CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217927Orig1s000

PRODUCT QUALITY REVIEW(S)

Table of Contents

NDA Executive Summary

1. Application/Product Information

NDA Number.	217927		
Applicant Name	Solubiomix, LLC		
Drug Product Name	Oxaprozin Capsules, 300 mg		
Dosage Form.	Capsule		
Proposed Strength(s)	300 mg		
Route of Administration	Oral		
Maximum Daily Dose	1200 mg (because the Cmax of the proposed product is 34% higher than the listed drug, which has an MDD of 1800 mg)		
Rx/OTC Dispensed	Rx		
Proposed Indication	Signs and symptoms of Osteoarthritis (OA), Rheumatoid Arthritis (RA), and Juvenile Rheumatoid Arthritis (JRA)		
Drug Product Description	White opaque capsule imprinted “403” on the cap in black ink		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	25ºC		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Zhixing Shan	Gaetan Ladouceur
	Drug Product/ Labeling	Eric Bow	Valerie Amspacher
	Manufacturing	Yeung Chan	Jingbo Xiao
	Biopharmaceutics	Bryan Ericksen	Ta-Chen Wu

	Microbiology	N/A	N/A
	Other (specify):	N/A	N/A
	RBPM	Teicher Agosto	
	ATL	Valerie Amspacher	
Consults	N/A		

2. Final Overall Recommendation - Approval with QPA(s)

3. Action Letter Information

a. Expiration Dating: An expiry of 24 months is acceptable when stored at controlled room temperature: 20°–25° (68°–77° F).

b. Additional Comments for Action

Biopharm PMC 4503

PMC Description:

 Development and validation of an optimized dissolution method for using a suitable dissolution medium with buffering capacity, instead of water.

 Collect dissolution profile data of your drug product from at least the first six manufactured commercial batches using the revised dissolution method. Submission of the dissolution method development report, validation report, and dissolution data and based on these data, provide your proposal for the dissolution acceptance criterion for your product.

Goal of the Study:

During the current review cycle, the Applicant's originally proposed dissolution method resulted in very rapid dissolution without proper justification and demonstration of method suitability. In response to the Agency's information request, the Applicant proposed a dissolution method using 2000 mL water with surfactant, 0.5 w/v SLS. This method did not result in complete dissolution according to the data submitted. In addition, water is lacking in buffering

capacity to serve as a suitable dissolution medium as per the Division of Biopharmaceutics' current review guideline. Therefore, the newly proposed dissolution method is not acceptable. Therefore, the currently proposed dissolution method and acceptance criterion for the proposed Coxanto™ (oxaprozin) immediate-release capsules are accepted only on an interim basis.

The studies to be performed under this PMC agreement are aimed toward developing an optimal/suitable dissolution method using a buffer medium suitable as a dissolution medium to ensure an adequate control of the quality of the proposed product at the time of batch release and during stability testing.

The specific goals of the study are outlined below:
 To develop and validate separate optimal dissolution methods using a buffered dissolution medium. We recommend developing a clinically relevant dissolution method and acceptance criterion.

 To provide the dissolution method development and validation reports including detailed justification and complete dissolution data supporting the selection of the dissolution method/testing conditions (e.g., selection of the equipment/apparatus, in vitro dissolution media and media volume, agitation/rotation speed, media pH, sink conditions, use of sinker, surfactant, and enzyme, if applicable, etc.).

 To provide a list of the critical material attributes (CMAs), critical formulation variables and critical process attributes (CPAs) affecting dissolution.

 To provide data supporting the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations in the most relevant critical material attributes, critical formulation variables, and critical process parameters (i.e., ± 10-20% change to the specification-ranges of these variables). Submit the dissolution profile data and similarity testing results obtained with appropriate statistical test (e.g., f2 values) comparing the test and reference drug products. In addition, if available, submit data showing that the selected dissolution method can reject product that is not bioequivalent to the reference-target drug product.

 To provide complete multi-point dissolution profile data [individual (n=12), mean, range, % CV at each time point, and mean profiles until complete release] for the unexpired clinical and registration batches undergoing stability testing using the new dissolution conditions. Also, to collect

complete dissolution profile data for the first six commercial batches of the drug product using the new dissolution methods. Provide all data in Microsoft Excel ".xls or .xlsx" format.

