suspension packaged in 2 sizes, i.e., as 120 mL in 150 cc round, white, opaque high-density polyethylene (HDPE) bottles and as 300 mL in 325 cc oblong, white, opaque HDPE bottles.

- **Drug product composition -**
  (3.2.P.1.)

The composition of Baclofen Oral Suspension drug product is reported below:

Name of Ingredient	Function	mg/mL
Baclofen, USP	Active	5
Anhydrous Citric Acid, NF	(b) (4)	
Sodium Benzoate, NF		
Propylene Glycol, USP		
Sucralose, NF		
Hydroxyethyl Cellulose, NF		
Simethicone Emulsion (b) (4), USP		
D&C Yellow No. 10, 21 CFR 74.1710		
FD&C Red No. 40, 21 CFR 74.1340		

Artificial Grape Flavor (b) (4)	(b) (4)
Purified Water, USP	

Assessment:

Adequate

- **Description of container closure system**
(3.2.P.1., 3.2.P.7.)

The drug product suspension is packaged in 2 formats, a 150-cc container closure system and a 325-cc container closure system. Drawings with specifications are provided for each container closure system (CCS). The CCS is shown in Table below:

Component	Material of Construction	Manufacturer
150-cc round HDPE bottle	(b) (4)	
325-cc oblong HDPE bottle		
Cap, (b) (4) foam liner and (b) (4) induction seal		

Assessment: The applicant provided an adequate description of the drug product composition and container closure system.

Adequate

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

7 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Aditi Das

Digitally signed by Aditi Das
Date: 8/27/2021 10:58:42AM
GUID: 59ce55a8001021f51621534263276c8f

Yuansha Chen

Digitally signed by Yuansha Chen
Date: 8/27/2021 11:50:06AM
GUID: 545289f5000727e1136ef94794e114b8

BIOPHARMACEUTICS

PRODUCT BACKGROUND

NDA: 215602; 505(b)(2)
Drug Product Name / Strength: Baclofen Oral Suspension / 5 mg/mL
Route of Administration: Oral
Indication: Treatment of spasticity resulting from multiple sclerosis (MS)
Submission Date: 04/05/2021 (Original)
Applicant Name: Azurity Pharmaceuticals, Inc.

BACKGROUND

The proposed product, a ready-to-use Baclofen Oral Suspension, 5 mg/mL, is a 'convenience dosage form' developed for patients who have difficulty swallowing tablets. It is indicated for the treatment of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity. The listed drug (LLD) for conventional baclofen tablets is LIORESAL® (baclofen) Tablets (Novartis NDA 017851); however, the LD has been discontinued for reasons other than safety or efficacy. Because the RLD has been discontinued, the Applicant conducted the relative bioavailability study using the designated reference standard (RS) listed in the Orange Book (Baclofen Tablet USP [IVAX/Teva ANDA 072235]) as the comparator.

The submission of this 505(b)(2) NDA is supported by a randomized, single-dose, three-way crossover, pivotal bioavailability study (# RM-05-PK001) under fasted and fed conditions. The objective of this study was to assess the relative bioavailability of a test formulation of a single 20 mg dose of Baclofen Oral Suspension [5 mg/mL (4 mL)] and Baclofen Tablet, USP (20 mg) in healthy adults. The current Biopharmaceutics review is focused on evaluation of the proposed dissolution method and acceptance criterion.

REVIEW SUMMARY

Dissolution Method: The Applicant's originally proposed dissolution method (b) (4) were not justified. (b) (4) Considering, the high solubility of baclofen across the physiological pH, and the nature/simplicity of the composition of the drug product, it dissolves very rapidly and hence it is not possible to develop a discriminating dissolution method. However, the biopharmaceutics risk is low for the proposed drug product owing to the characteristics of the drug substance and the drug product. Based on the provided information/data, the Applicant was recommended to revise the

dissolution method to 500 mL of 0.01N HCl using USP Apparatus 2 (paddle) at 25 rpm. The Applicant accepted the FDA recommendation and accordingly revised the dissolution method. The newly proposed dissolution method is deemed adequate for QC testing of the proposed drug product.

Dissolution Acceptance Criteria: The Applicant's originally proposed dissolution acceptance criterion of (b) (4), was permissive and not supported by the data. Based on the provided information/data, the Applicant was recommended to revise the dissolution acceptance criterion to 'NLT(b) (4)% (Q) at 15 minutes'. The Applicant accepted the FDA recommendation and revised the dissolution acceptance criterion accordingly. The Applicant's new dissolution acceptance criterion (not less than (b) (4)% (Q) in 15 minutes) is adequate for quality control testing of the proposed product.

