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RESEARCH**

APPLICATION NUMBER:

215431Orig1s000

PRODUCT QUALITY REVIEW(S)

Office of Pharmaceutical Quality

New Drug Application (NDA) Integrated Quality Assessment

NDA 215431
Symbravo™ (meloxicam and rizatriptan) Tablets

NDA Executive Summary

1. Application/Product Information

NDA Number	215431		
Applicant Name	Axsome Therapeutics Inc.		
Drug Product Name	Symbravo™ (meloxicam and rizatriptan)		
Dosage Form	Tablet		
Proposed Strength(s)	20 mg/10 mg		
NDA Classification	Type 4 - New Combination		
Route of Administration	Oral		
Maximum Daily Dose	20 mg/10 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Acute treatment of migraine with or without aura in adults		
Drug Product Description	White, modified capsule-shaped, debossed with “MXRZ” on one side and “20/10” on the other		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	20°C to 25°C		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	N/A	N/A
	<i>Drug Product/ Labeling</i>	Jizhou Wang	Martha Heimann/ Julia Pinto
	<i>Manufacturing</i>	Hong Yang	Shujun Chen
	<i>Biopharmaceutics</i>	Swapna Pamu	Okpo Eradiri
	<i>Microbiology</i>	N/A	N/A

	<i>Other (specify)</i>	N/A	N/A
	<i>RBPM</i>	Erica Keafer	
	<i>ATL</i>	Martha Heimann	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

Six (6) months for product stored at 20°C to 25°C.

b. Additional Comments for Action

There are no additional comments for the action letter.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

This is the second review cycle for NDA 215431. The proposed product, SYMBRAVO, is an immediate-release tablet containing meloxicam 20 mg and rizatriptan 10 mg (as rizatriptan benzoate). During the first review cycle, the review team identified significant deficiencies related to the tablet manufacturing process, control of drug product impurities including potential (b) (4) degradants, and biopharmaceutics (dissolution).¹ In the 7/31/2024 resubmission and subsequent amendments, the applicant has adequately addressed all outstanding product concerns. Based on our evaluation of the available information, the application, as amended, contains sufficient information to support an approval recommendation from the product quality perspective. The Applicant provided adequate information to ensure the identity, strength, purity, and quality of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements. Thus, the Office of Product Quality (OPQ) review team recommends APPROVAL of NDA 215431.

¹ NDA 215431 Integrated Quality Review, 3/31/2022
<https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80653a5a&showAsPdf=true>

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

Recommendation by Subdiscipline:

Drug Substance	-	Adequate first review cycle.
Drug Product	-	Adequate
Quality Labeling	-	Adequate
Manufacturing	-	Adequate
Biopharmaceutics	-	Adequate
Microbiology	-	Adequate

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

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments: N/A

Comparability Protocols (PACMP): No

Comments: N/A

Additional Lifecycle Comments:

There are no outstanding issues or lifecycle considerations.

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.
1/13/2025



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: **adequate**

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	SYMBRAVO™	N/A
Established name(s)	meloxicam and rizatriptan benzoate	Adequate
Route(s) of administration	Oral	Adequate
Summary of the dosage form(s) and strength(s) in metric system.	20 mg meloxicam-10 mg rizatriptan tablet	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	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	Adequate

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

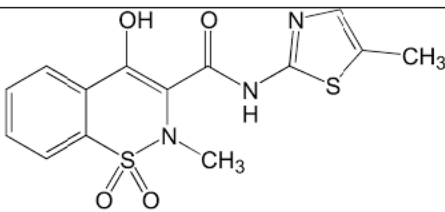
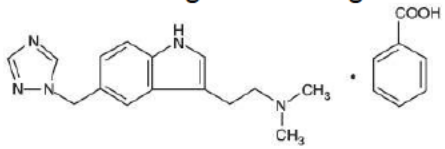
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	N/A

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Tablet	Adequate
Strength(s) in metric system	20 mg meloxicam and 14.5 mg rizatriptan benzoate, equivalent to 10 mg rizatriptan	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	14.5 mg rizatriptan benzoate, equivalent to 10 mg rizatriptan)	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	The tablets are white and modified capsule-shaped, debossed with "MXRZ" on one side and "20/10" on the other)	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
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.	N/A	N/A

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	SYMBRAVO (meloxicam and rizatriptan benzoate)	Adequate
Dosage form(s) and route(s) of administration	Tablet for oral	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	14.5 mg of rizatriptan benzoate equivalent to 10 mg rizatriptan	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose, partially hydrolyzed polyvinyl alcohol, polyethylene glycol, povidone, pregelatinized starch, sodium bicarbonate, sulfobutyl-ether- β -cyclodextrin sodium, talc, and titanium dioxide.	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	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Statement of being sterile (if applicable)	N/A	Adequate
Pharmacological/therapeutic class	meloxicam, a member of the enolic acid group of NSAIDs, and rizatriptan benzoate, a selective 5-HT _{1B/1D} receptor agonist.	Adequate

Chemical name, structural formula, molecular weight	 Meloxicam 4-hydroxy-2-methyl-N-(5 methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide molecular formula $C_{14}H_{13}N_3O_4S_2$ molecular weight of 351.4 g/mole.  Rizatriptan benzoate N,N dimethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-1H indole-3 ethanamine monobenzoate molecular formula $C_{15}H_{19}N_5 \cdot C_7H_6O_2$ molecular weight of the free base rizatriptan is 269.4 g/mole	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	N/A	N/A

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	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	N/A

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	tablets	Adequate
Strength(s) in metric system	meloxicam 20 mg-rizatriptan 10 mg	Adequate
Available units (e.g., bottles of 100 tablets)	Bottles of (b) (4)	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	SYMBRAVO tablets are white, modified capsule-shaped, film-coated tablets with "MXRZ" on one side and "20/10" on the other	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	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	N/A

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.)	N/A	N/A
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."	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP <i>Controlled Room Temperature</i>].	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	N/A	N/A

rubber latex. Avoid statements such as "latex-free."		
Include information about child-resistant packaging	(b) (4)	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 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.