☐ To propose the final dissolution acceptance criterion based on the dissolution profile data collected from three unexpired clinical and registration batches and the first six manufactured commercial batches, using the new dissolution methods. The acceptance criterion should be set at the time-point where ≥ (b)(4)% dissolution occurs (Q= (b)(4)%).

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The CMC recommendation for this application is approval with a biopharmaceutics PMC.

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

Recommendation by Subdiscipline:

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

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

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 1; eCTD 0001	22 Dec 2022	All, original submission

Supporting document 10; eCTD 0011	26 May 2023	Drug substance
Supporting document 11; eCTD 0009	2 Jun 2023	Drug product, manufacturing, biopharmaceutics
Supporting document 14; eCTD 0014	7 Jul 2023	Biopharmaceutics
Supporting document 16; eCTD 0016	8 Sep 2023	Drug product
Supporting document 17; eCTD 0017	18 Sep 2023	Drug product
Supporting document 19; eCTD 0018	4 Oct 2023	Biopharmaceutics

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CHAPTER IV: LABELING

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

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

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	N/A	

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

package and imaging bulk package.		
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	

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)	N/A	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets,	N/A	

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

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)

Appears this way on original

QUALITY ASSESSMENT

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	Added gelatin capsules
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	Adequate	
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)

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QUALITY ASSESSMENT

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	
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

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

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

(b) (4)

3.2 Carton Labeling

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

No carton labeling is used

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	N/A	
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).	Adequate	
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	

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

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	

QUALITY ASSESSMENT

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.	Adequate	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	Adequate	
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***

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

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 Name and Date: Eric Bow

Secondary Assessor Name and Date (and Secondary Summary, as needed): Julia Pinto

Eric Bow

Digitally signed by Eric Bow
Date: 9/27/2023 09:06:29AM
GUID: 5df160d800320e19970e198e30e1cc2e

Julia Pinto

Digitally signed by Julia Pinto
Date: 9/27/2023 10:46:01AM
GUID: 5050dbcb00001294a888a4bdc20a3a58

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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	NDA-217927-ORIG-1
Assessment Cycle Number	1
Drug Product Name/ Strength	Coxanto™ (oxaprozin) Capsules / 300 mg
Route of Administration	Oral
Applicant Name	Solubiomix, LLC
Therapeutic Classification/ OND Division	CDER/OND/ON/DAAP
RLD/RS Number	NDA 018841
Proposed Indication	(b) (4)
Primary Reviewer	Bryan Ericksen, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.

Assessment Recommendation: **Adequate**

Assessment Summary:

The Applicant seeks approval of immediate-release Coxanto™ (oxaprozin) Capsules 300 mg via 505(b)(2) regulatory pathway for (b) (4) (b) (4)

The Applicant developed an in-house dissolution method as QC test for batch release and stability testing for the proposed drug product. However, the selection of the test conditions/parameters are not considered adequate and the final proposed dissolution medium (water) lacks in buffering capacity. The Applicant will be requested to change dissolution medium to a more appropriate buffer medium. The Applicant proposed a dissolution acceptance criterion of "Q= (b) (4) % in 45 minutes", which is inadequate and will be subject to revision based on the newly generated dissolution profile data from registration/clinical batches and newly manufactured commercial batches using the revised dissolution method. The Biophamaceutics review is focused on evaluation and acceptability of the proposed dissolution method and acceptance criterion for the proposed product.

Dissolution Method and Acceptance Criterion – Accepted on an interim basis:

During the current review cycle, the Applicant's originally proposed dissolution method resulted in very rapid dissolution without proper justification and

demonstration of method suitability. In response to the Agency's information request, the Applicant proposed a dissolution method using 2000 mL water with surfactant, 0.5 w/v SLS. This method did not result in complete dissolution according to the data submitted. In addition, water is lacking in buffering capacity to serve as a suitable dissolution medium as per the Division of Biopharmaceutics' current review guideline. Therefore, the newly proposed dissolution method is not acceptable. This issue could not be addressed during the review cycle because of short review timeline for this NDA. Therefore, the currently proposed dissolution method and acceptance criterion for the proposed Coxanto™ (oxaprozin) immediate-release capsules are accepted only on an interim basis.