Formulation Bridging: In-vitro and/or in-vivo bridging studies are not needed for the proposed product as there were no changes in 1) composition of the proposed product between the clinical batch, exhibit batches, and the proposed commercial batches, 2) product manufacturing site, and 3) manufacturing process in the scale-up.

Conclusion and Recommendation: From a Biopharmaceutics perspective, Baclofen Oral Suspension, 5 mg/mL, is adequate and recommended for **APPROVAL**.

The approved dissolution method and acceptance criterion for the quality control of the finished immediate release drug product at batch release and during stability testing are summarized in Table 1.

Table 1: FDA's Approved Dissolution Method and Acceptance Criterion for Baclofen Oral Suspension / 5 mg/mL

Apparatus	USP Apparatus 2 (paddle)
Paddle Speed	25 rpm
Volume	500 mL
Medium	0.01N HCl
Temperature	37.0 ± 0.5°C
Acceptance Criterion	NLT (b) (4)% (Q) in 15 minutes

Primary Biopharmaceutics Reviewer Name

Kaushalkumar Dave, Ph.D.
Division of Biopharmaceutics, ONDP, OPQ

I concur with Dr. Dave's Biopharmaceutics assessment and recommendation.

Secondary Reviewer Name
Okpo Eradiri
Division of Biopharmaceutics, ONDP, OPQ

BIOPHARMACEUTICS ASSSESSMENT

1. LIST OF SUBMISSIONS REVIEWED

Submissions Reviewed		
eCTD sequence #	**Received date**	**Document**
0001	04/05/2021	Original NDA Submission
0004	06/24/2021	Quality/Response to Information Request
0007	10/05/2021	Quality/Response to Information Request
0010	12/06/2021	Quality/Response to Information Request

2. DRUG PRODUCT

The proposed drug product is an immediate-release, ready-to-use aqueous suspension with 5 mg/mL of baclofen. The composition of the proposed product is provided in ***Appendix 1***.

To establish bioequivalence, the Applicant studied relative bioavailability of the proposed/test product (a single 20 mg dose of Baclofen Oral Suspension, 5 mg/mL) under fasted and fed conditions versus Baclofen Tablet, USP (20 mg) (designated RS) under fasted conditions in healthy adults. The results of the study ((# RM-05-PK001) will be evaluated by the Office of Clinical Pharmacology.

3. BCS DESIGNATION: *NOT APPLICABLE*

Solubility

The Applicant studied the solubility of baclofen in the physiological pH range. The results of the experimental solubility study, summarized in Table 2, indicate that the solubility of baclofen is pH-dependent, with increasing solubility above and below its upper (9.62) and lower (3.87) pKa's, respectively. The amount of dissolved Baclofen in the proposed drug product was determined to be (b) (4) mg/mL, theoretically, leaving (b) (4) mg/mL or (b) (4)% of Baclofen drug substance suspended in the finished drug product.

Table 2: Aqueous Solubility of Baclofen

Buffer	pH	Solubility
20 mM KCl	1.2	75.7 mg/mL
20 mM Acetate	4.5	5.1 mg/mL
20 mM Phosphate	6.8	4.7 mg/mL
Baclofen Oral Suspension Vehicle Diluent	4.4	4.5 mg/mL
(b) (4)		

Permeability

The Applicant did not provide any permeability data. It is important to note that no BCS designation request has been submitted by the Applicant and no designation has been determined by the FDA for baclofen.