N/A

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Distributed by:	Axsome Therapeutics, Inc. New York, NY 10007	Adequate

2.0 PATIENT LABELING

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

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

3.0 CARTON AND CONTAINER LABELING

3.1 & 3.2. Container and Carton Label ([SN24](#))

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	yes	Adequate
Dosage strength	Yes	Adequate
Route of administration	N/A	N/A
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	10 mg rizatriptan (14.5 mg of rizatriptan benzoate equivalent to 10 mg rizatriptan, see Section 11)	Adequate
Net contents (e.g. tablet count)	Yes	Adequate
"Rx only" displayed on the principal display	Yes	Adequate
NDC number	Yes	Adequate
Lot number and expiration date	Yes	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Yes	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Bar code	Yes	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Yes	Adequate
Medication Guide (if applicable)	Yes	N/A
No text on Ferrule and Cap overseal	N/A	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	N/A
And others, if space is available	Yes	Adequate

Assessment of Carton and Container Labeling: *adequate*

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

ITEMS FOR ADDITIONAL ASSESSMENT

Overall Assessment and Recommendation:

Primary Labeling Assessor Name and Date: Jizhou Wang, PhD. 12/03/2024
Secondary Assessor Name and Date (and Secondary Summary: Julia C. Pinto, PhD. 12/10/2024

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Martha
Heimann

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Comments: For Jizhou Wang



Julia
Pinto

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Title:	NDA IQA Template CHAPTER VI-BIOPHARMACEUTICS		
Document ID:	OPQ-ALL-TEM-0047		
Effective Date:	18 Sep 2023	Revision:	00
Total Pages:	17		



Template Revision: 03

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CHAPTER VI: BIOPHARMACEUTICS

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

NDA Number	NDA-215431-ORIG-1-RESUB-25
Assessment Cycle Number	1
Drug Product Name/ Strength	Symbravo™ ((b) (4)) Tablet/ 20 mg Meloxicam - 10 mg Rizatriptan)
Route of Administration	Oral
Applicant Name	Axsome Therapeutics, Inc.
Therapeutic Classification/ OND Division	Division of Neurology
LD Number	Anjeso (Meloxicam) Injection (NDA 210583) and Maxalt (Rizatriptan benzoate) Tablets (NDA 020864).
Proposed Indication	Acute treatment of migraine with or without aura in adults.

Assessment Recommendation: Adequate

A. Assessment Summary:

The Applicant is seeking approval for the proposed drug product Symbravo™, a (b) (4) tablet with 20 mg Meloxicam and 10 mg Rizatriptan. In the original submission (NDA-215431-ORIG-1), the Applicant proposed same dissolution method and acceptance criterion for both API's of the drug product. Based on the submitted data, both dissolution method and acceptance criterion were found to be unacceptable. The original submission resulted in complete response (CR) due to deficiencies from multiple disciplines within the Agency and a CR letter (CRL) was sent to the Applicant on 04/29/2022¹.

Applicant responded to CRL in NDA-215431-ORIG-1-RESUB-24. However, the response was not acceptable, and RESUB-24 received an incomplete response. This NDA-215431-ORIG-1-RESUB-25 is to address the CRL comments appropriately. Biopharmaceutics deficiencies that were included in the CRL were regarding the need to develop two separate methods for both the API's. Applicant addressed those deficiencies in RESUB-25 and developed two separate methods (See Appendix 1 for details). Based on the provided dissolution method development and discriminating ability data, the revised dissolution methods are found to be acceptable. However, the proposed dissolution acceptance criterion of $Q = \frac{(b)}{(4)}\%$ in (b) (4) minutes for both APIs were permissive. Applicant was sent an IR on 12/13/24 to revise the criteria. Applicant responded to that IR on 12/17/24 and proposed to use the existing criteria on the interim basis. Applicant also stated that they would collect more dissolution data and submit a report in year 2026 to finalize the acceptance criterion.

¹ [\\CDSESUB1\EVSPROD\nda215431\0024\m1\us\1-2-reviewer-guide.pdf](#)

Agency did not accept Applicant's proposal and another IR was sent on 12/17/24 re-iterating the recommendation to revise the criteria based on the submitted data. Applicant responded on the same day and accepted agency's recommendation². Approved dissolution method and acceptance criteria are listed below in table 1.

Table 1: Approved dissolution method and acceptance criteria for both APIs:

API	USP Apparatus	Speed (RPM)	Medium	Volume/Temp	Acceptance Criteria
Meloxicam	II (Paddle)	75	50 mM KH ₂ PO ₄ , pH 7.2	900 mL/37°C	Q = ^(b) ₍₄₎ % at 30 minutes
Rizatriptan	II (Paddle)	50	50 mM KH ₂ PO ₄ , pH 6.8	900 mL/37°C	Q = ^(b) ₍₄₎ % at 30 minutes

The Biopharmaceutics review is focused on evaluation of (1) the adequacy of the proposed dissolution method and acceptance criterion, (2) formulation bridging and (3) risk assessment.

² <\\CDSESUB1\EVSPROD\nda215431\0033\m1\us\cover-letter.pdf>

Reviewer's Assessment:

I. Dissolution Method and Acceptance Criterion

In the original submission, Applicant proposed the same dissolution method and dissolution acceptance criterion for both API's of the drug product (see table 2) which were found to be unacceptable. The original submission resulted in CR and CRL was sent on 04/29/2022.

Table 2: Originally proposed dissolution method and acceptance criterion for both APIs:

USP Apparatus	Speed (RPM)	Medium	Volume/Temp	Acceptance Criterion
(b) (4)				

In the CRL, Agency recommended the Applicant to develop two separate dissolution methods. In response, Applicant developed two separate dissolution methods as listed below in table 3. Based on the provided method development and discriminating ability data (see Appendix 1 for details), the revised dissolution methods are acceptable.

Table 3: Revised dissolution method and acceptance criteria:

API	USP Apparatus	Speed (RPM)	Medium	Volume/Temp	Acceptance Criteria
Meloxicam	II (Paddle)	75	50 mM KH ₂ PO ₄ , pH 7.2	900 mL/37°C	Q = $\frac{(b)(4)}{(4)}\%$ at $\frac{(b)(4)}{(4)}$ minutes
Rizatriptan	II (Paddle)	50	50 mM KH ₂ PO ₄ , pH 6.8	900 mL/37°C	Q = $\frac{(b)(4)}{(4)}\%$ at $\frac{(b)(4)}{(4)}$ minutes

Based on the submitted data, dissolution for both API's is at least $\frac{(b)(4)}{(4)}\%$ by 30 minutes. Therefore, the proposed dissolution acceptance criterion of Q = $\frac{(b)(4)}{(4)}\%$ in $\frac{(b)(4)}{(4)}$ minutes is permissive. Applicant will be sent an IR on 12/13/24 to revise the acceptance criterion to Q = $\frac{(b)(4)}{(4)}\%$ in 30 minutes (see Appendix 2 for details). Applicant responded to that IR on 12/17/24 and proposed to use the existing criteria on the interim basis. Applicant also stated that they would collect more dissolution data from the registration and stability batches and submit a report in year 2026 to finalize the acceptance criterion based on a time-point where $\frac{(b)(4)}{(4)}\%$ (Q = $\frac{(b)(4)}{(4)}\%$) of the dissolution occurs.