The Applicant agreed to the Post-Marketing Commitment (PMC) on 10/04/2023, submitted under Amendment 0018 to the NDA, and will submit the interim and final PMC reports within 6 months and 24 months, respectively, from the NDA's action date, per the E-Mail communication on 09/28/2023 and agreement on 10/04/2023. Refer to Appendix 2 for the PMC # 4503.

The following dissolution method and acceptance criterion for batch release and stability testing of oxaprozin from the oral capsules are **accepted on an interim basis**:

USP Apparatus	Speed (RPMs)	Medium/ Temperature	Volume (mL)	Acceptance criterion
2 (Paddle) with spiral sinkers	75	Water with 0.5% w/v SLS/ 37°C ± 0.5°C	2000	Q= (b) (4)% at 45 minutes

Recommendation:

From the Biopharmaceutics perspective, NDA-217927-ORIG-1 for Coxanto™ (oxaprozin) Capsules 300 mg is recommended for approval. The proposed dissolution method and acceptance criteria for the batch release and stability testing of oxaprozin from the proposed oral capsule are accepted on an interim basis.

List Submissions Being Assessed:

12/22/2022	ANDA 217927/Sequence 0001/Original Submission
6/2/2023	ANDA 217927/Sequence 0009/Response to Information Request
7/7/2023	ANDA 217927/Sequence 0014/Response to Information Request

Concise Description of Outstanding Issues *(list bullet points with key information and update as needed)*:

- The Applicant is requested to develop optimized dissolution method for API of the proposed oral capsule product under PMC # 4503.

B.1 BCS DESIGNATION

No BCS designation was requested. The drug substance, oxaprozin, possess low solubility and high permeability characteristics of BCS Class II drug.

Solubility: Oxaprozin is a low solubility compound according to solubility measurements in buffers across the physiological pH range (pH 1.2-7.4) and based on the maximum single dose (1200 mg), per BCS criteria, as shown in Table 1.

Table 1: Oxaprozin Solubility data over the physiologic pH range

Oxaprozin Solubility/pH Relationship		
Buffer Solution	**Solubility (mg/mL)**	**Solubility (mg) per 1000 mL Media**
0.1N HCl 1.2010 g Oxaprozin/ 250 mL (pH of saturated solution, ~ 1.6)	0.09 mg/mL	90
pH 4.5 Acetate Buffer 1.2053 g Oxaprozin/ 250 mL (pH of saturated solution, ~ 4.6)	0.49 mg/mL	490
pH 6.8 Phosphate Buffer 1.2023 g Oxaprozin/ 250 mL (pH of saturated solution, ~ 6.9)	2.5 mg/mL	2500
pH 7.4 Phosphate Buffer 1.2010 g Oxaprozin/ 250 mL (pH of saturated solution, ~ 7.4)	3.1 mg/mL	3100

Permeability: High permeability as per the Applicant

Dissolution: See section B.2 for dissolution profile data

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: *{Inadequate}*

There is no published USP compendial dissolution method for the Oxaprozin Capsule drug product, nor is there an FDA recommended method. The Applicant developed an in-house dissolution method and provided justification in the dissolution method development report for the choice of apparatus, use of spiral sinkers, and paddle speed. However, the selection of the test conditions/parameters are not considered adequate and the newly or final proposed dissolution medium (water) which lacks in buffering capacity. The

Applicant will be requested to change dissolution medium to a more appropriate buffer medium (see PMC in Appendix 2). The proposed method is shown in Table 2.