4. DISSOLUTION INFORMATION

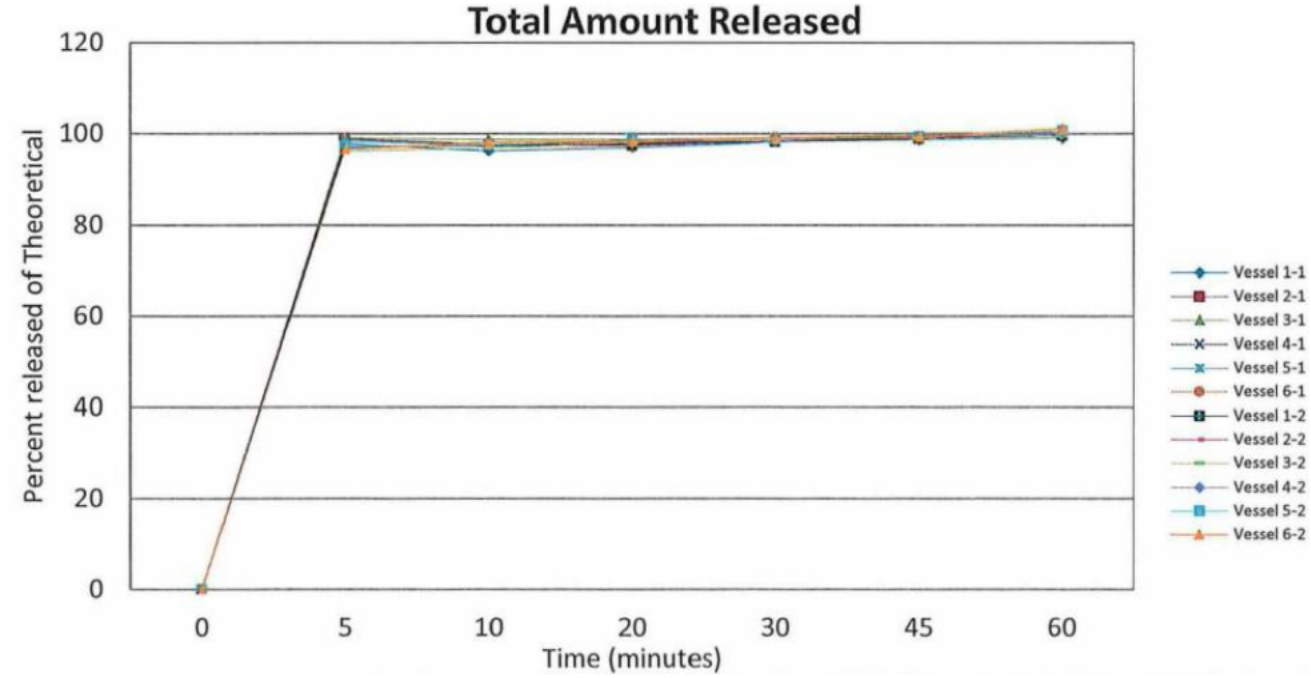
Selection of the dissolution method

In the original submission, the Applicant did not provide information/data justifying the selection of the proposed dissolution method (b) (4)
The Applicant provided a dissolution method development report on 06/24/2021 in response to an Information Request (IR), to justify the selection of the dissolution testing parameters.

The Applicant selected USP Apparatus 2 (paddles) for dissolution testing due to the nature of the dosage form. This is a commonly used apparatus for dissolution testing of suspension products. The Applicant's selection of dissolution apparatus (USP Apparatus 2) is justified.

To test the effect of paddle speed and the volume of dissolution medium, the Applicant performed a dissolution study [2 runs of six vessels each (n=12)] with 500 ml of 0.01N hydrochloric acid at the paddle speed of 25 rpm using USP Apparatus 2. The results of the study (Figure 1) indicate that the proposed drug product exhibits very rapid dissolution with complete drug release at the first time-point of 5 minutes.

Figure 1: Dissolution of Baclofen Oral Suspension, 5 mg/mL in 500 mL of 0.01N HCl using USP Apparatus 2 at 25 rpm



For selection of the dissolution medium, the Applicant conducted trials with (b) (4) . However, the Applicant selected 0.01N HCl as the dissolution medium (b) (4) The Applicant's selection of dissolution medium is adequately justified. (b) (4)

Based on the provided data, the Applicant was recommended (via an IR dated 09/03/2021) to

implement the following dissolution method for quality control testing of the proposed drug product for batch release and stability testing: 500 mL of 0.01N HCl using USP Apparatus 2 at 25 rpm.

Also, the Applicant was asked (via an IR dated 09/03/2021) to confirm whether the routine dissolution testing was performed using samples from different bottles/units of suspension for each of the dissolution vessels. We typically require dissolution data from 12 dissolution vessels where one unit/bottle of proposed oral suspension product, with the volume as per the dosing instruction in the labeling, is used per dissolution vessel. The Applicant was recommended to submit newly generated dissolution profile data according to the guideline if previously it was done by pooled sampling.