Agency did not accept Applicant's proposal and another IR was sent on 12/17/24 re-iterating the recommendation to revise the criteria based on the submitted data. Applicant responded on the same day and accepted agency's recommendation³. Approved dissolution method and acceptance criteria are listed below in table 1.

II. Formulation Bridging:

To-be-marketed formulation/product was used in the bioavailability study comparing to LD under fasting condition and food-effects. Therefore, formulation bridging is not needed.

Recommendation:

From the Biopharmaceutics perspective, NDA-215431-ORIG-1-RESUB-25 for Symbravo™ $\frac{(b)(4)}{(4)}$ Tablet/ 20 mg Meloxicam - 10 mg Rizatriptan) is adequate.

List Submissions Being Assessed:

Document(s) Assessed	Date Received
Sequence 0024 (Resubmission, CR response)	06/28/2024
Sequence 0025 (Resubmission, OPQ IR response)	07/31/2024
IR response	12/17/2024; 12/19/2024

Highlight of Key Issues from Last Cycle and Their Resolution:

None.

Concise Description of Outstanding Issues:

None.

B. BCS DESIGNATION

Assessment:

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

Primary Biopharmaceutics Assessor's Name and Date:

Swapna Pamu, MS; 12/20/2024

Secondary Assessor Name and Date:

Okpo Eradiri, Ph.D. 12/20/2024

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RECOMMENDATION: Complete Response

NDA 215431

Review #1

Drug Product Name	Symbravo™ (meloxicam and rizatriptan)
Dosage Form	Tablet
Strength	20 mg/10 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Axsome Therapeutics Inc.
US agent, if applicable	N/A

QUALITY TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Friedrich Burnett	Donna Christner
Drug Product	Jizhou Wang	Martha Heimann
Manufacturing	Hong Yang	Shujun Chen
Microbiology	N/A	N/A
Biopharmaceutics	Swapna Pamu	Ta-Chen Wu
Regulatory Business Process Manager	Erica Keafer	
Application Technical Lead	Martha Heimann	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

Submission(s)	Document Date	Discipline(s) Affected
SD-1, Original NDA	6/30/2021	All
SD-4, Response to IR	9/17/2021	Manufacturing
SD-5, Labeling, draft PI	9/27/2021	Drug product
SD-11, Response to IR	2/18/2022	Biopharmaceutics, drug product
SD-12, Response to IR	2/23/2022	Manufacturing, drug product
SD-13, Response to IR	3/1/2022	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)	(b) (4)	Adequate	8/9/2021	Reviewed by F. Burnett.
	II			Adequate	8/9/2021	Reviewed by F. Burnett.
	III			N/A ¹	--	
	III			N/A ¹	--	
	III			N/A ¹	--	

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

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

Document	Application Number	Description
IND		
NDA	21864	Maxalt (rizatriptan benzoate) tablets. Reference to support safety and efficacy of rizatriptan.
NDA	210583	Anjeso (meloxicam) injection. Referenced to support safety of meloxicam.

2. CONSULTS

None.

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The Office of Pharmaceutical Quality Review (OPQ) team has evaluated NDA 215431 with respect to drug substance and facilities and has determined that it meets all of those applicable standards to support the identity, strength, quality, and purity that it purports. However, the drug product, manufacturing, and biopharmaceutics disciplines have unresolved quality issues. Specifically, the proposed drug product specification is inadequate to control potential impurities, including potential (b) (4) degradants, manufacturing controls are inadequate to ensure consistent product quality, and the applicant has not provided adequate data to support the proposed dissolution test method. Therefore, from an OPQ perspective, this NDA is not deemed ready for approval in its present form until the above-mentioned issues are satisfactorily resolved. As such, OPQ recommends a **Complete Response (CR)** action from a product quality perspective.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The applicant, Axsome Therapeutics, is seeking under section 505(b)(2) of the FD&C Act approval for a fixed dose combination (FDC) tablet containing 20 mg meloxicam and 10 mg rizatriptan (as the benzoate salt). Rizatriptan is approved for this indication and marketed as MAXALT (tablets, NDA 20864) and MAXALT MLT (orally disintegrating tablets (NDA 20865). Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) approved for management of moderate to severe pain as Anjeso (injection, NDA 210583) and management of osteoarthritis pain (tablets/capsules, multiple applications). The applicant references NDAs 20864 and 210583 to support safety and efficacy of rizatriptan and safety of meloxicam, respectively.

Proposed indication(s) including intended patient population	Acute treatment of migraine with or without aura in adults
Duration of treatment	Chronic intermittent
Maximum daily dose	20 mg meloxicam/10 mg rizatriptan
Alternative methods of administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

Meloxicam

DMF (b) (4) was reviewed on 8/9/2021 and found ADEQUATE. The information was cross-referenced for this NDA and therefore has not been summarized in the body of the review.

Stability data submitted is sufficient to support a retest period of (b) (4) when stored at (b) (4)

Rizatriptan Benzoate

DMF (b) (4) was reviewed on 09-AUG-2021 by Friedrich Burnett, Ph.D. and found ADEQUATE. The information was cross-referenced for this NDA and therefore has not been summarized in the body of the review.

Stability data submitted is sufficient to support a retest period of (b) (4) when stored at (b) (4)

Drug Product: Inadequate

Drug product AXS-07¹ (SYMBRAVO™) is a fixed dose, combination of meloxicam and rizatriptan benzoate. AXS-07 drug product has been formulated as an immediate-release tablet for oral administration for acute treatment of migraine with or without aura. Each tablet contains 20 mg of meloxicam and 10 mg of rizatriptan (equivalent to 14.53 mg as benzoate salt).

(b) (4)
(b) (4)
(b) (4) The effects of attributes of the drug substance, excipients and formulation have been appropriately analyzed. The excipient compatibility studies have been performed to show the suitability of the chosen excipients. No critical physicochemical and biological properties including polymorph and particle size were identified that adversely affect the AXS-07 drug product performance.