Table 2. Originally proposed dissolution method and acceptance criterion

USP Apparatus	Speed (RPMs)	Medium/ Temperature	Volume (mL)	Acceptance criterion
2 (Paddle) with spiral sinkers	75	(b) (4)	(b) (4)	Q (b) (4) % at 45 minutes

(b) (4)

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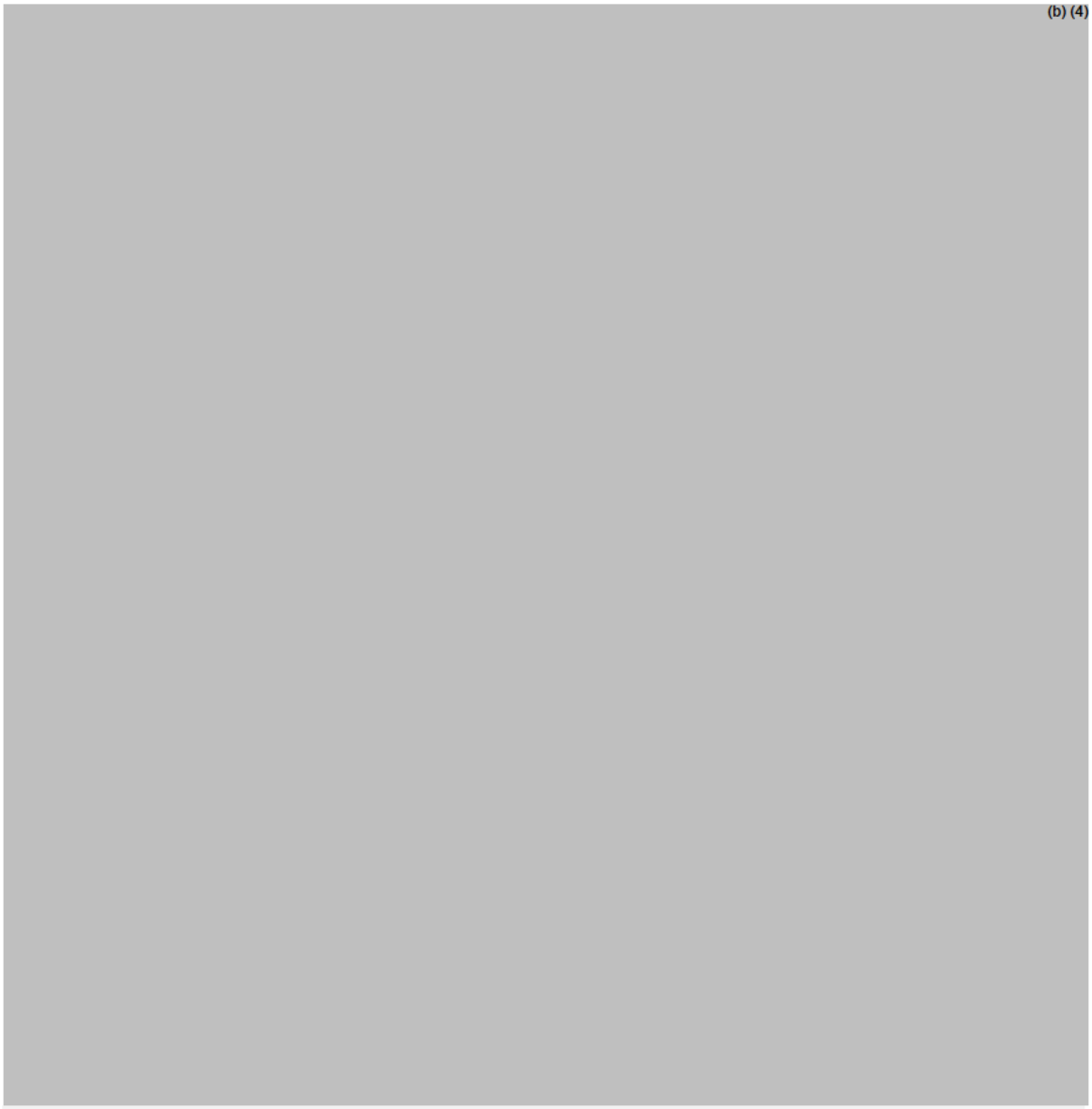
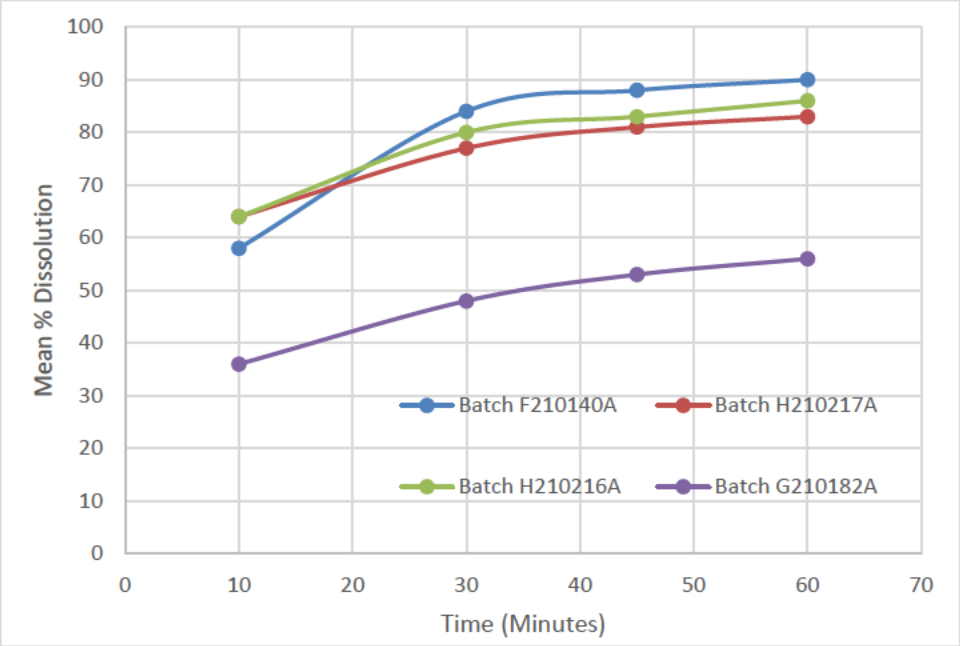
(b) (4)