In response (dated 10/05/2021), the Applicant agreed to implement the FDA recommended dissolution method for QC testing of the proposed drug product. The Applicant stated that it did not perform routine dissolution testing using samples from different bottles/units of suspension for each of the dissolution vessels. The Applicant revised the dissolution testing protocol and generated new dissolution profile data according to the recommended dissolution method for the six (6) registration batches. This testing was conducted using a unique sample from a single finished product unit/bottle for each of the 12 dissolution vessels. The results from this new dissolution profile data were then compared to the results from the dissolution profiles preformed according to the previous method ((b) (4) The dissolution profiles of the registration batches with the FDA recommended dissolution method were found to be complete and very rapid (Appendix 3), similar to those with the originally proposed dissolution method. Based on the provided data, the Applicant's selection of the dissolution testing parameters is justified and deemed adequate.

The proposed drug product is a suspension; however, the amount of dissolved Baclofen in the proposed drug product was determined to be (b) (4) mg/mL, theoretically, leaving (b) (4) mg/mL or (b) (4)% of Baclofen drug substance suspended in the finished drug product. Considering, the high solubility of baclofen across the physiological pH, and the nature/simplicity of the composition of the drug product, it dissolves very rapidly and hence it is not possible to develop a discriminating dissolution method. However, the biopharmaceutics risk is low for the proposed drug product is low owing to the characteristics of the drug substance and the drug product.

Based on the provided information/data, the newly proposed dissolution method (500 mL of 0.01N HCl using USP Apparatus 2 at 25 rpm) is deemed adequate for QC testing of the proposed drug product.

Selection of the Dissolution Acceptance Criterion

In the original submission, the Applicant proposed the dissolution acceptance criterion of ' (b) (4) for quality control testing of the proposed product. However, based on the

very rapid dissolution of the proposed product, the Applicant was recommended (via an IR sent on 11/30/2012) to implement the dissolution acceptance criterion of 'NLT (b)(4)% (Q) at 15 minutes'. In response (dated 12/06/2021[2]), the Applicant accepted the FDA recommendation and implemented the dissolution acceptance criterion of 'NLT (b)(4)% (Q) at 15 minutes' for quality control testing of the proposed product. The Applicant's respon is adequate.

5. FORMULATION BRIDGING

In-vitro and/or in-vivo bridging studies are not needed for the proposed product as there were no changes in 1) composition of the proposed product between the clinical batch, exhibit batches, and the proposed commercial batches, 2) product manufacturing site, and 3) manufacturing process in the scale-up.

6. BIOWAIVER REQUEST

Only one strength (5 mg/mL) is proposed under the current NDA and therefore no biowaiver request is submitted or is necessary.

7. LIST OF DEFICIENCIES

None

Appendix 1

Table: Composition of Baclofen Oral Suspension, 5 mg/mL

Component	Grade	Function	mg/mL
Baclofen	USP	Active ingredient	5.0
Anhydrous Citric Acid	USP	(b) (4)	
Hydroxyethyl Cellulose	NF		
Propylene Glycol	USP		
Simethicone Emulsion (b) (4)	USP		
Sodium Benzoate	NF		
Sucralose	NF		
D&C Yellow No.10	21 CFR 74.1710		
FD&C Red No. 40	21 CFR 74.1340		
Artificial Grape Flavor (b) (4)	DMF (b) (4)		
Purified Water	USP		

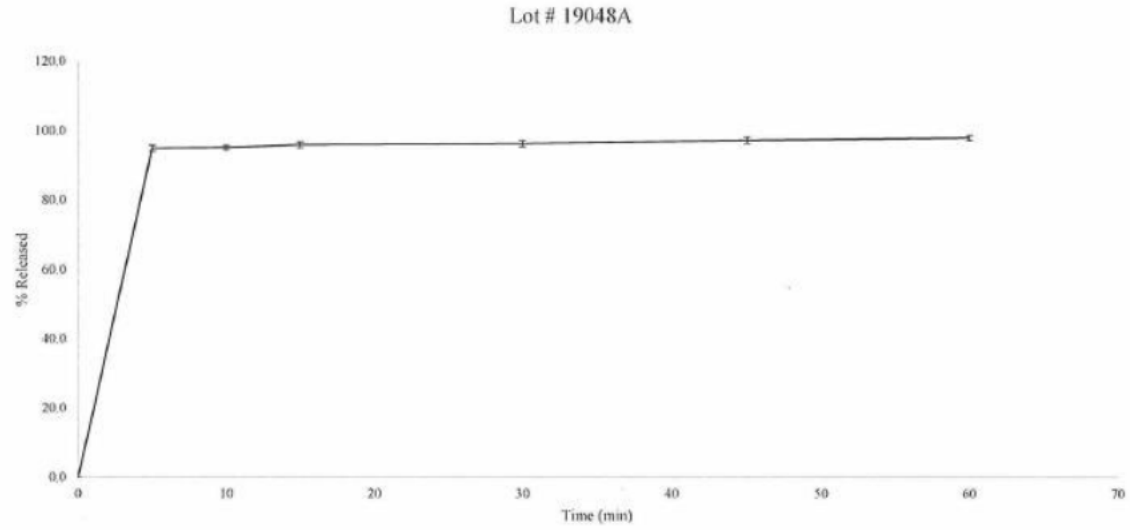
3 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Appendix 3