¹ AX-07 is the applicant's code for meloxicam and rizatriptan tablets 20 mg/10 mg.

The proposed release specifications for the drug product are based on USP General Chapters, ICH guidelines and in-house data trends. The provided data for three registration batches fall into the applicant's pre-determined release specification. However, as outlined below there are two issues for the impurity controls and the registration batches are not deemed acceptable for determination of product shelf life.

The proposed acceptance criterion for the specified impurity Rizatriptan N-oxide (RNO), a rizatriptan degradant, of not more than (NMT (b) (4) %). This limit exceeds the ICH qualification threshold of NMT 0.5% for the maximum daily dose (10 mg) and is higher than allowed for approved rizatriptan products². In this application, the acceptance criterion of NMT (b) (4) % for RNO was set based stability data trend and published literature; no nonclinical or clinical supporting data was provided. Thus, this acceptance criterion was deemed unacceptable from a nonclinical perspective.

The applicant did not perform a risk assessment and control of (b) (4) impurities. The possibility for the (b) (4) and other (b) (4) is medium to high during the manufacturing process and the storage condition due to the following reasons: (b) (4)

(b) (4) The applicant committed to control the potential (b) (4) by sensitive methods thorough the shelf life in response an IR issued on 1/22/2022 but did not submit an analytical method or requested data for the existing product batches.

The applicant provided stability data for three registration batches and supportive data from scale-up and clinical batches. During the manufacturing review, it was determined that the registration batches failed (b) (4) and therefore they cannot simulate a viable commercial process. Therefore, it is recommended that the applicant manufacture new registration batches with acceptable (b) (4). At this time, an expiration dating period cannot be granted due to the failed registration batches and outstanding impurity issues.

Labeling: Adequate

The proposed labeling is adequate from a product quality review perspective.

² Cf. USP monographs for Rizatriptan Benzoate Tablets and Orally Disintegrating Tablets.

Manufacturing: Inadequate

Meloxicam and Rizatriptan Benzoate Tablets, 20 mg/10 mg are immediate release tablets manufactured by (b) (4)

(b) (4)

During development, the product was initially manufactured by (b) (4)

(b) (4)

In the original submission, the applicant proposed a commercial batch size (b) (4) times the registration batch size. However, in the amendment submitted on 9/27/2021, the applicant stated that the commercial batch size will be the same as the registration batch size. In the amendment submitted on 2/23/2022, the applicant stated the commercial batch size for (b) (4)

(b) (4)

Based on data provided in the amendment dated 2/23/2022, none of the three registration batches manufactured using (b) (4)

(b) (4)

Additionally, there are remaining concerns

(b) (4)

(b) (4)

All facilities proposed for manufacturing meloxicam API, rizatriptan benzoate API, and meloxicam and rizatriptan benzoate tablets are currently acceptable. Facility status will be reevaluated during any future review cycle.

***Biopharmaceutics:* Inadequate**

The Biopharmaceutics review focused on evaluation of the adequacy of the proposed dissolution method and acceptance criterion and need for formulation bridging throughout product development. The applicant did not request a biowaiver because the proposed product has only one strength and clinical studies were conducted on the to be marketed product.

Dissolution Method and Acceptance Criterion:

The applicant proposed an in-house dissolution method for this test product as shown in the table below. The applicant provided summary dissolution data from the clinical and registration batches but not the full profile. The applicant did not provide the method development report for the selection of the testing conditions and parameters. Therefore, the applicant was asked to provide the full dissolution profile data from the clinical and registration batches and method development report.

USP Apparatus	Speed (RPM)	Medium	Volume/Temp	Acceptance Criterion
(b) (4)				

In response to the request for fill dissolution profiles and the method development report, the applicant submitted the method development report and proposed the revised method below.

USP Apparatus	Speed (RPM)	Medium	Volume/Temp	Acceptance Criterion
(b) (4)				

In the original submission, the applicant investigated the discriminatory ability of the proposed dissolution method toward the parameters including (b) (4)

(b) (4) Additional results were provided for studying drug release with changes in product formulation including variations in (b) (4)

(b) (4) composition and coating. However, the applicant did not provide justification how the studied parameters and ranges were selected. Therefore, the applicant was asked to provide justification for the selection of the studied parameters and ranges for discrimination ability studies.

In response to the deficiency, the applicant investigated the discriminatory ability of the proposed dissolution method toward the parameters including API amount variation, changes in formulation and coating process. However, the results indicate the proposed method did not demonstrate discriminatory ability. Therefore, the applicant will be asked to provide justification for the selection of the studied parameters and ranges for discrimination ability studies

Formulation Bridging:

Formulation product bridging is not needed because to-be-marketed formulation was used for clinical studies and in bioavailability (BA) studies comparing to listed drugs under fasting condition and food-effect BA studies.

Environmental: Adequate

The applicant's claim for categorical exclusion under 21 CFR 25.31(b) is granted.

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 – Meloxicam	Formulation, container closure, moisture, process parameters	Low	Choice of excipients, container, process parameters	Adequate	Confirmed in stability studies
Assay, stability – Rizatriptan		Low	Choice of excipients, container, process parameters	Inadequate	(b) (4)
Content Uniformity – Meloxicam	API physical properties, formulation, process parameters, equipment, scale	Moderate	Selection of process parameters	Inadequate	
Content Uniformity – Rizatriptan		Low		Inadequate	
Physical stability – Meloxicam (solid state)		Moderate	(b) (4)	Inadequate	
Physical stability – Rizatriptan (solid state)		Low		Adequate	
Dissolution – Meloxicam		Moderate	Applicant proposes single test method for both actives	Inadequate	
Dissolution – Rizatriptan		Low		Inadequate	Inadequate justification for selection of test parameters. Discriminating ability not established.
Microbial Limits	Formulation, container closure, moisture, process parameters	Low	Tested at release and on stability. Desiccant in packaging.	Adequate	