Discriminating Ability of the Dissolution Method and Exhibit Batch Dissolution

The Applicant also provide results of discriminating ability for the dissolution method using 2000 mL 0.5% SLS in water with sinkers with a paddle speed of 75 rpm. Dissolution profile data were generated using exhibit batches F210140A, H210217A, and H210216A and comparison batch G210182A. Results are shown in Figure 6.

Figure 6: Comparison of three exhibit batches compared to batch G210182A

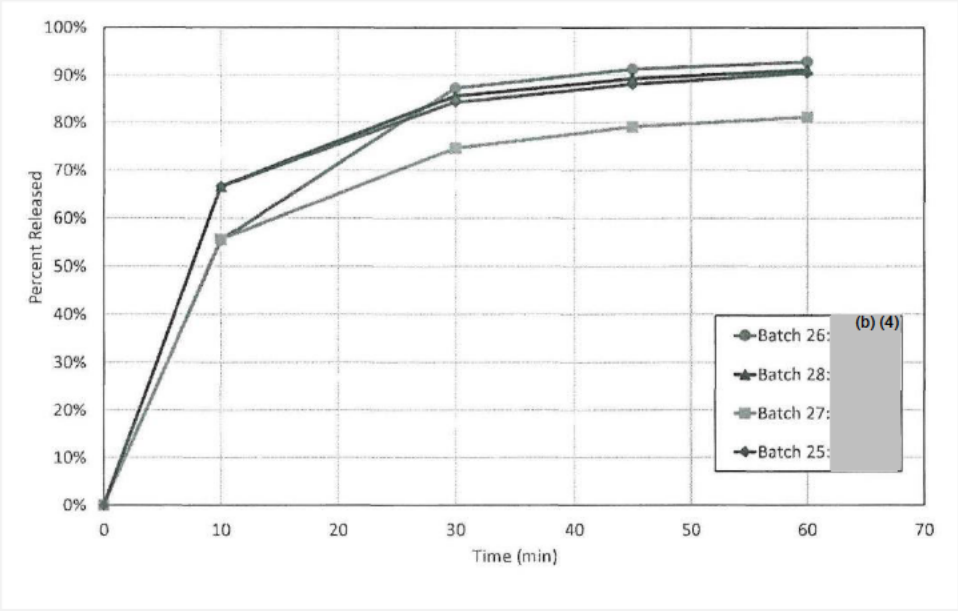


The Applicant did not propose this new acceptance criterion or submit a list of critical quality attributes. However, batch G210182A failed to meet the proposed acceptance criterion using the proposed dissolution method. During the manufacture of batch G210182A, (b) (4) (b) (4) However, since water is not a suitable dissolution medium or an accepted medium, the discriminating ability of the SLS/water method is not considered being adequately demonstrated.