Dissolution of registration bathes with the FDA recommended dissolution method (500 mL of 0.01N HCL using USP Apparatus 2 at 25 rpm)

	Vessel #													
Timepoint	1	2	3	4	5	6	7	8	9	10	11	12	Average	Std Dev
0												(b) (4)	0.0	0.0
5													94.8	0.9
10													95.1	0.6
15													95.9	0.9
30													96.2	0.9
45													97.2	0.9
60													97.9	0.7

Data presented as % Release

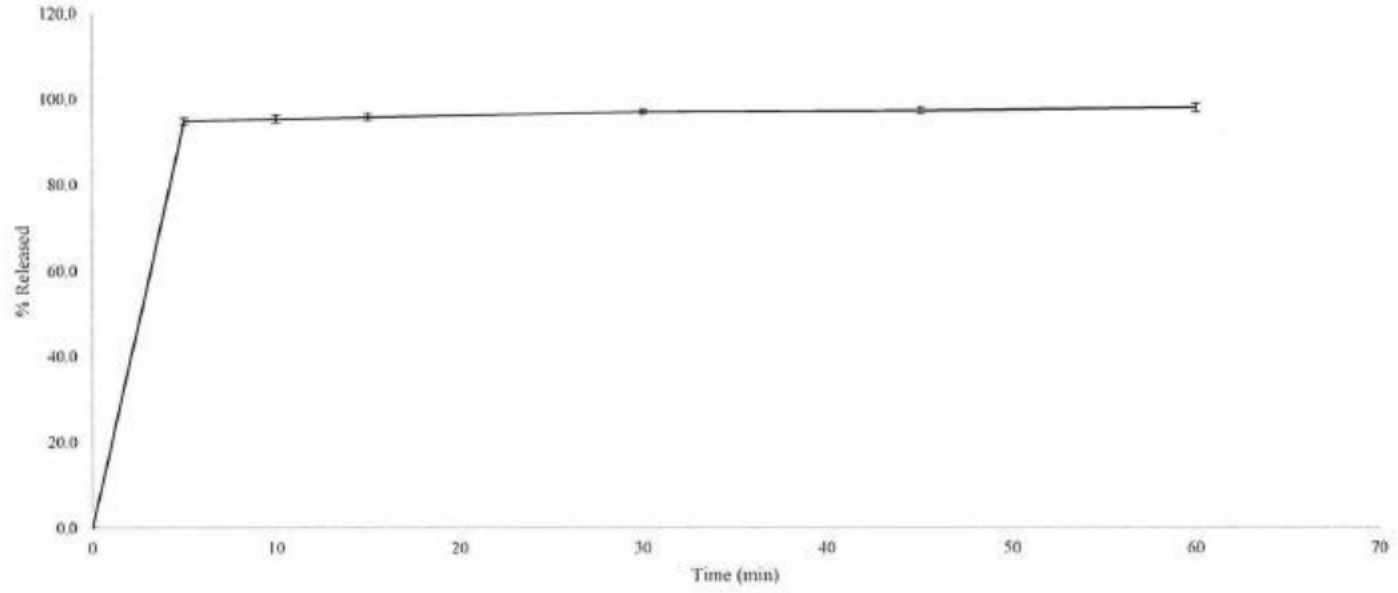


Vessel #

Timepoint	1	2	3	4	5	6	7	8	9	10	11	12	Average	Std Dev
0	(b) (4)												0.0	0.0
5													94.8	0.7
10													95.3	0.8
15													95.7	0.7
30													96.9	0.5
45													97.2	0.6
60													97.8	1.0