D. List of Deficiencies for Complete Response

Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

N/A

Drug Substance Deficiencies

N/A

Drug Product Deficiencies

1. We note your agreement in the response dated January 3, 2022, to develop validated sensitive methods to demonstrate the levels of any potential (b) (4) and your commitment to analyze the registration and process validation batches of AXS-07 drug product using these methods, and to continue to monitor such (b) (4) to the end of the stability studies for these batches. Provide validated methods for determining (b) (4) in AXS-07 and the results of testing on the registration batches and any process validation batches manufactured to date.
2. An acceptance of NMT (b) (4) % for rizatriptan N-oxide in your release and stability specification of drug product is not acceptable. Tighten it to NMT 0.5% consistent with the ICH Q3B (R) qualification threshold and USP Rizatriptan Benzoate Tablet monograph. Alternatively, submit adequate safety data to qualify a higher limit for the N oxide impurity. If such data are not available, perform the appropriate nonclinical studies to support your proposed limit; for a chronic indication, the general toxicity study should be of 3 months' duration.
3. Since you have failed in accelerated studies and intermediate stability studies for the drug product, perform statistical analysis to determine the shelf-life of the product per ICH Q1E.
4. Provide tabulated stability protocols for validation batches (manufactured at commercial scale and in commercial packaging), post-approval batches and annual batches. The stability protocol for the first commercial batches should include testing under ICH intermediate and accelerated conditions.
5. We acknowledge that you provided the ASTM statistics data for (b) (4) (b) (4) for the 3 registration batches in the response dated 2/23/22 (Seq 0012). We notice that for Meloxicam, 2 of 3 batches failed (b) (4) ASTM statistics test, whereas for the 3rd batch the (b) (4) (b) (4)

(b) (4) Therefore, none of the 3 batches would be considered passing (b) (4) ASTM statistics test. Since the registration batches failed (b) (4) they cannot simulate a viable commercial process. We also observe the (b) (4) varies between the registration batches. We recommend you manufacture three (3) new registration batches with acceptable (b) (4) and repeat the primary stability studies. (b) (4)

6. Include (b) (4) in both release and stability specification to show that there is no (b) (4) for meloxicam (b) (4) and rizatriptan benzoate during storage of drug product or provide justification for not including this test

Labeling Deficiencies

N/A

Manufacturing Deficiencies

1. In the amendment submitted on 2/23/2022, the commercial batch size for meloxicam (b) (4) was proposed to increase from (b) (4) kg to (b) (4) kg. We acknowledge you updated the batch formula for meloxicam (b) (4) in Section 1.11. Include the batch formula for meloxicam (b) (4) in Module 3.2.P.3.2. In addition, update the commercial batch record for meloxicam (b) (4) manufacturing to reflect the increased commercial batch size, in-process tests performed at (b) (4) site and proposed hold times for all process intermediates and final meloxicam (b) (4)
2. Address the following comments for meloxicam (b) (4) process and update Module 3.2.P.3.3 and Module 3.2.P.3.4 accordingly.

a.

b.

c. [REDACTED] (b) (4)

3. We acknowledge you agreed to [REDACTED] (b) (4)
[REDACTED] (b) (4)

4. We acknowledge you provided the dissolution profiles for both feasibility batch CDTCN and scale-up feasibility batch CFGBW to support your proposed upper limit of tablet hardness (b) (4) kp). However, the dissolution medium [REDACTED] (b) (4) [REDACTED] used for supporting the upper limit of the hardness is different from the proposed dissolution medium [REDACTED] (b) (4) for drug product release testing. We recommend you provide the dissolution study data obtained using the same dissolution method as that proposed for DP release testing to support your proposed hardness range (b) (4) kp with target (b) (4) kp). Note that the data from failed registration batches cannot be used to support your proposed hardness range.

5. In the amendment submitted on 2/23/2022, you proposed mitigation strategy to [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]. Update the commercial batch records accordingly and address the following comments.

a. [REDACTED] (b) (4)

b. [REDACTED]

- c. [REDACTED] (b) (4)
- d. [REDACTED]

6. We acknowledge you [REDACTED] (b) (4)
- [REDACTED] (b) (4)

7. We acknowledge you established [REDACTED] (b) (4)
- [REDACTED] (b) (4)

8. We acknowledge you confirmed there is no change for the proposed [REDACTED] (b) (4)
- [REDACTED] (b) (4)

Biopharmaceutics Deficiencies

1. For the fixed-dose combinational (FDC) drug products, the Agency typically recommends the development of separate/different dissolution methods for each of the two drug substances (or API) unless a single method can be satisfactorily demonstrated to be suitable and discriminating for the drug substances. Given

that, we do not consider that you have adequately justified the selection of (b) (4)
(b) (4)
(b) (4) for the proposed
single dissolution method. Specifically,

- While we acknowledge the demonstrated improvement in (b) (4)
(b) (4)
 - Based on the provided information and data, we do not believe that the use of (b) (4) for dissolution testing is justified. Please note that in principle, the Agency does not recommend the use of (b) (4) without appropriate justifications and supporting evidence. In addition, you reported that (b) (4)
(b) (4)
(b) (4) Based on the provided information and data/figures in your responses to the Information Request (dated 02/18/2022), you should explore the utility of (b) (4)
(b) (4)
 - We do not consider the reported investigation of discriminating ability of the proposed dissolution method being appropriately performed. While the Agency typically recommends $\pm 10\%$ range for the study, you should provide adequately justifications for the relevant or meaningful ranges of the critical material attributes (CMA) or critical process parameters (CPP) in the aberrant formulations tested.
2. The originally proposed acceptance criterion of (b) (4)
(b) (4) as quality control for both meloxicam and rizatriptan is permissive based on the submitted dissolution profile data from the biobatch/registration batches. Note that all the batches of the proposed product exhibited rapidly dissolving profiles with (b) (4)
(b) (4) In your resubmission, you should submit study report for the method development and generate complete dissolution profile data (n=12) of biobatch/registration batches and stability batches using the final selected dissolution method(s) for both drug substances. In addition, you should propose

a new set of acceptance criterion for each drug substance based on the biobatch/registration batches. The acceptance criterion should be set based on the time-point where ^{(b) (4)} % of the dissolution occurs.

Microbiology Deficiencies

N/A

Other Deficiencies (Specify discipline, such as Environmental)

N/A

Application Technical Lead Name and Date:

Martha R. Heilmann, Ph.D.