Two additional critical process parameters were varied: (b) (4) (b) (4) Only one change was made at a time. Batches with (b) (4)

(b) (4) were tested and the results are shown in Figure 7. It is noted that the Applicant did not provide tabular presentation to detail the changes.

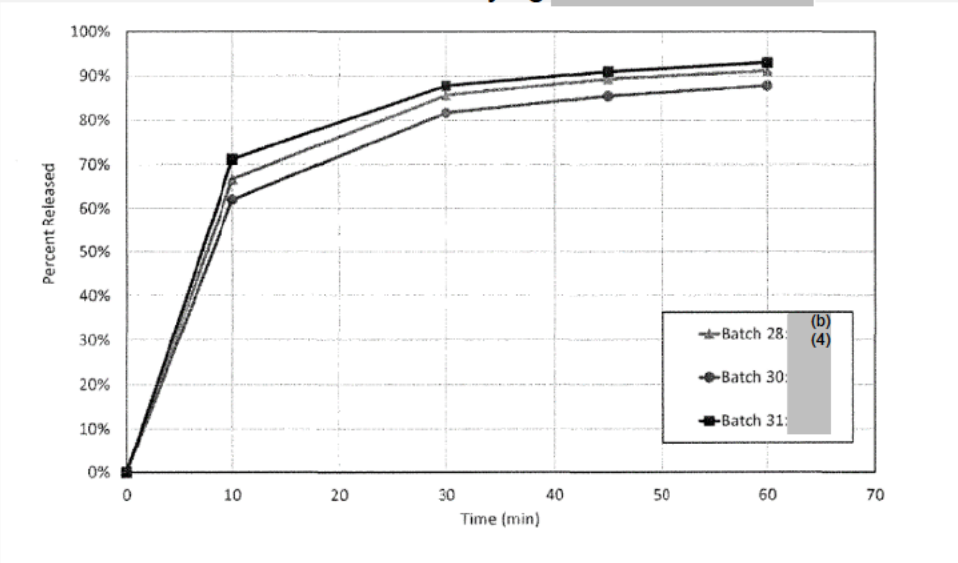
Figure 7: Dissolution of batches with varying (b) (4) (b) (4)



There is no clear trend among the results.

Batches with varying (b) (4) are shown in Figure 8.

Figure 8: Dissolution of batches with varying (b) (4)



(b) (4)

Reviewer's Assessment:

The discriminating ability of the dissolution method was not clearly demonstrated by varying the (b) (4) (b) (4). Additionally, per the Applicant, the discriminating ability of the dissolution method was not demonstrated with respect to particle size. Since water is not a suitable dissolution medium or accepted medium, the discriminating ability of the SLS/water method is not considered being adequately demonstrated. Further investigation will be requested after the dissolution method/test condition is optimized with an appropriate buffer medium (see PMC in Appendix 2).

Dissolution Acceptance Criterion

The Applicant proposed a dissolution acceptance criterion of "Q=(b) (4)% in 45 minutes" which will be subject to modification after the dissolution method is optimized with adequate discriminating ability of the method being demonstrated and new profile data are generated from registration/clinical batches and newly manufactured commercial batches using the revised dissolution method. Note that an appropriate acceptance criterion for an immediate-release product should be set where Q=(b) (4)% (≥(b) (4)% dissolution) occurs.

B.12 BRIDGING OF FORMULATIONS

Assessment: *{Adequate}*

The to-be-marketed product is the same product used in the clinical biobatch so no additional formulation bridging is necessary.

B. 13 BIOWAIVER REQUEST

Assessment: *{Adequate}*

There is only one strength, 300 mg. There is no biowaiver request.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

Appendix 1

Biopharmaceutics Information Request and Applicant's Responses

On May 8, 2023 in an information request, the following deficiencies were communicated to the Applicant.

5 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Bryan Ericksen

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Ta-Chen Wu

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Date: 10/04/2023 05:45:17PM
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Valerie Amspacher

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