Data presented as % Release

Lot # 19049A

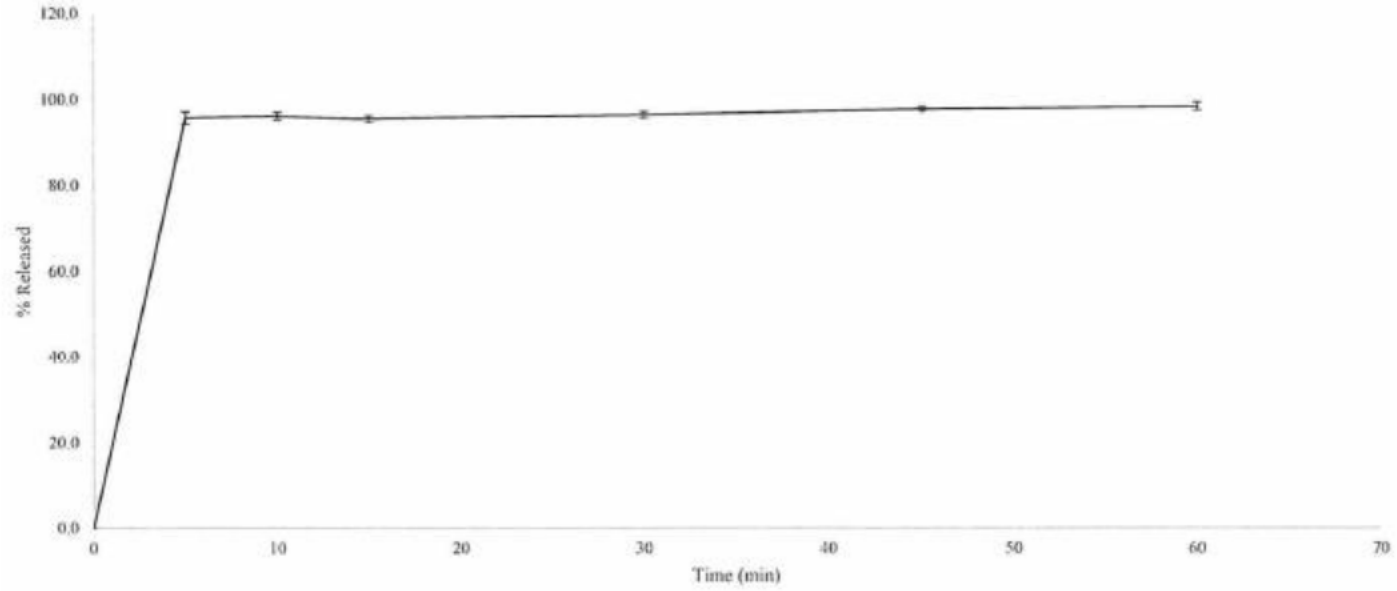


Vessel #

Timepoint	1	2	3	4	5	6	7	8	9	10	11	12	Average	Std Dev
0	(b) (4)												0.0	0.0
5													95.6	1.4
10													96.0	0.8
15													95.4	0.7
30													96.3	0.7
45													97.6	0.5
60													98.2	0.9