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

3/30/2022



Martha
Heimann

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BIOPHARMACEUTICS REVIEW

NDA Number	NDA-215431-ORIG-1
Drug Product Name	Symbravo™ (meloxicam and rizatriptan benzoate) Tablets
Dosage Form/ Strength	(b) (4) Tablet/ 20 mg Meloxicam - 10 mg Rizatriptan
Route of Administration	Oral
Applicant Name	Axsome Therapeutics, Inc.
Therapeutic Classification/ OND Division	Division of Neurology
Proposed Indication	Acute treatment of migraine with or without aura in adults.
Submission Date	6/30/2021 (Original); 02/18/2022 (IR response)
Primary Reviewer	Swapna Pamu, M.S.
Secondary Reviewer	Ta-Chen Wu, Ph.D.
Recommendation	Inadequate

EXECUTIVE SUMMARY

The Applicant is seeking 505(b)(2) approval for the proposed fixed-dose combination (FDC), Symbravo™ (meloxicam and rizatriptan benzoate) Tablets, 20 mg/10 mg (or AXS-07) The Listed Drugs (LD) for this proposed product are Anjeso (Meloxicam) Injection (NDA 210583) and Maxalt (Rizatriptan benzoate) Tablets (NDA 020864). The proposed drug product is indicated for the acute treatment of migraine with or without aura in adults. The recommended maximum dose is 1 tablet (20 mg of meloxicam and 10 mg of rizatriptan) administered orally with or without food at the onset of a migraine.

REVIEW SUMMARY:

The Biopharmaceutics review is focused on evaluation of (1) the adequacy of the proposed dissolution method and acceptance criterion, (2) need for formulation bridging throughout product development, and (3) risk assessment. The Applicant did not request Biowaiver because the test product has only one strength.

1) Dissolution Method and Acceptance Criterion:

The Applicant proposed an in-house dissolution method for Symbravo™ as shown in the table below but did not provide method development report or justifications for the selection of the testing conditions and parameters.

USP Apparatus	Speed (RPM)	Medium	Volume/Temp	Acceptance Criterion
(b) (4)				

Per the Agency's request, the Applicant provided method development report and revised the in-house method as shown in the table below. The submitted dissolution profile data from clinical and registration batches were generated using the revised method and show rapid dissolution (b) (4) for both drug substances. The proposed acceptance criterion is permissive.

USP Apparatus	Speed (RPM)	Medium	Volume/Temp	Acceptance Criterion
(b) (4)				

This Reviewer does not consider the selection of (b) (4)
(b) (4)
(b) (4) are adequately justified.

The Applicant investigated the discriminatory ability of the proposed dissolution method towards parameters, including (b) (4)
(b) (4) (b) (4) as well as (b) (4)
changes in (b) (4) composition and coating. However, the Applicant did not provide justification how the studied parameters and ranges were selected. The proposed dissolution method was not found to be discriminatory for the studied parameters.

2) Formulation Bridging:

Formulation/product bridging is not needed because the to-be-marketed formulation/product was used in the bioavailability study comparing to LD under fasting condition and food-effects.

3) Biopharmaceutics Risk Assessment:

Based on the initial risk assessment (by the ATL during the filing meeting), content uniformity (both actives), physical stability (meloxicam) and dissolution (meloxicam) are considered moderate risk critical quality attributes (CQAs). The remaining CQAs are considered low risk. Considering the immediate release nature of the drug product, the risk associated with dissolution and bioavailability of Rizatriptan (highly soluble, per BCS criteria) could've been considered "low". With lingering concerns regarding adequacy of the proposed dissolution method and permissive acceptance criteria as quality control, adding the reported (b) (4) the Biopharmaceutics risk and mitigation assessment for Symbravo™ is pending.

RECOMMENDATION:

From a Biopharmaceutics perspective, NDA 215431-ORIG-1 for Symbravo™ (meloxicam and rizatriptan benzoate) Tablets, 20 mg/10 mg, is deemed inadequate because of the outstanding biopharmaceutics deficiencies regarding the adequacy of in vitro dissolution method and the appropriateness of the acceptance criterion for each drug substance.

BIOPHARMACEUTICS ASSESSMENT

List Submissions being assessed:

Document(s) Assessed	Date Received
Original Submission	06/30/2021
Response to Information Request	02/18/2022

Drug Substance and Drug Product:

Symbravo™, an oral FDC of 20 mg meloxicam and 10 mg rizatriptan, is formulated into modified capsule-shaped, film-coated, immediate-release tablets. The proposed FDC tablets are formulated to improve the solubility and enhance the absorption of meloxicam for the migraine indication. According to the Applicant, “The meloxicam formulation in Symbravo™, which we refer to as MoSEIC™ (Molecular Solubility Enhanced Inclusion Complex), incorporates (b) (4)

(b) (4)

BCS DESIGNATION: *Not requested.*

Solubility:

The Applicant claimed that meloxicam belongs to the Biopharmaceutics Classification System (BCS) Class 2 with low solubility. Rizatriptan benzoate has good solubility across pH range from 1.20 to pH 9.18.

Meloxicam:

The provided solubility study results across the physiological pH range (pH 1 to 13) are summarized below in Table 1, which confirms that meloxicam is a low soluble drug substance, per the BCS criteria (b) (4)

Table 1. Aqueous Solubility of meloxicam¹

Aqueous Solubility at Various pH Values	At pH 1: solubility = 0.01 mg/mL At pH 3: solubility = <0.01 mg/mL At pH 5: solubility = <0.01 mg/mL, At pH 7: solubility = <0.01 mg/mL At pH 9: solubility = <0.01 mg/mL At pH 12: solubility = 0.01 mg/mL At pH13: solubility = 0.02 mg/mL
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The Applicant developed the formulation with improved solubility of meloxicam to enhance its absorption. To improve the solubility of meloxicam, (b) (4)

Table 2. Amount of meloxicam and (b) (4) dissolved in different media

Table 2: Amount of Metronidazole and		Observed in different media	
Media	Sample	Average (mg/mL) at (b) (4)	Average (mg/mL) at (b) (4)
(b) (4)			

Applicant was requested to provide justification for selecting [REDACTED] (b) (4) timepoints for meloxicam solubility measurement and provide meloxicam solubility improvement data at different pH conditions (see **Appendix 1**).

In response to the deficiency (dated 02/18/2022), the Applicant clarified that solubility of meloxicam (b) (4) is very low (b) (4)

[1 \\CDSESUB1\evsprod\nda215431\0001\m3\32-body-data\32s-drug-sub\meloxicam\32s1-gen-info\general-properties-mlx.pdf](#)

² [\\CDSESUB1\evsprod\nda215431\0001\m3\32-body-data\32p-drug-prod\axs-07\32p2-pharm-dev\pharmaceutical-development-2.pdf](#), page 12

(b) (4)

(b) (4)

(b) (4)

Rizatriptan:

The provided solubility study results across the physiological pH range (pH 1.2 to 9.18) are summarized in Table 3, which confirms that rizatriptan is a highly soluble drug substance, per the BCS criteria. Rizatriptan is a highly soluble drug substance (b) (4)

Table 3. Solubility of rizatriptan in aqueous buffers³

pH	Solubility (mg/mL)
1.2 pH buffer solution	130.38
4.00 pH acetate buffer	71.44
6.86 pH phosphate buffer	52.50
9.18 pH phosphate buffer	61.15
Water only	62.73

Permeability:

The Applicant did not provide permeability data for meloxicam and rizatriptan. However, the absolute bioavailability data from Mobic⁴ (F=89%) and Maxalt⁵ (F=45%) suggest that meloxicam and rizatriptan belongs to high permeability class.