Data presented as % Release

Lot # 19050A

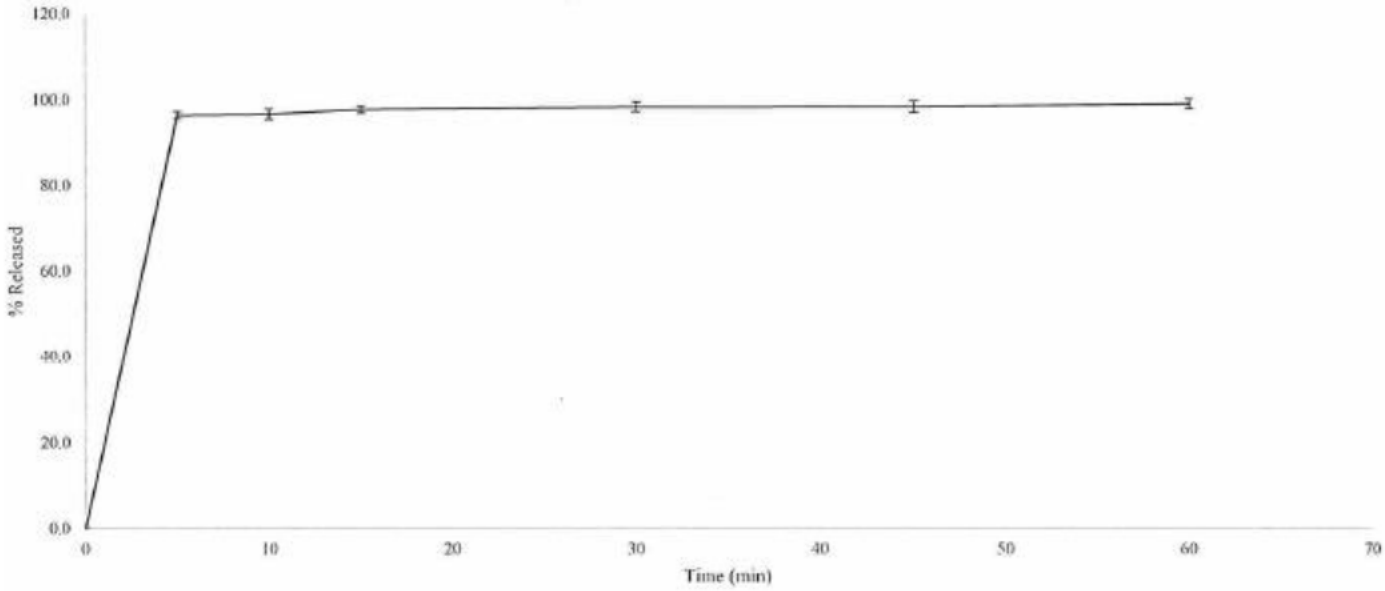


Vessel #

Timepoint	1	2	3	4	5	6	7	8	9	10	11	12	Average	Std Dev
0	(b) (4)												0.0	0.0
5													96.3	0.9
10													96.5	1.3
15													97.7	0.8
30													98.2	1.1
45													98.3	1.3
60													99.0	1.2