Dissolution:

The proposed meloxicam-rizatriptan (20 mg-10 mg) (b) (4) tablet is rapidly dissolving, i.e., more than (b) (4) (See below for dissolution profile data and specifications).

DISSOLUTION METHOD AND ACCEPTANCE CRITERION

Assessment: *Inadequate*

Dissolution Method Development

The Applicant proposed an in-house dissolution method for the proposed product as shown in Table 4. The Applicant did not provide method development report for the selection of the testing conditions and parameters. An Information Request (IR) was issued to request for the method development report (**Appendix 1**).

³ \\CDSESUB1\evsprod\nda215431\0001\m3\32-body-data\32s-drug-sub\rizatriptan\32s1-gen-info\general-properties-rzt.pdf

⁴ https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020938s028lbl.pdf

⁵ https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020864s023,020865s024lbl.pdf

Table 4. Originally proposed dissolution method and acceptance criterion

USP Apparatus	Speed (RPM)	Medium	Volume/Temp	Acceptance Criterion
(b) (4)				

The Applicant provided summary dissolution data for 6 clinical trial batches (3847-23-Phase 1, CBHCV (Phase 3), CCGVX (Phase 1&3), CCSGK (Phase 3), CCVNG (Phase 3), CCYKS (Phase 3) and 3 registration batches (CDTKD, CDTKM, CDTKN) as shown below in Table 5, without individual dissolution data. Additional information was requested (*Appendix I*).

Table 5. Dissolution Data for AXS-07 drug product Batches

(b) (4)				
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Figure 1. Comparison of Dissolution (n= 12)

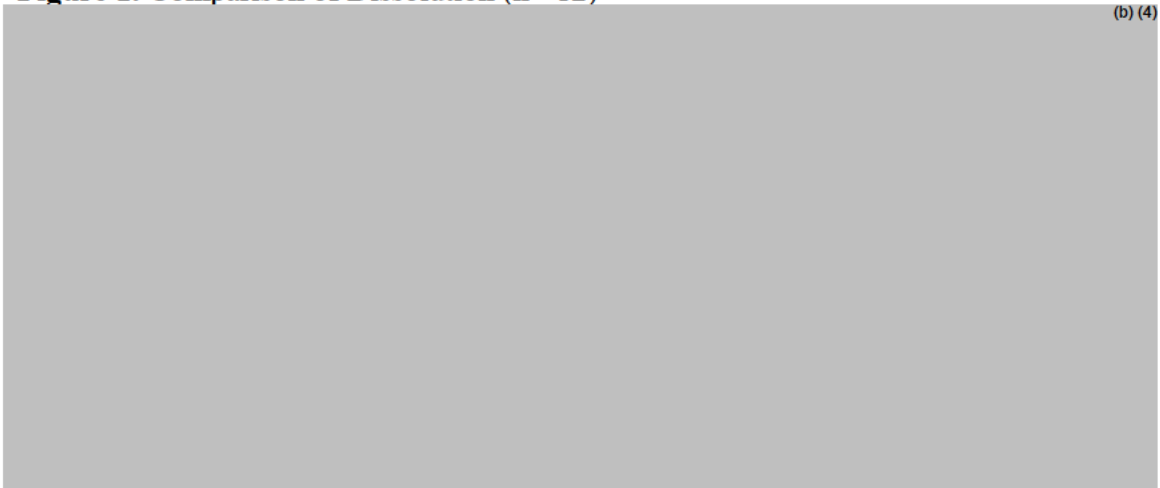


Figure 1 illustrates rapid drug release (b) (4) with low variability. Based on the submitted dissolution data, the proposed dissolution acceptance criterion is permissive and would not be acceptable. Data-driven acceptance criterion will be

recommended after new dissolution profile data from the biobatch/registration batches are generated using the suitable dissolution method(s) which is found acceptable (*Appendix I*).

In response to the IR (*Appendix I*), the Applicant provided method development report and revised the in-house method as shown below (Table 6). Additionally, per requested, the Applicant submitted the dissolution profile data from all clinical and registration batches generated using revised method⁶, as well as dissolution profile data from long-term (25°C ± 2°C/ 60% RH ± 5% RH) and accelerated (40°C ± 2°C/75% RH ± 5% RH) stability tests⁷. The Applicant also provided Individual unit dissolution profile data for each batch.⁸

Table 6. Revised dissolution method and acceptance criterion

USP Apparatus	Speed (RPM)	Medium	Volume/Temp	Acceptance Criterion
(b) (4)				

The Applicant did not adequately justify the selection of (b) (4) (b) (4) (b) (4) for the proposed single dissolution method. Specifically, while the Applicant demonstrated improvement in solubility of (b) (4) (b) (4) being physiologically not relevant for the proposed orally administered FDC tablets. The Applicant will be recommended to explore a dissolution medium at a physiologically relevant pH condition.

Based on the provided information and data, the use of (b) (4) (b) (4) for dissolution testing is not adequately justified. In addition, the Applicant reported that (b) (4) (b) (4) produced dissolution profiles similar to the control conditions (b) (4) (b) (4). Based on the provided information and data/figures, the Applicant will be asked to explore the utility of (b) (4) (b) (4).

Discriminating Ability of Dissolution Method⁹:

In the original submission, the Applicant investigated the discriminating ability of the proposed dissolution method toward API, formulation and process changes of the proposed drug product. The performed discriminating ability studies and the results are

⁶ [\\CDSESUB1\evsprod\nda215431\0011\m3\32-body-data\32p-drug-prod\axs-07\32p2-pharm-dev\pharmaceutical-development-2-3.xlsx](#)

⁷ [\\CDSESUB1\evsprod\nda215431\0011\m3\32-body-data\32p-drug-prod\axs-07\32p8-stab\stability-data.pdf](#)

⁸ [\\CDSESUB1\evsprod\nda215431\0011\m3\32-body-data\32p-drug-prod\axs-07\32p2-pharm-dev\pharmaceutical-development-2-2.pdf](#)

⁹ [\\CDSESUB1\evsprod\nda215431\0001\m3\32-body-data\32p-drug-prod\axs-07\32p2-pharm-dev\pharmaceutical-development-2-1.pdf](#)

summarized in Table 7. The dissolution profiles of Meloxicam and Rizatriptan (% released) were generated for the target (CDTKD-registration batch) and intentionally altered batches.