Data presented as % Release

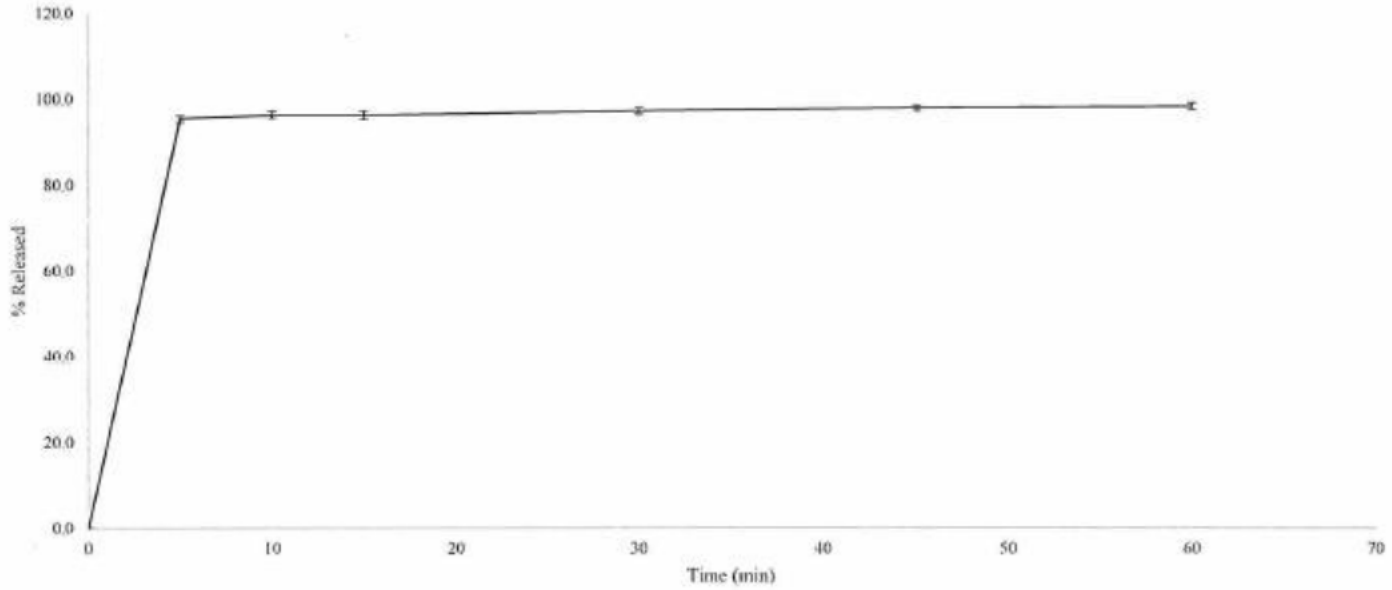
Lot # 19051A



	Vessel #													
Timepoint	1	2	3	4	5	6	7	8	9	10	11	12	Average	Std Dev
0	(b) (4)												0.0	0.0
5													95.3	0.7
10													96.3	0.8
15													96.2	1.0
30													97.2	0.7
45													98.0	0.6
60													98.3	0.7

Data presented as % Release

Lot # 20002A

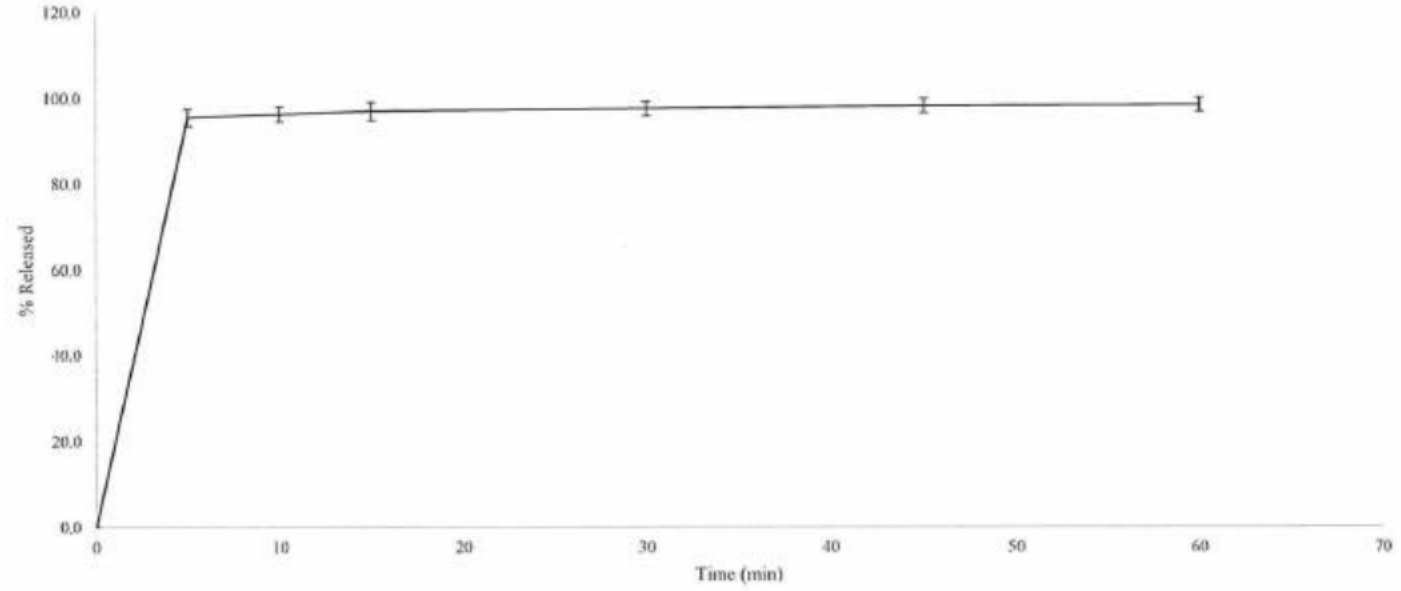


Vessel #

Timepoint	1	2	3	4	5	6	7	8	9	10	11	12	Average	Std Dev
0												(b) (4)	0.0	0.0
5													95.4	2.0
10													96.2	1.8
15													96.9	2.2
30													97.4	1.7
45													98.1	1.7
60													98.3	1.7

Data presented as % Release

Lot # 20002B



Kaushalkumar Dave

Digitally signed by Kaushalkumar Dave
Date: 12/14/2021 10:03:05PM
GUID: 5575db68006e2262805f2e6449c54250

Okponanabofa Eradiri

Digitally signed by Okponanabofa Eradiri
Date: 12/14/2021 11:40:44PM
GUID: 50bdfe8d00003559ede66be3fd299f65

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

/s/

MARTHA R HEIMANN
01/13/2022 02:54:56 PM