Table 7. Summary of test product made with intentional variations in formulation and process parameters

Item	Study	Dissolution samples (n=12)	Lot CDTKD *Target
(b) (4)			
*Target = reference table sample (registration lot CDTKD)			

Differences in dissolution profiles were reported (based on similarity factor f2 values <50) between the target and altered batches for some of the test combinations as shown in Table 8 below.

An f2 value of <50 is observed for the below combinations:

- Meloxicam: (b) (4)
- Rizatriptan: (b) (4)

Table 8. f2 values for meloxicam and rizatriptan dissolution (% released)

Excipient/Process Parameter	Test Value	Meloxicam f2 Values 10 to 30 mins	Meloxicam f2 Values All Time Points	Rizatriptan f2 Values 10 to 30 mins	Rizatriptan f2 Values All Time Points
(b) (4)		51.79	55.02	51.05	51.43
		63.16	63.97	63.85	68.19
		63.43	64.27	62.10	68.36
		64.87	67.94	62.13	68.26
		44.87	49.35	50.32	57.33
		41.25	46.83	42.38	49.04
		53.01	56.57	63.64	70.66
		70.41	70.16	67.81	70.75
		51.00	56.08	55.12	62.20
		57.51	59.44	63.41	69.83
		47.56	52.39	48.89	55.43
		73.26	63.87	93.28	89.46
		56.49	59.81	71.35	77.39
		60.20	60.77	78.05	83.25

*Target = reference table sample (registration lot CDTKD)

The Applicant was requested to provide justifications for the selection of the studied parameters and ranges for discrimination ability studies (see **Appendix 1**).

In response to the IR, the following variation to formulation were tested:

Parameter studied	Target batch	Variation in altered batch
(b) (4)		

This Reviewer does not consider the formulation variations studied meaningful, as in most of the cases, differences are greater than +/-10% without adequately justification. In addition, except at starting timepoint, there are no significant differences in the dissolution observed between target batch and altered batches. Therefore, the proposed dissolution method was not found to be adequately discriminatory for any of the studied parameters. The Applicant's response is deemed inadequate to this Reviewer.

Dissolution Acceptance criterion:

The Applicant proposed an acceptance criterion of (b) (4) minutes" for both meloxicam and rizatriptan. Based on the submitted dissolution profile data from the biobatch/registration batches, the proposed acceptance criterion is

permissive. All the batches of the proposed product exhibited rapidly dissolving profiles with (b) (4). Therefore, data-driven dissolution acceptance criterion will be recommended after the dissolution method is found to be acceptable (**Appendix 1**).

BRIDGING OF FORMULATIONS

Assessment: *Adequate*

The drug product formulation (shown below in Table 9) used in clinical trials is the same as the one used in the registration batches. However, modifications were made to the manufacturing process of registration batches (b) (4)

(b) (4) to support scale-up. To demonstrate the lack of impact of manufacturing changes on tablet quality or performance, the Applicant submitted comparative dissolution test results, using the proposed dissolution method/test condition. Batch release testing data for dissolution of meloxicam and rizatriptan for the clinical and registration batches are similar. Additional bridging is deemed unnecessary.

Table 9. Formulation composition¹⁰

Component	Function	Amount per Tablet	
		mg	% (w/w)
(b) (4)			
Meloxicam, USP	Active	20	(b) (4)
Rizatriptan benzoate (equivalent to 10 mg freebase), USP	Active	14.53	
(b) (4)	(b) (4)	(b) (4)	
Sulfobutyl-ether- β -cyclodextrin sodium (SBECD), USP/Ph. Eur.			
Microcrystalline Cellulose (b) (4) NF/Ph. Eur./JP			
Pregelatinized Starch, NF/Ph. Eur.			
Colloidal Silicon Dioxide, USP/NF/Ph. Eur./JP			
Povidone, USP/Ph. Eur./JP			
Crospovidone (b) (4) NF/Ph. Eur./JP			
Magnesium Stearate, NF/Ph. Eur./JP			
Sodium Bicarbonate, USP			
(b) (4)			
(b) (4)			

JP = Japanese Pharmacopoeia, NF = National Formulary; Ph. Eur. = European Pharmacopoeia; USP = United States Pharmacopoeia

(b) (4)

¹⁰ <\\CDSESUB1\evsprod\nda215431\0001\m3\32-body-data\32p-drug-prod\axs-07\32p1-desc-comp\description-and-composition.pdf>

BIOPHARMACEUTICS RISK ASSESSMENT

The Applicant claimed that the meloxicam belongs to the Biopharmaceutics Classification System (BCS) Class 2 (low solubility and high permeability). Per Mobic (meloxicam) capsules label, the absolute bioavailability of meloxicam capsules was 89% following a single oral dose of 30 mg compared with 30 mg IV bolus injection¹¹. Based on the submitted solubility study results of the proposed product and absolute bioavailability data from Mobic label, this reviewer considers meloxicam belongs to BCS Class 2. To improve the solubility of meloxicam, the Applicant (b) (4)

Rizatriptan drug substance has high solubility over the pH range of 1.2 to 9.18. Per Maxalt (rizatriptan) tablets label, rizatriptan is completely absorbed following oral administration. The mean oral absolute bioavailability is 45%¹². Considering the high solubility of the meloxicam (b) (4) and rizatriptan as well as the immediate release nature of the drug product, risk in dissolution is considered low. Note that time to peak drug concentration (Tmax) of the active ingredients is considered critical in view of the proposed migraine indication.

During the review cycle the OPMA review team reported that 3 registration batches had (b) (4) and, consequently, none of the 3 batches would be considered passing (b) (4) ASTM statistics test. With lingering concerns regarding adequacy of the proposed dissolution method and permissive acceptance criteria as quality control, adding the reported (b) (4) (b) (4) (reported by), the Biopharmaceutics risk and mitigation assessment for Symbravo is pending.

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

See **Appendix 1** for Biopharmaceutics Deficiencies.

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

¹¹ https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020938s028lbl.pdf

¹² https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020864s023,020865s024lbl.pdf



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